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WHAT'S ON
INSIDE SCIENCE
CNIC & SOCIETY

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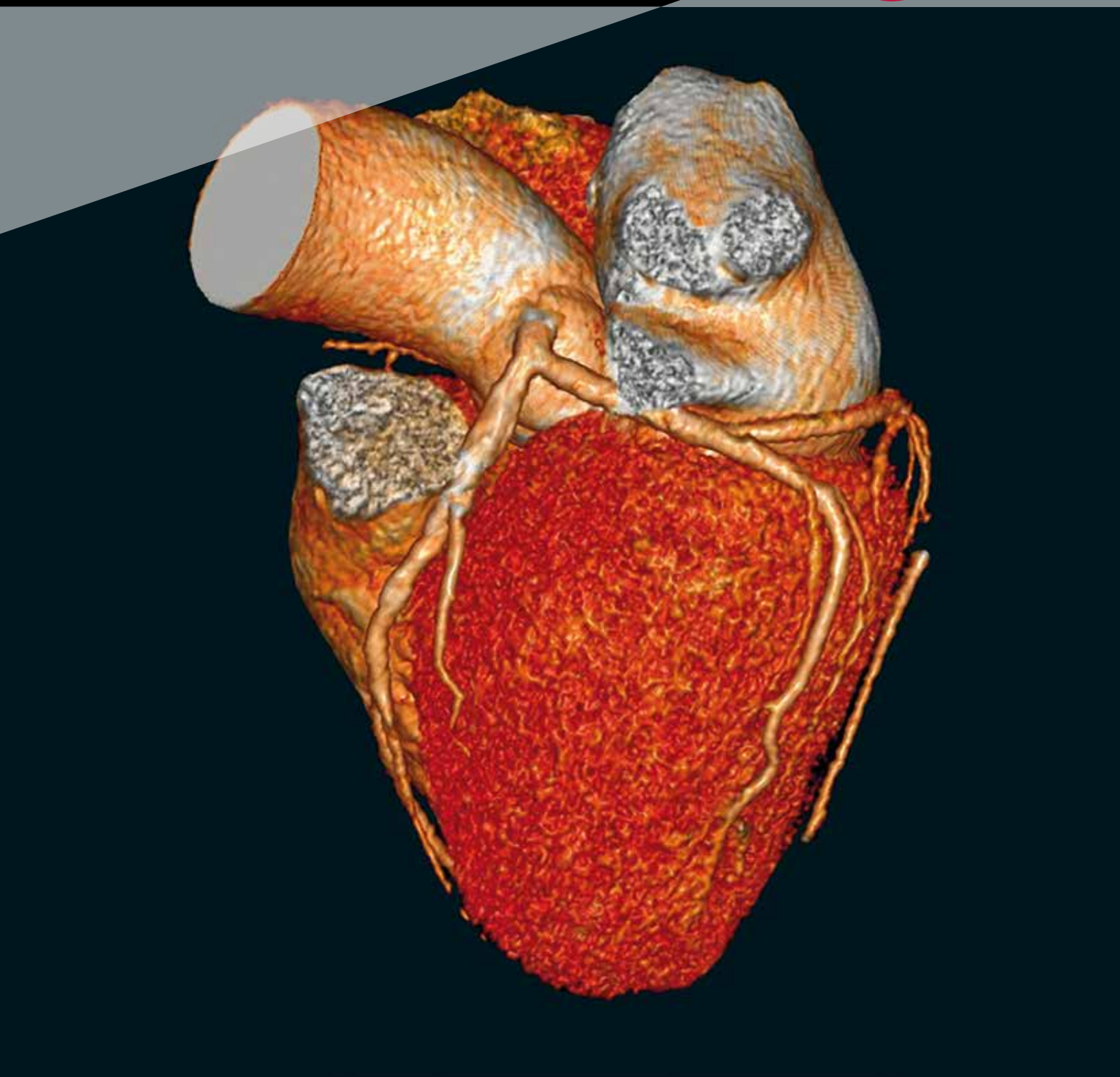

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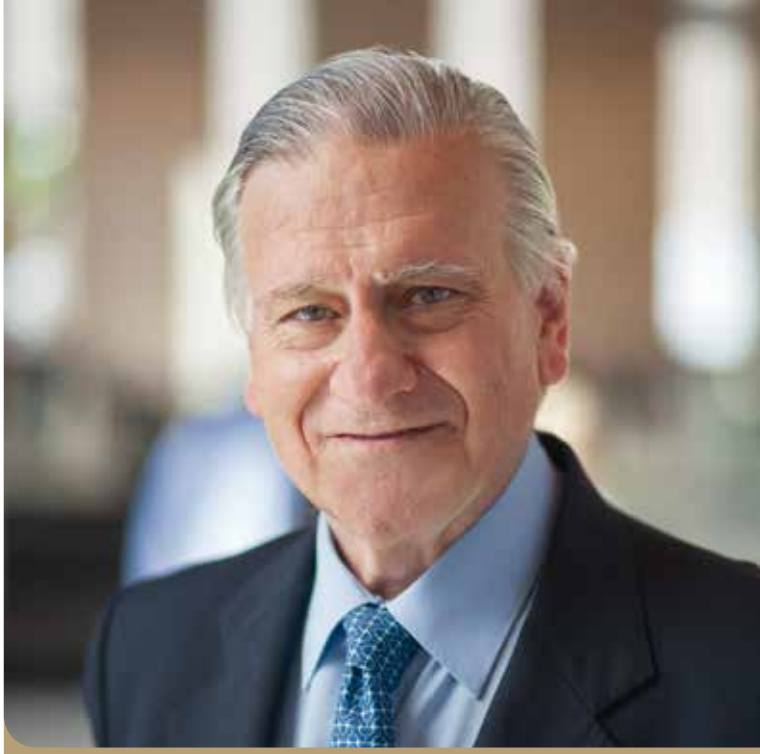


Dr. Valentín Fuster, General Director, Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC)

TECHNOLOGY AT THE SERVICE OF RESEARCH

One of CNIC's hallmarks is excellence, excellence that is also evident in the innovative technology we use to conduct our research. CNIC has state-of-the-art technology in clinical and preclinical imaging at its facilities, technology that enables us, for instance, to determine the presence of arterial inflammation in areas where the plaque of atherosclerosis does not yet exist thanks to the advanced PET/MRI imaging techniques used in the PESA study, or to design a revolutionary technique that allows cardiac magnetic resonance imaging (CMR) in less than one minute —a technique known as ESSOS— which enables precise assessment of heart anatomy and function.

But CNIC also puts this technology at the disposal of the scientific and industrial community through ReDIB, an officially recognised ICTS (Unique Scientific and Technical Infrastructure). ReDIB is a unique infrastructure in the field of biomedical imaging that was set up to create synergies between San Sebastian's CIC-biomaGUNE (Centre for Cooperative Research in Biomaterials), Valencia's Imaging La Fe at the University and Polytechnic La Fe Hospital and La Fe Health Research Institute (IIS La Fe), and BiolmaC (the Complutense University Bioimaging Centre) in order to develop joint projects, opt for more competitive funding programmes and foster the exchange of researchers to pursue excellence in scientific training.

Our ICTS offers equipment that few European centres can boast and represents a powerful, unique tool for diagnosis in molecular and functional imaging, and in the sphere of advanced and high-throughput imaging.

The Infrastructure for Advanced Translational Imaging (TRIMA) is located at CNIC, with a Molecular and Functional Imaging Unit, an Advanced Imaging Unit, a Nanotechnology, Organic Chemistry, and Radiochemistry Laboratory, as well as the High-throughput Imaging Unit.

As **Rafael Yuste**, the Spanish researcher and creator of the USA's Brain Initiative project, acknowledges in this edition of *CNIC Pulse,* it is thanks to these innovative technologies that we can begin to discover aspects of our brain that had previously been unreachable. As he himself says, "We'll know ourselves from the inside for the first time."

Roser Vento-Tormo is an expert in technological innovation whose team is part of the Human Cell Atlas (HCA) consortium, which aims to create an atlas of all the cell types in the human body at single-cell resolution, including all stages of human development/life cycle in 3 dimensions, to obtain a complete view of the human body during health and illness. Thanks to technology, we are seeing surprising results.

But technology always needs human capital. And at CNIC, we know a lot about that. A critical mass of human resources is essential to progress in the research we want to pursue. As **Dr. Vento-Tormo** explains, "It's not all about funding, which is, of course, important... For a person to develop their ideas, it is absolutely vital to part of a group where people think, where they discuss their ideas." We couldn't agree more.

INFRASTRUCTURE FOR ADVANCED TRANSLATIONAL IMAGING (TRIMA) & REDIB

CUTTING-EDGE RESEARCH

TO PRESERVE KNOWLEDGE

ReDIB, the Distributed Biomedical Imaging Network (www.redib.net), is a distributed Unique Scientific and Technical Infrastructure (ICTS) that depends on the Spanish Ministry of Science and Innovation. It consists of four nodes: TRIMA@CNIC, the Infrastructure for Advanced Translational Imaging at the Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC); CIC biomaGUNE, the Molecular and Functional Imaging Platform of the Centre for Cooperative Research in Biomaterials; PREBI-GIBI230, the Infrastructure of La Fe University Hospital (Imaging La Fe); and BiolmaC, the bioimaging unit at Madrid's Complutense University. The ICTS are large facilities, resources, equipment and services that are devoted to research and technological development, in addition to fostering the transmission, exchange and preservation of knowledge, technology transfer and innovation in Spain.

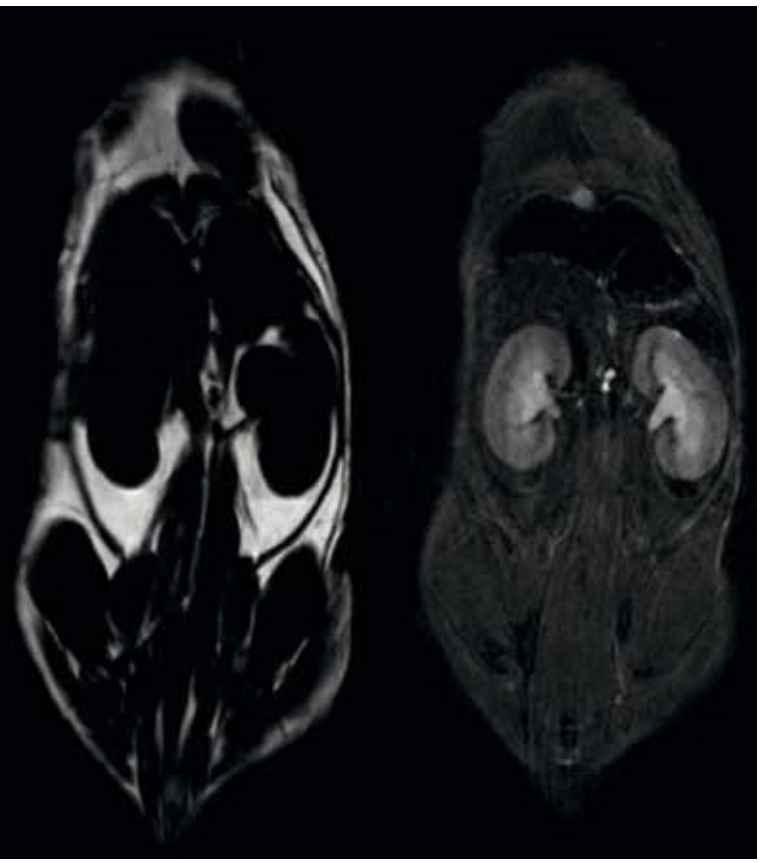
Their main objective is to make scientific and technical infrastructure and equipment available to the scientific, technological and industrial community both in Spain and internationally. These resources can be indispensable for conducting scientific and technological research that is unique or exceptional of its kind, which involves high costs in investment, maintenance and operation, but has a strategic nature and importance that justify their being accessible to the whole R&D&I collective.

All ICTS are unique and exceptional facilities of their kind. They conduct cutting-edge research of the highest quality and act as hubs for the transmission, exchange and preservation of knowledge and technology transfer as well as fostering innovation.

ICTS have three basic characteristics: they are publicly owned infrastructures, they are unique, and they are open via a competitive access process.

They are located at different points of Spain and can be seen on the Map of Unique Scientific and Technical Infrastructure. Depending on the level of integration and their capacities, ICTS may be a single-location infrastructure, form part of an ICTS network or be set up as a distributed ICTS, which is the case of ReDIB.

The ICTS map is dynamic and open, which means that the infrastructures included on the current map must continue to meet the necessary requirements to be an ICTS and, on the other hand, new infrastructures can be added as long as they are operational and prove compliance with the requirements.



The ICTS ReDIB has facilities that, in the opinion of external governmental evaluators, have unique characteristics that contribute to the singularity of the ICTS and are considered "essential".

The essential installations at TRIMA@CNIC include Clinical PET-CT (Vereos digital positron emission tomography/computed tomography), clinical 3T MRI (Elition X3 magnetic resonance imaging), preclinical PET/SPECT/CT (trimodal system) and preclinical 7T MRI (Agilent-Varian).

The equipment, personnel and organisation of this facility form a dynamic group that provides a service to the scientific community in the field of molecular and functional imaging and advanced imaging. It includes state-of-the-art technologies and resources.

- **TRIMA@CNIC**, located at CNIC, has functioned since 2010. The facility has a translational vocation and state-of-the-art technologies to progress in the study of different diseases and cardiovascular conditions from molecular level to tissues; from preclinical research, principally with murine models, but also with human subjects.
- The **Molecular and Functional Imaging Platform** is part of CIC-biomaGUNE-San Sebastian. It was designed, built and equipped to conduct multimodal longitudinal research projects in the preclinical context, and to develop applications in the sphere of preclinical molecular and functional imaging and nanomedicine.
- **BioImaC** is a facility that belongs to Madrid's Complutense University and consists of nuclear magnetic resonance, electron spin resonance, brain mapping and diagnostic imaging capabilities.
- The **Medical Imaging Unit at the University and Polytechnic La Fe Hospital in Valencia**, consists of the Biomedical Imaging Research Group, GIBI230, and PREBI, the Experimental Radiology and Biomarkers Imaging Unit, which have the mission of promoting and developing the use of imaging and biomarker techniques to optimise the diagnostic and therapeutic efficiency of medical imaging through a multidisciplinary, multimodal approach to healthcare research and experimentation with preclinical models.

The management body of ICTS has representatives from the four nodes that make up ReDIB, and a coordinator, **Dr. Gonzalo Pizarro**, CNIC clinical researcher and head of the Cardiology Service at Hospital Ruber Juan Bravo Quironsalud.

HOW TO ACCESS REDIB

Any researcher, whether Spanish or international, can access the facilities and services that are on offer via the website https://www.redib.net. All the facilities belonging to ICTS have the obligation to allot 20% of their time to external users via a competitive access process.

When a user generates a request that meets the conditions, the Coordinating Committee of representatives from the four nodes evaluates the technical feasibility of the request. Some requests are technically not viable and so cannot continue. The request must include a summary of the research project.

> Last year, 17 projects gained access to the TRIMA@CNIC facility via the open competitive access calls, and 12 projects did so through the on-demand access process

If the project is feasible, it is forwarded to the Access Committee, a group 30 national and international experts. This independent, external committee evaluates the proposal and issues a report qualifying whether the project has sufficient scientific merit to receive approval and be conducted within the ICTS. It also establishes the project's priority.

Once the call for projects has finalised, the applicant is informed.

ReDIB has three to four open competitive access calls each year; a form of access with logistic and financial

advantages for the researcher who applies. It is also possible to access ReDIB through an on-demand request process. This year, the 4th call for applicants closed on 31st August 2023.

REDIB EQUIPMENT

CLINICAL IMAGING

ReDIB offers clinical imaging services at two of its nodes: CNIC and Imaging La Fe PREBI-GIBI230. TRIMA, the Infrastructure for Advanced Translational Imaging, has PET-CT equipment (Vereos digital positron emission tomography/computed tomography), a 3T MRI and echocardiography with 4D image acquisition.
https://www.redib.net/imagen-clinica

PRECLINICAL IMAGING

The Molecular and Functional Imaging Platform at CIC-biomaGUNE has two magnetic resonance imaging (MRI) devices, hybrid PET-CT and SPECT-CT devices and an optical/X-ray imaging system. On the other hand, TRIMA has MRI, hybrid PET-CT imaging and fluorescence molecular tomography (FMT) imaging systems as well as luminescence and fluorescence tomography equipment. BioImaC has three magnetic resonance imaging (MRI) systems and a hybrid PET-CT device in addition to X-ray and ultrasound equipment. Finally, Imaging La Fe has a 3T MRI, a microPET-CT device and fluoroscopy equipment.
https://www.redib.net/imagen-preclinica

IMAGING ANALYSIS

Preclinical imaging: The preclinical imaging analysis platform, CIC-biomaGUNE, offers the computational infrastructure necessary to process and analyse images.

CLINICAL IMAGING

This includes analysis of the images acquired by echocardiography, magnetic resonance, PET and computed axial tomography equipment. Different software programmes exist for these analyses, both CNIC-developed and commercial software (i.e., EchoPac for echocardiography, QMASS for MRI, QLab-Philips for resonance, PET and CT). The staff responsible for the analysis at CNIC adapt the form and system of analysis for each study after direct consultation with the researcher.

RADIOCHEMISTRY

ReDIB offers radiochemistry services at two of its nodes. CNIC's Infrastructure for Advanced Translational Imaging has a radiochemistry lab with a shielded area, a 68Ge/68Ga generator associated with an automatic synthesis module and a fully equipped organic chemistry laboratory. CIC-biomaGUNE's Molecular and Functional Imaging Platform has a radiochemistry laboratory.

The 2022 ICTS national call resulted in approval for inclusion of the following facilities and equipment at the TRIMA@CNIC node:

- A SPECT, PET and CT imaging laboratory, including the imaging tools (SPECT-CT equipment) and set-up of the radiochemistry laboratory necessary for the synthesis and characterisation of new SPECT radioactive tracers.
- The system acquired has three imaging modes (PET, SPECT and CT), which can be used to study three to four preclinical models simultaneously, increasing the unit's capacity. It also provides improved image quality in cardiac synchronisation and/or respiratory studies.
- In 2022, 17 projects gained access to the TRIMA@CNIC facility via the open competitive access calls, and 12 projects did so through the on-demand access process. ■

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YALE SCHOOL OF MEDICINE
YALE CANCER CENTER
New Haven (United States)

Carla Rothlin

"RESEARCH IS AN INTELLECTUAL CHALLENGE THAT YOU CAN TAKE UP THROUGHOUT YOUR LIFE"

Dr. Carla Rothlin is Dorys McConnell Duberg Professor of Immunobiology and Professor of Pharmacology at the Yale School of Medicine, and co-leader of the Cancer Immunology Programme at Yale Cancer Centre. She studied biochemistry and pharmacology at the University of Buenos Aires, where she also undertook her postgraduate research under the direction of Dr. Ana Belén Elgoyhen, focussing on nicotinic receptors expressed in the inner ear. Later, she completed her doctorate and moved to San Diego to join Dr. Greg Lemke's laboratory at the Salk Institute for Biological Studies. In 2009, Dr. Rothlin was named Assistant Professor in Immunobiology at Yale Medical School.

Dr. Rothlin's research focusses on the mechanisms underlying inflammation regulation and homoeostatic control of immunological function. Her laboratory has been able to identify the function of TAM receptor tyrosine kinases in negative regulation of immune response and resolution of inflammation. Her contributions to this field have received the recognition of various institutions such as the Pew Foundation and the Howard Hughes Medical Institute. In addition to her research work, Dr. Rothlin is also committed to Yale's educational mission, and has been Director of Graduate Studies in Immunobiology since 2018.

Your training is in biochemistry and pharmacology. How did you come to immunology?

I studied biochemistry and pharmacology at the University of Buenos Aires and, in 2002, after completing my doctorate with **Dr. Belén Elgoyhen**, I went to the Salk Institute in La Jolla to work on my post-doc.

During my doctorate I studied nicotinic acetylcholine receptors, which are very special receptors that mediate information from the brain to the inner ear. What these receptors do is modulate the ear's sensitivity. And, very interestingly, without really looking for it, in my post-doc I ended up finding another family of receptors, tyrosine kinase receptors, which mediate regulation of inflammatory response.

That is to say, we change response and model, but I understood that in many physiological processes, or maybe also in physiopathological ones, there are regulation mechanisms. Our organism does not always want to always respond, or with the same intensity. But many mechanisms exist that regulate how response should be and how long it should last. In the same way that regulation exists at auditory level, there is also inflammation regulation. And that's what my laboratory does: try to understand the nature of the internal mechanisms our immune system has to be able to regulate how large your inflammatory response is and how long it should last.

We believe this is important because if you respond a lot or for a long time, this could be the origin of chronic inflammatory responses and of many of the diseases that affect humankind.

I made this first finding at the Salk Institute, despite not having trained as an immunologist. I knew that to be able to really understand the implications of what we had discovered in terms of inflammation, it was very important to set up my laboratory in a place where there were a large number of scientists devoted to studying the immune system.

And I was very lucky to start at Yale University's immunology department, an exceptional place for the analysis of immune response and, in particular, what is known as innate immune response, which is the response we are all born with and is largely responsible for forming inflammation.

It was a real honour for me, and a great opportunity, because I was able to surround myself with scientists who were very knowledgeable about inflammatory response.

To progress in science, it's essential to understand the importance of the environment where you ask your questions. The possibility of answering them in the best way doesn't just depend on the ideas you have, but also on how these ideas grow, on what is shared with colleagues in and outside the laboratory.

When a researcher formulates their questions, do they think about the possible medical benefits for society?

Yes, of course. Recent decades have seen giant leaps in recognition of immune response and its great impact on many biological functions; it isn't just a mechanism that lets us attack bacteria, viruses, parasites, fungi, and so on... Acting as a defence system against infectious diseases is one great role of the immune system. But it can also regulate functions inside our organism that are not part of what defence response is.

Our laboratory is devoted to understanding how immune response is regulated, not only when it's acting as a defence against external threats, but also, for instance, when it suddenly activates to try and eliminate a cell that has become cancerous. We are also very interested in understanding how the immune system activates when the cells of our organism die. For instance, if we have suffered a trauma and many cells have died, the immune system is also able to recognise this and activate a repair response for the damaged tissue.

We study how these responses are regulated in our laboratory. We have discovered mechanisms that allow us to develop a much more effective response against a cancerous or other cell, which offers us the opportunity to create a response against tissue damage that can regenerate the damage in an organ in a more efficient way.

New technologies have been added to this acquired knowledge in the field of immunology. How important have they been in producing this qualitative leap?

We are at the ideal moment to combine this foundational knowledge, gathered over many generations, thanks to which we know more about the immune system. But now we have more molecular knowledge and, what's more, we have mechanisms that allow us to modify how the immune system reacts. That's how we can ask what changes we have to make in an immune response to obtain a better response against cancer, to

stop the progression of Alzheimer's or to regenerate a damaged heart.

Immunotherapy has revolutionised the treatment of certain cancers and it looks like it will be the answer to many diseases, if not all of them. What about the possible collateral effects of manipulating the immune system?

Basic research is essential to be able to distinguish what physiological or pharmacological effects we want to induce to prevent Alzheimer's or to treat a cardiovascular event, etc. and not induce effects on the immune system that could be prejudicial.

We must be very careful, as human beings but particularly as scientists, not to say that by X day we will be able to cure a given disease. But I think that science has shown many times that understanding how a system works and how it does so aberrantly in a disease is basic for designing a way to intervene that could be successful.

We contribute to knowledge, but I believe that technology has brought unquestionable benefits. Both areas are very important and obviously, as a person who is devoted to basic science, I perceive how the system works in one way, which is not the only way, but is one of the ways that enables a potential therapy for all of these diseases.

> "We must be very careful, as human beings but particularly as scientists, not to say that by X day we will be able to cure a given disease"

> "You have to be committed because things don't always work out in experiments. The aim is always to be able to answer the questions we have set ourselves"

It is true that immunotherapy has made great progress in certain types of cancer. We have seen that certain types of cell in the immune system, T cells, attempt to eliminate the cancer but tire in the effort and become exhausted. We have seen that they can recuperate and attack the cancer.

But this is not the only reason we may have a cancer. As researchers, we have to know what the other causes are for a poor immunological response. And when we know these, we might find new strategies for the patients who do not yet respond to immunotherapy, which is a very high percentage. And the reason is probably because the target is different.

And how is it possible to modulate the immune system to treat a cardiovascular disease or Alzheimer's?

The first step is to understand whether there are certain immune system responses. For instance, in Alzheimer's, now we have started to discover that there is a response from cells with immunological functions —microglia— that prevent the progression of this disease in animal models.

If the microglia response also exists in humans and prevents the progression of Alzheimer's, then we could try to find certain targets, for instance receptors, in the microglia. And depending on the type of receptor we could design different molecules.

In fact, we have discovered a microglia receptor that causes the microglia to have the function of preventing the progression of Alzheimer's in animals.

Then, we have to ask ourselves if we can do the same in humans, if we have the same function and, if that is the case, a new therapy could be found, maybe not to cure, but at least to prevent at very early stages.

That's why early diagnosis mechanisms are important. In general, to treat diseases, first you need to have a good diagnosis and then a good treatment.

Could the immune system be used as a warning sign to identify other diseases?

If a person has an infection, the immune system warns us very soon if the infection is being responded to. Or something even simpler can be done, like measuring inflammation in blood to know that it has activated.

We can think of it as a sensor of both internal damage and the damage caused by external factors. I think it could be very interesting to use the immune system to diagnose and treat diseases in the future. In reality, it is a warning system that something is happening.

The pandemic revolutionised science and many researchers found themselves having to work on Covid. Did you have to interrupt any lines of study to devote yourself to this worldwide problem?

No. You have to remember that scientists train over many decades and that implies we have a high degree of specialisation. We are specialists. That's why we have to devote ourselves to our specialism, in which society has invested so much, in areas where we can help achieve progress. I did not have to pay to study at Buenos Aires University, I was trained for free, and afterwards I had the opportunity to continue this training thanks to many institutions. That's why I have the responsibility to apply my knowledge to make progress in inflammation regulation and give back to society, which is now global, what it has invested in me.

Do you remember how old you were when you became interested in science?

The truth is that I have a very personal reason, but one that is obviously influenced by what I have lived and read. My parents are physicians, my father is also a scientist, and I am the eldest daughter. But I remember that when I was a very little girl, I wanted to be a palaeontologist because I was blown away when they discovered Lucy. My parents had bought me a beautiful book with some spectacular pages on palaeontology.

Later, I became fascinated by biomedical aspects and that's why I chose to train in biochemistry. In Argentina, biomedical training allows you to go into research. So yes, I have wanted to be a researcher since I was little. And I love it because research is an intellectual challenge that you can take up throughout your life; you are always thinking about trying to answer new questions. For me, that's fascinating. The intellectual challenge of having to find answers to something we don't understand well.

As director of a laboratory how much time do you have for research?

All the time: I am co-director of my laboratory and all the activities I do are related to science. As I am a professor, there are certain aspects of what I do that are more related with service to my community, but everything is related to science.

Apart from the intellectual commitment, there is also the commitment to the scientific training of the people who are in the laboratory.

> "Science needs funding, but not just that. It also needs a critical mass, which is something I see at CNIC"

In science, as in many walks of life, there is commitment, and it is precisely because of that commitment that some days are hard, whereas others are incredible. But you have to be committed because things don't always work out in experiments. The aim is always to be able to answer the questions we have set ourselves.

I am Director of Graduate Studies in Immunobiology at the university and we have a programme with many people training to do their doctorate. In my opinion, it's important to generate the ideal critical-scientific atmosphere and provide the next generations of scientists with the tools they need.

I also have a general commitment to making sure that immunology, in reality science, reaches many people who have not had the privilege that I had of going to university.

Along with a good friend of mine, **Elina Zúñiga**, professor at California University San Diego, I began a programme called Global Immunotalks during the pandemic. The seminars take place on Zoom every Wednesday, except during vacations.

You talk about giving back to society what it has invested in you. Have you ever considered returning to your country to practice science?

I've thought about it a lot. For a scientist, like anyone else, it is very painful not to return to your country of origin. But I think that as we live in a more globalised world, one can be useful from another perspective.

In personal terms, and more so at my age, I realise that it has been one of the great costs of practising science as I do. Not living in Argentina means not being near many friends and family members. I've had to make a choice about my professional life. I understand a great investment is made in many of us who do not return. However, I think we can be a great positive influence on a worldwide scale, where one can make a contribution not only to one's country, but to more nations.

Obviously, each country has to think about the equation: how much is invested and how many people leave, because the people who leave don't return.

It's clear that science needs funding, but not just that. It also needs a critical mass, which is something I see at CNIC. It's an institution that has a critical mass that enables progress to be made in research.

Women and science. Are you tired of being asked the question?

I noticed a marked difference in the representation of women and other minorities when I began teaching. Before, I hadn't noticed it.

I think, as a professor, I have the responsibility to achieve a more balanced representation, not just of women but of other minorities. ■

Dr. Carla Rothlin participated in the seminar "Principles of resolving and non-resolving inflammation" in CNIC at the invitation of Dr. Guadalupe Sabio.

COLUMBIA UNIVERSITY
NEUROTECHNOLOGY CENTER
New York (United States)

Rafael Yuste

"BECAUSE IT ACCESSES THE CENTRE OF OUR MENTAL ACTIVITY, NEUROTECHNOLOGY BYPASSES ALL OF THE FILTERS THAT EXIST IN THE BODY"

Rafael Yuste studied Medicine at the Autonomous University of Madrid. He went to the United States to write his thesis and has now lived there for 36 years. He had to abandon his musical studies at Madrid Royal Conservatory because the time came when the disciplines of science and music each demanded 150% of his time. He set music to one side and devoted his life to science. He is currently Director of the NeuroTechnology Centre (NTC) at Columbia University, New York. Yuste is one of the proponents of the BRAIN Initiative project. His work focusses on understanding how perception and memories work, and he has experimentally altered "perceptions" in laboratory animals.

The BRAIN Initiative: A map of the brain

In September 2011, we sent the Obama Administration a proposal to conduct a project similar to the human genome one, but about the brain, on a large scale, with a 15-year duration and funding similar to or larger than that of the Human Genome Project. The aim was to develop techniques to measure and map brain activity. And the same day that we sent the proposal, they read it and sent it back. They loved it!

Obama chose this project as the Administration's star science project, he presented it to Congress and managed to convince them two years later, in 2013, with the goal

of developing methods to advance our understanding brain function and progressing both in the clinical context and also in economic terms. The latter aspect is what convinced Congress.

What do we really know about the brain? Do we have a map?

We don't even have a draft. The brain is a very complex organ with more types of cell than the rest of the body. We don't know exactly, but we estimate around 100,000 million neurons, each connected at a minimum with around another 100,000 neurons. The complexity of the brain network is three times greater than all of the internet on Earth. Which means that inside our heads there are three internets.

This tangle of connections, what **Santiago Ramón y Cajal** called the impenetrable jungle, is where thoughts, memory, imagination, behaviour, identity and awareness arise. And that is the greatest question in neuroscience, which remains unanswered. How does what we are —humanity, our mind— arise from the brain activity of all of these connections?

We are not talking about any organ of the body, like the liver, lungs or heart. This is the organ that generates the human mind, and it is there to be discovered. Neurobiologists have been pondering this for over 100 years. And the idea we presented to Obama is that we lack technology. We won't progress in this field if we don't construct the techniques to enter the brain and map what is going on, so as to be able to change it and help patients.

And that is the central goal of the BRAIN Initiative: develop the methods to record brain activity and change it. The American project has inspired similar projects in many countries: China, Japan, South Korea, Australia and Europe, Israel, Canada. In 2017, we created an international network, the International Brain Initiative, similar to that of the human genome.

We are halfway there, we're gradually developing techniques and the first major results are being seen: the brain activity of small animals has been mapped, but not yet decoded. It's like the genome: one thing is sequencing, and another is understanding what is written there.

So, having the map does not mean we understand what is going on in the brain?

First you need to have it. That is the prerequisite to understanding what is happening. It's what they call "necessary but insufficient". It's the same as with the genome, it was sequenced, and we are still trying to decode what is happening. It's such a complex system that we neurobiologists have tackled it from the outside, but still haven't got inside. And that is what these techniques allow us to do. It's not just about recording. First, we map and then we modify.

Your training was in Medicine. How did that influence you when it came to research?

One of the things I remember is the care given to schizophrenia patients when I was doing a clinical rotation in psychiatry at the Lafora Hospital in Madrid. At that time, we had bodyguards to interview some of the patients

who were dangerous. For me, that was a shocking experience because I remember one of the patients I interviewed was highly intelligent, and instead of helping society, contributing to progress, he was a self-destructive being. And I wondered if we could have entered his brain and seen what was going on, would it have been possible to turn a switch on or off and suddenly make all of that creativity and intelligence serve another purpose and improve his life.

I realised that intervention is not possible until we can see what happens inside the brain. To understand pathophysiology, first we have to understand the physiology of the organ.

At the turn of the 21st century there was talk of the "brain decade". And now we are in 2023.

More and more progress is being made. This is a taste of things to come. I completely agree that, in the same way that genetics and molecular biology represented a leap for biology in the 20th century, the 21st century will belong to neuroscience. We are talking about an organ of the body that generates the human mind and identity, the essence of who we are. We'll know ourselves from the inside for the first time.

It will be a revolution for humankind; I compare it to a new Renaissance. Knowing ourselves began in the Renais-

sance. And the repercussions will be of all kinds, in medicine of course, but also the human and economic spheres. To give an example: in the last 15-20 years mobile phones have revolutionised the world. What do smart phones do? They connect us to a network. They have changed our lives. Now, a phone is an accessory that forms part of our identity, and we access it with our fingers. But the next generation will be able to do all that with an interface.

These interfaces are now being tested for people with spinal cord injuries or ALS so that they can move their limbs or communicate by means of the interface.

The interfaces that spinal cord injury patients have are invasive. A lot of the neurotechnology being developed is not invasive. For instance, one of the goals of many companies is being able to write mentally without using our fingers. This would lead to an increase in cognitive capacities.

Isn't all of this available information a double-edged sword?

Here, we come up against ethical and social problems, which are very important, and many researchers like us, who are involved in the field, see them coming. There's no escaping them. Technologies are neutral: you can use them to cure a tetraplegic or to give someone access to what you are thinking. As we develop technology and support initiatives like that of the USA, we must develop ethical rules. We believe it is a question of human rights that protect the essence of what it is to be human, which is generated by the brain.

It's a rule of three: if the brain generates all mental and cognitive activities, and you can record and change brain activity with techniques, it follows that you can record and change cognitive activities. And that is not science fiction, we have done it in animals. In fact, at my laboratory we are specialists in recording, decoding and manipulating brain activity in mice. And we do this not because we want to enslave them, but to cure Alzheimer's or schizophrenia by understanding how the brain works in animals.

What can be done in a mouse today, will be possible in human beings in the future, which is why, before that happens, we have to protect human brain activity as a basic human right.

Yet again, science is a step ahead of the law.

The clearest example is what happened with nuclear power. It was the physicists who made the nuclear reactor that warned the humans who were in danger. And that's why the Atomic Energy Commission was created in Vienna. Something similar will happen with neurotechnology. We are going to become a different type of human being, and we need to think about that carefully and define what type of human beings we want to be. We have to protect basic rights before 'getting the car on the road'.

Will we have to add new rights to human rights?

If humankind progresses, why would human rights not progress too? The truth is that we are always changing. We have to improve, not only in medical techniques, but also in social rules, and in this case human rights.

What do we mean by neurorights?

The concept of neurorights refers to rights in the cerebral and mental domain. Current human rights refer to the body's need to eat, to a dwelling, etc.

Now we are talking about brain activity. We propose the right to mental privacy so that the content of brain activity cannot be decoded without consent; the right to personal identity and free will, so that brain activity cannot be modulated, because the essence and freedom of choice are going to change; and the right to equal access to sensory and cognitive augmentation technologies so that we don't end up with a two-speed human race: those that have neurotechnology and those who don't.

We scientists are working closely with experts in human rights, in cases of torture, disappearances, racial discrimination, protection of minors, etc.

> "We'll know ourselves from the inside for the first time. It will be a revolution for humankind; I compare it to a new Renaissance"

> "We are going to become a different type of human being, and we need to think about that carefully and define what type of human beings we want to be"

Methods to modify our conduct already exist, like social media, internet...

That's true, but that's just a taste of things to come. For instance, I can tell you what we do with mice, which is to modify their visual perception based on neurotechnology that stimulates the neurons in the visual cortex of the brain responsible for vision. And the animal behaves as if it were seeing things that we put into its brain. And we have proved that there is no difference in animal behaviour if the information comes from inside or outside. In fact, the animal interprets them as its own.

As it accesses the centre of our mental activity, neurotechnology bypasses all of the filters we have in our bodies; for instance, if we read information on internet that may be biased, although we believe it, we always know it is external. If we put it directly into the brain, we will believe it's what we think.

That's why it is so important to protect ourselves. There must be a red line that is not crossed. We have reached the essence of what it is to be human, and we can change it. It sounds like science fiction, but we are already doing it in laboratories.

We have the example of Chile, where a constitutional amendment was unanimously approved to protect brain activity as a fundamental right of all Chilean citizens, so that brain activity cannot be altered or decoded without consent. The idea is that the United Nations should champion this legislation and spread it worldwide so that brain activity is sacrosanct and cannot be touched.

Do we see what we think we see?

One of the few things we know about the brain is that we are seeing that the world we live in is generated internally. That is related to what Plato and Kant said, that the reason the human mind fits in with the world is not because it is a refection of the world but the opposite: the world is a reflection of our minds. What we believe we see we already have in our brain. That is what we are beginning to find in mice.

> "The concept of neurorights refers to rights in the cerebral and mental domain. Current human rights refer to the body's need to eat, to a dwelling, etc."

And I believe it fits in with many of the discoveries that are being made now in neuroscience, which say that we have a machine that is generating a kind of virtual reality that is no other than the world we live in.

That would explain, for instance, how millions of people see a single fact in many different ways?

That predicts that each of us lives in an isolated universe, which is the universe of our mind. But the brain has 700 million years of evolution behind it, and it has evolved as a machine to predict the future.

And we perceive all of this through our senses —the systems of sight, smell, touch— which are fantastic. With that, the virtual model adapts to the world and it's so good that it makes us believe that it is the world.

A human being is no more than that: the human mind, what it knows, everything it is, thoughts, memories, emotions. It must be protected because if you don't, yours might be decoded or altered.

I am optimistic, I think that this type of technology and knowledge will take us to a better and fairer society. Historically, that is what has always happened: science shines a light, long-held prejudices disappear and ignorance ends.

Does it mean we will be able to communicate with people who suffer cognitive deterioration like Alzheimer's or ALS?

That's one example of the benefits of neurotechnology. One of the things they are starting to do with implanted interfaces is precisely that; to decode the mental activity of patients who cannot communicate.

My colleagues at Stanford University and the University of California San Francisco (USA) have been able to decode speech through internal brain sensors. So, it is possible that Alzheimer's or ALS patients could establish two-way communication.

One of my first medical experiences at Madrid's Fundación Jiménez Díaz was with an ALS patient. It was there that I perceived the importance of being able to help these patients communicate, because one of the last things that stops working is the brain. Patients with ALS are locked in their own body, which is paralysed, but they can't communicate. Neurotechnology could represent a route to freedom for them. In the future, assisted neurotechnology will enable control of robotic equipment, prostheses of legs and arms, or even living without that death sentence.

That is one example of the benefits. But the same technology can be used on a normal person to find out what they are thinking. For instance, in a police interrogation. That is why rights must be protected.

And they aren't?

Not yet. In the proposal we sent to the Obama government in 2011, we highlighted the importance of tackling the ethical and social issues of neurotechnology and the need for regulation. And that aspect still lags behind the technological developments.

Sometimes we speak about setting up guide rails so that this technology develops within an ethical system that is compatible, but also strict so there are no deviations.

What is the role of private business?

Private business plays an important role because it can be the driving force behind neurotechnology and bring benefit to patients and humankind in general. But it has to understand that certain rules must be followed. We are collaborating and working with many private companies, IBM, Google, Facebook, etc., and they understand that this is a field of interest to them which should be developed within an ethical framework.

The idea is that this new human rights platform should also receive support from the private sector. ■

Rafael Yuste gave the seminar "The neural code: emergent properties of neural circuits" at the invitation of Jorge Alegre-Cebollada.

WELLCOME SANGER INSTITUTE
Cambridge (United Kingdom)

Roser Vento-Tormo

"WORKING IN ACADEMIC SCIENCE IS A PRIVILEGE, AS IT ALLOWS US TO DEVELOP OUR CREATIVE SIDE"

Dr. Roser Vento-Tormo runs her laboratory at the Wellcome Sanger Institute, Cambridge (United Kingdom). Her research focusses on the adaptation of immune cells in tissues and their function in steady state and inflammation. Her team uses genomics, spatial transcriptomics and bioinformatics tools to reconstruct the microenvironment that will shape immune cell identity and function.

Vento-Tormo completed her PhD with Esteban Ballestar in Barcelona, where she studied the influence of cytokines on innate immune cell differentiation. She later did her post-doc with Sarah Teichmann at the Wellcome Sanger Institute as an EMBO and HFSP Fellow. She was finalist in the 2023 edition of the Michelson Philanthropies & Science Prize for Immunology for her essay "Decoding foreign antigen tolerance: Cell atlases of human tolerogenic milieus guide transformative immunotherapies". Her research focusses on how cell-cell communication and the tissue micro-environment regulate cell identity and function in the context of immunity and development.

She also designed CellPhoneDB, a novel repository of ligand-receptors and their interactions, and applied CellPhoneDB to study cellular connections from single-cell transcriptomic data.

Your team is part of the Human Cell Atlas project, which has recently published new results.

Our team is part of the Human Cell Atlas (HCA) international consortium, which aims to create an atlas of all the cell types in the human body at single-cell resolution, including all stages of human development/life cycle in 3 dimensions to obtain a complete view of the human body during health and illness. Recently, one of the initiatives participating in the HCA, called the Human BioMolecular Atlas Programme (HuBMAP) has generated new results. Some of these results were published in three articles in ***Nature***. This research is an excellent resource for researchers like myself who study human biology and diseases, and an essential contribution for the HCA. Understanding the human body at single-cell resolution level will allow us to develop better diagnoses and treatments.

In other words, the goal of HCA is to draw up a cell map of all the cells located in all our organs, first in healthy ones, to later compare them to diseased ones. It's like having a Google Maps (a map of healthy cells) that also lets us detect deviations from the route (a map of diseased cells).

Technology plays a very important role in this work because, as we progress further, we increase the resolution of results, and in that way obtain more information about the cell and the tissue. So, these cell atlases are developing in parallel with technologies like genomics, bioinformatics, big data, etc. The use of computers is essential because, in the end, it isn't only about generating data, but about learning to understand them. You have a map, and you have to understand how to read it.

One of the studies recently published in *Nature* follows your group's line of research in the study of placenta cells.

That's right, in the Greenbaum study, the authors focus on the development of placenta and how the mother's immune system helps in this process. The work complements a study that my team published some months ago in the same review [Arutyunyan et al. (2023) ***Nature***. doi: 10.1038/s41586-023-05869-0], which is a continuation of my post-doc studies characterising placenta at single-cell resolution [Vento-Tormo et al. (2018) ***Nature*** doi: 10.1038/s41586-018-0698-6]. Both papers published this year (Greenbaum et al. and Arutyunyan et al.) help us better understand the vascular reorganisation in the uterus that is necessary to sustain the development of placenta and the embryo. Uterine reorganisation is essential for a pregnancy to continue, and therefore is very important to understand diseases that affect pregnancy, such as preeclampsia.

What information have the recently published atlases contributed?

The articles published as part of the HuBMAP initiative in ***Nature*** describe the cell maps of three organs: the placenta, intestine and kidney. This allows us to obtain views of the different cell types and their organisation in tissues, as well as help us understand the functioning of healthy tissues and those damaged by a disease.

To generate cell atlases, we use a technology called "single-cell resolution transcriptomics". The transcriptome gives us exclusive information about the cell since, despite almost all the cells in the body of an individual having the same genome, only some genes are active in each of them. The set of genes that are active in a cell is known as the cellular transcriptome. That's why single-cell resolution transcriptomics is such a powerful tool as it allows us to make inferences about cell identity and function. Because it requires an initial step of tissue digestion, the technology's greatest limitation is loss of information about the spatial distribution of cells.

To overcome this limitation, we combine single-cell resolution transcriptomics with another technology called spatial transcriptomics. Spatial transcriptomics lets us measure the transcriptome directly on the tissue and therefore obtain the spatial coordinates that each cell occupies in the tissue. In some ways, spatial transcrip-

tomics is as if you did a high resolution histology, contributing exact information about the cells and which genes they express.
Our group generates cell atlases of different parts of the human body, with special focus on mucosa-associated lymphoid tissue to study how they are formed and their abnormalities in different diseases. In our recently published article (Arutyunyan et al. ***Nature*** 2023) we analyse the transcriptome of human uterus samples during the first trimester of pregnancy. These samples also contain placenta, a transitory organ formed by the embryo during its development, which plays an essential role in the nutrition, protection and development of the embryo. To do so, the placenta, which surrounds the embryo, is in direct contact with the uterus. Our work allowed us to study communication between the uterus (maternal) and the placenta (foetal) after implantation in humans.
What happens in the period of development after implantation is fascinating. The epithelial cells of the placenta, called trophoblasts, which are of foetal origin, migrate towards the maternal uterine tissue and invade the uterine arteries. This allows remodelling and broadening of the uterine arteries to increase the amount of maternal blood that reaches the placenta, facilitating the exchange of nutrients between the embryo and the mother. This is a unique condition, where foetal and maternal cells share a space to perform a common function: the development of the foetus.

> "Our group generates cell atlases of different parts of the human body, with special focus on mucosa-associated lymphoid tissue, to study how they are formed and their abnormalities in different diseases"

> "An idea doesn't come from nothing. If you read, you pay attention and think differently, out of the box

The transformation of the arteries during the first trimester of pregnancy is essential, because abnormalities in this process are related with common problems in pregnancy like preeclampsia or intrauterine growth restriction. What's more, the migration of trophoblasts has characteristics that are specific to humans, which cannot be reproduced in mice. This may be due to the length of a human pregnancy (9 months) compared to that of mice and, therefore, the need for a much higher amount of nutrients, which are supplied via blood flow.
Our study is really interesting because, for the first time, we define the mechanisms by which trophoblasts migrate to the uterus and maternal arteries. And they key to this is communication between the foetal (trophoblasts) and maternal (uterine) cells.

How do cells communicate?

Tissues and organs form organised communities. So that each cell does not act individually, coherence and structure are necessary, and for that to happen, they need to speak to each other. There are different spaces in the tissue that specialise in different functions and determine communication hubs of cells. This allows the control of more complex functions, for instance, how much an organ should grow and when the growth should stop.
There are many forms of communication, and many have not yet been studied. One of the most common forms of cell communication, and what we study, is through ligand-receptor interaction. In this case, the cell that sends the signal, secretes or expresses a molecule called a ligand on its surface. This ligand can interact with another molecule called a receptor, which is expressed on the cell surface of another receptor cell of the signal. As these two molecules interact, a signal is activated in the receptor cell, which ultimately activates a specific expression of genes that may have an impact on cell function.

So, a defect in development means that communication has failed?

It could be due to many reasons, but it is often the case that one of the cells is not talking correctly to the next cell along and so communication is not established, and the cell doesn't know what to do. Communication guides all of the processes, from a cell that migrates to a place until it proliferates. If there is a defect in this communication, a cell may proliferate more than it should, for instance, and produce something it should not. Or conversely, it doesn't proliferate, and something doesn't happen, or goes to the wrong place.

This approach, performed on healthy cells, serves to study disease?

In this study we only looked at what happens in healthy placentas and uteri. What we know is that the migration of trophoblasts in the uterus is controlled by the communication between trophoblasts and uterine cells. We know this happens because when there is an ectopic pregnancy —the embryo is implanted outside the uterus, for example in the fallopian tube— an uncontrolled migration of trophoblasts occurs that endangers the life of the mother and the embryo.
One of the things we have seen is that the mother's immune cells, and in particular macrophages, control the invasion. That's why we think that maybe controlling the cells of the mother could tackle these complications; but this is pure speculation because we haven't yet worked with diseased cells.
In the future we are interested in studying ectopic pregnancy to discover what specific part of the uterus allows this anomalous invasion.

It sounds like immunology is the 21st century panacea for many diseases.

Immune cells have mobility, they are found all over the body and can access different tissues and organs. They have also developed very specific mechanisms to distinguish one thing from another, and so differentiate between elements that come from the body itself or those that are external. These two properties of the immune system —knowing where we want to go and what we want to attack or eliminate— open up many translational opportunities. This means we have before us an opportunity that makes medicine progress. In this context, tools for gene editing increase the potential of immune cells in the field of immunotherapy. This is because gene editing offers us the ability to add molecules to the immune cells to a) improve their mobility —for instance, to allow them access to places in the body they would not usually be able to—; b) increase their specificity —e.g., allow them to detect a foreign body, like a carcinogenic cell—; or c) add or repair new functions.

You work on designing tools that can help research. Your team created CellPhoneDB. What is it?

I developed CellphoneDB when I was doing my post-doc research in Sarah Teichmann's lab. Since then, my group has continued to implement CellPhoneDB and added new functionalities. CellPhoneDB is a bioinformatics tool that allows us to discover cell-cell communication processes using single-cell transcriptomic data. Recent updates of the tool include adding spatial data to consider the proximity between the interacting partners and multiomic data to connect external and internal cell circuits.

Many researchers at CNIC are deciding what to do in their careers. You work in an academic research institution. Can you give them any advice?

I believe that working in academic science is a privilege as it allows us to develop our creative side. For me, working on something that motivates you is very important because I don't like being told what to do, or doing something I see no point in. Industry has other positive things, but the creative aspect is usually less important and that's why I'm still interested in staying in the academic world. At times, the creativity can be scary because it involves uncertainty, but there is the potential that what you are doing might change the world.

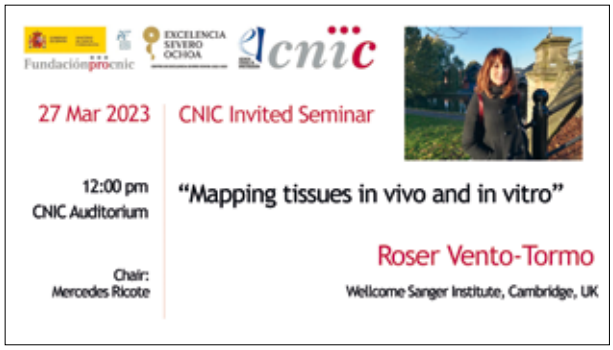
> "CellPhoneDB is a bioinformatics tool that allows us to discover cell-cell communication processes using single-cell transcriptomic data"

Talent, work, or both?

I think that everything can be learned; the important thing is to read a lot, listen, and have time to think and get things wrong. An idea doesn't come from nothing. If you read, you pay attention and think differently, out of the box. In my opinion, that's something you can be trained to do. Of course, there are people who have more talent, but I think that everything can be learned. At the end of the day, it's about not being scared to think something new or make mistakes, but it's also about reading a lot, listening and openly debating ideas.

That's why it is so important to work in a centre of excellence, like CNIC, that has a good level of scientific debate. It's not all about funding, which is, of course, very important, but in my opinion for a person to develop their ideas it's absolutely vital to be part of a group where people think, where they discuss their ideas. A critical mass is essential. ■

Roser Vento-Tormo gave the seminar "Mapping tissues in vivo and in vitro" at the invitation of Mercedes Ricote.



JOHNS HOPKINS UNIVERSITY
BLOOMBERG SCHOOL OF PUBLIC HEALTH
Baltimore (United States)

Edward Pearce

"PREVENTION IS ALWAYS MORE ECONOMICAL THAN TREATING A HEART ATTACK OR A HEART TRANSPLANT"

Dr. Edward J. Pearce is an expert in immunobiology, who investigates the role of cellular metabolism in immune cell function and fate during infection and cancer in order to identify ways to inhibit or promote metabolic pathways to modulate immune responses. Dr. Pearce's long-term goal for his work is the modulation of metabolic processes to develop new therapies.
Dr. Pearce joined Johns Hopkins University as a Bloomberg Distinguished Professor in 2020 from the Max Planck Institute of Immunobiology and Epigenetics.

Gene therapy in cardiovascular disease, when and how?

One of the main problems in the use of gene therapy in clinical practice is the rush there was to apply it, particularly in the 1990s. This meant that it was used before we had full knowledge of this disruptive treatment, and it caused the death of some patients. This affected the use of the therapy and meant no work was done on it for many years

When things are done in a hurry, the outcomes are not what you expect, and the possible risks are not properly considered.

We only recently understood how to administer viral vector therapy more safely, which had been a challenge, particularly in the field of cardiovascular gene therapy as we could not make a large enough amount of the modified genes or proteins reach the heart to obtain the desired effect. This is something we have recently been able to resolve, for the time being, in mice. This was a bottleneck that, once solved, allows us to continue progressing.

And now, what's the next step?

The technique's safety. We have to be sure that we administer not only the necessary, sufficient amount of protein to treat the heart or liver lesion, but also enough of the virus used as the vehicle to administer the gene therapy. That means we need to use the right amount of virus to avoid triggering an immune response that is more harmful than beneficial. Too much virus can trigger an unnecessary response that is prejudicial for the patient. It is a bit like what happens in transplants; you have to inactivate the immune system a specific amount, not too much not too little. In that way, we avoid the immune system itself triggering a response and attack on the virus used as the vehicle.

> "The idea that gene therapy could be the solution for cardiac anomalies makes a lot of sense and should be proactively studied"

Are you convinced that gene therapy will play an essential role in heart treatment?

Conceptually, the idea that gene therapy could be the solution for cardiac anomalies makes a lot of sense and should be proactively studied. I don't think that gene therapy will be the solution for all patients with genetic cardiovascular diseases. To do so, in addition to this treatment, research is needed on other therapeutic alternatives for patients with cardiovascular diseases that are not of genetic origin. We have already started to see results in diseases like amyloidosis and hypertrophic cardiomyopathy.

Something that sounds like science fiction is what some pharmaceutical companies are researching. It's a gene therapy for the liver so that a person can never develop hypercholesterolemia; so you could eat whatever you want

without the risk of having high cholesterol. It would be a kind of immunisation against heart disease. That means we would modify the genes in the liver using gene therapy so that our cholesterol would be like that of a vegetarian. Like I say, it sounds like science fiction, but we already have the tools to alter genes in a mouse model.
So, one of the questions that particularly worries me is who will have access to these therapies. These are clearly very expensive treatments, a million dollars per patient, so I think they will only be accessible for a very small group of people and people who really need the treatment wouldn't be able to afford it. This is a serious problem that requires careful consideration.

These are very expensive treatments, but the costs of lifelong hospital and chronic care for patients with heart failure seem much more expensive. If costs were slightly lower, these might be cost-effective therapies.
Of course. Prevention is always more economical than treating a heart attack or than a heart transplant. It would make particular sense to use gene therapy for people with a higher risk of cardiovascular disease, but not for the majority of the population.

> "The biggest challenge for me is that there should not be a gap in access to these new technologies"

> "If you love what you do, there's no sacrifice"

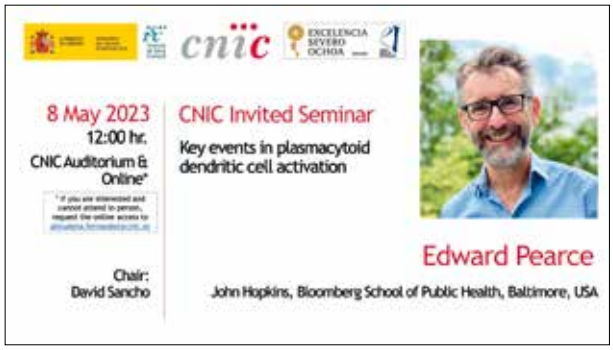
You have been head of heart transplants at La Jolla for some years. Animal organs for transplants in humans?
The case of the patient who received a pig's heart that had been genetically modified to be more similar to a human heart, who unfortunately died, was because there was no other option. In my opinion, the concept of xenotransplantation and its ramifications is something that is beyond me, because I imagine farms of animals, for instance pigs, destined to generate organs for transplants… I find it difficult to imagine.
I see it as more feasible for kidney transplants. In the case of the heart, we have to refine gene therapy to modify the genes of the pig's heart and minimise possible risks. Again, it sounds like science fiction, but really it isn't.

Thirty years ago, nobody would have imagined that mobile phones would mean in our lives…
That's right. I always remember that my father went to school on a horse. It's the same thing that happened in biology, where changes have occurred in areas like cancer, or immunotherapy that we would never have imagined. Like I said, the biggest challenge for me is that there should not be a gap in access to these new technologies. At the same time, we have seen the great potential of artificial intelligence in areas, for instance, like early identification of patients. In gene therapy, AI can be very useful, for instance, to discover why, in the case of two siblings who have the same gene defect, only one develops the disease.

And the risks of AI?
Recently, my centre did a study in which a patient contacted the doctor to make a complaint but didn't know whether the person they were speaking to was a human doctor or AI. And, surprisingly, when the results of this small study were analysed, it was found that patients were more satisfied with the AI responses, which they perceived as being more sympathetic and a better listener. I find this really surprising because I would never have believed AI to be more sympathetic and understanding than a person.
And if we talk about possible risks, AI is the same as many other technologies; it depends on how they are used. For instance, insurance companies can use the information to decide whether to insure you or not: that's a bit scary!

Why science?
I studied literature at university. One day, speaking to one of my cousins who is a physician, I realised that the great stories are in medicine. Patients share their vulnerability with you, their fears, their lives… There are many writers who are physicians. So, I went back to university to study medicine. And thanks to that I was able to work with **Dr. Valentín Fuster** in New York. For me, that was transformative. At the start of my fellowship in New York, when I still wasn't sure if I wanted a career in research or in cardiology, **Dr. Fuster** showed me the satisfaction that comes from innovation and research. He's always thinking about the future, he never stops. I remember, right at the beginning of my training, I would spend more than 17 hours in the laboratory working on a project for a grant, even weekends and some days sleeping in the hospital. Many people wondered why I did that; it was a sacrifice… but for me it wasn't. Quite the contrary; it was pure pleasure and satisfaction. If you love what you do, it's no sacrifice. I can say that **Dr. Fuster** taught me the joy of research. For me, he's been a great influence on my life. ■

Edward J. Pearce gave the seminar "Key events in plasmacytoid dendritic cell activation" at the invitation of David Sancho.



UNIVERSIDAD DE VALLADOLID
HOSPITAL CLÍNICO UNIVERSITARIO DE VALLADOLID
Valladolid (Spain)

Juan Francisco Arenillas

IF THERE IS NO REGULATION OF PROTECTED RESEARCH TIME, THERE WILL BE LESS AND LESS RESEARCH"

Dr. Juan Francisco Arenillas has been continuously devoted to field of vascular neurology since he trained in neurology as a fellow at Barcelona's Vall d'Hebron Hospital Stroke Unit (1998-2005) under José Álvarez Sabín and Carlos Molina.

A vascular neurologist at the Stroke Unit, Germans Trias i Pujol University Hospital in Barcelona, in 2008, he moved to Valladolid University Hospital (HCUV) to become Director of the Stroke Programme. In 2013, he became head of the Department of Neurology, and in July 2015, Associate Professor of Neurology at the University of Valladolid, obtaining full professorship in October 2022. During this period, the HCUV has become a regional reference centre for stroke treatment.

Dr. Arenillas is currently responsible for developing the Castile and Leon regional stroke plan. Intracranial atherosclerosis has been one of his main areas of research since his doctorate in 2003, and he is particularly interested in biomarkers, inflammation, progression of the disease from its asymptomatic onset stage, and characterisation of high-risk plaques using HRMRI vessel wall imaging.

What is intracranial atherosclerosis?

It's atherosclerosis that affects the intracranial arteries within the brain, which until recently represented a great unknown. A large part of my research activities focus on this disease.

Twenty years ago, there were many myths and deep-seated preconceived ideas about this disease, but today's reality is otherwise. The key has been the methods we have to study it better. These are imaging methods that take us directly to the intracranial arteries. What was the problem? These arteries are hidden inside the head, and we don't have access to them, as we did, for instance, with coronary or carotid arteries or ones in the leg.

Ultimately, the conclusion you reach is that atherosclerosis is a systemic disease, which affects the whole body, and although we tend to compartmentalise, it is really not so different from atherosclerosis in other parts of the body as we thought 25 years ago.

So, for both prevention and treatment, we are getting closer to what has proved effective for atherosclerosis in general.

Is stroke a preventable disease?

The difficult thing about preventing a stroke is that, unlike what happens with ischaemic heart disease, which in 90-95% of cases is generated by atherosclerosis of coronary arteries, in the case of stroke, that percentage is lower. We have cardioembolic stroke, small vessel stroke, and stroke from other causes like artery dissection, inflammatory diseases, vasculitis, etc.

Although all of these manifest as a stroke eventually, the differential diagnosis is more complex.

There is another peculiarity, however, which is that in most cases of patients with vascular risk factors, several causes co-exist; for instance, the same person may have heart disease and small and large vessel disease. And although this is not the cause, what does it mean that a person simultaneously has small vessel disease and intracranial atherosclerosis apart from atrial fibrillation?

We're seeing that what this usually means is that they are people at higher risk, who respond worse to treatment and have a worse prognosis because they present a cocktail of diseases, not a single causal disease.

The same thing happens with the distinction between what is neurodegenerative or vascular. We insist on compartmentalising. We've discussed this a lot, and almost come to verbal blows about it!

In the end, it's been seen that we mustn't compartmentalise, we are speaking about a spectrum where a person may be closer to one end or the other, but really various problems coexist. Each person is unique and so is their disease.

The fact that atherosclerosis exists in arteries implies a risk of its presence in intracranial vessels too...

That's right. The truth is that intracranial arteries have peculiarities, and that the intracranial territory is more protected, which means that when atherosclerosis eventually develops in intracranial arteries many protective mechanisms have failed. Which means that these patients are per se very high risk, since under normal conditions the intracranial territory should not develop atherosclerosis until a very advanced age.

We also see the influence of metabolic syndrome, insulin resistance, factors that accelerate the process of atherosclerosis at intracranial level.

> "Each person is unique and so is their disease"

> "I studied medicine with an investigative vocation: I wanted to be a doctor in order to research"

Genetic predisposition is also a factor: there is a documented predominance among people of Asian ancestry, for whom intracranial atherosclerosis is the most frequent cause of stroke, but also among people of African or Hispanic ancestry. And we do not know if this is because of genetic or environmental factors, or even dynamic factors due to the different morphology of the head and arteries.

It is also associated with worse control of risk factors, extreme poverty and environmental contamination.

And the neurodegenerative/vascular "war"...

We used to argue about this a lot more 15 years ago. It's probably related with how research is organised, how we obtain funding for research. It's all about reasons that are more mundane.

I can clearly see a continuum; there are probably some people with a purely neurodegenerative component, but

there is usually an overlap, and in some cases that is very clear, to the point of not knowing if there is vascular dementia or an Alzheimer's dementia, not only from a clinical perspective but also from the neuroimaging abnormalities we see.
I think that the more we observe, with a flexible attitude and acceptance of what arises, the better for our research and the better for our patients.

In recent years we have been warned that strokes occur at younger ages. What are the causes?
Now, it's not unusual to have patients in the stroke unit between the ages of 40 and 50, whereas until recently the age was 60 or 65.
Although this is not new, I had observed it during my training period in Barcelona, and since my move to Valladolid to develop the stroke programme, we have seen the trend increase.
The causes? The causes are probably to do with lifestyle, diet, toxic habits and other factors I think are important, like stress management.
What we eat, how we move and how we manage stress —which is the difference between what we expect and what happens, the difference between expectations and reality—, how each person manages that, makes them more or less unwell. Specifically cardiovascular and cerebrovascular disease is very susceptible to stress.
And in recent years, a final factor that we are considering is contamination, which probably influences the acceleration of all vascular damage.
Studies undertaken in large metropolitan areas have found that, curiously, the incidence of stroke increases in areas more exposed to the exits of city bypasses. We have our lifestyles, but we are also taking risks with our health.

Physician and researcher...
From an early age, I knew that's what I wanted to do. I studied medicine with an investigative vocation: I wanted to be a doctor to research. I think what I said when I was little was, "I want to cure cancer". And when I started in medicine, I realised that what really fascinated me was the nervous system, the brain. I specialised in neurology with a great vocation for research, but then I started clinical practice and I realised how difficult it is to be both a clinician and a researcher. It's very complicated, particularly in a system like the Spanish one where there is no protected research time —the concept doesn't exist— and all research activity is at the cost of your leisure time, personal and family life.
Ultimately, that limits the goals you can achieve in research because, if patients take up your time every day, you don't have the energy you need.
Although it is true that being in contact with patients makes you more sensitive to problems and you have more ideas, when it comes to developing them, you don't have the capacity.
And I see that now even more with younger doctors. This generation has a lot of good things but also has a more utilitarian, practical attitude to life. And what we did, devoting our free time to research... I think that either we regulate the concept of protected research time or there will be less and less research. I'm not judging which is better or worse.
It's important to acknowledge that the system needs to change and understand that clinical researchers must have protected research time, as happens in more developed countries in Europe and North America. That means that a person does their healthcare work within a limited time and the rest of their time is devoted to research projects, which also involve a lot of responsibility, managing public funding, etc.
In Germany, for instance, you have working conditions, and you are oriented to scientific production, which is what you are assessed on at university. In the United States and Canada, you negotiate the amount of protected research time. They understand that you can't do everything at night or during the weekend, with your children, even though that's what happens in the end. There should be a more solid network for research.

> "What we eat, how we move and how we manage stress —which is the difference between what we expect and what happens, the difference between expectations and reality—, how each person manages that, makes them more or less unwell"

And if you don't research, you don't get projects.
That's right. You have to find a way to carry on doing all of those things. One solution is collaboration and working in a network. There are times when there is no time available to write an article, but you have a team who can do it.
There are five of us on the stroke team at the hospital and four at the university.
My goal is to have some protected research time so I can continue investigating. ■

Juan Francisco Arenillas gave the seminar "Unraveling Intracranial Atherosclerosis" at the invitation of M. Ángeles Moro.

UNIVERSIDAD DE SALAMANCA
INSTITUTO DE BIOLOGÍA FUNCIONAL Y GENÓMICA
Salamanca (Spain)

Juan Pedro Bolaños

"WE OFTEN THINK WE HAVE A GOD-GIVEN UNDERSTANDING OF HOW TO DO CERTAIN THINGS"

Juan Pedro Bolaños is a biochemist and researcher in neuroscience specialised in neuroenergetics and metabolism. He is Professor of Biochemistry and Molecular Biology at the University of Salamanca. His research focusses on understanding the molecular mechanisms that regulate metabolism and redox homeostasis in cells of the central nervous system. Specifically, he studies the proteins and signalling pathways responsible for adaptation of neuronal metabolism to the continuous, high energy demands and antioxidants imposed by neurotransmission. He has received various awards throughout his scientific career, among which are the 2021 Castile and Leon Prize for Scientific and Technical Research and Innovation.

Your work has focussed on the study of cerebral metabolism. What's that got to do with cardiovascular disease?

The regulation mechanisms of the metabolism are, to a large extent, common to all tissues. What is explored in the brain can also be extrapolated, but with its peculiarities because there are important differences.

What interests me is cerebral metabolism and knowing how the brain adapts to the different situations we face every day.

It's understood that if we eat more fat, we are going to get fat and, if you do exercise, you lose weight. It seems we have everything well under control in terms of knowledge about how the metabolism regulates itself for the whole body, particularly in terms of adipose tissue.

However, we know very little about how that directly affects the brain.

What we intend to do is to attempt to understand what the adaptation mechanisms of neural cells are, I mean nerve cells, not just neurons.

There are other cells called glial cells, for instance, astrocytes that have a unique morphological peculiarity, which is that they are the intersection between blood and the neuron. To explain this graphically, we could say that they are cells that hug onto the brain blood vessels, which is where they obtain nutrients, and on the other end of the same cell they are in direct functional, but not physical, contact with the synapsis.

And since **Cajal** we have known that the astrocytes must have, let's say, a bridging mission between the composition of blood and function of the neuron. But this was not studied because we didn't have the necessary technology.

> "My father was a pharmacist, and he had a clinical analysis laboratory, where I used to play. Instead of playing with chemistry set toys I had the real thing, made by my father, and I did all kinds of experiments"

The astrocyte is a type of neural cell that, as it does not have either synaptic or nerve activity, does not transmit impulses, but it does possess a very high metabolic dynamic, which means it can adapt itself metabolically, which in turn means that the biochemical reactions that take place in the cells can adapt on a large scale to very disparate conditions and survive. This does not happen in neurons, whose metabolism is a bit more rigid and more difficult to adapt.

And we don't know why.

Currently, in my laboratory in Salamanca, we are trying to understand how, through the chemical composition of blood, astrocytes are capable of sensing changes in lifestyle, for instance, diet, exercise, etc.

For many years, I have been working to decipher what the main pathways are that regulate the metabolism in astrocytes, in neurons, to establish their differences in

order to achieve a better understanding of them. Over the years, this has led me to the conclusion that astrocytes are enormously plastic from a metabolic point of view.

This plasticity, the quality to change metabolic substrate and precursor of energetic fuel, the quality they have to change from one to the other with hardly any apparent effects, does end up slightly altering the metabolic product.

The metabolism has a decomposition pathway of metabolites that is ultimately going to generate energy or produce other metabolic intermediaries which are released to the synapse, and which are used by neurons as, for instance, signals to regulate and modulate synaptic transmission, or even to obtain their own energy.

Without any doubt, these changes that simple astrocytes can undergo as a consequence of changes in lifestyle have an impact on neuronal activity.

Could we say that astrocytes are a possible therapeutic pathway for neurocognitive decline?

I don't think we should lose sight of them.

Why are you so interested in cerebral metabolism and specifically in astrocytes?

The truth is that sometimes you specialise in something by chance. I was in London doing my post-doc and we decided to cultivate the nervous system cells of a mouse, and we saw that it was easier to do it with astrocytes. Then I realised the potential of this line of research.

At that time, I was studying the respiratory chain. We added a substance of nitric oxide, which is an important

cardiovascular regulator, although we were more interested in nitric oxide as a regulator of mitochondria in the nervous system. Working with neurons and astrocytes, we added the same dose of nitric oxide, and we observed that the neurons died within minutes, whereas the astrocytes were happy. That also started to motivate me: I wanted to understand what differences exist between neuronal metabolism and that of astrocytes that allows them to adapt in such a different way.
Astrocytes adapt so well that, even with the respiratory chain blocked, without the cell's main source of energy, the mitochondria survived.

Like a kind of supercell?
That's it, they are supercells. They are able to readapt their metabolism, obviously, changing other things, supplementing energy by obtaining it from different sources. That's what readaptation is.
That capacity to resist attracted my attention. I wanted to know what makes them so resistant. Maybe what we have to do is find out how we can add these resistance mechanisms to neurons and maybe prevent neurodegeneration that way. That was more or less the idea I had at that time, but it turned out not to be so easy.

> "I think it's good to have a work-life balance. It's true that before, research consumed you and it was much more difficult to devote yourself to research"

Technology has advanced a lot since then.
Now we can quite easily answer questions that were almost impossible back then. I'm still answering questions I asked myself at that time.
It is true that the field of cerebral metabolism is slightly less advanced than, say, cancer cell metabolism or that of cardiomyocytes, due to the intrinsic difficulty involved in working with a biological material of great complexity, where different types of cells take different metabolic pathways.

Coming from a family of pharmacists, your path was clear.
I was certain from an early age that I liked pharmacology, I liked research. My father was a pharmacist, and he had a clinical analysis laboratory, where I used to play. Instead of playing with chemistry set toys I had the real thing, made by my father, and I did all kinds of experiment. It was a daily thing for me. And my father always encouraged me. He challenged me to think: do this, and why? he would say. My scientific vocation was unavoidable.
That's where it all began. I went to study a degree in Pharmacology at Salamanca and did my PhD under the supervision of **José María Medina**, the biochemistry professor who has just retired. I went to London for the postdoc; I was there for two years and worked very hard.
At that time, we could say that metabolism was an area of research that was of no great interest to anyone and, least of all, that of the nervous system, which was what I liked. During those two years I published three original papers that are, curiously, the most cited of my scientific career.
On my return to Spain, I did the competitive entrance exam for a teaching position at the University of Salamanca and, after passing, I applied for my first National Plan project. That's when I created my group, without a penny to my name.

And suddenly you found yourself up against something you had no training for: leading a group.
Right. We often think we have a God-given understanding of how to do certain things. For instance, nowadays, for a National Plan project, you have to explain a series of things that are not just scientific. For instance, your approach to gender or how the data is going to be stored..., all of these aspects that we have no training for and don't know how to tackle. And the people who assess you are people like me, who don't have training in this field.

How has the profile of a researcher in Spain changed since those times?
It's more or less the same. There are people who know they want to research, whereas others, when they realise what it takes to get a tenured position in an institution, in terms of time, effort and sacrifice, decide they are not willing to make that sacrifice. Let's say they are more practical.
What I notice is that there are more and more practical people who prefer the pharmaceutical industry, etc. It's not because they don't want a career in research, but because they see the personal sacrifice as too great for what they will receive in return.
Science is very demanding. I think it's good to have a work-life balance and it is true that before, research consumed you and it was much more difficult to devote yourself to research. Before, it was normal to work at the weekend or keep going until 12 o'clock at night. And you don't see that anymore. Also, now, in some places you aren't allowed to work at the weekend. ■

Juan Pedro Bolaños gave the seminar "Peculiarities of brain energy metabolism" at CNIC at the invitation of Dr. Mercedes Ricote.

ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI
CARDIOVASCULAR RESEARCH INSTITUTE
New York (United States)

Cameron McAlpine

"THERE ARE MANY REASONS WHY WE HAVE TO SLEEP, SOME OF WHICH WE DON'T EVEN KNOW YET"

Cameron McAlpine's laboratory focusses on the study of brain-body interactions in cardiovascular and neurological pathologies and incorporates innovative tools and approaches to study at the interface of immunology, cardiology, and neuroscience to study the fundamental impact of neuro-immune interactions and brain-body communication in heart and brain diseases. Specifically, he studies how a lack of sleep is associated with inflammation. His research has determined that when we get the right number of hours of good quality sleep, levels of inflammation go down and, therefore, there is less cardiovascular risk.

How many hours should we sleep and what is good sleep?

Many studies have tackled this subject. In principle, for a healthy adult, it is recommendable to sleep between 7 and 8 hours each day. And that's very important because it's related with better cardiovascular health. Also, more and more studies show that it is also important to have a sleep routine. That means sleeping and getting up, more or less at the same time every day. In fact, it has been found that sleep patterns at the weekends compared to weekdays should be as similar as possible because they have an impact on cardiac health.

What happens while we sleep that is so healthy?

There are many reasons why we have to sleep, some of which we don't know yet. One of them is that during our sleeping hours our brain carries out a kind of cleaning in its metabolism. But there are many more, other systems, signalling pathways, etc. that use this time to reset themselves.

In the laboratory, we analyse a series of immune cells in the context of sleep, including stem cells and progenitor cells. It seems that sleep keeps these cells in a healthy state through, for instance, influencing their epigenetic programmes or maintaining a balance in cell production

so that, for instance, there is not an exacerbated production of monocytes, which would be prejudicial for the immune system.

What connection is there between sleeping well and longevity?

My group doesn't research the connection between sleep and longevity. But it is true that clinical data suggest that inadequate sleep is associated with higher mortality, not just cardiovascular but from other inflammatory diseases or cancer. That's why it is likely that a relationship exists between a person's sleep patterns throughout their life and longevity.

Sleep is associated with cardiovascular diseases, depression, Alzheimer's, etc. Should adequate sleep be prescribed as a preventive therapy?

Because we now know more about how sleep influences our health, it would be more than logical for primary care physicians in particular, to consider it as a factor to manage. In my opinion, we haven't paid enough attention to sleep as a factor in the management of many diseases, whereas emphasis has been put on other things, such as a healthy diet or exercise, which are also important. My work consists of proving that sleep is a factor that is as determinant as other parameters and, as such, forms part of a healthy lifestyle. Little by little, we are getting there. Last year, the American Heart Association Foundation noted that sleep is a key factor in controlling cardiovascular disease, on a par with blood pressure, cholesterol, diet, physical activity, etc. Primary care physicians should talk to their patients about it.

Is that something that usually happens?

Questions about rest habits are probably not asked as often as they should be.

As we get older, we sleep less and worse. Is that pathological or is it a normal part of the ageing process?

The truth is that we don't fully understand. The number of hours sleep we need changes according to age. From a baby's 20 hours, to the 6 or 7 of an older person. We don't know why this need changes over the years, nor how it influences diseases like Alzheimer's or cardiovascular disease. We have to continue studying, on the one hand, why we sleep less as we get older, and on the other, the connection between sleep and certain diseases.

One of the greatest problems of the 21st century is insomnia and sleep problems.

There is a worldwide epidemic of insomnia. More and more people have sleep problems. The causes? There are many, but it is clear that technology —screens, mobile phones, etc.— represents a major external factor.

This situation is particularly worrying in adolescents, among whom we are seeing an increase in sleep pattern disorders. Screens are changing their sleep habits, and we don't know the repercussions this will have on their health as adults. That is the question... whether the bad sleep patterns of adolescents and young people will increase their risk of chronic conditions, like cardiovascular diseases or Alzheimer's in the future. A lot of research remains to be done in this field.

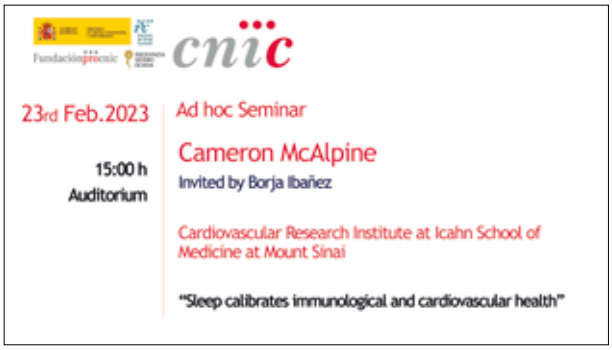
We are conducting studies, with animals and mice, about sleeping habits —few hours, segmented sleeping, etc.—. But we need more research on adolescents.

Your work combines clinical and basic research.

I don't have medical training, but I work in a hospital, which has made me understand how important it is that our work should combine clinical and basic research. This is important for any research, but particularly when studying sleep. Animals have sleep patterns that are very different to those of humans, which is why it is essential.

I hope that my research has impact on the general public, on how to identify new therapies or influence public health policies that promote good sleeping habits. But I would be lying if I didn't say that what really interests me is the discovery of new basic principles in biology. ■

Cameron McAlpine gave the seminar "Sleep calibrates immunological and cardiovascular health", at the invitation of Dr. Borja Ibáñez.



FUNDACIÓN "LA CAIXA" AWARDS GRANTS TO FIVE YOUNG CNIC RESEARCHERS

Five researchers received grants for excellent research to carry out their projects at CNIC. The INPhINIT doctoral and Junior Leader post-doc fellowships awarded by Fundación "la Caixa" have the dual aim of supporting young talent to conduct their research in Spain or Portugal and of attracting foreign researchers to these countries.

The recipients for 2022 are **Andra Cristina Dumitru**, who received the post-doctoral Junior Leader grant, and **Jorge Peña**, **Aurora Semerano**, **Danielle Medina-Hernandez** and **Manuel Gavilán Herrera**, who received an INPhINIT doctoral grant.

The awards offer competitive salaries and transversal training. In the case of the doctoral grants, they strengthen capacities like scientific communication, emotional wellbeing for researchers, leadership and funding opportunities. On the other hand, the post-doctoral fellowship training focusses on fostering an independent scientific career as a future professional option and fostering innovation and leadership.

Fundación "la Caixa"'s programme is the most important of its kind sponsored by private enterprise in Spain and Europe, both for the number of awards and for the variety of disciplines. In this edition, the foundation will award 20.2 million euros in doctoral and post-doctoral grants. Both programmes have been co-funded by the European Commission under the Marie Skłodowska-Curie grant agreement within the Horizon 2020 framework.

ANDRA CRISTINA DUMITRU

Post-doctorate in Biophysics

Andra Dumitru graduated in Chemical Engineering from the Universitatea Politehnica din București (Romania) and then completed a master's in Organic Chemistry at the Complutense University, Madrid, in 2012. After finishing the master, she changed route to begin a doctorate in Physics at the Instituto de Ciencia de Materiales de Madrid (CSIC) with a JAE predoctoral fellowship. As a

chemist, she is drawn to multidisciplinary approaches, which inspired her to expand her knowledge in biophysics and surface chemistry within the field of atomic force microscopy.
As a post-doc researcher her focus combines high-resolution atomic force microscopy and live-cell confocal imaging to study the mechanical and biophysical properties of single molecules and cells.
She returned to Spain in 2021 thanks to a Juan de la Cierva Incorporacion fellowship and joined the Molecular Mechanics of the Cardiovascular System Group at CNIC under **Dr. Jorge Alegre**. She is currently developing her own line of research that focusses on studying the mechanical regulation of nuclear proteins in pathogenic conditions. Her goal is to tackle biomedical problems that are important for society, such as diabetes mellitus, cancer or ageing using a multidisciplinary approach that combines the latest advances in nano-biophysics with single-molecule techniques, protein biochemistry and animal models.

MANUEL GAVILÁN HERRERA
Doctorate in Molecular Biosciences

Manuel Gavilán is an aerospace engineer (with a degree and a master's) from the Universidad Carlos III, Madrid. After an academic year at the Neil Armstrong Hall of Engineering, Purdue University (Indiana, USA), where he worked as a flight dynamics engineer in charge of keeping satellites in position at optimum altitude, he decided to change route and do a master in Biochemistry, Molecular Biology and Biomedicine at Madrid's Complutense University (2022). With Fundación "la Caixa"'s INPhINIT Retaining grant he hopes to capitalise on his double experience to complete his doctorate at CNIC's Molecular Mechanics of the Cardiovascular System Laboratory. During the doctorate, he will research the role of the giant protein, titin, in the mechanobiology of cardiomyocytes and its importance for heart function in healthy and pathological states.

DANIELLE MEDINA-HERNANDEZ
Doctorate in Molecular Biosciences

Danielle Medina-Hernandez graduated in Health Sciences and Exercise (2018) at Wake Forest University (North Carolina, USA) and holds a master's in Biomedical Sciences (2019) from the same university. In 2017, she participated in the "Excellence in Cardiovascular Science" programme and became interested in anthracycline-induced cardiotoxicity and obtaining cardiovascular MRI images. Her master's dissertation studied neruokinin-1 receptor blockers as a treatment strategy for anthracycline-induced cardiotoxicity in a murine model.

In 2021, she joined **Dr. Borja Ibáñez**'s laboratory as a Fullbright fellow, where she will continue as a doctoral student. Her research aims to understand the cardioprotective mechanisms of sodium-glucose co-transporter-2 inhibitors and develop strategies for the treatment of anthracycline-induced cardiotoxicity in a porcine model.

JORGE PEÑA
Doctorate in Biochemistry, Molecular Biology and Biomedicine

In 2016, **Jorge Peña** began his degree in Biochemistry and Biomedical Sciences at the Universitat de València. In 2019, he received a grant from his university to study at the North Carolina State University (Raleigh, USA) for a semester. He completed his degree in 2020 at the top of his class and received the Premio Extraordinario de Grado (Extraordinary Degree Award) and recognition of the Spanish Society of Academic Excellence as best Biochemistry graduate in the country. That same year, he moved to Madrid to complete a master's in Molecular Biomedicine at the Autonomous University of Madrid with a CNIC-Acciona grant.
Jorge began his research career after the second academic course when he joined **García-Verdugo**'s laboratory at Valencia University. He worked for two years on the neurogenesis and biology of oligodendrocytes. He also undertook a short internship at CNIC in 2019 thanks to the CICERONE programme. For his master's dissertation, he chose a different subject: the cell competition of cardiomyocytes. This biological process, with major implications in heart regeneration, is the main subject of the research for his doctoral thesis, which he is preparing at CNIC's Genetic Control of Organ Development and Regeneration Group.

AURORA SEMERANO
Doctorate in Biomedical Research

Aurora Semerano is a physician (Università Vita-Salute San Raffaele, Milan, Italy, 2013) who specialises in neurology (Neurology Department and Neuroimmunology Unit, Ospedale San Raffaele, Milan, Italy, 2019) and has a particular interest in cerebrovascular diseases. During her residency, she obtained a clinical research fellowship at the Cerebral Vascular Pathologies Unit at the Hospital Clínic de Barcelona. She has also undertaken clinical practice fellowships at the Neurovascular Intensive Care Unit (Hôpital Fondation Adolphe de Rothschild, Paris, France) and at the Stroke Centre (Inselspital, University Hospital of Berne, Switzerland), where she researched in the field of stroke immunology and thromboinflammation. She is currently undertaking her doctorate at CNIC under the supervision of **Dr. Mª Ángeles Moro** and **Dr. Marta Cortés**, with the support of a Fundación "la Caixa" fellowship grant. ■

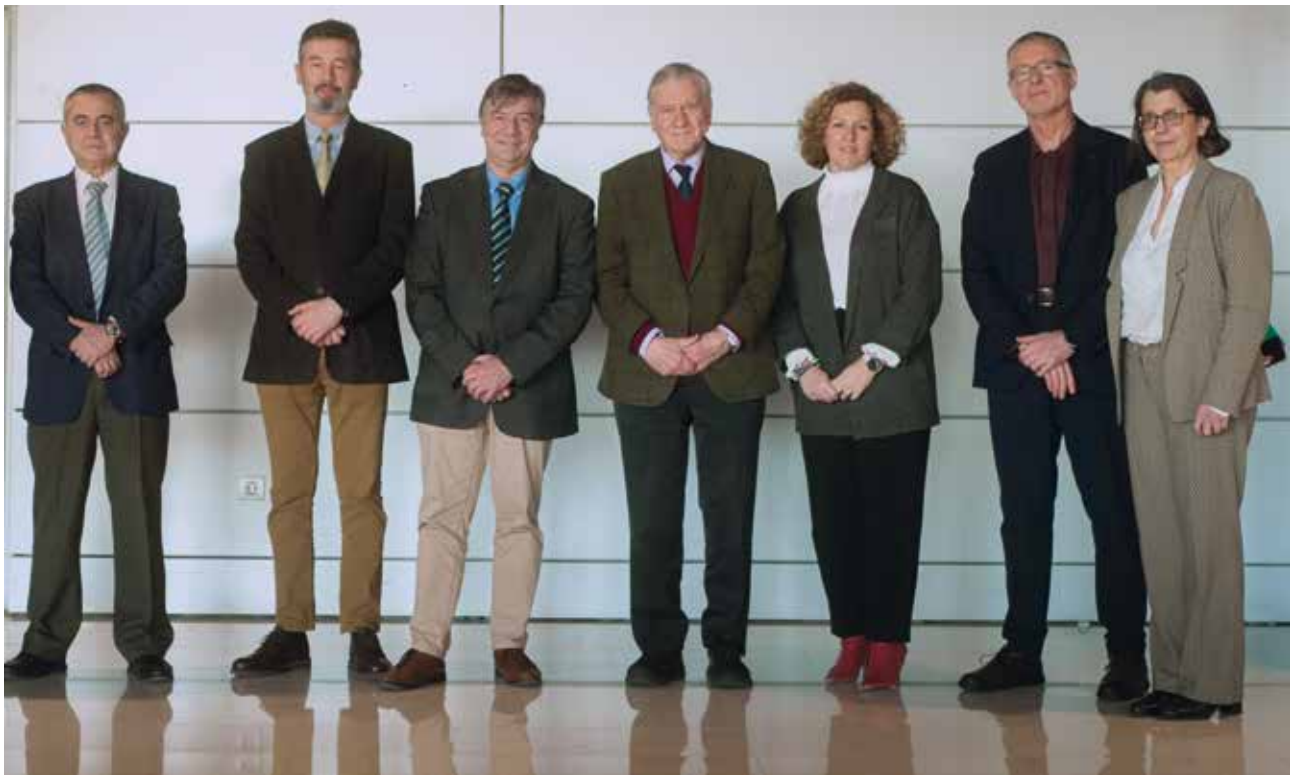
CNIC AND FUNDACIÓN CAROLINA PRESENT THEIR GRANT PROGRAMME FOR MASTER'S STUDENTS

CNIC and the Fundación Carolina signed a collaboration agreement to develop a joint programme of grants for students studying for a master's at a Spanish university to conduct an experimental project (master's dissertation) in a CNIC laboratory and so contribute to the training of future researchers in the cardiovascular area.

The award will have three programmes: University Master in Biochemistry, Molecular Biology and Biomedicine-Complutense University of Madrid; University Master in Therapeutic Targets in Cellular Signalling-University of Alcalá, and University Master in Biomedical Engineering-Technical University of Madrid.

The basic goal of this postgraduate awards programme is to train citizens of Latin American countries, member states of the Comunidad Iberoamericana de Naciones or Portugal who have proven professional or academic capacity and an outstanding CV, bringing them to Spain to conduct their experimental project (master's dissertation) at a CNIC laboratory. ■

The basic goal of this postgraduate awards programme is to train citizens of Latin American countries, member states of the Comunidad Iberoamericana de Naciones or Portugal who have proven professional or academic capacity and an outstanding CV



EXCELLENCE IN COMMUNICATION SCIENCE

LEADING JOURNALS PUBLISH CNIC SCIENCE

NATURE CARDIOVASCULAR RESEARCH
The 'guardian of the genome' protects against cardiovascular disease

A team at the CNIC, working in collaboration with institutes in the USA, has demonstrated that acquired mutations in the gene encoding the protein p53 contribute to the development of atherosclerotic cardiovascular disease. Known as the Guardian of the Genome, p53 helps to maintain the integrity of the hereditary material inside cells by regulating multiple cell functions in response to cellular stresses.

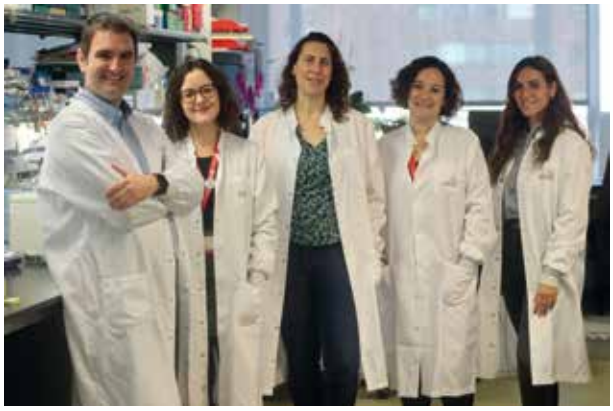
Every day, an adult person generates hundreds of thousands of blood cells. Though essential, this process unavoidably promotes the appearance of mutations in the progenitor cells responsible for this production.

The presence of acquired p53 gene mutations in blood cells increases the risk of developing various types of cancer, including blood cancers.

In the new study, published in ***Nature Cardiovascular Research***, the CNIC group led by **José Javier Fuster** demonstrates that p53 mutations also accelerate the development of atherosclerosis, the underlying cause of most cardiovascular disease, which is the leading cause of death in the world and places an enormous burden on health care systems.

The scientists analyzed sequencing data from the blood cells of more than 50,000 people.

"We found that carriers of acquired mutations in p53 had a higher risk of developing coronary heart disease and peripheral artery disease, and this effect was independent of established cardiovascular risk factors like hypertension or elevated blood cholesterol," explained **Dr. José Javier Fuster**.



Based on these results, the CNIC scientists conducted functional studies in animal models of atherosclerosis, into which they introduced cells carrying p53 mutations.

The results showed that mice carrying these mutations developed cardiovascular disease more rapidly, mostly due to an abnormally elevated proliferation rate of immune cells in the artery walls.

"This combination of observations in humans with experimental studies in animals provides solid evidence that these mutations increase the risk of developing cardiovascular disease," said **Dr. Fuster**.

For **Dr. Valentín Fuster**, CNIC General Director and an author on the study, these findings "broaden our knowledge of how the acquisition of mutations in blood cells,

a phenomenon called clonal hematopoiesis, acts as a cardiovascular risk factor."

The researchers highlight that mutations in different genes contribute to cardiovascular disease through distinct mechanisms. "In the future, this could be exploited to design personalized prevention strategies targeting the specific effects of different mutations," said CNIC scientist **Nuria Matesanz**, one of the co-first authors on the study.

The CNIC study team received support from Fundación "la Caixa", the Leducq Foundation, a Fundación BBVA 2019 Leonardo grant for researchers and cultural creators, and the Instituto de Salud Carlos III (ERA-CVD 'CHEMICAL' consortium).

The study was also supported by the US National Institutes of Health and the Department of Veterans Affairs.

Zekavat SM, Viana-Huete V, Matesanz N, et al. *TP53-mediated clonal hematopoiesis confers increased risk for incident atherosclerotic disease.* ***Nature Cardiovascular Research***. 2023 In press.
doi: 10.1038/s44161-022-00206-6

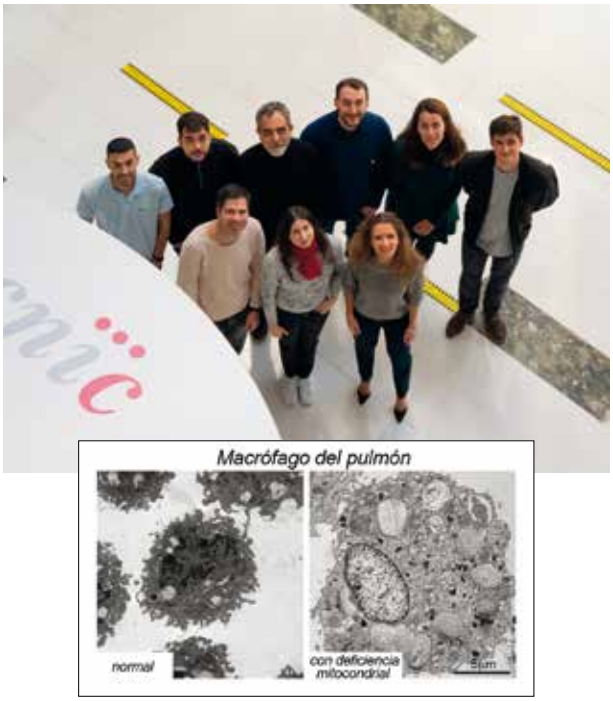
IMMUNITY

CNIC scientists identify a new therapeutic target in macrophages for the treatment of obesity-related diseases

A team at the CNIC has discovered that the metabolic requirements of macrophages differ depending on the organ in which they reside. In other words, these cells adapt to the needs of the organ in which they are located. The discovery "gives us a better understanding of how macrophages regulate their metabolism according to the organ in which they reside. In addition, our results reveal a vulnerability of macrophages that contributes to chronic inflammatory diseases and that could be exploited therapeutically for the treatment of conditions associated with obesity and metabolic syndrome, such as cardiovascular disease," said study leader **Dr. David Sancho**, who heads the CNIC Immunobiology group. The study was published in an article in the journal ***Immunity***.

Macrophages are immune cells that are normally distributed throughout the body and help to cleanse organs of all types of biological material that needs to be removed, from harmful particles such as mineral crystals or viruses to proteins or larger complexes that arise during development. Macrophages are also important for removing dead cells, thus contributing to tissue renewal.

The new study reveals that macrophages adapt their metabolism and function to the organ in which they reside. "In tissues with abundant extracellular fat and cholesterol, such as the lungs and spleen, macrophages adapt their metabolism to degrade these fats through mitochondrial respiration," explained first author **Dr. Stefanie Wculek**. "Using genetic or pharmacological methods to disrupt mitochondrial respiration, mitochondria can be eliminated from lung and spleen, whereas the macrophages in other organs, which don't depend on mitochondrial respiration, survive."



Another example is provided by the macrophages located in body fat, or adipose tissue. "Macrophages residing in the body fat of a person of normal weight are unaffected by mitochondria-disrupting treatments because their metabolism is less dependent on mitochondrial respiration. This is because the fat cells, called adipocytes, are fully functional, leaving the macrophages in a resting state," said **Dr. Sancho**. "However, in obese individuals, the excess fat surpasses the capacity of the adipocytes, and the resident macrophages become activated, converting into inflammatory cells that promote the development of insulin resistance, type 2 diabetes, and fatty liver."

But this change in adipose tissue macrophages also makes them vulnerable.

The investigators conclude that this finding opens the way to new treatments for conditions linked to obesity and metabolic syndrome, like cardiovascular disease.

The studio was supported with grants from the International Human Frontier Science Program Organization; Fundación "la Caixa"; the Spanish Ministerio de Ciencia e Innovación (MCIN); the Agencia Estatal de Investigación (AEI) with the European Regional Development Fund (EDRF); the Spanish biomedical research network on frailty and healthy aging (CIBERFES-ISCiii); an ERC-2016-Consolidator Grant from the European Union

Horizon 2020 Programme; and the Community of Madrid regional government (Inmunothercan-CM).

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doi: 10.1016/j.immuni.2023.01.011

ECLINICALMEDICINE
Imaging the adolescent heart

Magnetic resonance imaging (MRI) has allowed scientists at the CNIC to produce an accurate picture of the healthy heart in adolescence. Using this advanced technology, the research team was able to determine reference values for anatomical and functional parameters in the heart during adolescence. This information, pubished in ***eClinicalMedicine***, has direct implications for clinical practice.

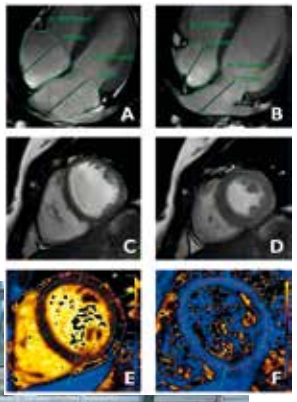
"Magnetic resonance imaging has become a very important method for studying the heart because it avoids exposing patients to radiation and provides more information, and with greater precision, than ultrasound, currently the most frequently used cardiac imaging technique," said CNIC General Director **Dr. Valentín Fuster**, a co-author on the study.

Nevertheless, most published MRI data from adolescent subjects come from patients with congenital heart defects or other heart conditions. As a result, there is a lack of knowledge about the 'normal' values of cardiac parameters in the general adolescent population. "These reference values are essential for a proper interpretation of cardiac MRI studies in this population group," said lead study author **Dr. Rodrigo Fernández-Jiménez**, leader of the Cardiovascular Health and Imaging group at the CNIC and a cardiologist at Hospital Clínico San Carlos.

These reference values are precisely what the CNIC team set out to define. As part of the EnIGMA project (Early ImaginG Markers of unhealthy lifestyles in Adolescents), the team managed, in the middle of the Covid-19 pandemic, to recruit 123 adolescent participants (64 girls and 59 boys) from seven public-funded secondary schools within the Comunidad de Madrid. The schools and adolescents were already signed up to the SI! Program for Secondary Schools, a program dedicated to promoting healthy lifestyle habits that is coordinated by Fundación SHE-"la Caixa" in partnership with the CNIC and the University of Barcelona.

"The response of the participants and their families was incredible," said first author **Dr. Carlos Real**, a CNIC investigator and a resident cardiologist at Hospital Clínico San Carlos. "Some of the schools are located more than 60 km from the city, and the participants and at least one parent or guardian visited the CNIC's advanced imaging facility on an entirely voluntary basis. Without their willingness to participate the project would not have been possible."

Dr. Borja Ibáñez, CNIC Scientific Director and a co-author on the study, stressed that "the results have direct implications for clinical practice because they providde a list of reference values for multiple cardiac parameters used in daily practice, including measures of the size and functioning of the heart chambers (atria and ventricles) and cardiac tissue composition." **Dr. Fernández-Jiménez** concluded that "with this information, physicians at any center can determine if cardiac MRI data from an adolescent's heart fall within the normal range for this age group, and prescribe closer follow-up and additional tests if needed."



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JACC
High-dose anticoagulation can reduce intubations and improve survival for hospitalized Covid-19 patients

High-dose anticoagulation can reduce deaths by 30 percent and intubations by 25 percent in hospitalized Covid-19 patients who are not critically ill when compared to the standard treatment, which is low-dose anticoagulation. These are the significant findings from the large-scale international "FREEDOM" trial, led by **Valentín Fuster**, General Director of CNIC, President of Mount Sinai Heart and Physician-in-Chief of the Mount Sinai Hospital.

The study results were announced at the American College of Cardiology Scientific Sessions, together with

World Congress of Cardiology in New Orleans (USA), and simultaneously published in the ***Journal of the American College of Cardiology (JACC)***.

"What we learned from this trial is that many patients hospitalized with Covid-19 with pulmonary involvement, but not yet in the intensive care unit (ICU), will benefit from high-dose subcutaneous enoxaparin or oral apixaban to inhibit thrombosis and the progression of the disease," says **Dr. Fuster.** "This is the first study to show that high-dose anticoagulation may improve survival in this patient population—a major finding since Covid-19 deaths are still prevalent."

This work was prompted by the discovery early in the pandemic that many patients hospitalized with Covid-19 developed high levels of life-threatening blood clots. Mount Sinai research showed that treatment with prophylactic (low-dose) anticoagulation was associated with improved outcomes both in and out of the intensive care unit among hospitalized Covid-19 patients. Researchers further observed that therapeutic (high-dose) anticoagulation might lead to better results. Then, they designed the FREEDOM Covid Anticoagulation Strategy Randomized Trial to look further into the most effective regimen and dosage for improving outcomes of hospitalized Covid-19 patients who are not critically ill.

Researchers enrolled 3,398 hospitalized adult patients with confirmed Covid-19 (median age 53) from 76 urban and rural hospitals across 10 countries —including hospitals within the Mount Sinai Health System in New York City— between August 26, 2020, and September 19, 2022. Patients were not in the ICU or intubated, and approximately half of them had signs of COVID-19 impacting their lungs with acute respiratory distress syndrome (ARDS). Patients were randomized to receive doses of three different types of anticoagulants within 24-48 hours of being admitted to the hospital and followed for 30 days. Equal numbers of patients were treated with one of three different drug regimens: prophylactic subcutaneous enoxaparin, therapeutic subcutaneous enoxaparin, and therapeutic oral apixaban. They compared the combined therapeutic groups to the prophylactic group.

The primary endpoint was a combination of death, requirement for ICU care, systemic thromboembolism, or ischemic stroke at 30 days. This endpoint was not significantly reduced between the groups. However, 30-day mortality was lower for those treated with therapeutic anticoagulation (high dose) compared with those on the prophylactic regimen (low dose). Seven percent of patients treated with the prophylactic anticoagulation died within 30 days compared with 4.9 percent of patients treated with therapeutic anticoagulation—an overall reduction of 30 percent. The need for intubations was also reduced in the therapeutic group: 6.4 percent of patients on the therapeutic regimen were intubated within 30 days compared with 8.4 percent in the prophylactic group—a 25 percent reduction.

The study showed therapeutic anticoagulation to be especially beneficial for patients with ARDS, a condition where Covid-19 damages the lungs. Among patients with ARDS at the time of hospital admission, 12.3 percent in the prophylactic anticoagulation group died within 30 days compared with 7.9 in the therapeutic anticoagulation group.

All groups had low bleeding rates, and there were no differences between the two therapeutic blood thinners for safety and efficacy.

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NEJM
A Spanish team presents the first pharmacological treatment able to improve cardiac function in stiff-heart syndrome

The results of a study published in the ***New England Journal of Medicine (NEJM)*** promise to radically alter the prospects of patients with this disease. The study was led by **Dr. Pablo García-Pavía**, who heads the Inherited Cardiac Diseases Section at Hospital Universitario Puerta de Hierro and is a research scientist at the CNIC and within the Spanish cardiovascular research network (CIBERCV). Coinciding with the publication of the study, **Dr. Pablo García-Pavía** presented the results of the first clinical trial with an amyloid-removing drug for the treatment of cardiac amyloidosis.

The study represents a major advance in the treatment of the disease. Although currently available treatments effectively prevent the accumulation of more amyloid fibrils and delay disease progression, they do not directly remove any amyloid protein already deposited in the heart.

Current treatment options include transthyretin-stabilizing therapy and measures to control associated cardiovascular complications. The only intervention currently

able to restore cardiac function in this disease is heart transplantation.

The initial results of the trial, which included 40 patients in France, the Netherlands, Germany, and Spain and was coordinated by **Dr. García-Pavía**, show that the new drug is safe and appears to reduce the amount of amyloid protein deposited in the heart.

Developed by the Swiss company Neurimmune, the new medication is an antibody that binds to transthyretin amyloid protein. The antibody was first isolated from memory B cells obtained from healthy elderly individuals.

In the study, the antibody was used to stimulate the patients' own defense systems, resulting in the elimination of cardiac amyloid fibrils. The antibody was administered to patients intravenously in progressively increasing monthly doses over a 12-month period.

"Patients who received higher antibody doses seemed to show a greater reduction in amyloid deposits in the heart and greater improvements in a range of cardiac parameters," said **Dr. García-Pavía**.

The ***NEJM*** article concludes that the phase I proof-of-concept study demonstrates the safety of this treatment in patients and supports further clinical trials of this antibody.

Dr. García-Pavía is a world-leading expert on transthyretin-related cardiac amyloidosis and is the leader of the European Society of Cardiology guidelines on the diagnosis and treatment of this disease, which are followed worldwide.

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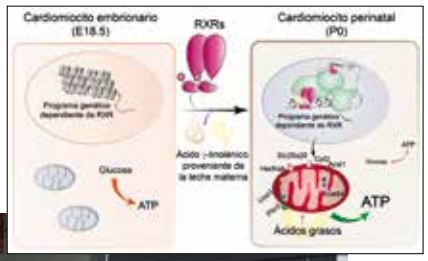
NATURE

GLA, the fatty acid that makes the heart function properly after birth

A study conducted in mice and led by researchers at the CNIC has revealed that maternal milk provides an essential signal that triggers the maturation of heart metabolism after birth, allowing the neonatal heart to function correctly and ensuring postnatal survival.

The study shows that the fatty acid gamma-linolenic acid (GLA), present in breast milk, binds to the retinoid X receptor (RXR) protein found in heart cells. RXR acts as a nutritional sensor of lipids and vitamin A derivatives, altering gene expression and influencing biological functions such as immunity, cell differentiation, and metabolism. Once activated by maternal GLA, RXR initiates genetic programs that equip mitochondria, the energy centers of the cell, with the enzymes and other proteins they need to start consuming lipids, the primary source of energy in the mature heart.

The results, published in ***Nature***, could have significant therapeutic implications for cardiovascular disorders involving mitochondrial and metabolic dysfunction, as well as diseases related to alterations in postnatal developmental processes, explained study leader **Dr. Mercedes Ricote**, who heads the Nuclear Receptor Signaling group at the CNIC.



In a mouse model, the research team found that the absence of RXR in the heart or the lack of GLA in maternal milk prevented mitochondria in the hearts of newborn mice from producing energy correctly, leading to severe heart failure and death 24-48 hours after birth.

The heart of a newborn mammal must quickly produce energy to sustain cardiac contraction outside of the womb. To achieve this, cardiomyocytes, the contracting cells of the myocardium (the cardiac muscle), need to activate their mitochondria to use lipids as the energy source for the generation of ATP (adenosine triphosphate—the essential energy currency of the cell). Although this process is crucial for the survival of the organism, until now, little was known about the signals that trigger the physiological adaptation of the heart after birth.

"The need to maintain a constant and uninterrupted beat places an immense energy demand on the heart", explained **Dr. Ricote**. "To meet their energy needs, cardiomyocytes maintain a tight control over the cellular pathways that produce energy. Any imbalance in these

bioenergetic mechanisms can lead to the development of serious cardiovascular pathologies."

For **Dr. Ricote**, part of the study's novelty "lies in demonstrating that RXR plays a critical role in cardiac muscle, contrary to what was previously thought. This is an important conceptual advance in the field of nuclear receptors."

According to first author **Dr. Ana Paredes**, the study presents a new framework for understanding the postnatal adaptations that occur in newborn mammals to meet the requirements of the extrauterine environment. "Birth is a physiological challenge for the newborn," **Dr. Paredes** explained. "With this study, we show that maternal milk, besides its nutritional function, plays a signaling role by instructing cardiomyocytes that they need to activate their metabolism because they are no longer supported by maternal physiology."

The research involved multidisciplinary approaches and advanced sequencing techniques, including key contributions from the CNIC teams led by **Dr. José Antonio Enríquez**, **Dr. Fátima Sánchez-Cabo**, and **Dr. Jesús Vázquez**.

Contributions from outside the CNIC included several Spanish centers: Centro Nacional de Biotecnología and Centro de Investigaciones Biológicas Margarita Salas, both belonging to the Consejo Superior de Investigaciones Científicas (CNB-CSIC, CIB-CSIC); Universidad Complutense de Madrid (UCM); Universidad de Barcelona (UB); Instituto de Biología Funcional y Genómica/Universidad de Salamanca (IBFG/USAL); CIBERCV, and CEMBIO/CEU San Pablo. International collaboration came from the Karolinska Institute (Sweden).

In conclusion, the study shows that the fatty acid GLA, found in breast milk, is the key signal that ensures correct cardiac function after birth. GLA activates the cell protein RXR, which then directs coordinated gene expression changes to ensure that cardiomyocyte mitochondria mature so that they can produce energy in the extrauterine environment.

The results open the way to treatments to modulate RXR activity in cardiomyocytes with specific drugs, including some that already have approval from the US Federal Drug Administration for cancer treatments. "Our study proposes RXR as a possible therapeutic target for neonatal heart disorders and systemic diseases triggered by metabolic errors," concluded **Dr. Ricote**.

The study was supported by funding from the Spanish Ministry of Science and Innovation, Fundación La Marató de TV3, and the Community of Madrid regional government.

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NATURE CARDIOVASCULAR RESEARCH

Scientists identify how some angiogenic drugs used to treat cancer and heart disease cause vascular disease

Research by scientists at the CNIC has demonstrated that most of the molecular effects of medicines used to modulate the formation of new blood vessels (angiogenesis) in cardiovascular disorders and cancer are not responsible for the toxicity and vascular pathology triggered by these drugs. The study is published in ***Nature Cardiovascular Research***.

Study leader **Rui Benedito** commented that "our results not only significantly increase our understanding of the biology of blood vessels, but will also help in the selection of the most effective and safe way to modulate angiogenesis in ischemic tissues or in cancer."

The vascular system supplies oxygen and nutrients to the tissues and organs of the body. But the blood vessels do more than just conduct blood; they contribute actively to the physiology and homeostasis of all tissues and organs throughout life. Most blood vessels in the body are in an inactive state, which they maintain by expressing a large number of genes, including the genes of the signaling pathway mediated by Delta ligands and Notch receptors.

Several drugs have been developed in recent years that either block or induce angiogenesis in cardiovascular disorders or cancer.

A group of these compounds in clinical use inhibit different components of the Delta-Notch signaling pathway, which plays important roles in angiogenesis and in the maintenance of blood vessels in the inactive state. These compounds, by modulating the growth of blood vessels, efficiently block tumor growth. These compounds are also able to induce angiogenesis in ischemic tissues, thereby improving tissue regeneration and function.

However, these drugs can also cause vascular injury in organs with no previous disease, including the liv-

er and heart, and this has reduced clinical interest in their use.

Until now, this vascular toxicity was thought to be due to the expression of genes that promote angiogenesis, leading the appearance of neoplasms or tumors in the affected blood vessels.

Thanks to the use of advanced genetic mouse models, high-resolution confocal microscopy, and single-cell sequencing and proteomics techniques, the team discovered that the vascular toxicity linked to these drugs is instead due to a change in the vascular architecture that impedes correct blood flow.

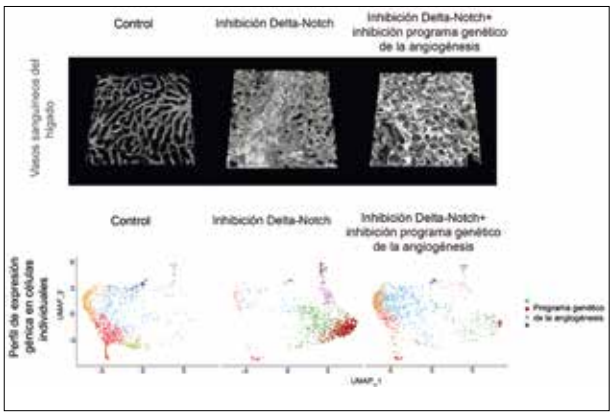
"Our study shows that the vascular pathology that can result from treatment with these drugs is unrelated to the expression of genes involved in angiogenesis or the appearance of neoplasms" said **Rui Benedito**.

The researchers showed that these changes happen even when they blocked cell activation and the expression of angiogenesis-related genes.

Therefore, explained **Rui Benedito**, "although the neoplasms and the expression of genes associated with angiogenesis are associated with the change in vascular architecture, they are not the cause of this change."

First autor **Macarena Fernández Chacón** explained that "after analyzing different genes and drugs targeting blood vessels, we have found new ways to control pathological angiogenesis without significantly affecting vascular architecture in other organs, thus avoiding toxicity."

The study was supported by the European Research Council (ERC) through Starting Grant AngioGenesHD and Consolidator Grant AngioUnrestUHD, the CNIC Severo Ochoa Intramural Program, the Spanish Ministry of Science and Innovation, and Fundación "la Caixa".



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EUROPEAN HEART JOURNAL
Atherosclerosis accelerates aging

Atherosclerosis—the much-feared 'hardening' of our arteries—impacts our health long before the appearance of symptomatic cardiovascular disease. A new study by a team at the CNIC shows that atherosclerosis at subclinical stages accelerates the aging process.

The study was published in the ***European Heart Journal***. Lead author and CNIC General Director **Dr. Valentín Fuster** emphasized that the results underline the benefits of reducing inflammation by adopting a healthy lifestyle (healthy diet, regular physical activity, etc.) or taking specific medication, such as colesterol-lowering statins "that can block, or at least slow, the transition from the subclinical phase of atherosclerosis to the appearance of severe cerebrovascular events, like myocardial infarction or stroke."

The study shows that there is a strong association between the presence, extent, and progression of atherosclerosis at the subclinical level and accelerated epigenetic aging in otherwise healthy young individuals, said **Dr. Enrique Lara Pezzi**, an author on the study.

Epigenetic age is a measure of a person's biological age (the functional age of their cells and tissues) based on the idea of the epigenetic clock. Epigenetic clocks use machine learning algorithms to predict a person's biological age and life expectancy based on their level of DNA methylation, explained study first author **Fátima Sánchez Cabo**.

But sometimes, said **Sánchez Cabo**, this prediction does not correspond to a person's chronological age (the time elapsed since birth), "so that someone's epigenetic age can be older than their chronological age, whereas someone else might have an epigenetic age younger than their chronological age."

Fortunately, unlike the germinal mutations we carry in our genome, "changes in DNA methylation are reversible, opening up the possibility of 'slowing down' our epigenetic aging," assured **Lara Pezzi**.

The identification of an association between subclinical atherosclerosis and reduced life expectancy based on epi-

genetic clocks was possible thanks to a massive analysis of data from the PESA-CNIC-Santander study, which is led **Dr. Valentín Fuster**. Since 2010, the PESA-CNIC-Santander study has analyzed the progression of subclinical atherosclerosis in more than 4,000 Banco Santander employees aged 40 to 54 years at the start of the study and with no prior history of cardiovascular disease.

"The follow-up of this cohort constitutes one of the most important cardiovascular prevention studies in the world," said **Dr. Fuster**.

The ***European Heart Journal*** study combines data on the progression of atherosclerosis obtained with advanced imaging techniques with detailed information on participants' lifestyle and data from molecular omics studies.

"These molecular data allowed us to advance our knowledge of the causal mechanisms of subclinical atherosclerosis, as well as its clinical consequences, providing key information for a more personalized treatment of the disease in its early stages," said **Lara Pezzi**.

Using transcriptomic and proteomic data, the study demonstrates that systemic inflammation triggered in individuals with a high burden of atherosclerotic plaques may be a key factor in accelerating their epigenetic aging.

The authors conclude that the study identifies a solid association between the presence, extent, and progression of subclinical atherosclerosis and accelerated epigenetic aging, mediated in part by low-grade chronic inflammation induced by inflammatory cytokines. The authors nevertheless recognize that further longitudinal studies are needed over a longer follow-up period and supported by more experimental data, in order to provide a more thorough characterization of the effect of atherosclerosis on health and life expectancy and to identify underlying mechanisms.

The PESA-CNIC-Santander study is cofunded by the CNIC and Banco Santander.

The study received funding from the Instituto de Salud Carlos III and the European Regional Development Fund (A way to build Europe) and the Spanish Ministry of Science and Innovation. ■

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doi: 10.1093/eurheartj/ehad361

cnic AWARDS AND SCHOLARSHIPS

AWARDS

THE CITY COUNCIL OF BARCELONA AWARDS THE GOLD MEDAL OF SCIENTIFIC MERIT TO DR. VALENTÍN FUSTER

Dr. Valentín Fuster, General Director of CNIC, received the Gold Medal for Scientific Merit, awarded by the City Council of Barcelona. With this medal the city council recognises his scientific career, his academic dedication and his social commitment.

DR. FRANCISCO SÁNCHEZ-MADRID RECEIVES THE ROBERT KOCH PRIZE 2023

Dr. Francisco Sánchez-Madrid, Director of the CNIC's Intercellular Communication in the Inflammatory Response Group, Head of the Immunology Service at La Princesa University Hospital, Director of the IIS Princesa Healthcare Research Institute and Professor in Immunology at the Autonomous University of Madrid, was awarded the Robert Koch Prize 2023 alongside the researcher **Timothy Springer**, for their important joint research in immunology. Both were pioneers in discovering the importance of cell adhesion molecules for the function of immune cells. This major finding opened up new possibilities for the treatment of immune diseases with monoclonal antibodies.

GUADALUPE SABIO AWARDED THE XXVII CARMEN AND SEVERO OCHOA AWARD FOR MOLECULAR BIOLOGY

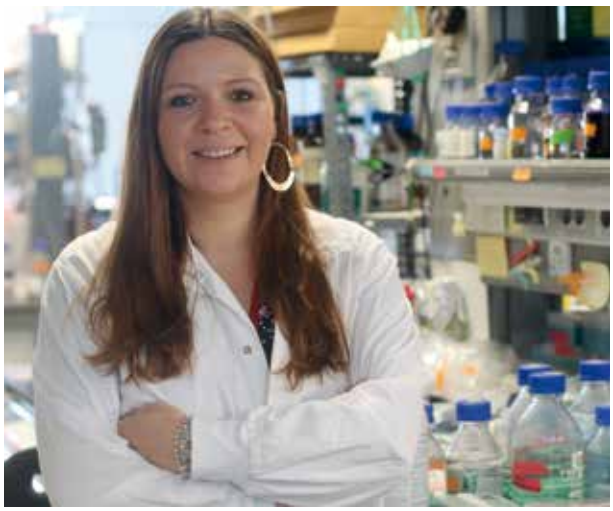
Dr. Guadalupe Sabio Buzo received the XXVIII award for research in molecular biology that the Fundación Carmen y Severo Ochoa awards each year, in recognition of her brilliant career in this field.

The prize is awarded for the research work of scientists in the field of molecular biology who mainly conduct their research in Spain, for which the jury takes into account all of the work undertaken in the last five years.

DR. VALENTÍN FUSTER AND DR. BORJA IBÁÑEZ AMONG THE 25 MOST INFLUENTIAL PEOPLE IN SPANISH HEALTHCARE

Dr. Valentín Fuster, Director General of CNIC, is one of the most influential people in healthcare in Spain, according to the Forbes list of the 25 most influential people in Spanish healthcare, a list that is, according to WHO data and that of other international organisations, one of the best in the world.

Dr. Fuster holds second position, but he is not the only CNIC representative, because **Dr. Borja Ibáñez**, CNIC's Scientific Director and Fundación Jiménez Díaz cardiologist, is also included among the 25 professionals with the best reputation in Spanish healthcare.



THE EUROPEAN ASSOCIATION FOR THE STUDY OF OBESITY AND THE NOVO NORDISK FOUNDATION GIVE PRIZE TO CINTIA FOLGUEIRA

The CNIC researcher **Cintia Folgueira Cobos** received the prize of the European Association for the Study of Obesity and Novo Nordisk Foundation in the category of Basic Science for her excellence and commitment. The award consists of some 40,000 euros in funding and **Folgueira**'s participation in the European Congress on Obesity.

SUPPORT FROM THE AECC - THE SPANISH ASSOCIATION AGAINST CANCER

The researcher **Anabel Díaz-Guerra** has received an award of 88,000 euros from the Spanish Association Against Cancer (AECC) in Madrid to contribute to her predoctoral work in the Translational Laboratory for Cardiovascular Imaging and Therapy headed by **Dr. Borja Ibáñez**, scientific director of CNIC.

The project is an attempt to better understand the consequences that treatments against cancer have on the hearts of survivors, with the ultimate goal of developing innovative treatments to reduce associated cardiac toxicity.

INSPIRATIONAL WOMEN - PESA HEALTH CNIC-SANTANDER

On 8th March, CNIC held an event designed to introduce young people to four of the Centre's women who are part of the PESA Health CNIC-Santander project. The goal of the CNIC video aimed at secondary, pre-university and vocational training students is to introduce young people to the experience, talent and profiles needed to work in this area of interesting scientific challenge.

The video is part of the initiative #EmpresasQueInspiran of the Fundación Bertelsmann, that aims to awaken vocation in the field of science and technology. This goal is also shared in the series of organised activities that include student visits to the CNIC.

VISITS

Vocational training clinical and biomedical laboratory students from the Enrique Flórez secondary school, Burgos, visit CNIC.

Students from La Serna school's 4th year visit CNIC thanks to the joint programme with the Fundación Bertelsmann.

Visit of students from the dual vocational training course on imaging for diagnosis and nuclear medicine, from San Juan de la Cruz school.

Students from the auxiliary care in nursing vocational training module at Sapere Aude school also visited CNIC. ■

TRAIN2GAIN
WHAT'S ON
INSIDE SCIENCE
CNIC & SOCIETY

cnïcPULSE

#16