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CNIC & SOCIETY

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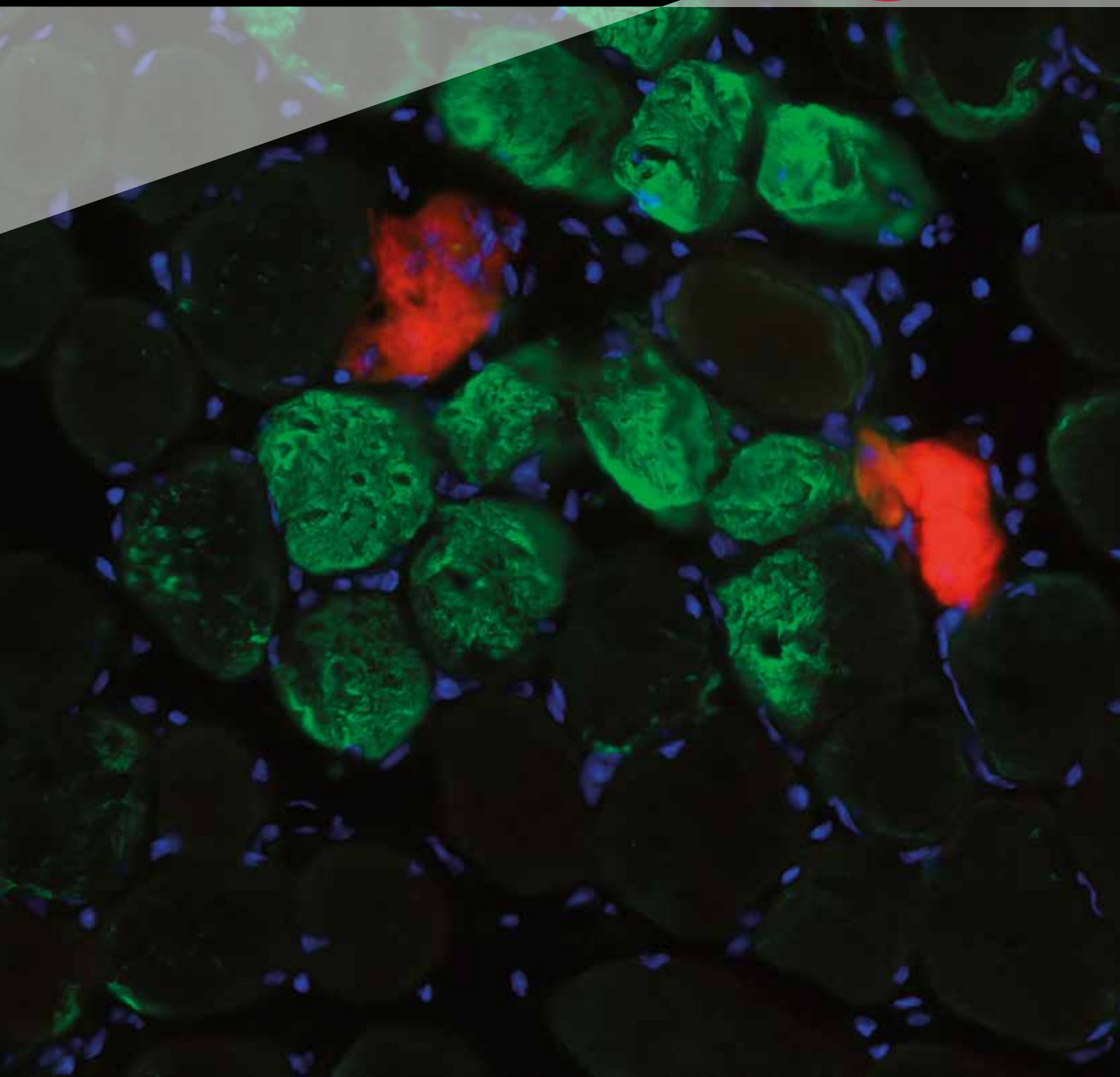

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Dr. Valentín Fuster, General Director of Carlos III National Centre for Cardiovascular Research (CNIC)

RESEARCH IS ESSENTIAL FOR A COUNTRY'S FUTURE

The Centro Nacional de Investigaciones Cardiovasculares Carlos III or CNIC (the Spanish National Centre for Cardiovascular Research) has set itself the primary mission of improving the population's cardiovascular health through research. Indeed, one of CNIC's hallmarks is the translation of basic research to the clinical setting. We work to understand what constitutes health within the context of the changes occurring in medicine. Understanding what health consists of is fundamental when it comes to comprehending disease.

The CNIC's 2022-2025 Strategic Programme does not modify the organisation's structure, but does contemplate diverse actions in the area of science that will facilitate consolidation of the CNIC as an international reference centre for translational research in the cardiovascular field and in the study and promotion of cardiovascular health. These are the main objectives of the CNIC Severo Ochoa Project strategic plan (2022-2025), under the auspices of Spain's Ministry of Science and Innovation.

This strategic plan brings the main focus of CNIC scientific activity from 2022 onto five large Research Programmes that aim to tackle the challenges arising in the cardiovascular field in coming years.

And one of the challenges we have to face is the need for clinical research scientists capable of integrating basic and clinical research. Another is the promotion of young researchers within the Spanish research system.

I believe that although the situation of research in Spain has improved over the last 10-15 years - today we have a more deeply rooted culture of research than 15 years ago - work still needs to be done to ensure a higher proportion of GDP reaches research.

And it is here that the PERTE (Strategic Projects for Economic Recovery and Transformation) will play a major role, as **Dr. Cristóbal Belda**, Director of the Carlos III Health Institute has indicated, because these projects cover the need to transform our way of undertaking R&D as well as the efficiency with which the R&D is ultimately transferred to society.

The road ahead is, therefore, to continue working on public awareness that research is essential for a country's future.

DIRECTOR OF CARLOS III HEALTH INSTITUTE

Cristóbal Belda

"PERTE REPRESENTS AN OPPORTUNITY TO HELP OUR COUNTRY"

Dr. Cristóbal Belda became Director of the ISCIII (Carlos III Health Institute) last August. Until his appointment, he had served as the Institute's Deputy Director General with direct responsibility for operational management of Acción Estratégica en Salud, the main strategic actor in coordinating and fostering biomedical research in Spain. He is a specialist in medical oncology and Doctor in medicine, who is an expert in the design and execution of highly complex clinical trials and cancer biomarkers, co-author of over 100 articles published in international journals, tens of book chapters and advisor for nine doctoral theses. Since 1999, he has attended patients and families diagnosed with brain tumours and lung cancer, as well as undertaking research to improve their quality of life.

The Strategic Projects for Economic Recovery and Transformation (known as PERTE) have just been approved. What research opportunities do they represent for the Carlos III Health Institute (ISCIII)?

The ISCIII is one of the organisations with greatest involvement in PERTEs, and we are extremely proud of this. What's more, the ISCIII itself has invested considerable funds within these strategic projects. What we have to understand is that the ISCIII is a scientific body anchored in healthcare and, therefore, we simultaneously represent both science and healthcare. We play an important role in PERTEs, in the sense that this dual focus is necessary in order to meet the majority of PERTE objectives. As well as this dual focus, PERTEs contemplate the need to transform our way of conducting R&D, and the efficiency with which this R&D is ultimately transferred to society. And this can be achieved in many ways: transfer may be in the form of industrial wealth or highly qualified jobs, but we can also direct it at transgenerational training for different people: from the youngest, who need training in different pre-doctoral or post-doctoral routes, to people who are more mature and have greater professional skills but need to adapt to new and more complex environments.

What does the term *salud de vanguardia* mean?

Vanguard Health, *salud de vanguardia* in Spanish, is a combination of all possible technologies and information sources to achieve optimum prevention, diagnosis, treatment and rehabilitation for each individual. That is to say, taking all the data we can obtain about the collective, employing big data analytics, and applying this information at the level of a specific individual, with the final goal of preventing and avoiding problems this person may experience by delaying them as long as possible or, in the case of the onset of problems, solving them as quickly as possible so that the individual can enjoy a full life. In turn, this result should enable us to obtain feedback to add to the collective dataset and improve the precision of the various derived actions.

> "The global transformation of our National Health System represents a historic opportunity for scientists, businesses and our National Health System itself, because ultimately, it is people who are at its centre"

Could we say that we are much closer to personalised or precision medicine?

Over and above population studies, we need many other things, because precision medicine is a goal. In addition to precision medicine as a goal, we have to include certain types of therapy that are highly precise treatments, practically tailor-made for the individual. This has to be combined with a data system that allows us to include information taken from social and environmental areas, data about health and disease, in addition to lifestyle habits.
Ultimately, the four goals set out in PERTEs are inseparable in nature, despite the fact that in order to correctly carry them out, each has to be individually conceptualised. In any case, to achieve precision, you need data, to obtain data, digitization is necessary, to achieve advanced therapies, you need digitization and precision: we have distinguished four objectives or goals, with very specific leads, but the truth is that they form an inseparable unit.
There are also transversal or interdisciplinary lines that completely determine the objective, bearing in mind that the aim of PERTEs is to create wealth and highly qualified employment, but through health, and the enormous developments in health R&D.
And at this point it is worth remembering that Spain has been able to carry out academic R&D at the highest level. If we consider the size of our economy and make a rank list comparing the position we have to Spanish scientific production, it becomes clear that there is an imbalance, since our position in scientific production is vastly superior compared with the size of our economy. It is amazing how much we have achieved in recent decades. Moving on from this point, the next thing we need to do is analyse the capacity of this scientific production to be transformed into industrial wealth. And it is here that we find the gap. So, we need to be able to take advantage of the opportunity offered by PERTEs to help us bridge this gap. It should be the seed, a seed that generates a strong, firm root that will enable us to bridge the distance, providing a clear and definite path between academic scientific production and industrial wealth. What's more, managing to achieve this objective will allow us to bring scientific fact both to the lives of the people who go to hospital at a given time because they are ill, and to the creation of employment and industrial wealth.

One objective of PERTEs is to encompass both the public and private sectors. How do you intend to do that?

Each sector knows how to do one thing, sometimes several things, but in general, when you focus talent, it is very productive. We, as the public sector of science, know how to produce science at a very high level. The business and industrial sectors know about business and industry, and they do it very well. If we add to these factors the fundamental principle of public-private cooperation, maintaining a two-way perspective that surpasses the linear idea of sales as the basis of this collaboration, we achieve a truly winning combination. To do this, we have to align both worlds so that they share the same line of vision, even though this may mean that we have to adapt our initial points of view. As well as that, we would have to be able to add regulatory science, which is often lacking in the academic sector, and is what the business sector probably knows a lot about. You could be capable of developing the best biomarker in the world, but in order for it to get into the system it has to pass a series of regulatory filters in the same way as any drug, medical device, etc. And we, as scientists, don't always have good knowledge of this, despite the common language that may exist in both sectors.

How can PERTEs be made attractive for private businesses so that they become fully involved?

I believe that there is a basic attraction, which is that this is a project for the entire country. Throughout the public health crisis caused by COVID, we heard many voices saying that everyone wants to help their country. PERTEs represent an opportunity to help our country.
As citizens, we have to try to develop the capacity to build the industrial fabric, to create employment that is highly competitive. Secondly, academic R&D has to have an industrial application, a result that will generate wealth and returns for the population. There are a good number of our businesses that need high-value R&D to be competitive at an international level. The PERTEs should be able to focus common interests and bring them into the same line of vision.
In addition, the global transformation of our National Health System represents a historic opportunity for scientists, businesses and our National Health System itself, because ultimately, it is people who are at its centre. At times the people are scientists, at others they are patients, and sometimes they are industry. Now is the time, so, as our Minister of Science always says: "people".

> "We cannot consider PERTEs as a fixed entity, as a box with a specific, limited capacity. PERTEs are a blueprint, with very specific funding - almost 1,500 million euros, that will achieve a series of objectives"

> "As scientists, we can do as much as possible to promote health, but the reality is that this is achieved by educating people. Health by learning. And we haven't taken this step yet, but Dr. Fuster has"

So, given that CNIC has experience in public-private collaboration, how will it participate?

PERTEs represent an umbrella covering a series of objectives and a number of financial tools. Under this umbrella there will be subsidies, partially repayable loans, and it

even contemplates the creation of a company. So, what will the CNIC's role be? CNIC is an institution with an enormous capacity to generate knowledge applied to people. What we hope is that the CNIC will be able to help us hold up the umbrella and generate new projects that come under the umbrella. We cannot consider PERTEs as a fixed entity, as a box with a specific, limited capacity. PERTEs are a blueprint, with very specific funding - almost 1,500 million euros, that will achieve a series of objectives. But on this foundation, other pieces will be added whose aims, obviously, will align with PERTE general objectives, but will also help us to steer this boat in a direction that will help us achieve our goals.

The ISCIII's previous Director, **Dr. Raquel Yotti**, was very interested in improving the relationship between health and science within hospitals. Do you share this idea?
Absolutely. My project as ISCIII Director is a continuation of **Dr. Raquel Yotti**'s project. **Dr. Yotti**'s role at ISCIII was revolutionary: when we see things with more historical perspective we will realise the dimension of what **Dr. Yotti**'s did here, and of what she continues to do from her current position as Secretary General for Research.
So, the policy that we are going to follow is the one that **Dr. Yotti** began. We will continue along the same path and in the same direction begun by her. We will continue with the Strategic Plan that she promoted. Bearing in mind my time as Deputy Director under her, and that as such I participated in the strategic plan, it would be strange if we did not follow that path.

What challenges do you face in your new position as Director?
The major challenge is to be able to comply with the Strategic Plan with sufficient flexibility to respond to new challenges.

When you became Director of ISCIII we were in the middle of the COVID-19 pandemic. How has the pandemic conditioned research at the ISCIII?
The ISCIII response was, and is, excellent. The professionals who work here do so for their fellow citizens, and often go far beyond the requirements of their positions. Obviously, the main focus of ISCIII's work in research is transmissible diseases, however, we do also research non-transmissible diseases. At present, with a pandemic of a transmissible disease, naturally, our main effort is directed at this.
Nevertheless, it is true that from the Institute, we have accessed additional funding that has been distributed to different external groups and has enabled health-focused research activity to continue in a way that would have been difficult if we had only concentrated on the pandemic.

What do you mean by that?
We have increased our funding for research into cancer, cardiovascular diseases, neurological diseases, etc. In our efforts to fight COVID, what we could not allow to happen was to detract funding from science against cancer, ischaemic heart disease, high blood pressure, diabetes, etc. We could not allow that. The government made a firm commitment to science that would combat COVID and the support that we have had over the last two years has been very firm; however, over the same period, we have increased funding for the rest of science in order to protect health.

The Institute, unfortunately, has been able to respond very well. And I say "unfortunately" because that response has been conditioned by the existence of a pandemic which is, obviously, unfortunate.

So, the creation of the biomedical research network for infectious diseases, CIBERinfec, is a step in this direction... towards being alert to the possibility of new viruses?

For many years, we have been thinking about a research network for infectious diseases, and to tell the truth, the pandemic gave us the final nudge to set up CIBERinfec.

How important is it to generate scientific knowledge to combat situations like the one we are living nowadays?

We have to generate knowledge aimed at three essential aspects. The first aspect is knowledge for its own sake. Science is valuable for its own sake. This is something that we have to be quite clear about in a world where everything is focused on utilitarianism, which is also essential, because we have to be capable of transferring scientific fact to citizens, industries, businesses, the country. But we should not forget something quite basic, which is that science, for its own sake, is an absolute value that we must protect.

The second aspect is science to avoid or delay disease: this is another of the major aspects we need to focus on.

And finally, science to reverse or alleviate disease. Because sooner or later, each of us will become ill. We try to avoid or delay it as far as possible and, if we cannot, it is very important that we should be able to try and reverse or alleviate it.

The CNIC Director General, **Dr. Valentín Fuster**, says that the time has come to stop talking about disease or illness and to start talking about health, of taking care of ourselves.

There are two important aspects here, and **Dr. Fuster** is one of the great champions of this approach. At the end of the day, the way to promote health is through education. As scientists, we can do as much as possible to promote health, but the reality is that this is achieved by educating people. Health by learning. And we haven't taken this step yet, but **Dr. Fuster** has. He has taken health education to children, because educating a child is probably easier than changing the habits and behaviour that we have as adults. As adults, our attitude, our habits, are as formed and inflexible as our bone structure, whereas children are still flexible, and in all likelihood, this is the time when it is possible foster healthy habits.

If we promote healthy lifestyle habits from infancy, it will probably change us and protect us when we are older. It is a very complicated exercise to undertake. Science is fundamental but, at the end of the day, what is most important are schools and families: these are the places where health can really be promoted. I remember something that **Dr. Fuster** said, "if a child eats well, the parent will do what is necessary to eat well." For me, that is the message.

We could say that the pandemic has brought some good things and that society now perceives the value of science, the value of innovation in research. Can this trend be used to make society aware of how important it is to take care of our own health?

If we don't take care for our own health, who will? What I mean is that each of us has to have sufficient discipline to eat fruit and vegetables every day, because nobody is going to come along and eat that fruit and vegetables for us. Each of us should avoid cigarettes or alcohol or certain types of bad habits.

But it is also important to bear in mind something that I consider essential: although self-care is, without a doubt, primordial, we have to help with very clear public health policies that protect it. The crisis that has accompanied the pandemic, the crisis that occurred ten years ago, any crisis, has an impact on the health of people. All of us try to foster healthy lifestyles among the most disadvantaged people, but the problem is that often difficult to understand the situations of living conditions, social environment or the workplace. And even if it is possible to understand these aspects, it may be impossible for us to change them.

Indeed, what we are seeing is that certain types of food are easier to acquire and are much cheaper than others. If what we are trying to do is introduce mechanisms that stop the spread of these types of food, but we do it in such a way that some foods become so expensive that certain segments of the population cannot afford them, then we will be back to where we were, and a person's health will be mainly determined by their income. This would lead us to fail anew. And we cannot allow that to happen. We are an advanced society. Apart from fostering health, fostering self-care, we have to be capable of generating economic and social environments that mean fostering health can be effective. If buying a product with an enormous amount of trans fats is much cheaper than buying fresh vegetables, what we are doing is making access to a healthy life dependent on income. And this is something that, in principle, should be combatted using any policy that is necessary. Income cannot become the determinant factor for a healthy life.

Another priority of the previous Director was attracting both Spanish and foreign talent. Are you going to continue this line?

Without a doubt. But this means that we must make a series of regulatory changes that have to go further than finance, and make Spain a magnet for scientific talent, regardless of whether that talent has a Spanish passport or not. Nationality is irrelevant; the most important thing is talent.

When the pandemic ends, or is more or less under control, will ISCIII be easier to lead?

I have no idea whether ISCIII will be easier or more difficult to lead when the pandemic is over. But it will always be a weighty responsibility. We are the State's main biomedical research institution. We have the tools for funding science, which is to say that we act like a bank, we act to push back the frontiers of knowledge, whether under the flag of ISCIII, CNIC, CNIO, etc. or under the flag of a CIBER research network. And with that comes a responsibility that is not always easy to manage, bearing in mind that our ultimate objective is science as a tool to protect health. ■

STRATEGIC PLAN 2022-2025

Since January 2015, under the supervision of its Director General, **Dr. Valentín Fuster**, the scientific activity of the Spanish National Centre for Cardiovascular Research (CNIC) has been organised in two overarching departments: Basic Research and Clinical Research, both of which are fully interconnected via three Research Areas:

- Vascular Physiopathology
- Myocardial Physiopathology
- Cellular and Developmental Biology

Now, in 2022, without changing the structure of these two departments, the CNIC plans various actions in the scientific area that will allow the CNIC's consolidation as an international reference centre for translational research in the cardiovascular field and in the study and fostering of cardiovascular health, which is the main objective of the strategic plan of CNIC's Severo Ochoa Project (2022-2025), awarded by the Spanish Ministry of Science and Innovation.

Cardiovascular disease (CVD) is the principal cause of death worldwide, and the exponential increase in the cost of treating CVD in its symptomatic phase places an insurmountable burden on patients, families, and health systems. In response to this challenge, the CNIC has defined three major goals: to increase the understanding of cardiovascular health, to improve disease prevention, and to generate treatment advances for the prevalent manifestations of CVD. These goals require mechanistic studies to gain insight into the molecular and cellular processes underlying disease, coupled to the translation of these findings into improvements in health promotion, diagnosis, and disease management.

To meet these challenges, the CNIC is moving from a research organization based on three broad research areas to one comprising seven highly focused and integrated programs:

1. **Novel mechanisms of atherosclerosis**
   Coordinated by **José J. Fuster**, with **Valentín Fuster** and **Inés García-Lunar** as Clinical Leaders, this programme has nine research groups, seven cardiologist scientists and three technical units.
   Its primary objective is translational research into new genetic, molecular and cellular mechanisms that regulate the development of atherosclerosis.
   Its two main pillars are human studies on the development of subclinical atherosclerosis in the PESA Health cohort, led by **Dr. Valentín Fuster**, and experimental research into new regulatory mechanisms of atherosclerosis using cellular and animal models.

2. **Myocardial homeostasis and cardiac injury**
   Coordinated by **Enrique Lara-Pezzi**, with **Borja Ibáñez** as Clinical Leader, this programme has six basic research groups and seven cardiologist scientists.
   Its primary objective is to study the pathological mechanisms underlying different forms of cardiac injury, with a particular interest in diseases of genetic origin, and disease secondary to cancer treatment, as well as the development of diagnostic tools and specific therapies that are efficient in improving the treatment of these conditions. Both cellular and animal models (mainly murine and porcine) will be used and there will be clinical trials.

3. **Cardiovascular regeneration**
   Coordinated by **Miguel Torres**, this programme has eight basic research groups, and the primary objective of identifying endogenous mechanisms that stimulate the regenerative capacity of the heart and blood ves-

sels, and application of the knowledge generated to develop therapies based on cardiovascular regeneration in the clinical context. Different strategies, animal and cellular models will be used as a first phase prior to future clinical trials.

4. **Novel arrhythmogenic mechanisms**
   Coordinated by **Silvia Priori**, with **David Filgueiras-Rama** as Clinical Leader, the core work of this programme includes three basic research groups, two clinical research cardiologists and two technical units.
   Its main objective is the study of structural and electrophysiological abnormalities in the heart that cause the pathological remodelling associated with the intracellular dysregulation of calcium in hereditary and acquired heart diseases. Research will cover genetic, molecular and cellular mechanisms in cellular and animal models (murine and porcine) and clinical trials will be conducted.

5. **Cardiovascular risk factors and brain function**
   Coordinated by **Mª Ángeles Moro**, with **Valentín Fuster** and **Rodrigo Fernández** as Clinical Leaders, the programme comprises ten basic research groups and has four clinical cardiologist researchers.
   Its objective is to study the mechanisms involved in cognitive deterioration associated with cardiovascular disease and its cardiovascular risk factors, and apply the new knowledge generated to promote cardiovascular health and prevent cognitive deterioration with ageing. The programme will include cellular and animal models and well as human studies.

6. **Cardiovascular Health Promotion**
   Led by **Rodrigo Fernández-Jiménez** and **Valentín Fuster**, this transversal program includes research staff from different disciplines (cardiology, nutrition, physical activity, biology, education, biostatistics). Its objective is to deepen the knowledge of cardiovascular health and develop strategies for health promotion and cardiovascular prevention from early ages of life, which allow reducing in the future the burden of cardiovascular disease that affects our society.

7. **Technology Development**
   Led by **Beatriz Álvarez Flores**, it includes 11 technical units and its objective is to keep the CNIC at the forefront of cardiovascular health research through the development and application of cutting-edge biomedical technologies.

These programs span from basic research to advanced health-changing clinical trials and build on the CNIC's deep-rooted and proven expertise in state-of-the-art technology, cellular and animal models, imaging modalities, and large-scale data gathering and analysis.

TECHNICAL UNITS

The Technical Units will continue to provide fundamental scientific services to the CNIC's research laboratories and external users, as well as offering specialised training in the use of equipment and implementation of different techniques.
The CNIC currently has the following Technical Units, organised into three broad groups: OMICs (proteomics, genomics and bioinformatics), Imaging (microscopy and dynamic imaging, flow cytometry, and advanced imaging) and Models (transgenesis, viral vectors, and pluripotent cell technology) in addition to the Comparative Medicine Unit and the Clinical Trials Coordination Unit.

GENERAL OBJECTIVE FOR 2022

- Start up the Centre's new strategic research programmes focused on atherosclerosis, myocardial homeostasis and cardiac injury, arrhythmias, cardiovascular regeneration and cardiovascular risk factors and cognitive function as pillars of the CNIC's Severo Ochoa Project.
- Continue to develop new cellular and animal (small and large) models for cardiovascular disease to undertake preclinical studies.
- Continue optimisation and development of new technologies in the Centre's Technical Units.
- Strengthen the computer and bioinformatic infrastructure and installations necessary for big data analysis (Systems Biology).
- Consolidate activities of the Clinical Trials Coordination Unit (CTCU) in clinical research with medicines and sanitary devices, created in 2018 with the aim of increasing CNIC leadership at national and international levels in the field of cardiovascular clinical trials.
- Establish new collaborations and mechanisms of dissemination and participation in order to reinforce placements of visiting scientists and training programmes, both in general and those aimed at clinical researchers in particular.
- Increase the Centre's internationalisation and competitivity by setting up new international collaborations and increased participation in the new EU programme, Horizon Europe, and other international competitive calls.
- Increase the CNIC's visibility and impact within the scientific community (international scientific events, publication of a larger number of scientific articles in high-impact reviews and in Open Access format) and among the general public (informational/educational activities aimed at the general public, news and interviews in the media and on social networks, etc.)
- Start up measures included in the new Equality Plan. ■

DUAL VOCATIONAL TRAINING: LEARNING AND COLLABORATION

CNIC HAS AGREEMENTS WITH TWO VOCATIONAL TRAINING COLLEGES IN THE FIELD OF PUBLIC HEALTH WITHIN THE AUTONOMOUS COMMUNITY OF MADRID:

► IES MORATALAZ – CLINICAL AND BIOMEDICAL LABORATORY

► IES SAN JUAN DE LA CRUZ – IMAGING FOR DIAGNOSIS AND NUCLEAR MEDICINE

One of CNIC's training programmes is Dual Vocational Training, which combines a first year of academic study at an educational institution with a nine-month internship at CNIC during the second year, instead of the more customary three month work placements.

The CNIC has educational collaboration agreements with the only two schools or technical colleges that offer higher dual training in public health within the Autonomous Community of Madrid. IES San Juan de la Cruz: Advanced Vocational Training in imaging for diagnosis and nuclear medicine, and IES Moratalaz: Advanced Vocational Training in clinical and biomedical laboratory work.

Students work full-time in accordance with the established schedule for the place of work. The advantage of this type of internship is that it facilitates a practical learning experience thanks to spending a prolonged period in a real working environment.

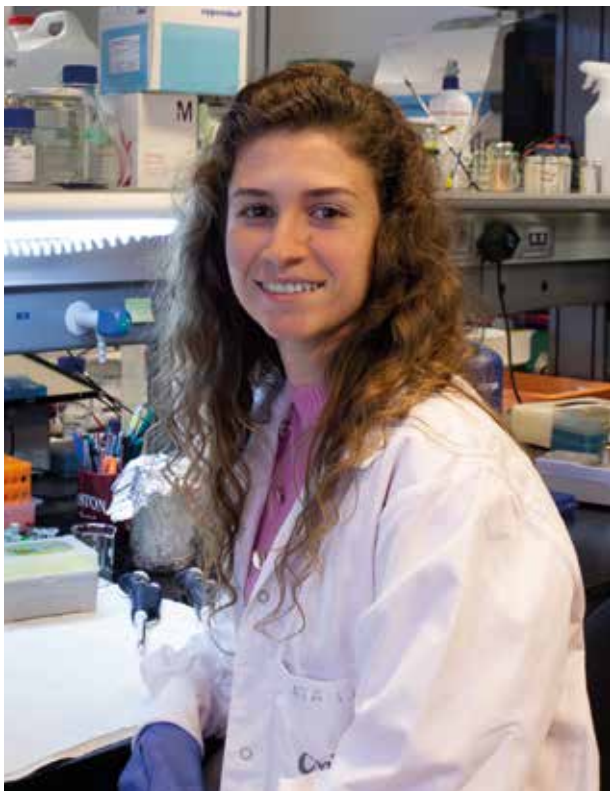
The programme offers advantages for students, but also for the CNIC. Specifically, Dual Vocational Training represents a great opportunity to acquire training at the same time as first-hand experience of real working life.

Students experience practical training in a business, so that they "learn by doing" and the learning experience is focused on the needs of the business. As well as gaining access to an authentic productive environment and increasing their possibilities of accessing future employment, the students receive a training grant of 300 euros per month, and they figure as employed interns in the national social security system. For their part, businesses actively participate in training students as future professionals.

As **Dr. David Sancho**, Group Leader of CNIC's Immunobiology Laboratory comments, this type of programme, like all of its training programmes, are very positive "because they allow us to train students, which is a highly motivating task for us." He goes on to say that students, "receive training in the tasks we do in a research laboratory that goes far beyond the theory they have studied."

CRISTINA ÁLVAREZ:

"It allows you to acquire knowledge in areas that interest you as you gain experience. This means that the possibility of finding a job in the future is made easier, as it was in my case"



The benefit is mutual, he adds, because for the group that the student joins, "although it invests in training, the group quickly reaps the benefits of the intern's thirst to learn and participate."

Since the CNIC began its collaboration with Dual Vocational Training internships in the 2017-18 academic year, 15 students have trained at the Centre (6 in Imaging and 9 in clinical laboratories). Currently, two of the participants in this programme are under contract.

Cristina Álvarez Diago is one of the students who took advantage of the opportunity offered, and is now working in the CNIC's Pluripotent Cell Technology Unit, led by **Dr. Giovanna Giovinazzo**.

Cristina had completed a degree in chemistry at the Universidad Autónoma of Madrid (UAM) in 2020 and found out about the programme when she was studying a two-year Dual Advanced Vocational Training in Clinical and Biomedical Analysis. The first year consisted of academic study, whereas the second was spent training in the workplace. "The college itself provided a list of centres, some focused on clinical analysis and others on research. Since I was interested in research, I chose the CNIC."

The most serious problem that Cristina encountered is that she joined CNIC in the middle of the COVID-19 pandemic, but her first impressions were favourable, "within the limits imposed by the extraordinary situation at the time."

She soon adapted to the workplace and had hopes of staying on to work at CNIC. "The working atmosphere was so good, and I felt so comfortable; of course I wanted to stay, and I never lost hope, but I also knew how difficult it is to get an offer of a contract at a research centre like CNIC."

She now works as a laboratory technician in the Pluripotent Cell Technology Unit, on murine embryonic stem cells (mESC) and human induced pluripotent stem cells (hiPSC), as well as participating in all of the molecular biology techniques and work undertaken in the cell culture and other laboratories.

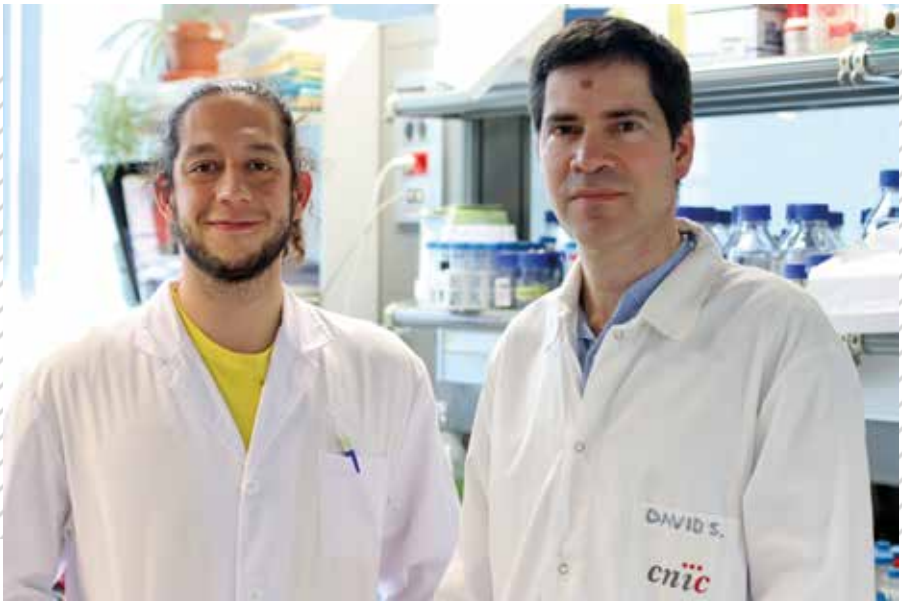
Eva Martínez Jiménez holds an Advanced Vocational Training Diploma in anatomical pathology and cytology and a dual higher vocational training qualification as Clinical and Biomedical analysis technician; she currently works as a laboratory and animal facility technician in the laboratory led by **Dr. José Antonio Enríquez** at CNIC.

Before this, however, she had spent two years at the CNIO, the Spanish national cancer research centre, with a grant from the Autonomous Community of Madrid, and when this could not be renewed, she decided to study the first year of the dual qualification while working the last year of her contract.

EVA MARTÍNEZ:

"They began my employment contract in August just after I completed the internship period, knowing that I was going to have a baby at the beginning of September, and the truth is that I am very grateful for that"

"Afterwards, I did the placement for the dual with **Dr. Enríquez**'s group, and as the CIBER research organisation had money, that organisation offered me a contract. Initially, I wanted to be a forensic assistant, which is why I studied anatomical pathology and did an internship at Madrid's Anatomical Forensics Institute, but it was very difficult to get work there, and I managed to get a contract with CNIO, the Spanish national cancer research centre,



where I discovered what science was like on the inside, and I loved it."

Eva highlights the fact that, at the time, she was pregnant, but this did not represent an obstacle for the group. "They began my employment contract in August just after I completed the internship period, knowing that I was going to have a baby at the beginning of September, and the truth is that I am very grateful for that. First, I had a CIBER contract to work with a CNIC group, and later I came top in a competitive selection process for candidates to work directly at CNIC." She currently works in the animal facility.

Manuel Rodrigo Tapias is one of the students currently studying the programme. Manuel heard about the programme while he was applying for vocational training, and admits that he did not expect to find something that so fully coincided with what he was looking for. "I was pleasantly surprised to find that all of the theory was condensed into one year, and that the second was an internship."

In **Dr. David Sancho**'s laboratory, Manuel focuses on genotyping functions and performing histological sectioning, and although he dreams of spending a longer time in this laboratory, he tries not to think about it.

For Eva, the length of the programme is very important. "A year is a very good amount of time in which to learn. Before, internships were six months, which was then cut to three, and in three months it is impossible to get practical experience of a job like this."

For her part, Cristina highlights, "The high level of training that you have achieved once the year is over, and the many areas in which you can work autonomously."

She considers that the programme might, "improve if there were a wider list of Advanced Vocational Training courses that could be taken in this dual mode, and I think that, little by little, this will be possible."

She does not hesitate to recommend this type of training programme. "It allows you to acquire knowledge in areas that interest you as you gain experience. This means that the possibility of finding a job in the future is made easier, as it was in my case."

Eva has a similar opinion. "With a bit of effort, you can learn the theory in one year, and then you have another to get the necessary work experience. Various students have come to do internships and there is an enormous difference between the ones that stay three months and those who spend a year."

Manuel adds that the CNIC is, "A place full of wonderful people who have been willing to support and teach me both in and outside the centre." He also remarks on how condensed the course is and how quickly the studies are completed. "This course is quite demanding and dense, but it is, without a doubt, well worth the effort."

So he enthusiastically recommends this type of training. "Not only is it an excellent way to acquire the skills that you are really going to use in the world of work as a technician, but you also learn theory that is enormously useful if you intend to continue formal training."

For **Dr. Sancho**, it is essential that students join the group with, "confidence, motivation, enthusiasm and a desire to learn," and that they look on it as a "...unique opportunity to learn in a unique environment of researchers who not only have high scientific but also high human values, and who will be their colleagues in the laboratory. The main thing" -he adds- "is that they take advantage of this opportunity and adopt a proactive, organised attitude to make the most of their experience."

Manuel is convinced that, even if he does not end up working at CNIC, "I will take a small part of it with me." His motto is, "Manuel, make the most of the experience and the advice they give you here." ■

BARCELONABETA BRAIN RESEARCH CENTER
SPANISH NATIONAL CENTRE FOR CARDIOVASCULAR RESEARCH

Juan Domingo Gispert

"COMBINING CNIC AND BBRC DATA WILL ALLOW US TO ANSWER QUESTIONS OF GREAT RELEVANCE FOR THE PREVENTION OF ALZHEIMER'S IN HEALTHY SUBJECTS"

Juan Domingo Gispert López, head of the Barcelonaβeta Brain Research Center and CNIC (Spanish National Centre for Cardiovascular Research) researcher

Can Alzheimer's disease be prevented?

Right now, the answer is "partially", and we hope that, in the future, the answer will be an emphatic "yes".

But this answer has two caveats. Although most people don't know it, up to a third of Alzheimer's cases can be prevented by adopting healthy lifestyles, which are basically the same as the ones recommended for cardiovascular health: taking care of your heart, doing exercise, etc. In the case of Alzheimer's, we know that it is also important to participate in activities that stimulate the brain and avoid depression: working, listening to music, playing an instrument, speaking to the neighbours, playing chess... Anything that stimulates the brain's sensorial or cognitive activity.

The people most genetically at risk are also the ones who benefit most from this type of preventive action. For instance, it has been shown that for carriers of the APOE4 gene, who have a very high risk for Alzheimer's and present very early signs of the disease such as higher concentrations of the protein beta-amyloid in the brain, taking up this type of activity reduces their risk to a level that is practically the same as that of subjects who do not have the risk factor.

What is the relationship between depression and Alzheimer's disease?

We know that there is a very close relationship between depression and Alzheimer's, to the extent that there is some speculation as to whether depression may even be an initial symptom of the disease. It is also possible that, if a person perceives that their intellectual capacity is diminishing, this could facilitate, or make them more vulnerable to, a state of depression.

In addition, there is the fact that people with depression tend to socially isolate themselves, and this reduces sensorial stimulation in the brain, which is counterproductive.

Does genetic screening currently exist that can tell us which people have higher or lower risk of developing this disease?

In the case of genetically determined, autosomal dominant Alzheimer's, there are well identified mutations that are the cause of the disease. In these cases, screening is indicated for people whose father or mother is known to have had the variant associated with the disease and wants to know if they will have it or not. This is done through genetic counselling programmes. But these cases are a very small fraction of Alzheimer's, less than 1%. And the families are clearly identified.

But most cases are what is known as sporadic Alzheimer's. In these cases, there are genetic risk factors, but that doesn't mean that someone with this risk factor will

eventually develop the disease, or that someone who does not have it will not develop the disease.

So, can we prevent the disease or not?

This is what can be done now; but the world of Alzheimer's is rapidly changing. We now have biomarkers that allow us to detect the most frequent abnormalities that occur in the disease decades before symptoms appear. And those biomarkers are now easy to obtain with a simple blood test. So, we are starting to find biomarkers in blood that will allow us to identify which people have begun a pathological process, even though they are completely healthy.

Once we have detected the people who are at a higher risk of having experienced onset of the disease, what we need is a way of changing its course. In June, the United States approved a drug, aducanumab, that eliminates amyloid plaque from the brain, and it seems that this could have a beneficial effect on the cognition of patients who have incipient Alzheimer's disease.

At the present time, clinical trials exist that are attempting to prevent the disease. This does not mean the type of drugs that eliminate amyloid protein in patients who have a diagnosis and established disease, people who have symptoms and therefore already present accumulated neurodegeneration. The idea is that they are investigating healthy people who show evidence of having amyloid in the brain, but whose cognition is intact. The objective is to preserve cognitive activity. These trials are already ongoing and that's why I believe that, in the not-too-distant future, we will be able to prevent this disease.

This drug's approval in the USA was extremely controversial. As a scientist, what is your view?

It is true that the evidence the pharmaceutical company provided to the FDA (Food and Drug Administration) on the clinical benefits of the drug is irregular and incomplete. It was based on a trial that the company halted after an intermediate analysis, which later, when the data was reviewed and to everyone's surprise, showed that in one of the two trials that had been conducted in parallel, the drug seemed to work and be effective in reducing the cognitive loss preestablished for the trial. So, the data from one trial were positive, whereas the data from the other were not.

But for the later study, they performed an unplanned, retrospective analysis of only the subjects who had really completed the regimen, and they observed that among those people the positive effect on cognition was confirmed.

This was what encouraged the company to present its data to the FDA. However, the US health authorities found themselves in a very difficult position because the evidence that this drug works did not meet the standards for approval.

During the approval process, the independent scientific panel unanimously voted against. But the FDA used its accelerated approval pathway, which establishes that a drug can receive temporary approval if there is a plausible effect on a surrogate marker that is predictive of the clinical effect. What this means is that the FDA has no doubt that the drug eliminates amyloid plaque from the brain. It also means that although the data of the clinical trials does not allow approval of the drug for its clinical effectiveness, it does allow us to think that elimination of amyloid plaque from the brain may have a beneficial effect on cognition.

Which is to say that the trial allowed us to confirm that amyloid plaque is eliminated from the brain. And this surrogate marker of the clinical effect is what the FDA used for their approval.

In my opinion, the FDA took a brave decision and, I believe, the correct one. I also think that it should be made quite clear that this drug does not cure Alzheimer's and that it has a limited clinical effect. The trials are clearly not conclusive, and we need further information to see whether this drug, this type of drug, really has an impact on cognitive capacity. But in this case, it is highly unlikely that another phase III clinical trial would have been undertaken.

So, now it is possible to begin administering this drug to patients and by doing so, obtain additional information about the clinical effects of the medication, and on management of adverse reactions.

And then there is another question that the clinical trials did not address. It has been shown that after 18 months, this drug reduces amyloid plaque in the brain to the levels of a young person. The question is whether administration of the drug should continue once these levels have been reached. This type of question is what the phase IV trials agreed by the FDA and the company must answer.

> "We now have biomarkers that allow us to detect the most frequent abnormalities that occur in the disease decades before symptoms appear. And those biomarkers are now easy to obtain with a simple blood test"

Likewise, there should be some kind of criticism of scientists, because sometimes it is easier to limit ourselves to criteria of scientific rigour, to state that something has not been absolutely proven, and to forget that there are people in the world who are suffering and need this type of drug. Ultimately, patients want something that is useful, and they are willing to accept the risk. Patients already know the bleak outlook of this disease and so, as I mentioned before, I think that the FDA made the right decision and has been brave.

There are other drugs undergoing clinical trials that follow similar lines of investigation, and also medicines aimed at other targets. In the future, will therapies to prevent or treat Alzheimer's be a combination of medications, as also happens for other diseases?

Nowadays, as well as aducanumab, there are another two drugs which control the production of amyloid and are the

subjects of trials that end in 2023 and 2024. There is also another study on prevention among healthy people, which is scheduled to end in 2027. These are the next milestones for elimination of amyloid protein.
But apart from those studies, we already have several clinical trials that have completed phase II, with results in combatting Tau, another protein characteristic of Alzheimer's. And the first results suggest positive effects on cognition. There are also studies aimed at modulating the inflammatory effect on the brain, among other mechanisms. There is more than one route to attack this disease.

We are living in times of biomarkers and imaging for all diseases, including Alzheimer's. In this case, what is the contribution of innovative imaging techniques?

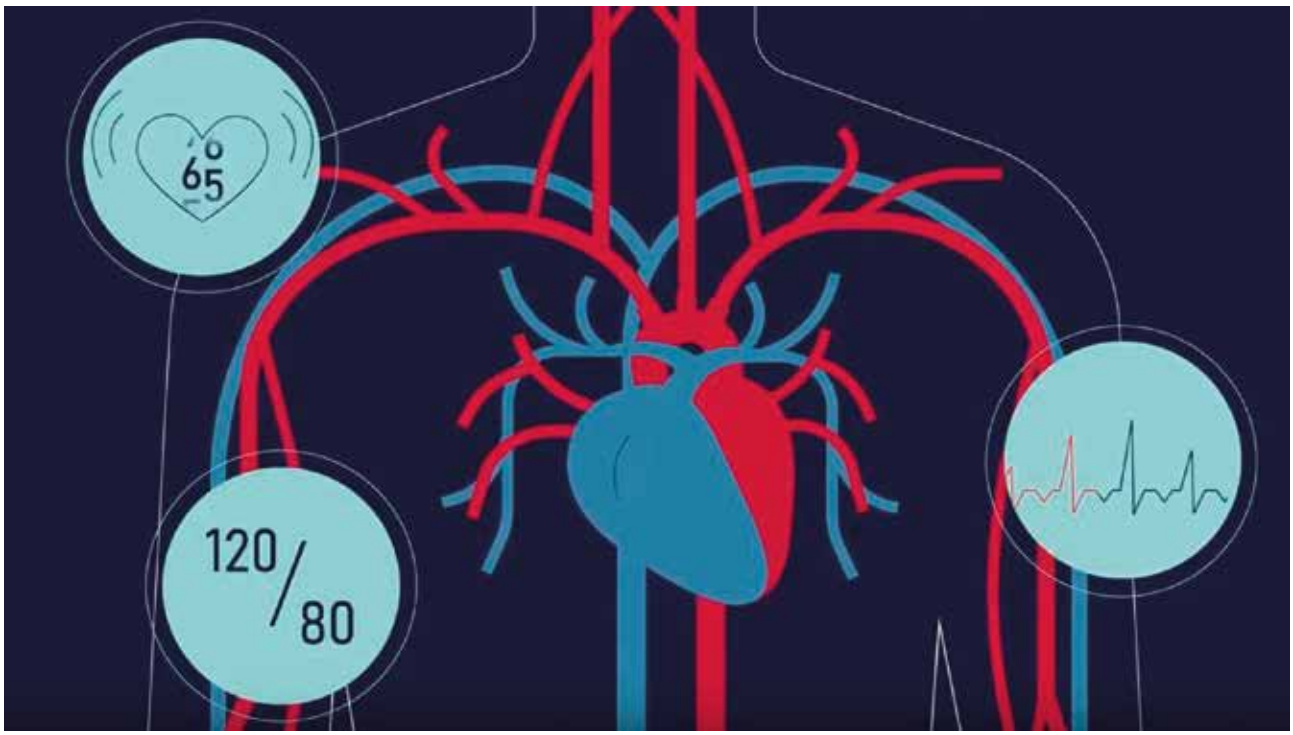
Drugs target Alzheimer's disease, tau and amyloid, so we have to identify which patients or healthy individuals have abnormalities in these two proteins. Until two years ago, this was done using extremely expensive and highly invasive techniques such as PET or lumbar puncture (spinal tap), which is painful.
These are also techniques that, apart from their expense, are not suitable when it comes to screening the general population to identify specific individuals who already have tau or amyloid abnormalities. So, the development of biomarkers in blood will facilitate prevention efforts in the world of Alzheimer's in the same way as they do in the cardiovascular field for evaluating cholesterol and so on.
What this means is that we had techniques that were only valid for research and in the experimental field, but now they are going to reach clinical practice in the short-term, if there are finally drugs that modify the progression of this disease. It's a combination: the two things must go together.
We need not only the tools that change progression of the disease, but also the means to detect which people might benefit from the drugs.
There is also a synergistic effect since this is not simply progress in parallel. To date, there have not been studies on prevention because they were logistically almost impossible, it would have been necessary to recruit thousands of healthy people who showed evidence of anomalous markers.
And until now this type of population was only found in research cohorts, like those we have in the Pasqual Maragall Foundation. Recruiting 1,300 healthy people with amyloid abnormalities worldwide was practically impossible.
Another aspect is that studies on prevention last a long time because we are talking about a disease that has a very slow progression.
We know that when amyloid protein is present, decades may elapse until the onset of symptoms, which means that it is not enough to find people who have amyloid protein abnormalities, we need to clearly know what moment of the preclinical phase the subjects are in and select people who are closer to cognitive decline. If not, you have a study in which there are two groups: one who receive a placebo and the other who receive the drug. If neither of these two groups of patients experience cognitive decline because almost all of them are far from the onset of disease symptoms, you cannot show the drug's effectiveness.
Now, the fact of having markers in blood is of great help in making this type of study much easier and realistically feasible. Which means that markers, apart from their use in future clinical practice, will help in the development of new drugs, particularly in preclinical phases.

What information will be obtained from the combination of Barcelonaβeta Brain Research Center's Alfa database and PESA-CNIC-Santander?

I think that the two cohorts, the BBRC's Alfa and the PESA, share the same perspective on prevention in general and in characterising risk factors that can have great future impact. The CNIC has done this in the cardiovascular area. But they are established cohorts with complementary characteristics: in ours, the volunteers have a higher risk of Alzheimer's, evidently, and a very low cardiovascular risk because they are individuals who are concerned about looking after themselves, whereas PESA places more emphasis on cardiovascular effect, in characterising vascular risk and identifying subclinical atherosclerosis.
I believe that combining the data from the two cohorts will allow us to answer an important question, which is, we know that controlling cardiovascular risk factors has an impact on Alzheimer's, what we don't know is why. Why does doing physical activity protect against Alzheimer's? It really is not clear.
It has been shown that vascular damage contributes to the severity of symptoms after onset of the disease. But there is probably a closer connection between cardiovascular health factors and Alzheimer's disease.
So, the CNIC cohort is ideal to answer these questions, and combining the data of CNIC and the BBRC will allow us to answer relevant questions about prevention of this disease in healthy subjects.

How did your interest in the field of Alzheimer's arise?

I am an engineer by training, and studied biomedical engineering, which is where my knowledge in the field of biology comes from. I have always worked in research and in neuroimaging. First in Madrid's Gregorio Marañón hospital, which allowed me to take my first steps in the world of clinical medicine, understand what questions arise in it, and how neuroimaging can respond to these questions.
In 2004, I worked in a molecular imaging centre where we did imaging of patients from the Hospital del Mar, but also clinical trials for pharmaceutical companies and on laboratory animals. It was rewarding because I had access both to clinical and experimental phases.
In 2010, I began to work at the Pasqual Maragall Foundation on the Alfa project as an expert in neuroimaging.
In addition to my scientific interest in Alzheimer's, which I believe is the greatest challenge facing medicine from a scientific point of view, and in neuroimaging, which has become my specialism and has had a central role in contributing to better understanding of the disease, I have a personal interest. Some years ago, my father died of Alzheimer's, at a time when there were almost no treatment options, and this was one of the reasons that inspired me to follow this route. ■



REBOOT

AIMING TO CHANGE THE CLINICAL PRACTICE GUIDELINES FOR MYOCARDIAL INFARCTION

In March 2019, CNIC (the Spanish National Centre for Cardiovascular Research) and the Spanish Society of Cardiology (SEC) presented a pioneering project in Spain. TREatment with Beta-blockers after myOcardial infarction withOut reduced ejection fracTion (REBOOT). In the words of its principal investigator, **Dr. Borja Ibáñez**, this project "...has the ambitious vocation to change clinical practice guidelines after acute myocardial infarction." To do so, the effect of maintaining beta blocker treatment after hospital discharge for heart attack will be tested among 8,468 patients. To date, over 6,000 patients have been recruited.

Beta blockers are drugs that reduce heart rate, blood pressure and myocardial contractility (the heart's strength) favouring diastole (refill) of the heart and, therefore, improved heart function and blood flow to the coronary arteries. Despite most evidence dating from a time when reperfusion therapy was not given to patients, for decades, beta blockers have been approved by all European and American clinical practice guidelines for treatment of patients after acute myocardial infarction.

Currently, clinical practice guidelines recommend beta blockers. However, this approval is based on trials carried out decades ago when the treatment for heart attack was less sophisticated, at a time before reperfusion therapy. At that time, coronary arteries were not unblocked and the prognosis for patients was a lot worse than nowadays.

Today, patients who survive acute myocardial infarction without deterioration of the heart's ability to pump blood have a much better prognosis and, therefore, we need to take a fresh look at whether beta blockers continue to offer clinical benefits.

Specifically, for the first time in the era of reperfusion therapy, REBOOT aims to study whether administering beta blockers to this type of patient influences the incidence of death, reinfarction or hospital admission for heart failure.

For more than four decades, beta blocker drugs have almost universally been prescribed on discharge after acute myocardial infarction (AMI), despite the fact that there is no clear evidence of their benefit for all types of infarction.

Several thousand researchers and over 100 small, medium and large hospitals in Spain and Italy will participate in REBOOT, which aims to change the clinical practice guidelines related with myocardial infarction

Although the precise figures are difficult to calculate, in Spain each year there are approximately 100,000 heart attacks without left ventricular systolic dysfunction. Almost all of these patients are discharged with a prescription of two antiplatelet drugs (aspirin and a P2Y12 inhibitor), statins, ACE inhibitors, beta blockers and a gastric protector. In many cases other types of medication are associated. Except for the P2Y12 inhibitor and the gastric protector, the other medication is currently prescribed for life.

Beta blockers, despite being inexpensive (they are no longer under patent) and having a very high safety profile, may have potential adverse reactions that could limit a patient's quality of life, which include physical weakness, loss of strength and, in some cases, impotence. We should consider that may patients who suffer a heart attack are middle-aged, have many years of life ahead of them, and their quality of life is an important factor to bear in mind. This is why knowing whether this type of drug is really necessary for these patients is of major importance. If it is shown that they are not effective in this type of post-infarction patient, they will not be prescribed, which could result in an increase of patient adherence to medication that has been shown to be effective, and also avoid possible adverse reactions that might limit patient quality of life.

The study will recruit a total 8,500 patients who have suffered a myocardial infarction with a left ventricular ejection fraction greater than 40%, who will be randomised to receive a placebo or beta blockers.

They will undergo a minimum two-year, maximum three-year follow-up. The incidence of clinical events and adherence to the randomised treatment will be recorded and documented at 3, 15 and 36 months. A sub-sample of 1,000 patients will be used to assess patient quality of life during follow-up.

Dr. Borja Ibáñez, principal investigator of the REBOOT study, comments that several thousand researchers and over 100 small, medium and large hospitals in Spain and Italy will participate in REBOOT, which aims to change the clinical practice guidelines related with myocardial infarction.

The study will be coordinated by CNIC's Clinical Trials Coordination Unit, and will compile data on the incidence of death, reinfarction or hospitalization for heart failure among the patients during a three-year follow-up.

This is the first large-scale, independent clinical trial developed in and led by our country. To date, it has not been possible to undertake a study of this size without a connection to industry.

"The study design is highly innovative, in that it is a pragmatic trial closely related to real life, which is to say, there are no great restrictions as far as inclusion criteria are concerned..." **Dr. Ibáñez** comments, "...although the most novel aspect of this trial is that it is the first large-scale study to be carried out in our country that has no connection with industry. This type of study is common in countries like Sweden or the United Kingdom, but so far not in Spain. Spain has a great deal of talent, but so far it has been difficult to get any project of this nature off the ground," he adds.

Beta blockers, despite being inexpensive and having a very high safety profile, may have potential adverse reactions that could limit a patient's quality of life, which include physical weakness, loss of strength and, in some cases, impotence

The subject under study is of such clinical relevance that another three clinical trials similar to REBOOT are to start in Sweden, Norway and Denmark. In total there will be over 20,000 patients with similar characteristics, randomised to receive a placebo or beta blockers after a heart attack without ventricular dysfunction. "The fact that different studies are going ahead simultaneously will not only measure our capacity to be on a par with counties that have a tradition of carrying out large-scale clinical trials, but also allow us to perform meta-analysis by pooling all of the cohorts," **Dr. Ibáñez** concludes. ■

EXCELLENCE IN COMMUNICATION SCIENCE

LEADING JOURNALS PUBLISH CNIC SCIENCE

JACC

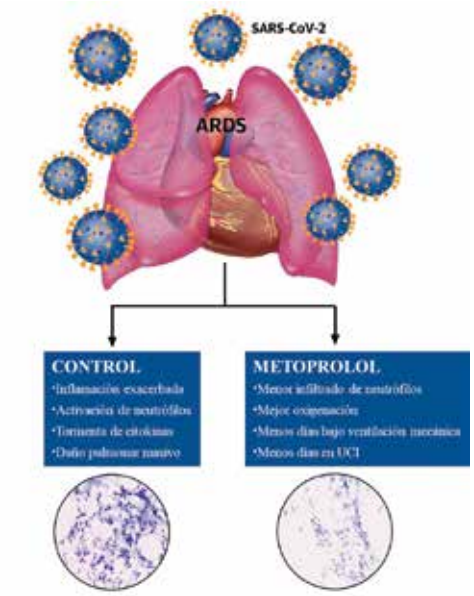
A drug costing less than €2 a day helps in the treatment of severely ill COVID-19 patients

The most severe form of COVID-19 is severe respiratory failure, which requires intubation and is associated with a high mortality rate. Pulmonary infection with the SARS-CoV2 virus can progress to acute respiratory distress syndrome (ARDS), in which inflammation and neutrophil hyperactivation play a central role. There is currently a lack of therapies for ARDS associated with COVID-19.

The study was led by **Dr. Borja Ibáñez**, group leader of the Translational Laboratory for Cardiovascular Imaging and Therapy at the CNIC, cardiologist at the Hospital Universitario Fundación Jiménez Díaz (FJD) in Madrid, and member of the CIBERCV cardiovascular research network. The research team recently discovered that metoprolol, a well-established beta-blocker, has a highly selective effect on hyperactivated neutrophils during situations of acute stress such as a myocardial infarction. Given the central role played by neutrophils in ARDS, the team postulated that metoprolol might be an effective treatment for patients with severe COVID-19.

Madrid-COVID is a randomized clinical trial conducted in close collaboration between the CNIC and cardiology, ICU, pulmonology, and biobank services at FJD Hospital. This pilot trial examined the effect of intravenous metoprolol administration on lung inflammation and respiratory function in severe COVID-19 patients intubated after developing ARDS.

The team "randomized 20 intubated COVID-19 patients to receive intravenous metoprolol (15 mg per day over 3 days) or to a control group that did not receive metoprolol. We analyzed the inflammatory infiltrate in bronchoalveolar fluid before and after treatment and also monitored clinical progression parameters such as oxygenation and days on mechanical ventilation." The intravenous metoprolol treatment significantly reduced neutrophil infiltration of the lungs and improved oxygenation.



Dr. Ibáñez added that "while we need to be cautious with these results of a pilot trial, we have observed that metoprolol treatment in this clinical setting is safe, is associated with a very significant reduction in lung infiltration, and appears to lead to very rapid improvements in patient oxygenation."

The researchers therefore propose intravenous metoprolol as a "promising intervention that could improve the prognosis of severely ill COVID-19 patients." They also emphasize that metoprolol is a safe and cheap drug (daily treatment cost below €2) that is readily available.

Joint first author **Agustín Clemente-Moragón** added that "the effect of metoprolol on the hyperactivation of inflammatory cells implicated in ARDS is exclusive to this beta-blocker." In a previous experimental study, the same group recently demonstrated that other apparently similar beta-blockers have no effect on exacerbated lung inflammation.

The research team led by **Dr. Ibáñez** was awarded funding from the Instituto de Salud Carlos III (ISCIII) for a clinical trial to definitively demonstrate the clinical benefits of metoprolol in 350 ADRS patients admitted to 14 ICUs across Spain. The MAIDEN clinical trial will be coordinated by the cardiovascular CIBER research network and will include the participation of cardiovascular and respiratory specialists.

The study was partly funded by the European Comission (EERC-CoG grant N° 819775) and the Ministerio de Ciencia e Innovación (MCN; 'RETOS 2019' grant N° PID2019-107332RB-I00). The study was also supported by the Programa de Atracción de Talento de la Comunidad de Madrid.

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CIRCULATION RESEARCH

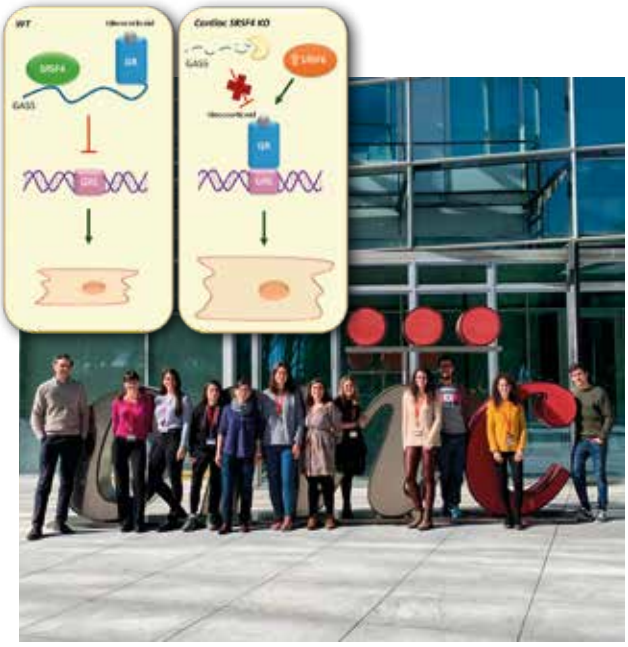
CNIC scientists describe one of the mechanisms underlying cardiac hypertrophy

Scientists at the Centro Nacional de Investigaciones Cardiovasculares (CNIC) have identified a new mechanism involved in the regulation of cardiac hypertrophy. The mechanisms underlying this disease remain largely unknown, and this situation is impeding the development of effective treatments.

The findings, published in ***Circulation Research***, may spur the development of new tools for the treatment of cardiac hypertrophy, especially in Cushing syndrome patients.

The results, explained principal investigator **Dr. Enrique Lara Pezzi**, who leads the Molecular Regulation of Heart Failure group at the CNIC, reveal that the "protein SRSF4 binds to and stabilizes the non-coding RNA GAS5, enabling it to block the action of the glucocorticoid receptor and thus prevent cardiac hypertrophy."

The contractile function of the heart depends on the action of cardiomyocytes. Although in the adult heart these cells have almost no ability to divide, **Dr. Lara Pezzi** explained that they have a remarkable ability to adapt to the changing demands placed on the heart.



One example of this capacity is the response to aortic stenosis. "During stenosis, the aortic valve cannot open fully, and the narrowing of the opening obliges the left ventricle to pump blood with greater force. This requires the heart muscle to contract more strongly," continued **Dr. Lara Pezzi**.

Although cardiomyocytes cannot divide, **Dr. Lara Pezzi** explained that "to increase contractile capacity, these cells become enlarged, a process known as hypertrophy."

However, while this response is effective at first, the thickening of the left ventricular wall (cardiac hypertrophy) triggers structural changes in the heart that cause a progressive loss of contractile capacity.

Continuing lack of knowledge about the mechanisms underlying cardiac hypertrophy is impeding the development of effective treatments.

Dr. Lara Pezzi's group, in partnership with researchers at Hospital Puerta de Hierro in Majadahonda, the Spanish Cardiovascular Research Network (CIBERCV), and the University of Frankfurt, has analyzed possible mechanisms underlying the development of this disease.

The researchers found that mice lacking the RNA-binding protein SRSF4 develop cardiac hypertrophy and have an impaired ability to relax the heart muscle, a condition known as diastolic dysfunction.

Further analysis showed that the absence of SRSF4 severely reduces the expression of the non-coding RNA GAS5. "SRSF4 binds directly to GAS5, preventing GAS5 degradation in the cell. GAS5 is an inhibitor of the glucocorticoid receptor, whose activation contributes to the development of cardiac hypertrophy," explained **Dr. Lara Pezzi**.

First author **Dr. Javier Larrasa** clarified that "the absence of SRSF4 triggers the degradation of GAS5, and this results in activation of the glucocorticoid receptor. In contrast, overexpression of GAS5 with a viral vector inhibits the glucocorticoid receptor and reduces cardiac hypertrophy."

The research team concludes that the identification of the SRSF4-GAS5-glucocorticoid-receptor cell signaling pathway is a major advance in the characterization of the molecular mechanisms underlying cardiac hypertrophy and could serve as the basis for new treatments.

Furthermore, the findings could be "particularly applicable to patients with Cushing syndrome, who develop cardiac hypertrophy in part through glucocorticoid receptor activation."

An analysis of samples from Cushing syndrome patients revealed a degree of dysregulation of SRSF4 and GAS5 expression; however, the possible role of this pathway in this disease will require further research.

The study received funding from the European Union (CardioNeT-ITN-289600 and CardioNext-ITN-608027), the Ministerio de Economía y Competitividad, and the Community of Madrid (2010-BMD-2321 "Fibroteam"). Funding was also provided by the Plan Estatal de I+D+I 2013-2016 and the European Regional Development Fund "A way to build Europe" program.

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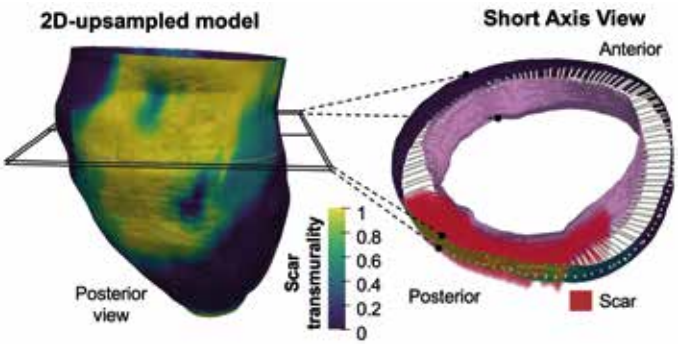
SCIENTIFIC REPORTS
3D mapping of post-infarction scarring increases the prognostic potential of cardiac magnetic resonance imaging

A multidisciplinary team of scientists based at the Universidad de Valladolid and the Centro Nacional de Investigaciones Cardiovasculares (CNIC), has developed a highly efficient method for identifying the 3-dimensional features of the scar tissue formed after a myocardial infarction. The study was carried out in partnership with scientists and clinicians at Hospital Clínico San Carlos, Hospital Universitario La Paz, Fundación Jiménez Díaz, Hospital Ruber Juan Bravo Quironsalud, Universidad Politécnica de Madrid, Centro de Supercomputación de Barcelona, Philips Healthcare Iberia, CIBERCV and CIBERBBN.



The new method allows 3-dimensional transmural (across the ventricular wall) mapping of scar tissue in the infarcted muscle. Transmural mapping of the infarcted tissue enables highly detailed characterization of the morphology of the damaged tissue and provides an accurate measure of infarct size relative to myocardial wall thickness, a parameter known as transmurality.

According to CNIC scientist **David Filgueiras**, "a major advantage of this new method is its full compatibility with standard cardiac magnetic resonance (CMR) sequences that take just a few minutes to acquire. This approach can thus significantly shorten the time needed for image acquisition, easing access to in-demand nuclear magnetic resonance scanners."

"This novel methodology may provide an efficient approach in clinical practice after manual or automatic segmentation of myocardial borders in a small number of conventional 2D slices and automatic scar detection," write the authors in an article published in ***Scientific Reports***.

The results of the study show that low scar transmurality on CMR (below 10% of ventricular wall thickness for 3D sequences or 20% for 2D sequences) is associated with the clinical presentation of tachycardias involving infarcted ventricular tissue, known as ventricular tachycardias.

Describing the results study first authors **Susana Merino**, of Valladolid University, and **Lilian Karina Gutiérrez**, of the CNIC, said that the results reveal a significant correlation between low scar transmurality and the cardiac frequency of spontaneous ventricular tachycardia episodes.

The results also show that patients with low scar transmurality values had a higher probability of ventricular tachycardia recurrences during long-term follow-up.

The new method is especially promising because it uses conventional 2D delayed gadolinium-enhanced CMR sequences and requires only a limited number of slices. This technology is available at all centers that carry out CMR studies, and the method does not require 3D CMR studies.

The method was developed through technical, experimental, and clinical collaboration under the umbrella of a specific partnership between Valladolid University and the CNIC. Joint lead author **Carlos Alberola** explained that the technical advances of the method are built on procedures developed in the Image Processing Laboratory at Valladolid University, located in the Escuela Técnica Superior de Ingenieros de Telecomunicación.

"The first of these advances is a method for interpolating images that preserves topology. This allows high-resolution 3D images to be generated with a high level of precision from the images obtained with conventional CMR procedures."

"A second advance is a mathematical method for characterizing fibrous tissue formed in the myocardial wall after an infarction. This tool provides a measure of the full

3D morphology of the scar relative to the thickness of the myocardium, a parameter known as transmurality." The method uses a procedure based on partial differential equations to provide point-wise correspondences between the endocardium and the epicardium. These correspondences allow the definition of multiple indicators of the extent of the infarction.

The experimental arm of the study involved input from the Advanced Development in Arrhythmia Mechanisms and Therapy group at the CNIC, led by **Dr. David Filgueiras**. This group provided expertise in experimental models of myocardial infarction, essential for validating the methodology.

The CNIC laboratory also coordinated the study of the clinical application of the new method, in partnership with a multidisciplinary team of experts in the diagnosis and treatment of complex cardiac arrhythmias.

The study received funding from the Ministerio de Ciencia e Innovación (TEC2017-82408-R y PID2019-109329RB-I00); Fondo Europeo de Desarrollo Regional (CB16/11/00458); Heart Rhythm Association de la Sociedad Española de Cardiología; Fundación Interhospitalaria para la Investigación Cardiovascular (FIC); Fundación Eugenio Rodríguez Pascual; programa H2020 de la Unión Europea; Ministerio de Asuntos Económicos y Transformación Digital, and Fundación Carolina-BBVA.

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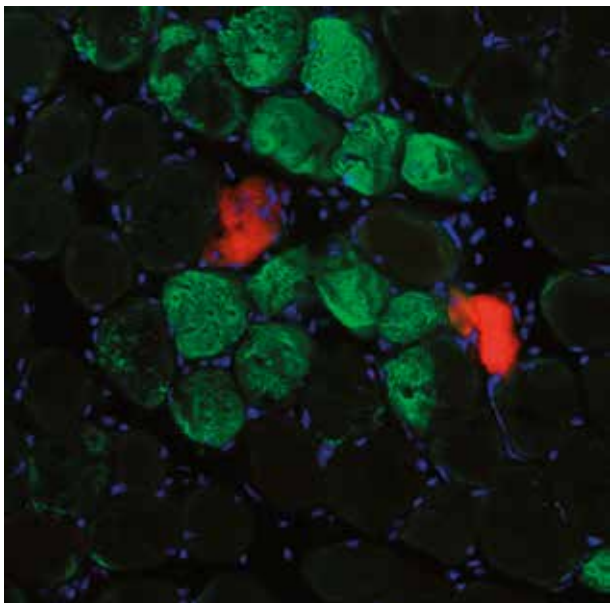
SCIENCE

A rapid mechanism for muscle self-repair independent of stem cells

Muscle is known to regenerate through a complex process that involves several steps and relies on stem cells. Now, a new study led by researchers at Universitat Pompeu Fabra (UPF), Centro Nacional de Investigaciones Cardiovasculares (CNIC) / CIBERNED and Instituto de Medicina Molecular João Lobo Antunes (iMM, Portugal), published on 15 October in the journal ***Science***, describes a new mechanism for muscle repair after physiological damage relying on the rearrangement of muscle fibre nuclei, and independently of muscle stem cells. This protective mechanism paves the way to a broader understanding of muscle repair in physiology and disease.



Skeletal muscle tissue, the organ responsible for locomotion, is formed by cells (fibres) that have more than one nucleus, an almost unique feature in our body. Despite the plasticity of these fibres, their contraction can be associated with muscle damage. **William Roman**, first author of the study and researcher at UPF, explains: "Even in physiological conditions, regeneration is vital for muscle to endure the mechanical stress of contraction, which often leads to cellular damage." Although muscle regeneration has been investigated in depth in recent decades, most studies centred on mechanisms involving several cells, including muscle stem cells, which are required when extensive muscle damage occurs."

"In this study we found an alternative mechanism of muscle tissue repair that is muscle-fibre autonomous," says **Pura Muñoz-Cánoves**, ICREA professor and principal investigator at UPF and the CNIC, and study leader. Even in physiological conditions, regeneration is vital for muscle to endure the mechanical stress of contraction, which often leads to cellular damage.

Researchers (including **Antonio Serrano** (UPF) and **Mari Carmen Gómez-Cabrera** (Universitat de València e INCLIVA) used different in vitro models of injury and models of exercise in mice and humans to observe that upon injury, nuclei are attracted to the damage site, accelerating the repair of the contractile units. Next, the team dissected the molecular mechanism of this observation: "Our experiments with muscle cells in the laboratory showed that the movement of nuclei to injury sites resulted in the local delivery of mRNA molecules. These mRNA molecules are translated into proteins at the site of injury to act as building blocks for muscle repair," explains **William Roman**. "This muscle fibre self-repair process occurs rapidly both in mice and in humans after exercise-induced muscle injury, and thus represents a time- and energy-efficient protective mechanism for the repair of minor lesions," adds **Pura Muñoz-Cánoves**.

In addition to its implications for muscle research, this study also introduces more general concepts for cell biolo-

gy, such as the movement of nuclei to injury sites. "One of the most fascinating things about these cells is the movement during the development of their nuclei, the biggest organelles inside the cell, but the reasons why nuclei move are largely unknown. Now, we have shown a functional relevance for this phenomenon in adulthood during cell repair and regeneration," says **Edgar R. Gomes**, group leader at the Instituto de Medicina Molecular and a professor at the Faculty of Medicine at the University of Lisbon, who co-led the study.

This finding constitutes an important advance in the understanding of muscle biology, in physiology (including exercise physiology) and muscle dysfunction.

On the importance of these discoveries, **Pura Muñoz-Cánoves**, **Antonio Serrano** and **Mari Carmen Gómez-Cabrera** agree that: "This finding constitutes an important advance in the understanding of muscle biology, in physiology (including exercise physiology) and muscle dysfunction."

The work was conducted at UPF/CNIC/CIBERNED and at the iMM in collaboration with the University of Valencia/INCLIVA. This study was funded by the European Research Council, Association Française contre les Myopathies, the European Molecular Biology Organization, the Human Frontiers Science Programme, and the Spanish Ministry of Science.

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doi: 10.1126/science.abe5620

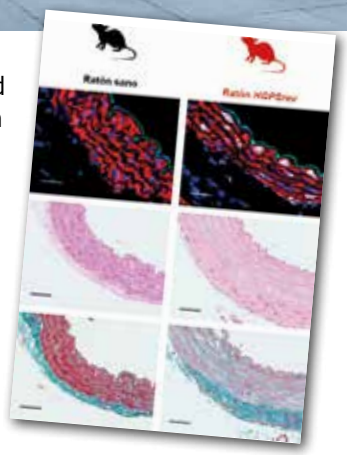
CIRCULATION

It's never too late to treat progeria

Scientists at the Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC) and the Spanish Cardiovascular Research Network (CIBERCV), led by **Dr. Vicente Andrés**, have generated the HGPSrev experimental mouse model. This is the first animal model to develop Hutchinson-Gilford Progeria Syndrome (HGPS) and also allow its suppression through the controlled regulation of the expression of progerin, the aberrant protein that causes the disease. Using the new model, the researchers have demonstrated that it is never too late to treat HGPS.

The study, published in ***Circulation****,* also establishes that the cardiovascular alterations and early death associated with HGPS can be prevented with treatments specifically targeting cells of the cardiovascular system.

HGPS is an ultra-rare genetic disease that affects fewer than 400 children worldwide and for which there is no known cure. The disease is caused by a mutation in the



LMNA gene and is characterized by accelerated aging and death in the second decade of life, principally due to cardiovascular complications derived from atherosclerosis.

In the absence of mutations, LMNA encodes type A lamin proteins (Lamins A and C). The mutation found in HGPS patients results in the synthesis of progerin, a mutant protein that provokes multiple molecular and cellular alterations in the tissues where it accumulates, causing their life to pass at an highly accelerated rate, where minutes are hours and hours are lost days.

Now, thanks to the HGPSrev mouse generated by the CNIC Molecular and Genetic Cardiovascular Pathophysiology group, the research team has managed to suppress progerin expression and reestablish lamin A expression in mice of different ages, both throughout all body tissues and in specific cell types. The characterization of the animal model was carried out with the participation of researchers at Queen Mary University of London.

Joint first authors **Drs. Amanda Sánchez López** and **Carla Espinós Estévez** explained that while some palliative therapies are effective in animal models and are the subject of clinical trials, their therapeutic benefit is very limited. "A true cure would require the elimination of the culprit mutation," commented **Dr. Sánchez López**. However, this is not yet possible, and progeria is only diagnosed once the first symptoms have already appeared. "We therefore sought to reverse symptoms once they are already present and to determine how long treatment could be delayed and still have a beneficial impact," explained **Dr. Espinós Estévez**.

The extent to which the damage caused by progerin can be reversed is currently not known, and patients often do not start to receive treatment until symptoms are quite advanced. The investigators therefore addressed a key question: Can the progression of HGPS be stopped or slowed if treatment commences when the disease is advanced,

or does therapeutic benefit depend on starting treatment early, when symptoms are mild?

Another important question is how treatment should be targeted. Progerin is expressed in many tissues, but it was not known if treatment needs to be directed at all affected cells or if it would be effective if targeted at a specific cell type. To answer these questions, **Dr. Andrés**'s team used CRISPR-Cas9 technology to generate HGPSrev mice.

The results published in ***Circulation*** show that HGPSrev mice develop the major features of the human disease, including growth retardation, lipodystrophy, cardiovascular alterations, and early death.

The investigators also showed that elimination of progerin and restoration of lamin A expression increased life expectancy by 84.5% in HGPSrev mice with very mild symptoms and, moreover, extended lifespan by 6.7% even in mice with very advanced symptoms.

These results establish not only that starting treatment when symptoms are mild has a huge positive impact, but also that treatment can be beneficial no matter how late it is started.

"We managed to prevent vascular alterations and normalize survival in progeric mice by eliminating progerin expression and restoring lamin A expression specifically in vascular smooth cells and cardiomyocytes, even though other cell types remained diseased," explained **Dr. Andrés**.

The investigators conclude that these results "could contribute to the design of future clinical treatments, given that they suggest that strategies exclusively targeting the cardiovascular system could have a very significantly beneficial effect on patients' life quality and expectancy."

The study received funding from the Ministerio de Ciencia e Innovación (MCIN)/Agencia Estatal de Investigación (AEI)/10.13039/501100011033 (grants SAF2016-79490-R, PID2019-108489RB-I00, SVP-2014-068334, FJCI-2017-33299); Instituto de Salud Carlos III (ISCIII; grant AC17/00067-TREAT-HGPS), an E-Rare Joint Transnational call project, European Union Horizon 2020 Framework Programme 2017); the Fondo Europeo de Desarrollo Regional ("a way to build Europe"); the Wellcome Trust (grant 098291/Z/12/Z); the Comunidad Autónoma de Madrid (grant 2017-T1/BMD-5247); the Asociación Apadrina la Ciencia-Ford España-Ford Motor Company Fund; and the Fundación "la Caixa".

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SCIENCE ADVANCES

CNIC scientists identify the essential role of a gene in placental development

Scientists working with an experimental mouse model at the Centro Nacional de Investigaciones Cardiovasculares (CNIC) have identified the essential role of the gene GPR126 in the development of the placenta during pregnancy.

The results, published in ***Science Advances***, show that GPR126 (adhesion G protein-coupled receptor 126) is essential for the development of a specific placental cell type that regulates the remodeling of the uterine vasculature. Cardiac defects in mouse Gpr126 mutants are secondary to placental defects, reflecting the intimate relationship between the placenta and the fetal heart.

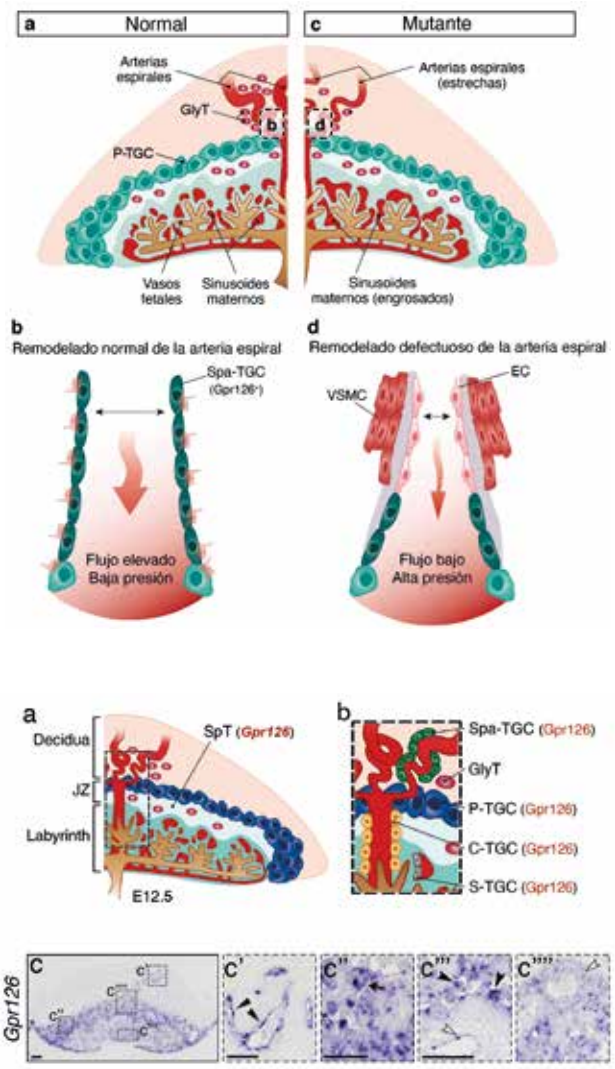
There is evidence that GPR126 may play a similar role in placental development in humans. The babies of women who carry mutations in GPR126 die during gestation or soon after birth, and 30% of these women develop preeclampsia. This pregnancy complication, which affects 5-8% of pregnancies in the general population, is characterized by high blood pressure that damages both mother and fetus and can result in fetal death.

Experiments in animal models have shown that GPR126 is required for the maturation of the peripheral nervous system (PNS), the formation of bone and cartilage, and the development of the inner ear. In humans, mutations in GPR126 are associated with skeletal malformations and muscle cramping in the limbs.

The CNIC Intercellular Signaling in Cardiovascular Development and Disease group, led by **Dr. José Luis de la Pompa**, initially identified GPR126 as a gene regulated by the NOTCH signaling pathway (a highly conserved intercellular signaling system in animals) during heart development.

This suggested that GPR126 might influence the proliferation and differentiation of cardiomyocytes (heart muscle cells) in the developing heart.

Other groups had already proposed a requirement for GPR126 in heart development in mice and zebrafish, but



research had not provided conclusive evidence to confirm this hypothesis.

In the new study published in ***Science Advances***, the CNIC team demonstrate using genetic techniques that GPR126 is not necessary for heart development in the mouse but plays an essential role in the formation of the placenta, a process known as placentation.

Explaining the results, **Dr. De la Pompa** said that "We observed that whole-body inactivation of GPR126 in mice caused thinning of the walls of the heart and resulted in embryonic death. However, when we inactivated the gene specifically in the heart, embryonic development was unaffected and heart function unaltered."

The investigators also found that the lethal effect of whole-body GPR126 deletion "was not reversed by specific re-expression of GPR126 in the heart, indicating that embryonic death in the mutants was not due to a defect in cardiac development," explained first author **Rebeca Torregrosa.** Further studies in the zebrafish model confirmed that GPR126 "is not involved in heart development."

During embryonic development, GPR126 is expressed in giant trophoblast cells, a cell type specific to the placenta. "These cells," indicated **De la Pompa**, "are vitally important for the implantation of the embryo and the maintenance of pregnancy."

The research team demonstrated that GPR126 inactivation in the embryo is compatible with survival if the placenta retains at least one normal copy of the GPR126 gene. However, inactivation of the gene in both the embryo and the placenta causes embryonic death.

"One of the crucial steps in placental development is the remodeling of the maternal arteries. Known as the spiral arteries, these vessels increase their diameter to increase blood flow to the embryo. Defects in this process are associated with pregnancy complications such as preeclampsia, restricted fetal growth, and even miscarriage," said **José Luis de la Pompa**.

The study shows that trophoblast GPR126 is necessary for the expression of specific proteases involved in spiral artery remodeling, which is essential for the viability of the fetus.

Based on these results, the investigators herald mice lacking GPR126 as an experimental model for studying spiral artery remodeling and preeclampsia. This animal model, moreover, has possible clinical applications in preimplantation genetic diagnosis.

The study was funded by the cardiovascular research network CIBER CV (PID2019-104776RB-I00, CB16 / 11/00399), TERCL (RD16 / 0011/0021) of the Ministerio de Ciencia, Innovación y Universidades (MCIU), BBVA Foundation, "la Caixa" Foundation, EMBO fellowship, Boehringer Ingelheim Fonds, and the Programa de Atracción de Talento of the Comunidad de Madrid (Ref.2016T1 / BMD1540).

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doi: 10.1126/sciadv.abj5445

FRONTIERS IN IMMUNOLOGY

CNIC scientists show that trained innate immunity protects against SARS-CoV-2 and increases the immunogenicity of COVID-19 vaccines

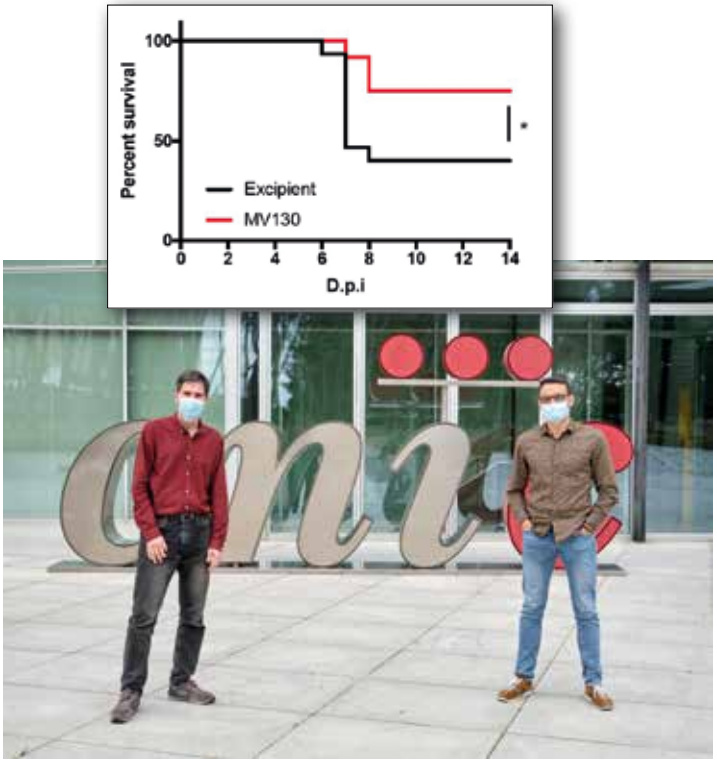
COVID-19 vaccines provide the best weapon against the pandemic caused by the SARS-CoV-2 coronavirus. But these vaccines have also highlighted the need for effective and fast acting responses against future viral threats. This can be achieved by activating—or training—a part of the body's natural defense system called innate immunity. This is the conclusion of a multicenter study coordinated by Spanish scientists **Carlos del Fresno**, of the Instituto de Investigación Sanitaria del Hospital Universitario La Paz (IdiPAZ), **Juan García Arriaza** and **Mariano Esteban** of the Centro Nacional de Biotecnología

(CNB)/Consejo Superior de Investigaciones Científicas (CSIC), and **David Sancho** of the Centro Nacional de Investigaciones Cardiovasculares (CNIC).

In the study, published in ***Frontiers in Immunology***, the team demonstrate that immune therapy with the MV130 dead bacterial preparation, produced by the Spanish biotech company Inmunotek S.L. in Alcalá de Henares, protects against SARS-CoV-2 infection in susceptible mice. The study was carried out at the Centro de Investigación en Sanidad Animal (CISA), part of the Instituto Nacional de Investigación y Tecnología Agraria y Alimentaria (INIA-CSIC), in Madrid. The mortality rate after SARS-CoV-2 infection was significantly lower in mice that had previously received the MV130 immune therapy. This treatment trains the innate immune system by introducing epigenetic changes into innate immune cells, as demonstrated in previous studies in **Dr. Sancho**'s laboratory.

The research team investigated whether this immune therapy might improve the immune response generated in response to subsequent vaccination against COVID-19. In experiments carried out at the CNIC, mice treated with MV130 or a control preparation were inoculated with one of two types of vaccine: one based on the CSIC MVA-CoV2-S vaccine (generated by **Drs. García Arriaza** and **Esteban**) and another based on recombinant protein S with adjuvant. Two vaccine administration routes were tested: intramuscular injection and the intranasal route.

"Animals treated with MV130 before vaccination, which therefore had a trained innate immune system, had a better immune responses to vaccination," explained **Carlos del Fresno**. "MV130 treatment increased the activation of cytotoxic CD8 T cells, which eliminate infected cells, as well as the levels of IgA-class antibodies to SARS-CoV-2 protein S in mucous membranes."



Summarizing the impact of the findings, **Juan García Arriaza** said: "The study shows that immune therapy with MV130 directly protects against death from SARS-CoV-2 infection and shows the ability of trained innate immunity to improve immune responses generated by COVID-19 vaccines."

The authors conclude that MV130 immune therapy will improve vaccine efficacy and immunogenicity, especially in vulnerable population groups or against variants against which vaccines are less effective, thus contributing to better community protection against COVID-19.

The study was supported by funding from the Fondo Solidario Juntos Banco Santander for **Dr. David Sancho**'s research at the CNIC and the Fondo COVID-19 Instituto de Salud Carlos III for **Dr. Juan García Arriaza**'s work. Other supporting bodies were the Fundación Asociación Española Contra el Cáncer (AECC); Fondo Supera COVID-19 (Crue Universidades-Banco Santander); Fundación 'la Caixa'; Programa Horizonte 2020 and Beca Marie Skłodowska-Curie de la Unión Europea; an EMBO fellowship; Comunidad de Madrid and Fondo Social Europeo y Desarrollo Regional Europeo; Consejo de Investigación Europea (ERC-2016-Consolidator Grant 725091); Agencia Estatal de Investigación (PID2019-108157RB); Comunidad de Madrid; Inmunotek S.L., and Fundació La Marató de TV3.

Del Fresno C, García-Arriaza J, Martínez-Cano S, Heras-Murillo I, Jarit-Cabanillas A, Amores-Iniesta J, Brandi P, Dunphy G, Suay-Corredera C, Pricolo MR, Vicente N, López-Perrote A, Cabezudo S, González-Corpas A, Llorca O, Alegre-Cebollada J, Garaigorta U, Gastaminza P, Esteban M, Sancho D (2021). *The Bacterial Mucosal Immunotherapy MV130 Protects Against SARS-CoV-2 Infection and Improves COVID-19 Vaccine Immunogenicity.* ***Front. Immunol.*** 12:748103.
doi: 10.3389/fimmu.2021.748103

PLOS BIOLOGY

CNIC scientists identify two proteins essential for postnatal cardiac metabolism

Scientists at the Centro Nacional de Investigaciones Cardiovasculares (CNIC) have identified essential roles for two proteins in cardiac metabolism after birth. The study, published in ***PLoS Biology***, shows that forced premature activation of these proteins in the mouse heart during the first days of life causes irreversible damage and alters whole-body metabolism, leading to diabetes and impaired thermoregulation later in life.

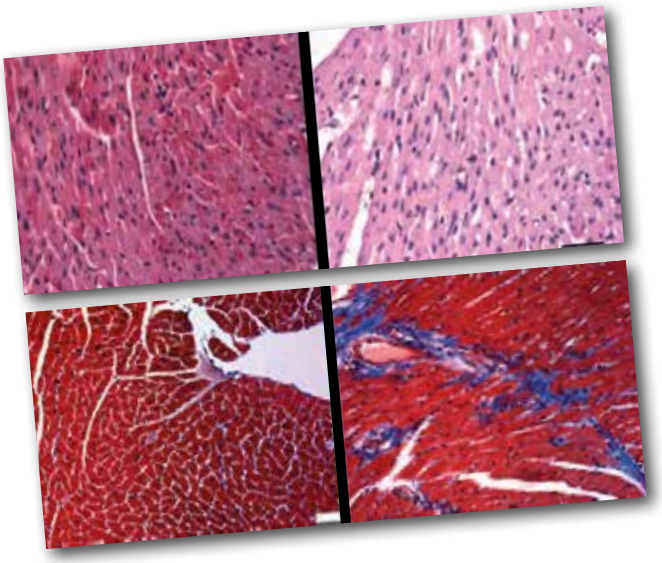
Lead investigator **Dr. Guadalupe Sabio** explained that, fortunately, the study shows that "these effects could in principle be treated through a change in diet."

During fetal development and the first days after birth, the heart derives most of its energy from the metabolism of glucose, stored in the form of glycogen. But first author **Ayelén Santamans** explained that, soon after birth, the rapid growth of the heart increases the organ's energy demands, requiring the heart to become "much more efficient at obtaining energy."

The ***PLoS Biology*** study shows that the proteins p38γ and p38δ are activated in the heart shortly after birth and reduce the activity of the enzyme responsible for glycogen synthesis. This precipitates a metabolic change in the heart, which begins to use fatty acids as its main energy source.

Perturbation of cardiac metabolism by forced premature p38γ and p38δ expression during the postnatal period causes irreversible damage that manifests in adulthood as insulin resistance, glucose intolerance, and an impaired ability to maintain body temperature.

But the new study shows that, since the problem is an insufficient supply of energy to the heart, the damage can be repaired by a change in diet. To demonstrate this, the researchers fed female mice a high-fat diet during pregnancy and lactation.



Newborn mice in these experiments had no cardiac damage and did not go on to develop diabetes symptoms even when p38γ and p38δ expression was prematurely activated.

The study is the first to show that heart metabolism in the postnatal period determines whole-body metabolism. "Our results show that the gradual increase in p38γ and p38δ activity is tightly regulated and that premature activation produces an energy deficit that is deleterious both for the heart and for the metabolism of the rest of the body," said **Dr. Sabio**.

The scientists think that both p38γ and p38δ might underlie some congenital cardiometabolic diseases that currently have no known cause, suggesting that dietary supplementation could be a valid treatment for these conditions.

The study was supported by the following funding bodies: EFSD; Lilly European Diabetes Research Programme; Ministerio de Ciencia, Innovación y Universidades; Comunidad de Madrid; Fundación Jesús Serra; Instituto de Salud Carlos III; and Fundación "la Caixa". ■

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https://doi.org/10.1371/journal.pbio.3001447

cnic AWARDS AND SCHOLARSHIPS

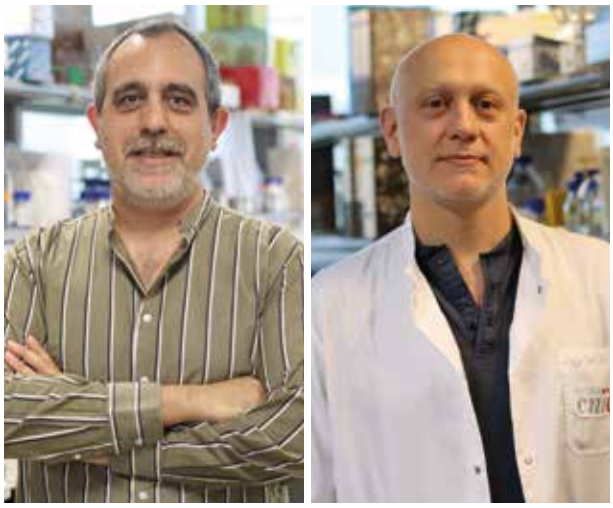
DR. BORJA IBÁÑEZ, AWARDED THE CRUZ AZUL ZENDAL-BALMIS MEDAL FOR HIS CONTRIBUTION DURING THE FIGHT AGAINST THE PANDEMIC

Dr. Borja Ibáñez, CNIC's Scientific Director and Fundación Jiménez Díaz interventional cardiologist, received a Zendal-Balmis Cruz Azul gold medal at the organisation's awards ceremony, which acknowledges people and institutions who have made a contribution in the fight against health crises at the start of the 21st century. The medal was awarded in recognition of his praiseworthy work, sacrifice, commitment and dedication during the pandemic.

The award highlights his research work from the outset of the health crisis caused by coronavirus and his discovery of the therapeutic use of metoprolol in cases of severe COVID-19.

JOSÉ ANTONIO ENRÍQUEZ AND ANDRÉS HIDALGO, WINNERS OF THE CONSTANTES Y VITALES PRIZE FOR BEST BIOMEDICAL PUBLICATION OF THE YEAR

José Antonio Enríquez and **Andrés Hidalgo** have been awarded the Constantes y Vitales prize for best biomedical publication of the year for "A Network of Macrophages Supports Mitochondrial Homeostasis in the Heart."



The study "A Network of Microphages Supports Mitochondrial Homeostasis in the Heart" published in ***Cell***, was the result of a collaboration between two CNIC groups under the direction of **Dr. Andrés Hidalgo** and **Dr. José Antonio Enríquez**. The article, which presents the conclusions of more than five years of research and collaborations with European, Asian and US laboratories, shows that macrophages, a type of immune system cell, help heart cells eliminate their waste material, thus maintaining the metabolic and contractile capacity of the heart.

The data that this discovery contributes suggest that cardiac dysfunction may, in some cases, stem from defects in these resident immune system cells instead of cardiomyocytes, a concept with major consequences for the diagnosis and treatment of heart disease.

DR. ALEGRE-CEBOLLADA AWARDED THE IUPAB MICHÈLE AUGER PRIZE

Dr. Jorge Alegre-Cebollada received the Michèle Auger prize awarded by the International Union for Pure and Applied Biophysics (IUPAB) through its scientific journal ***Biophysical Reviews***. This award recognises the work of young scientists who carry out research in the field of biophysics and who, at the time of proposal, are under the age of 40.

The prize was created in 2019 to honour the memory of university professor Michèle Auger, a dearly loved and respected member of the ***Biophysical Reviews*** editorial panel, who died in 2018.

The research of **Dr. Alegre-Cebollada**, who directs the CNIC Molecular Mechanics of the Cardiovascular System Laboratory, is related with understanding the nanomechanical principles that govern the structure, function and regulation of proteins.

CONFERENCE: BRAIN AND HEART
DR. VALENTÍN FUSTER, DIRECTOR GENERAL OF CNIC - SCIENCE WEEK, 2021

The CNIC again participated in Science and Innovation Week, held in the first fortnight of November, which in the Community of Madrid is led by the foundation "Fundación para el Conocimiento Madri+d". The goal is to bring science closer to society, foster knowledge and interest, and involve the general public in its activities. This year, science week's slogan is 'Science for the great challenges facing humankind'.

With the title "Heart and Brain", our Director General, **Dr. Valentín Fuster**, participated in an online conference.

DR. PURA MUÑOZ-CÁNOVES RECEIVES THE SANTIAGO RAMÓN Y CAJAL NATIONAL PRIZE

The Ministry of Science and Innovation awarded the Santiago Ramón y Cajal National Prize for research in the field of Biology to **Dr. Pura Muñoz-Cánoves**, professor in Cellular Biology at the department of Experimental and Health Sciences of the UPF (DCEXS), research professor at the Catalan Institution for Research and Advanced Studies (ICREA) and group leader at CNIC (the Spanish National Centre for Cardiovascular Research) and CIBERNED (the Neurodegenerative Diseases Research Centre Network) for her scientific contributions in the field of tissue regeneration.

Dr. Pura Muñoz joins two other CNIC researchers to have won this same award, **Dr. Francisco Sánchez Madrid** in 2020, and **Dr. Valentín Fuster**, in 2019.

CNIC RESEARCHER, JESÚS VICTORINO SANTOS, WINS THE FINAL OF FAMELAB SCIENTIFIC PRESENTATIONS

After winning the national finals, presided over by **Queen Letizia**, the CNIC researcher **Jesús Victorino Santos** went on to represent Spain in the international finals of the FameLab presentations.

Famelab is a prize for scientific presentations which aims is to present reliable scientific knowledge to the general public in an entertaining way.

NEW BREASTFEEDING ROOM

The CNIC's new breastfeeding room was inaugurated in 2020, days before the outbreak of COVID-19 pandemic, and is now open for use by workers of CNIC and collaborating organisations.

The CNIC's breastfeeding room was sponsored by Philips, who have provided equipment.

CNIC AT THE NOCHE EUROPEA DE LA INVESTIGACIÓN RESEARCH FAIR PROMOTED BY THE "LA CAIXA" FOUNDATION

CNIC researchers participated in the CaixaForum Madrid research fair, an event that uses live demonstrations and activities to showcase the scientific research carried out at different research centres and universities, among which the CNIC is the most participative organisation, represented by experiments carried out by its researchers. ■

TRAIN2GAIN
WHAT'S ON
INSIDE SCIENCE
CNIC & SOCIETY

cnïcPULSE #13