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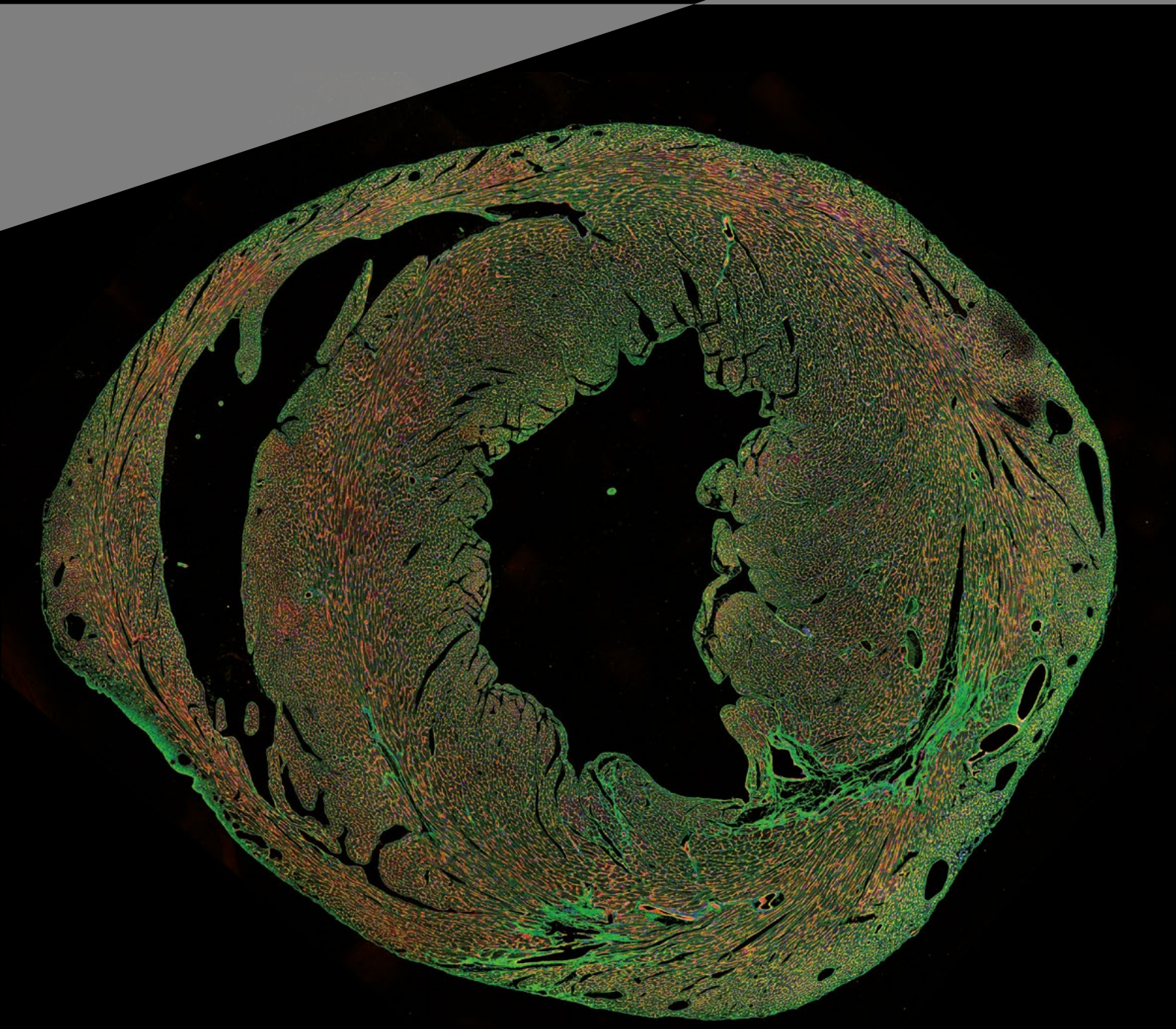

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PROTECTING THE HEART INCREASINGLY MEANS PROTECTING THE MIND

The relationship between the cardiovascular health and cognitive deterioration of older people is increasingly clear. Far from being a disorder exclusively related with the brain, Alzheimer's seems to have a significant vascular basis, which requires a re-think of the approach taken to this type of neurodegenerative disease.

During the 2024 CNIC Conference, "Cardiovascular Risk Factors and Brain Health", participants discussed the pivotal role cardiovascular risk factors play in the onset and progression of different forms of dementia. The conference highlighted that vascular abnormalities affect not only the heart and blood vessels but also the brain. These abnormalities, which may appear many years before the first cognitive symptoms, offer a vital window of opportunity for intervention before damage becomes irreversible.

One of the chief findings discussed is that cardiovascular risk factors, such as high blood pressure, diabetes, smoking and a sedentary lifestyle not only increase the risk of heart diseases but can also cause long-term damage in the brain's capillary network. Any chronic abnormality in these blood vessels can trigger or accelerate cognitive deterioration.

The traditional approach to neurodegenerative diseases has prioritized their study exclusively from the perspective of the brain; however, recent evidence indicates that the vascular system also plays a pivotal role. This change of paradigm is essential to design more effective prevention and treatment strategies. If they are detected in time and controlled, cardiovascular risk factors can offer a way to reduce the incidence of diseases such as Alzheimer's.

This inclusive approach, which brings together the fields of cardiology and neurology, opens up new possibilities for the treatment of diseases affecting millions of people worldwide. With a better understanding of how the cardiovascular and brain systems interact, inroads can be made in prevention of, and eventually the search for, possible cures for neurodegenerative diseases.

Science is leading us towards a more holistic vision of health, in which the heart and mind are interconnected. Taking care of cardiovascular health by following healthy lifestyle habits and controlling risk factors not only prolongs life, but can also preserve quality of life, avoiding the cognitive deterioration so many people suffer in later life. Increasingly, protecting the heart means protecting the mind.

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

Population ageing and the sophistication of treatments in developed countries has made it clear that research into prevention is, in general, more efficient than investing in treatment, as Marina Pollán, Director of the Carlos III Health Institute (ISCIII) explains in this issue of CNIC Pulse. Delaying the onset of diseases, she says, not only improves the population's health, but is also the key to maintaining sustainability of the health system. Unlike treatment, in prevention, the challenge is that beneficiaries do not always understand what is happening because the patients of the future don't know that their disease has been avoided or delayed.

Marina Pollán, Director of the Carlos III Health Institute (ISCIII)

"TALENT IS EASIER TO ATTRACT WHEN YOU HAVE A CRITICAL MASS"

Marina Pollán has been a research professor of the Spanish National Epidemiology Centre at the Carlos III Health Institute since 2016, and scientific director of CIBERESP, the Biomedical Research in Epidemiology and Public Health Consortium, since 2017. Last February, she became Director of ISCIII, the Carlos III Health Institute, an institution dependent on the Spanish Ministry of Science, Innovation and Universities. She is the first ISCIII Director to have spent her whole career at the institution, which she joined in 1990. Pollán was head of the Spanish National Epidemiology Centre from February 2019 to October 2022, where she was responsible for coordinating the centre's work during the COVID-19 pandemic. She was also scientific coordinator of the internationally recognized Seroepidemiological Study on the Prevalence of SARS-CoV-2 in Spain (ENE-COVID). She has participated in coordinating the evaluation of projects both at ANEP, the Spanish National Agency for Evaluation and Prospection, and at FIS, the Spanish health research funding body.

In addition to sitting on numerous national and international scientific committees and panels of experts, since 2021, she has coordinated the Predictive Medicine axis of the IMPaCT (Precision Medicine Infrastructure associated with Science and Technology) project, which aims to create a large primary care-based national cohort with the help of all the Spanish regional public health services, ultimately providing a nationwide research infrastructure.

You took up your position as Director of ISCIII in February 2024, although you have worked at the Carlos III Health Institute for over 30 years. How have these first months been?

First, despite having had a connection with the ISCIII for many years, I've realized that there are many more things I didn't know about it, particularly ones related with the Centre's external activities. During this short period of time I've been able to get to know many people who are connected with this institution, and really interesting projects that I had no idea about. For instance, I didn't know that Spain has such a prominent place in the international ranking of clinical trials - we are in second place after the USA; I didn't know that, as a country, we had such a high position in advanced therapies, and I didn't know the CNIC, the CIEN foundation (the Research Centre for Neurological Diseases) or the CNIO (the Spanish National Cancer Research Centre) very well.

How has having worked at the ISCIII for so many years helped you in this challenge?

I love and value the ISCIII, which I think can be seen in the decisions we are taking. It is a responsibility, but also a little scary, because the ISCIII is very large and my colleagues may have great expectations about how things are going to change quickly, which is not always so easy because changes take time, and we also need more staff

Budgets are important because when you want to do new things without setting to one side what already exists, the easiest way is to get more funding

and a bigger budget. I believe that changes occur little by little in all organizations and ISCIII will be no different. So the first thing I did when I was appointed was write to all of my colleagues and tell them that I intended to care for the institution and improve it, and they should be patient because I was then aware, but am now even more so, that it is a complicated task. One that is further complicated by the extended budget situation we have in Spain.

Did you think twice before taking on the responsibility?

I got a call while I was on holiday, and my first reaction was to say no. I thought, I'm not going to get involved in that. But then I began to think it could be an opportunity, and I set myself two strategic objectives. First, to care for the institution, i.e. improve the situation, the research and leadership capacities of the good researchers and technicians we have in ISCIII. The other important objective for me at the time - now I have new objectives because I know the institution better - was to support development of the IMPaCT [Precision Medicine Infrastructure associated with Science and Technology] cohort. I thought it was an opportunity and I had to say yes.

You mentioned the extended budget situation...

Budgets are important because when you want to do new things without setting to one side what already exists, the easiest way is to get more funding. For instance, centres of excellence like CNIC, CNIO or the CIEN Foundation already expected increased funding justified by the activities they undertake. The same situation existed with the CIBER (biomedical research networks) and some other funding initiatives under the auspices of the sub-directorate for evaluation and promotion of research, such as the Fortalece programme aimed at health research institutes, or at the CDTI (Centre for Technological Development and Innovation) to fund joint projects between teams from the National Health System and certain biomedical sciences businesses, which we won't be able to start due to this year's national budget which is an extension of last year's. The same situation exists with the centres themselves: to consolidate their work, strengthen and promote the new objectives we should adopt as the foremost public health institution, we need more staff. The budget dictates a great deal of what can be done, it isn't everything, but it says a lot.

I believe changes occur little by little in all organizations, and the ISCIII is no different. So, the first thing I did when I was appointed was write to all of my colleagues and tell them I intended to care for the institution and improve it, and they should be patient because I was then aware, but am now even more so, that it's a complicated task

In these months of work, what needs have your team identified and how are they going to be tackled?

The management committee have discussed some potential ideas to foster collaboration between the different ISCIII centres. Sometimes, the fact of being located on different sites -the ISCIII has always had its Majadahonda campus and another in Chamartín (Madrid)- means that the potential of joining a research group is not fully appreciated as you don't work side by side. And now we have a new campus in Moncloa, where the anti-doping laboratories are located. So we want to make an internal call for collaborative projects.

Collaboration is part of my DNA, maybe it's a needs must, because after having learned a lot of method and wanting to develop cohort studies, which was very difficult in this country, I began to collaborate with clinics, geneticists, etc. I've always found it very attractive because it's stimulating to see what other people know that you don't. I think that fostering collaboration is going to lead us to better projects.

What other challenges are you facing?

Another challenge is the 100th anniversary of the National School of Public Health. This is our organization's oldest institution. I myself am an alumna of the National School of Public Health. We have a unit linked with the School to train specialist physicians in preventive medicine and public health. The current Director General of Public Health at the Ministry of Health, Paco Gullón, is an alumnus, as is the Minister of Health herself, and she wants to promote the School. It also represents a strategic area of the ISCIII in supporting the ongoing training of specialists in the National Health System. That is why we need to strengthen the School.

The biggest problem we have, which is probably one shared by all Public Administrations, is the lack of administrative staff and management. We know that General State Administration salaries are not competitive and, compared to autonomous community salaries, are rather low; for years we have been suffering a decapitalization of staff, which is now a serious problem. We can't solve this problem on our own because the salaries, categories, etc. are set by the civil service. This is a major problem that must be solved. ■

We are currently in a process of stabilization and offering positions, but what happens is that the lower levels are not attractive, and the vacancies go unfilled. We are working on this issue because we know that to carry out good research, we also need technicians, managers, etc.

Attracting talent. How can the Institute be made more attractive for researchers?

I still don't know the situation in all of the centres in great depth, but my centre, the Spanish National Epidemiology Centre, has been able to attract talent in recent years. Researchers like to be in an environment where there is a critical mass they can share ideas with. When you have a critical mass it's easier to attract talent, despite the more competitive salaries of other centres. Many people place more value on an intellectually stimulating workplace than on earning a lot of money. The fact of working with colleagues you can share and learn with is an important part of research.

And the ISCIII is also a known brand. We have talent attraction programmes both in strategic health actions, which is the term for the series of calls we launch from the ISCIII, and in-house. We have specific contracts for the health research institutes to attract talent. But in addition to attracting talent, our objective is to retain it because, for instance, the calls we have for the health research institutes come with the commitment of the Autonomous Community to give stability to the people after the 4 or 5 year contract. And this is a challenge, because to carry out research in a hospital, sometimes we need figures or categories that do not exist in statutory personnel like, for instance, bioinformaticians, biologists, biochemists, etc. These specialists contribute to research in the hospital but the regions experience problems finding solutions to retain them.

You spoke about funding. Is ISCIII considering new funding models with private companies?

When I began working at the ISCIII it wasn't possible to work with the private sector. Things have changed a lot. In fact, last year we held a call that brought together research groups from the health service and biotech companies to collaborate with each other. The National Health System part was funded by ISCIII, and the Centre for Technological Development and Innovation (CDTI) supported the companies. We also have agreements with the AECC, (the Spanish Association Against Cancer) which is the main non-governmental organization funding cancer research. All funding is welcome. Coordination, for instance, with the AECC to fund major projects has enabled successful outcomes. It's a win-win, but the role of business has to be limited because we are a public research institution.

You mentioned the IMPaCT project as one of the factors that encouraged you to take on the position of ISCIII director.

IMPaCT is an initiative started in 2020 by the ISCIII to promote research in precision medicine; it has an element of genomic medicine and another of data science. Its foundations are the IMPaCT Cohort, which consists of generating an infrastructure of a cohort with at least 200,000 people whose data, extracted from questionnaires, imaging tests, biological samples, etc. is available to the scientific community. The model that we followed, in common with most developed countries, is the UK Biobank. When I was director of the Epidemiology and Public Health Networking Biomedical Research Centre, I had already convinced Raquel Yotti, then director of the ISCIII, that Spain, as a large country within the European Union, deserved to have its own cohort. Because, although many researchers use the UK Biobank data, it does not represent us well: not our lifestyle nor our genetics because we have a genetic structure with a large influence from the Arabs who were here for 8 centuries. In fact, we have seen that polygenic risk score (PRS) models don't work as well here as they do for the populations of the Anglosphere. I'm not just saying this for the sake of it: it's so that we have our own infrastructure that allows us to obtain results which are applicable to our context.

One of the novelties the IMPaCT Cohort includes, which was stipulated in the call, is that it is generated within the primary care system of each autonomous community. That makes it more difficult to start up because primary care has its own problems, but at the same time it involves a higher participation rate, which in turn means a cohort that is more representative of our country's population.

So, while the UK Biobank has 5% participation, ours is over 30%, which is unusual. To date, none of the cohorts of this type have such high participation.

When we talk about population cohorts, the Scandinavian model always comes up.

Scandinavian countries represent the gold standard. But extrapolating that model here is difficult. They are small countries with a single data collection system, whereas we have 17 Autonomous Communities. So we are like a federal country and the Scandinavian model cannot be automatically transferred here.

It is a great model, because you have all of the information collected ad hoc for you to exploit and use, what is called Real World Data. The IMPaCT Cohort is different because the general population does not usually undergo so many tests. Having more in-depth information and biological samples of people who do not necessarily come into the system for a health problem, but rather are recruited by sampling based on their health card, allows us access to information before disease appears. For instance, CNIC has projects like that, like the PESA cohort, which serve as a model for all of us.

It is an attempt to anticipate disease, as Valentín Fuster [CNIC's Director General] says, a vision that will become increasingly generalized. The ageing population, the sophistication of treatments, etc. in most developed countries has shown that investing in prevention is generally more efficient than investing in treatment. Postponing disease may be a key aspect that allows the health system to continue functioning, apart from improving the population's health. The problem with prevention is that, unlike treatment, the future patient does not always understand that in their case the disease has been avoided or postponed.

Yet again we come up against the problem of funding that is only short-term...

A long-term vision is more complicated. It's about convincing the funding bodies that what we are doing in the IMPaCT cohort is going to have results in 10 to 20 years' time. We know that the UK Biobank began to produce a large volume of publications 10 years after recruitment.

At ISCIII, we want to accelerate the process. We have a 3-year, maximum 4-year, funding structure for projects, which makes it difficult to conduct a cohort because they require more time. We hope that when we complete implementation in all of the Autonomous Communities, and the rules about how to use the information are established, the Spanish scientific community will take advantage of this resource to show it is useful and can produce interesting outcomes because if not, I don't think it can be maintained over time.

Also, bearing in mind current funding, we have designed a cohort for which we collect a lot of information at the baseline visit so that, if it cannot be maintained over time, we have enough data to conduct a follow-up using the medical history, which would be enough to at least take advantage of the effort.

How do you see the ISCIIII in 10 years?

I would like the Institute to continue to be a reference institution in biomedical research, both from an in-house and an external perspective. What's more, I would like the existing inequalities to have been reduced thanks to ISCIII research into the health of the populations of different Autonomous Communities, and I would hope that there will not be first and second-class Communities in terms of research. Research is a driving force. And, of course, I hope that the IMPaCT Cohort continues to exist in 10 years and has produced articles and information that is important for the public health of our country. ■

CNIC CONFERENCE 2024.
CARDIOVASCULAR RISK FACTORS AND BRAIN HEALTH

There is increasing scientific evidence supporting the idea that a relationship exists between cardiovascular health and cognitive deterioration in older people. Certain studies also highlight the role of cardiovascular diseases and their risk factors as coadjuvant in the expression of certain types of dementia, mainly Alzheimer's, which was already described as a vascular dysfunction by Alois Alzheimer in his first report on the disease.

The 2024 CNIC Conference discussed this relationship in 'Cardiovascular Risk Factors and Brain Health' organized by Valentín Fuster, General Director of CNIC; María Ángeles Moro, Head of CNIC's Neurovascular Pathophysiology Laboratory; Marta Cortés Canteli, CNIC / FJD-Health Research Institutes, and Costantino Iadecola, Director of the Feil Family Brain and Mind Research Institute of Weill Cornell Medical College.

The CNIC Conference is the result of the Severo Ochoa Programme: Cardiovascular Risk Factors and Health, designed to tackle the impact of cardiovascular risk factors on cognitive deterioration and dementia. "The initiative arose from the need to pay more attention to vascular abnormalities in the study of dementia, a field hitherto dominated by research from a neurobiological perspective," says María Ángeles Moro.

The conference highlighted the importance of vascular factors in signs of dementia, which often develops at an advanced age, whereas its underlying causes can begin to manifest a lot earlier. "This interval of time offers a crucial opportunity to intervene and preserve brain health, avoiding damage to the neural substrates responsible for cognition, thus preventing dementia." Dr Moro commented.

Marta Cortés Canteli points out that neurodegenerative diseases have traditionally been considered as exclusively related with the brain. However, recent evidence suggests the brain's blood vessels play a significant role. "We have over 500 km of brain capillaries and any chronic abnormality in these vessels can have a considerable impact on brain health," she clarifies.

The conference assembled experts from all over the world who are working to bring the brain and vascular fields closer for a better understanding of how to treat, prevent and even cure neurodegenerative diseases.

Dr Cortés Canteli underscores the need for an open mind about the multi-factor nature of these diseases. "For some patients, vascular damage can come before deterioration of the brain, whereas for others the opposite is true. It is essential to acknowledge that these processes can coexist and be interrelated."

The conference also highlighted the importance of controlling known cardiovascular risk factors to prevent cognitive deterioration. "Controlling these factors is essential, and we know how to do it" adds Dr Valentín Fuster. ■

Director of the Feil Family Brain and Mind Research Institute

Costantino Iadecola:

"THE IDEA IS THAT ALZHEIMER'S COULD HAVE A VASCULAR ELEMENT WAS NOT PART OF OUR THINKING"

Dr Costantino Iadecola is Director and President of the Feil Family Brain and Mind Research Institute and Anne Parrish Titzell Professor of Neurology at Weill Cornell Medicine. His research focusses on the basic mechanisms of neurovascular function and on the molecular and cell abnormalities underlying ischaemic brain injury, neurodegeneration and other dysfunctions associated with cognitive deterioration.

Neurological diseases of the brain are on the increase more than any others in the world, and they are also the ones with the fewest therapeutic opportunities...

That's right. To a large extent, this rapid growth is due to population ageing. Many of these neurological diseases are related with age, particularly the ones that affect cognition. As the population gets older, the incidence of these diseases increases. At the same time, there are no effective therapies for these conditions, which causes an increase in their prevalence. There are increasing numbers of people affected as they get older.

That's why there is so much interest in understanding how to prevent the cognitive problems related with age and, if possible, how to treat them. For many years, neurological diseases have been the domain of neurologists. I am a neurologist myself.

Until recently, the role that vascular abnormalities played in these neurological diseases had not been considered, except in the case of stroke or other major disorders related with the brain's blood vessels. The idea that Alzheimer's could have a vascular element was not part of our thinking.

In fact, the diagnostic criteria for Alzheimer's did not include the possibility of a vascular problem. For instance, if someone had suffered a stroke, the possibility of Alzheimer's was automatically ruled out. This created an erroneous perception of the disease. However, when

Until recently, the role that vascular abnormalities played in these neurological diseases had not been considered, except in the case of stroke or other major disorders related with the brain's blood vessels

you analyse the real situation, you see that the majority of people with cognitive deterioration in the community have a combination of diseases, like Alzheimer's and vascular problems. Mixed dementia is the most common cause; it isn't only Alzheimer's or just vascular, it is a combination of the two.

So neurologists, physicians and scientists should change their way of thinking...

Exactly. For instance, if you go to a memory clinic, where many of these people end up going first, the physicians don't even take your blood pressure. They only focus on the brain, without worrying about the rest of the body. This eliminates one of the most important factors contributing to dementia: blood pressure. There are other cardiovascular factors, such as cholesterol and diabetes that are also crucial.

Our generation grew up with TV and films, but young people today think in terms of social networks, which is where things happen now. What your teacher at school says, what you watch on TV, is not important anymore, it's what your peers say

The CNIC Conference brought together world experts who cover both intrinsic neural aspects of the brain and peripheral vascular aspects. We also have experts in epidemiology, who understand how diseases evolve in the population, and specialists in the immune system, whose role in these diseases is increasingly evident.

Maybe we should consider dementia as a disease that affects the whole body, not just the brain.

Exactly. This is a concept that the neurological community finds difficult to accept because we have been trained to focus only on the brain. We measure reflexes, not blood pressure. It is a change of paradigm we need to encourage, and we hope that the message resonates in the next generation. Today's postdoctoral students are the people who will have greatest impact in the future.

We no longer have the mental flexibility to think of new ways to tackle these problems. For instance, someone asked Valentín Fuster about social networks. Our generation grew up with TV and films, but young people today think in terms of social networks, which is where things happen now. What your teacher at school says, what you watch on TV is not important anymore, it's what your peers say.

In your teens, which is a critical period of life, you acquire certain habits that you maintain throughout your life. For instance, you remember that they taught you the importance of exercise and how to avoid being sedentary, which is an important risk factor for Alzheimer's and high blood pressure.

All of this is important for prevention, but the problem is that we don't have effective treatments for these diseases. Could this change of paradigm lead us to new treatments or ways of finding treatments for dementia, not just Alzheimer's?

Absolutely. But you have to understand that the field of dementia is closely linked to ageing.

Although we can't control ageing, some people say we will live a lot longer...

Yes, but we aren't made to live forever. Nevertheless, if we keep our body healthy, the impact of ageing will not be so severe.

You mentioned the importance of keeping the body young and avoiding risk factors...

Exactly, and the habits we acquire, like not smoking, are crucial. In the USA people smoke a lot less than here in Europe.

It's an enormous problem, particularly among young people...

That's right, and many young people think that smoking or vaping doesn't have consequences, which is a mistake. As Dr Fuster says, prevention strategies must begin at a very early age because risk is cumulative and also, when you are young, you are more likely to acquire good habits.

One of the most interesting aspects, but also one of the most depressing, is that the risk factors associated with blood vessels are more dangerous in middle age. When you already have memory or cognition problems, controlling blood pressure doesn't make a big difference. What really helps is having controlled it 20 years previously. The ideal thing is to identify the risks as early as possible, to change our lifestyle or seek medical help.

In your opinion, do you think society and governments are receiving the messages and understanding the importance of controlling blood pressure and other factors? And society?

Society tends to react instead of being proactive. You can't worry about controlling infections until there is a pandemic, for instance. The same thing happens with individuals. We don't act until we realise that something is wrong. It would be ideal to have a healthy lifestyle as the norm. ■

Stroke Branch Chief at the National Institute of Neurological Disorders and Stroke (NINDS)

Rebecca F. Gottesman:

"TELLING SOMEONE THEIR RISK OF DEMENTIA WOULD DROP IF THEY TREATED THEIR HIGH BLOOD PRESSURE WOULD IMPACT THEM MORE THAN THE POSSIBILITY OF A HEART ATTACK OR STROKE"

Dr Rebecca Gottesman joined the National Institute of Neurological Disorders and Strokes as Stroke Branch Chief in May 2021. In addition to the Branch, she is also Chief of the Stroke, Cognition and Neuroepidemiology Section. Before joining NINDS, Dr. Gottesman was an investigator at the Johns Hopkins University, where she made significant research contributions to understanding the cognitive impacts of stroke and other vascular diseases, as well as short- and long-term associations between vascular risk factors, vascular disease, and dementias.

Your presentation is about new imaging technologies and their use in dementia and vascular problems. What is the future of these techniques?

I am a vascular neurologist but also an epidemiologist. I mainly work with population studies. For me, neuroimaging is the way to understand the mechanisms of diseases. If I am interested in understanding how vascular risk factors like high blood pressure, diabetes, high cholesterol, smoking and obesity could be related with dementia or even specifically with Alzheimer's, I can't do an experiment on humans and expose them to these factors to see what happens, because it would obviously be unethical and unreasonable to do so. But I can use images of the brain to understand what the connections could be, if it is through certain changes in the brain's structure or through functional changes.

The imaging technique isn't a very new one: we are using images that are quite accessible in a study based on a large population, using magnetic resonance and some positron emission tomography (PET).

I am interested in understanding how vascular risk factors like high blood pressure, diabetes, high cholesterol, smoking and obesity could be related with dementia or even specifically with Alzheimer's

We use imaging techniques on a wide population of people. That said, there is a lot of excitement surrounding the new ways of using imaging to study diseases and mechanisms. There are other types of PET that can evaluate different biomarkers of a disease. There have been great changes in the field leading to the use of biomarkers in blood, particularly for Alzheimer's biomarkers, which we now know can be detected in plasma much more easily than with imaging data. With magnetic resonance we can also analyse not only structure but function, such as cerebral blood flow (CBF), the health of blood vessels and the characteristics of the main arteries that go to the brain. All this information is useful to understand what is happening in the brain related to the risk factors and with the cognitive changes we observe.

With all this information and the data collected with these techniques, can you understand what is really going on with the relationship between vascular factors, dementia and stroke?

A large part of this conference has been about the mechanisms that lead to cognitive deterioration or stroke in certain people. But given that I work with large populations and epidemiological studies, my focus is on considering the risks of dementia that can be modified.

These risk factors are important because they are things we know how to treat and, therefore, are examples of how we can prevent dementia. An important observa-

That said, there is a lot of excitement surrounding the new ways of using imaging to study diseases and mechanisms. There are other types of PET that can evaluate different biomarkers of a disease

tion we have made is that these risk factors, like high blood pressure and diabetes have a stronger connection with cognitive deterioration and dementia when they are anomalous in middle age. This is a crucial observation we have made from long-term follow-up epidemiological studies: if you have high blood pressure when you are young it is likely that you should control it from an early age to benefit your future cognitive health. From the perspective of prevention, it is important not to wait too long to start thinking about these risk factors. For middle-aged, or even younger people, prevention will be the key to modifying the risk of disease.

Images tell us a little about what is happening and at what stages we can intervene. They do not tell us with any certainty, if we see certain findings in the images, it is too late to treat the high blood pressure, but because they show the potential mechanical connections between, say, high blood pressure and dementia, they can indicate at what point along the road we can change the trajectory. These studies are not conclusive, they do not show the causal relationships that a clinical trial or animal studies might, but they reveal strong associations, and, in some cases, we need these long-term longitudinal studies in humans because these associations take decades to develop.

We also have an epidemic of obesity, diabetes and probably high blood pressure, since more than half of the people with high blood pressure don't know they have it. The future is not looking bright...

Absolutely not. If you look in terms of population, the rate of strokes has gone down, as have rates of dementia, which is encouraging, but it is mainly for old people. If you observe the younger population, we do not see the same reduction in rates of stroke, what worries me and other people is that when that sector of the population ages, the rates of dementia will increase again due to lifestyle factors, many of which would probably modify the risk of dementia. If we see an increase in these risk factors, even if they are more controlled, as you mentioned, if someone doesn't know they have a risk factor, they are not taking treatment and are not being controlled. I 100% agree that there is concern about the future.

Major advances have been made in the field with therapies that modify Alzheimer's disease. We have some available treatments, but they are controversial, have many side effects and are expensive...

Images tell us a little about what is happening and at what stages we can intervene

Very controversial. But the reality is that even if we are successful in the sphere of treatment, it is likely that we will also need to treat the vascular factors because most people, including the ones who clinically seem to have Alzheimer's, show a mixed pathology with a vascular component in post-mortem studies. So, treating Alzheimer's alone, even if we can do it really well, will not be enough. Anyway, we have to think of the vascular factors and risks that can be modified.

According to your research, is it possible to make recommendations to the public or governments to prevent the next pandemic?

I think it is fundamental to make an effort in education and in carrying out tests to detect many of these risk factors, particularly high blood pressure. Smoking is another important factor. I am here in Spain, and I see many more people smoking here than in the USA, where this aspect has improved. This is an example of how you sometimes need to modify risk factors with large-scale public health initiatives in order to really make a change. In the USA you can't smoke anywhere now, so people don't smoke. I think that if we somehow manage to improve access to healthy communities, it would be a great advance, at least in the USA where the lack of resources is a major problem. Physical activity probably has a direct benefit on cognitive health, and indirect advantages in the reduction of high blood pressure, obesity and diabetes. We need a public health campaign on the subject.

People are scared of things like heart attacks and strokes, but they are a lot more scared of dementia. Telling someone that if they treat their high blood pressure, their risk of dementia would drop, would have more impact on them than the possibility of a heart attack or a stroke, which are also terrifying. I think this is a convincing message.

Mayo Clinic College of Medicine and Science in Jacksonville, Florida

Sandro Da Mesquita:

"WHAT REALLY MOTIVATES ME IS UNDERSTANDING THE MECHANISMS AND THE POTENTIAL CLINICAL BENEFITS"

Sandro Da Mesquita is an assistant professor of neuroscience at the Mayo Clinic College of Medicine and Science in Jacksonville, Florida. Dr Da Mesquita's research focusses on the pathophysiology of brain ageing and neurological disorders, with a special interest in the role of the recently characterized meningeal lymphatic system. His main objectives are to advance the basic knowledge of disease mechanisms involving meningeal lymphatics and to develop novel bench-to-bedside therapeutic strategies that would prevent age-associated neurodegeneration, and the cognitive decline associated with age, particularly in the context of Alzheimer's.

What is important in this scenario where we know more about the association between dementia and vascular factors?

What I am looking for at these conferences are new concepts in the field that I can later take to my lab and enrich, so to speak, my research programme at Mayo Clinic. I feel that I study a very particular type of vasculature that drains the brain, and I am already part of a highly specialized niche of research that is in constant development. And although I carry out experiments that are not always completely aligned with the rest of the research in the cardiovascular and neurovascular field, I always try to attend this type of meeting to learn about what is out there and then apply it to my own research at Mayo Clinic. The study of the lymphatic system is still at a very early stage, particularly in comparison to blood vasculature and circulation, which is why I always try to meet experts to understand what affects blood circulation and then transfer it, so to speak, to lymphatic vasculature and function.

Your research revealed crucial information about the lymphatic system...

I don't want to attribute credit for the discovery to myself, also because... although I contributed to a greater understanding of the lymphatic vasculature that drains the central nervous system, I don't think that even the group where I did my postdoctoral research, led by Jonathan Kipnis at the University of Virginia and now at the University of Washington in Saint Louis, would want to take credit for having discovered the lymphatic system.

The study of the lymphatic system is still at a very early stage, particularly in comparison to blood vasculature and circulation, which is why I always try to meet experts to understand what affects blood circulation and then transfer it, so to speak, to lymphatic vasculature and function

When you go centuries back in history, there were already observations that the system was there, but the observations went ignored for centuries because they didn't have the right techniques to completely understand it. However, now, with the technology and the right experimental approach, the work of his group and the one I was part of helped to rediscover it. In the last decade, we have attempted to fully understand it. It is not a completely new type of vasculature; it is similar to the lymphatic vasculature we have in peripheral tissues, but now we know that it also extends to the central nervous system. Given the nature of the tissue, the lymphatics that drain the brain are a little different, and now our work is to continue research into how they work, how they change during ageing and in the context of disease, and how we can intervene to develop better therapeutic strategies, for instance.

Do you have any clues about how to intervene, prevent or promote the mechanisms?

We are at a very early stage. In my laboratory we use a lot of animal models, but any model has its limitations. We are researching some potential molecules that could help improve lymphatic drainage of the brain, such as therapies based on vascular endothelial growth factor C (VEGF-C). But again, we know that molecule works in the peripheral lymphatic system and is also important for the lymphatics that drain the brain. Nonetheless, we are also discovering that there are many differences: not everything that works for a lymphatic vessel that drains the skin or the intestines works for one that drains the brain, which also changes a lot during ageing. Ageing leads to a degeneration of these lymphatics and finally, to a better lymphatic drainage to cervical lymph nodes. This does not happen in peripheral lymphatics; an old person may have good drainage of peripheral lymphatics, but this does not seem to be the case for brain lymphatics. We still don't understand why this happens, which is why I think attempting to understand it using different models would be a great step, whether that is small mammals or more complex in vitro models, before we can really move on to better therapeutic strategies.

When you started your career, did you have translational medicine in mind?

Absolutely not. Working at the Mayo Clinic really means you deepen your understanding of the importance of translational research. But to be honest, what really motivates me is understanding the mechanisms and the potential clinical benefit. I'm fascinated when, sometimes by chance, someone discovers that a medicine or a compound has a particular effect on the heart, even without understanding how. I understand the great importance of finding therapies and getting clinical benefits but understanding the "why" also drives me. I think that both aspects are extremely important. At times, in basic research using animal models, many things work well in mice, but not all of them translate

to clinical results. That's why the translation of these findings is crucial and it's important to combine the best of both worlds. Animal models should always be used in combination with analysis of human tissue to see if our observations are the same.

It would be interesting to see that in human tissues...

Exactly. It's important to keep open communications between basic research and clinical practice and foster translational research. Mayo Clinic is one of the best places in the world to put this into practice.

Are you thinking of any collaborations with CNIC researchers?

Potentially, yes. I've met many new people and learned a lot. I've always been really interested in barriers in the brain, like the blood-brain barrier, and different niches and places where blood communicates with the brain environment. I am currently studying a different type of vasculature, lymphatics, which are also very important. Coming to this conference has allowed me to revisit all of my early interests and learn a lot. There are researchers here who really are leaders in the field, and it is gratifying to interact with them, learn from them and, potentially, begin new collaborations. I believe that a subject we should explore in the future is communication between the lymphatic system and the cardiovascular system. Anatomically, they always seem to go hand in hand; where you find a blood vessel you generally find a lymphatic vessel nearby. I think there is a dialogue between them that we need to understand better and maybe we could collaborate in this area. ■

Laboratory of Pharmacology and Physiology of the University of Montreal (Canadá)

Dra. Hélène Girouard: "IN ALZHEIMER'S DISEASE, HIGH BLOOD PRESSURE IS THE MAIN RISK FACTOR AFTER AGE"

Dr Hélène Girouard leads the Pharmacology and Physiology Laboratory at Montreal University (Canada). Her laboratory is interested in the mechanisms controlling cerebral circulation and the mechanisms underlying cerebral neurovascular coupling (NVC) in healthy, aged or diseased organisms. Although this area has been the subject of research for over 100 years, we still do not fully understand the mechanisms by which synaptic neuronal activity translates to blood vessel dilation. Fundamental research on NVC forms the foundations of modern neuroimaging and understanding it could explain the outcomes observed in neuroimaging, enabling the diagnosis of certain neurological diseases. These neurovascular functions can also worsen certain conditions such as ageing, Alzheimer's, migraine, high blood pressure and strokes.

What is your main area of research?

I have two main areas. One is the study of the impact of vascular dysfunctions in the brain. The other area is the mechanisms underlying neurovascular coupling. Neurovascular coupling is the connection between neuronal activity and the increase in blood flow in the same region, which ensures that active neurons receive enough oxygen and nutrients.

What is the relationship between these two areas, neurological diseases such as Alzheimer's or dementia and cardiovascular diseases?

Yes, because we are finding out more and more. Years ago, researchers, or rather, neuroscientists, thought that everything was down to neurological disorders. Before, it was thought that blood vessels were the origin of neurological diseases, but around the 1960s, our opinion changed and neurologists thought that blood vessels were not important, that everything was related to neurons. Now, we are coming back to the idea that both are important. We talk of the 'neurovascular unit', which includes blood vessels, glia and neurons. All of the components of this unit need to be healthy to keep the brain healthy. Whether the disease begins with a dysfunction of blood vessels or neuronal dysfunction, there is always an impact on both. This is important, particularly for Alzheimer's disease, where high blood pressure is the main risk factor after age, which suggests that there is an important vascular element in the pathogenesis of Alzheimer's.

In some way, the way we see these diseases is changing, going back to the start, joining vascular factors with neurological ones.

When I began studying cerebral blood flow in the context of high blood pressure, I remember the first time I presented my work, a gerontologist told me, "I've seen many patients with cardiovascular diseases and many of my Alzheimer's patients also have them. I'm pleased that someone is finally paying attention to that." Because, with his clinical experience, he felt that there was something important in the relationship between the two. The epidemiological data linking, for instance, high blood pressure with the incidence of Alzheimer's disease and cognitive decline is quite recent. It began in the 1970s, and only recently, many researchers, in both clinical and basic research have started to study this aspect in more depth, particularly for Alzheimer's. But as well as Alzheimer's disease there is a very important vascular element in cognitive deterioration that is not necessarily related with Alzheimer's but is connected with vascular health and its impact on cognition.

You mentioned high blood pressure as the most important factor for dementia after age, but whereas we cannot stop ageing, we can prevent, treat or control high blood pressure. The problem is that high blood pressure is on the increase in developing countries since it is related with obesity, diet and a seden-

tary lifestyle. It's also a disease that doesn't present symptoms, so many people don't know they have it...

Exactly. As it doesn't present symptoms, it is considered a risk factor rather than a disease. What we are seeing is an increase in blood pressure, but this is the consequence of many things: it could be genetic, mechanical or related with inflammation and the production of free radicals. There are many aspects involved in a rise in blood pressure, which makes it a complex topic. We think it is simple, just blood pressure, but really, the drugs administered to people only reduce blood pressure without necessarily tackling the root of the problem. If high blood pressure is an inflammatory disease, for instance, because now it is considered a subclinical inflammatory disease, then we should administer anti-inflammatory medication.

So, do you think that there are different types of high blood pressure and that each should be treated specifically?

Exactly, there are different profiles. I don't believe that just by reducing blood pressure we will solve the problem. We are working on aspects related with high blood pressure, which is the stiffening of blood vessels, a risk factor for Alzheimer's and cognitive decline. This is only one aspect of high blood pressure. There are people with hardened arteries who do not have high blood pressure but are still in danger of suffering brain damage. Another subject we study is the "early morning high" in blood pressure, because in the morning there is a significant increase in pressure, which could lead to stroke. We have also seen a relationship between this increase and a reduction in cerebral blood flow.

Do current treatments for high blood pressure just treat the symptoms?

Yes, they treat blood pressure but don't necessarily normalize other aspects, like vessel stiffness. There are drugs that could do that, like statins or osteoporosis medication, which help prevent calcification of the blood vessels. But we still don't know from what level of stiffness we need to treat patients.

Are drugs being developed to treat these problems?

There are many drugs that already exist and many possibilities. With artificial intelligence and personalized imaging we can move forward in this field. The first step is to change lifestyle . But there are people who continue to suffer high blood pressure despite an exemplary lifestyle. Nevertheless, controlling blood pressure is always better than not doing anything. ■

Spanish National Research Council (CSIC), Institute of Biomedicine of Seville (IBiS) and coordinator of the National Research Network on Hypoxia

Alberto Pascual:
"WANTING TO LIVE FOREVER IS NOT THE BEST THING FOR A SPECIES"

Alberto Pascual holds a degree and doctorate in biology from the University of Seville. His thesis in biochemistry and molecular biology was about ribonuclease P, an RNA enzyme involved in the maturation of tRNAs. He took up a postdoctoral fellowship in France at the laboratory of Dr Thomas Preát. Pascual returned to the Spanish science system with a Ramón y Cajal contract (2003) at the Virgen del Rocío University Hospital (HUVR) in collaboration with Professor José López Barneo and obtained his position as CSIC senior scientist at IBiS in 2007. As principal investigator at IBiS (from 2007) he has pursued a new, independent line of research on Alzheimer's disease (AD) and the hypoxia signalling pathway with a special focus on non-neural cells, in particular the endothelium and microglia. He has led regional, national and international projects with both public and private funding. He is currently secretary of SENC (the Spanish Society of Neuroscience), coordinator of the National Research Network on Hypoxia and a CSIC Scientific Researcher.

What do the brain, cardiovascular health and Alzheimer's disease have in common?

Many cases of Alzheimer's are related with genetic factors. They are very interesting to discover what the disease can be like and how it can progress. Genetic factors give us clues about how it develops but, of course, they are genetic and that cannot change. They are what we call unchangeable. However, there are many other factors associated with a higher risk of many types of dementia in general and Alzheimer's specifically.

For instance, there are some very surprising things that most people don't know about, such as social isolation. Deafness in adults or schizophrenia multiply by almost 7 the chances of developing Alzheimer's as you age. And we have no idea what could be happening.

It seems that, for the brain, social interaction is very demanding and when a person is using their brain to communicate and has to relate to others, it is kept active. It's like a muscle, when you stop using it, it atrophies. The same thing happens to the brain.

There are some very surprising things that most people don't know about, such as social isolation. Deafness in adults or schizophrenia multiply by almost 7 the chances of developing Alzheimer's as you age

As we get older and there are more problems with our body, it is likely that the brain does not receive the necessary attention due to cardiovascular problems and other types of abnormalities in the organism. And when you stop using it and don't have enough energetic input, there are likely to be structural failures.

We are very interested in the idea of changeable risks because certain studies say that the incidence of Alzheimer's could be reduced 35% just by lowering changeable risks.

On the other hand, a large part of the risks associated with Alzheimer's are cardiovascular factors; for instance, diabetes, atrial fibrillation, having had heart problems, atherosclerosis, even sleep apnoea or chronic obstructive pulmonary disease (COPD). All of these parameters increase the possibility of having dementia.

In the last 15-20 years many treatments have been developed to control atherosclerosis, high blood pressure or vascular function. In the wealthiest countries, most older people receive chronic treatment with this type of drug. If this is right, we should see a reduction in the incidence of Alzheimer's in the years to come. Several recent review articles exist, and we observe that once we correct for age, which is the largest risk factor for the development of dementia, there is a reduction in the prevalence of Alzheimer's in society. Which is to say that controlling cardiovascular risk seems to have a very interesting effect, not only on our daily lives, but also for the future. It is also protecting the integrity of the brain.

And how can we begin to control the risk?

Through lifestyle. Curiously, in the population studies conducted in the USA, Sweden and Spain, we observe a reduction in the incidence and prevalence of Alzheimer's, but not in Japanese one. Because Japan precisely has a diet and genetics that are not related with cardiovascular problems; that's why we see no change.

But all of this is correlations. Our approach is different: we want to know if cardiovascular risks really affect the brain, how they change it and how they predispose to Alzheimer's. The disease itself, how it interacts with the vasculature; i.e. the development of Alzheimer's, which may be independent of cardiovascular risks: a lack of blood flow in the brain, a lack of nutrients and less oxygen also favour the situation, and how this affects brain function. These two lines are what we are working on.

In reality, conventional wisdom has it that when a person starts to forget things it's because blood isn't reaching their brain...

Yes, oxygen and nutrients. It's very difficult to just reduce the amount of oxygen. There are situations in which a pulmonary obstruction, for instance, reduces the amount of oxygen. But really, if there is a reduction in the input of nutrients or oxygen, they go hand in hand. And we believe that this is interesting because the cell pathways that control them are completely different.

After much consideration, we are studying two main cell populations: one is blood vessels and how they change. We proposed a novel mechanism through which a disease can locally affect vessels and foster cardiovascular risks.

It seems that for the brain, social interaction is very demanding and when a person is using their brain to communicate and has to relate to others, it's kept active

The next thing we did was to see how this affects the cells that defend us from disease, such as microglia, the immune system. And what we see is that precisely in these conditions, these cells are not able to respond to disease and over time they lose their capacity to protect. These studies were published in 2021.

Now, on the one hand, we are studying how activity of the immune system depends on mitochondria and is, therefore, dependent on a good supply of oxygen and nutrients. We have very interesting data, very similar to a study conducted here at CNIC by David Sancho with peripheral macrophages, which studied the function of mitochondria, and we are doing the same thing but with the macrophages found in the brain, microglia.

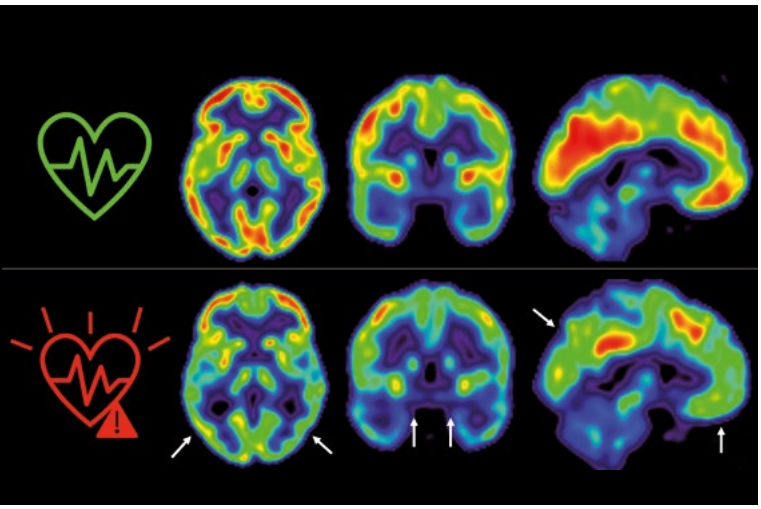
On the other hand, we are researching how to undo the vascular damage we find that is associated with disease. We have several approaches, one of which is pharmacological, that we don't think is going to get very far just yet. What we see is that because of this lack of oxygen and nutrients, the vessels try to grow in the brain, which is a typical response to the loss of oxygen, and when they come across an amyloid protein, the angiogenesis is interrupted and the vessels that are being generated are lost, but the vessels they come from also die. Which is to say, the attempted recovery makes the disease worse. This process is called non-productive angiogenesis, and we are studying how to revert the situation genetically or pharmacologically.

Is there a drug that can do this?

We have seen that when angiogenesis begins it becomes unproductive and destroys the vessels that were there. The first hypothesis was to block angiogenesis so that the point of destruction of local vessels would not be reached. It would be a transitory rather than a long-term solution, We were lucky in that many antiangiogenic agents have been developed for cancer. We have managed to partially rescue the amyloid load and the behaviour of animals with memory defects.

However, it isn't feasible to administer antiangiogenic drugs to an older person. The problem is that there aren't many studies on angiogenesis in the brain.

In collaboration with Rui Benedito and Henar Cuervo, at CNIC we are currently testing genetically mending the molecular pathway that we



know is destroyed. It's about acting one step ahead. We have seen that the vessel doesn't have a Notch pathway, a cellular signalling identity that goes a bit mad around the amyloid plaques, and under these conditions what we try to do is recover this Notch pathway. We do this genetically with viral vectors we have made in collaboration with Juan Bernal at CNIC's viral production unit. With these virus we manage to recover memory behaviour and vascularization that had been lost around the plaques quite well.

Why could this be so important? Because amyloid accumulates in the bran, above all when there are problems clearing. Normally, when we sleep, we change the pressures in our body and sleep clears the amyloid from the brain. What is more associated with the accumulation of amyloid in humans is fragmented sleep; i.e. people who do not sleep continuously well or who get up several times during the night, their amyloid load increases.

To clear it we need the vascular system. If we have a vascular problem associated with amyloid deposits, that is a problem that aggregates. In the end, it's a question of time and error, simply a series of situations that lead to a reduction of brain activity. We think that if we partially recover the vasculature, we could clear this amyloid and delay the onset of a disease.

As a joke, I usually say that the biggest contribution to the onset of Alzheimer's was the invention of antibiotics. We have prolonged life, and we have other problems that we weren't prepared for.

Our immune system and defences are in a state of natural selection during the time we are active and fertile, maybe up to the age of 50. From then on life normally doesn't continue much longer

Our immune system and defences are in a state of natural selection during the time we are active and fertile, maybe up to the age of 50. From then on, life normally doesn't continue much longer.

In some ways, the machine was not prepared to live so long.

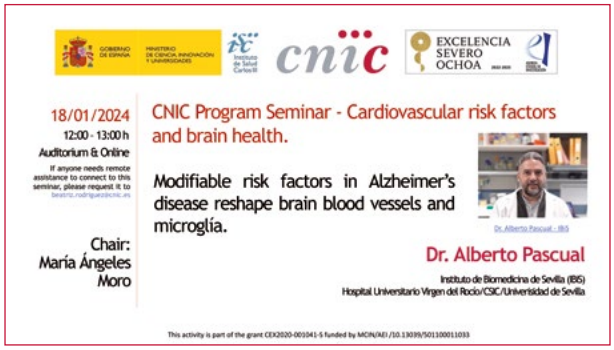
It's not that we have a sell-by date. It's that the selection of things needed to live for 40 or 50 years has been made; what comes after was irrelevant.

But some say our lifespans will get increasingly longer...

Not just that, you have to keep your body healthy over the age of 80. Evolution is the selection of what works, but of course, what works for the times you live in. For instance, our previous director, José López Barneo, often says that people have already been born that are going to live 130 or 140 years.

There is debate in the field between people who say there is a maximum number of years we can live and that, however much we optimize our life with healthy habits, medicine, etc, the species has a limit. Longevity really depends on the size of the species. Small species have a very fast metabolism and live short spans, whereas larger species who have a slower metabolism live many more years. So maybe what we have to do is live slower, but how can we do that? As the poet said, "I want to die living," it's not a case of anything goes. What I mean is, everyone wants to live longer, but in good conditions and with quality of life.

And then there is the ethical debate. How far can we prolong life and in what conditions? We live in an overpopulated world. Wanting to live forever is not the best thing for a species. I don't think we are the best thing for the planet either. ■



Deputy Director and Head of Astrocyte-Neuron Network Unit

Cristina García Cáceres:

"NOT EVERYONE HAS TO BECOME A GROUP LEADER; THERE ARE OTHER IMPORTANT ROLES"

Dr Cristina García Cáceres began her career at the Helmholtz Munich Centre in 2012 after coming from the Autonomous University of Madrid, and in 2015 she became Head of Astrocyte-Neuron Network Unit at the Diabetes and Obesity Institute. Since then she has established and consolidated her own research group focussing on the study of the properties and physiological consequences of communication between neurons and astrocytes in order to understand the role of these glial cells in physiological and pathological aspects of brain function in the neuroendocrine control of metabolism. Her work has won prestigious awards like the ERC Starting Grant and constitutes a shift of paradigm on how glucose gets into the brain and how hypothalamic astrocytes tune sympathetic outflow towards cardiovascular target organs to control blood pressure. Within the CNIC Late Winter Seminar Programme on Cardiovascular Risk Factors and Brain Health, Cristina García Cáceres gave the seminar entitled "Beyond Neurons: Exploring Hunger Regulation in the Brain."

How did your career as a researcher begin?

I completed my thesis at the Hospital Niño Jesús in Madrid under the supervision of Dr Julie Chowen and Dr. Jesús Argente. After a couple of fellowships in the United States and Sweden, I decided to do post-doctoral research abroad. I ended up in Germany, in Munich, first as a postdoctoral fellow and later as head of group. Now I am also a Professor at the University of LMU and associate director of the Institute for Obesity and Diabetes in Helmholtz Munich.

I was interested in biomedicine, particularly in areas that could have applications in advancing knowledge and even in treating patients

Really, I never thought I would end up in Munich. At first, I was just going to do a post-doc, but then everything seemed to just flow. Things went well for me. I got a grant, the ERC Starting Grant, which was the decisive step to consolidate my research group in Munich. They offered me a permanent contract there and funding possibilities to carry on my line of research and I went for it. And here I am.

And now it seems you've swapped the benchtop for an office?

That's right, now they almost don't want me in the lab, I get in the way. These last few years, I have focussed on training and consolidating my research group with experienced technicians who have been with me from the start, doctoral and post-doctoral students who are at different stages of their scientific career and writing their first theses and getting my first publications as head of group. In order to do this and continue in the same way, you need to continue applying for funding in the form of grants and projects. It's a non-stop job that's competitive and very demanding.

Do you get any training to do that?

It's really quite self-taught. There are always mentors or people who have influenced your scientific career at key moments; they are your guides, have a lot more experience than you, have lived similar situations and can guide you. But most of it is self-taught. Each person has their own style or personality and way of seeing things, but nobody specifically teaches you how to write a grant application. Like they say, it's trial and error; experience brings knowledge.

I studied a degree in biology, but I specialized in the branch of biomedicine. But when you finish your degree, you don't have the training necessary to lead a group or the necessary tools to face what is coming. To a certain extent it is about knowing how to explain your research, even to people who don't work in your area, and who see the potential in your studies to advance in scientific knowledge and its future applications. In general, we researchers don't have that training. Fortunately, I think that at the moment students are being encouraged to take training courses about how to write a scientific article, how to give a talk, etc. You need to know how to transmit the importance of your studies, even for a non-scientific audience, but at the same time be rigorous and careful not to generate unreal expectations. We also have to remember the language barrier, since for most of us English is not our first language, which is an added difficulty for non-native speakers.

Could you give some advice to students about a career in science?

I don't think so because every person and situation is different. But if they like research, I'd recommend exploring different possibilities and considering all of the options. Having doubts about what we like or the direction we want our career to take is normal. Of course, the decision to move abroad also depends on each individual's personal circumstances, but it is true that having international experience can be beneficial when it comes to trying to go back home because internships abroad are valued, and even sometimes a requirement.

A career in science is one of continuous learning, with different stages, like the doctorate, the post-doc, consolidation and leading a research group. Not everyone has to become a group leader; there are also other important roles, such as that of a project manager, both in academia and the pharmaceutical industry. It is important to identify our strengths, interests and limitations, both professional and personal. You should never be afraid to explore new opportunities and try out new things, particularly when you are young. We often don't know what we really like until we try it. That's why I encourage people to take on challenges and step outside their comfort zone because it can help us to discover what we are really looking for.

Fortunately, I think that at the moment students are being encouraged to take training courses about how to write a scientific article, how to give a talk, etc.

As a biologist, when you began your studies, did you think this was going to be your line of research?

I liked it and I really liked nature and animals. At that time I had also considered studying veterinary science or medicine. Biology has always been something I loved. But I wasn't clear whether I wanted to do a thesis or a post-doc. At that time, I never thought about all of those possibilities.

I was interested in biomedicine, particularly in areas that could have applications in advancing knowledge and even in treating patients. But the reason I began my career as a researcher was by chance. During my degree, I had to do an internship in a laboratory and my mother, who at that time worked at the Hospital Niño Jesús, suggested that I could do it there. That's where it all began; I did the laboratory internship, and I was offered the opportunity to prepare my end of degree dissertation. Later, the research group I had been with offered me the opportunity to work on my thesis. Finally, I spent over 5 years completing the doctorate, which also gave me the chance to do internships abroad. That allowed me to find out how research is carried out in other places and encouraged me to consider the possibility of taking up a postdoctoral fellowship abroad.

And how did you come to your current line of research? The brain, diabetes, obesity etc.

My supervisor, Dr Julie Chowen was one of the pioneers in the study of astrocytes in the hypothalamus, particularly in relation to metabolic diseases. During my research, we explored subjects such as type 1 diabetes, prenatal stress and hormonal response, among others. I began to work with this type of cell during that period and I still continue to do so.

I think that experience was crucial because it allowed me to establish myself in a relatively unexplored area of work. Working in a field that is not well known opened doors for me to find my niche. When you carry out post-doctoral research, it is important to understand your singularity compared to other researchers because there are a lot of us in the field. You should stand out in a specific scientific area that represents your work. For instance, if you are invited to give a talk, it's because other scientists acknowledge the importance of your work in a specific area and consider you are the right person to speak about it. Having experience in a specific area is also important

when it comes to applying for subsidies, since it shows your suitability to carry out the work you are proposing, making you a safe pair of hands for the project.

What are your current lines of research?

I focus on understanding how diabetes, obesity and other metabolic disorders can influence brain health in the long term. There is an increasing body of evidence indicating that resistance to insulin associated with obesity and type 2 diabetes not only affects the body on a peripheral level, causing cardiovascular changes and higher cardiovascular risk, but also has a significant impact on brain health, increasing the likelihood of suffering neurodegenerative and cognitive diseases in the future. In our research, we focus on exploring the relationship between metabolic health and brain health, because I consider that they are intrinsically related.

What is your opinion of CNIC?

I think the CNIC is a reference centre of scientific excellence in Spain for the study of cardiovascular diseases. Its scientists are highly recognized in the field and publish high-level research that significantly contributes to the advance of knowledge in this area. ■

Mayo Clinic Rochester (USA)

Esther Lutgens:

"SCIENCE IS THE BEST JOB THERE IS"

Esther Lutgens is a foremost expert in experimental vascular immunopathology. She obtained her degree in science and medicine simultaneously aged 25. Lutgens went on to take postdoctoral fellowships at Harvard and Dartmouth. When she returned to the Netherlands in 2004, she set up her own laboratory within the Cardiovascular Research Institute Maastricht (CARIM) and become Full Professor aged 35.

Lutgens has been the recipient of many prestigious grants and funding including a Veni, Vidi, Vici grant and the Sofja Kovalevskaja award. In 2011, she became Full Professor at the Amsterdam University Medical Centre and in 2021, she joined the Mayo Clinic to lead the Experimental Vascular Immunopathology Laboratory.

Her research on the role of the immune system in atherosclerosis particularly focussed on the CD40-CD40L pathway was innovative. She founded Cartesio Therapeutics in order to pursue development of this research in the clinical field. As a committed mentor and teacher, she has guided many students and postdoctoral researchers on their successful careers.

Can you briefly explain your approach to research in experimental cardiovascular immunology and its possible impact on health?

My focus is on immune system communicators, co-stimulatory and co-inhibitory molecules that determine whether an immune response worsens or attenuates. We have identified some that are crucial for atherosclerosis, like CD40. Blocking CD40 in mice significantly reduces atherosclerosis in the laboratory, but in humans it cause immunosuppression. Our aim is to solve this problem.

CD40 is expressed in the atherosclerotic plaque of many cell types, such as endothelial and smooth muscle cells. Each type of cell has different functions. If we understand the signalling pathway in each cell type, we can direct CD40 so that it reduces the atherosclerosis without compromising the immune system.

We have designed therapies that block the interaction between CD40 and TRAF6 in macrophages. This inhibitor reduces atherosclerosis in mice without suppressing the immune system

We have designed therapies that block the interaction between CD40 and TRAF6 in macrophages. This inhibitor reduces atherosclerosis in mice without suppressing the immune system. We are developing this therapy for clinical trials, using nanoparticles to make it more specific. We have already undertaken studies on large animals, and we are creating compounds suitable for clinical use.

Regarding funding, is it easier in the United States than in Europe?

It's different. In Europe there are more small awards. In the USA, the funding is for larger quantities but adapting to the system takes time. The probabilities of obtaining funding in the USA are greater thanks to funding from benefactors and internal bursaries like those of the Mayo Clinic.

The therapies that are being designed are for when atherosclerosis is already present, would it be possible to direct CD4 before the disease progresses?

Yes, we can find the CD40 in early atherosclerosis. In mice, we focus on CD40-TRAF6 interactions both before presentation of atherosclerosis and after it has developed. In studies on prevention, we found out that focussing these interactions could prevent atherosclerosis. In

mice that already had atherosclerosis, treatment slowed down progression. The lesions did not disappear, but they became more stable and less inflammatory. We are also testing this focus on animal models that already have atherosclerosis lesions to halt progression. We are also creating an atlas of the expression of cell-type specific co-stimulatory and co-inhibitory molecules at all stages of atherogenesis in mice and humans. We have found some new targets, like GITR, which belongs to the same family as CD40 but works differently. We are getting promising results with GITR, and we are starting to explore it in greater depth.

In the future, could multiple targets be found to tackle the disease?

Certainly. The immune system is complex, and these molecules interact with each other. CD40 could be a key regulator, but there are more molecules involved.

Immunology has been sidelined for a long time, not in basic research, but in the application of interventions in the immune system for certain diseases

It seems that immunology could solve many problems.

Immunology has been sidelined for a long time, not in basic research, but in the application of interventions in the immune system for certain diseases. The field of cancer triggered an interest in immunology thanks to the success of immunotherapy. All diseases involve the immune system. Current treatments for atherosclerosis are insufficient; they reduce the risk but don't eliminate it. There is an enormous field to explore, and immunology could be the answer. Inflammation plays an important role, but we need definitive proof of its effectiveness. Nowadays business and researchers are making great efforts in immunology. Maybe immunology will be the next great answer.

You are an immunologist, how or when did you come into contact with cardiovascular disease for the first time?

I was a medical student, and I ended up in a cardiovascular biology lab to do a project. I never left immunology. I completed my doctorate doing vascular research and I stayed in the field.

Did you always want to be a scientist?

I always like basic sciences and biology. I wanted to become a doctor to save people, but during my medical studies I discovered research, and I preferred it to medicine. I trained as a pathologist, but I chose to focus on research. Now I am a full-time scientist.

I like people and my medical training, but a large part of medical work is routine and obligatory. I don't like being on call or being constantly asked questions. I prefer the creativity of basic science and understanding how things work I enjoy being a physician, but I prefer science.

Having both specialities, a physician and a scientist, how do you find a balance?

I focus more on knowledge than on the clinical application. Although it is gratifying to see compounds move towards a clinical application, there comes a time when companies are better prepared to manage development and all the bureaucracy. As a scientist, I enjoy finding new mechanisms and molecules rather than focussing on taking a compound to the clinical setting.

How about your work as a mentor?

I guide students on a daily basis. I enjoy seeing how they develop and become independent people. They bring new ideas and perspectives, which is one of the best parts of the job.

Do you have any advice for students who are considering a career in science?

Science is the best job there is. They should always follow their heart. Try new things, take advantage of opportunities to work in international laboratories or in different fields and take their own decisions.

What do you think of the CNIC?

I am a member of its Scientific Advisory Council. I admire its laboratories and the close collaboration between the researchers who work on cardiovascular diseases from different angles. Its emphasis on students, even at secondary school level, is impressive. ■

Associate Professor in Molecular Medicine and Principal Researcher of the Vascular Surgery Division at Karolinska Institute.

Ljubica Matic: "MENTORS ARE NECESSARY AT EVERY STAGE OF A CAREER"

Dr Ljubica Matic is Associate Professor of Molecular Medicine and Principal Researcher of the Vascular Surgery Division of Sweden's Karolinska Institute. She obtained her degree in molecular biology at the University of Belgrade, Serbia, and holds a doctorate in biochemistry from the Karolinska Institute. Since 2019, she has been Leader of the Translational Vascular Medicine Group whose aim is translational research on novel therapeutic and diagnostic targets for the management of cardiovascular disease, specifically atherosclerosis and the complications of restenosis. Her group uses innovative, integrated multi-omics in silico pipelines to explore the Biobank of Karolinska Endarterectomy (BiKE) and identify smooth muscle cell related targets with a direct causal relationship to human vascular disease With this multidisciplinary approach, Dr Matic's mission is to create a platform for extrapolation of the outcomes of basic research to diverse realms of clinical cardiovascular disease, which will lead to accelerated development in areas ranging from target discovery to patient treatment.

Your group works in different areas...

I have always been fascinated by the changes that occur in cells during human diseases. In the field of cardiovascular diseases, for instance, we have discovered that certain types of cell present in human vascular disease, like smooth muscle cells, are not so different as we previously thought. They can adapt and transform under different conditions, particularly in environments such as atherosclerotic plaque, where the cells need to survive for decades. My interest lies in understanding how the cells transform and adapt to these environments, essentially focussing on the mechanisms of cell survival. Atherosclerotic plaque is a micro-environment in which cells are trapped and exposed to the influence of the environment for 20, 30 or 40 years; but plaque grows for decades and many of the cells don't want to die. They want to survive, but they somehow have to transform their own cell identity into something new in order to do so. In my opinion, this is an incredibly interesting area of study because it is about determining how a cell will decide to transform itself and how it will carry out the transformation. It is basically about survival.

At the start of your career you were more interested in scientific knowledge per se than in applied science. How has your perspective changed over time?

I initially focussed on basic science and on understanding fundamental processes. However, I became more interested in translational research when I realized its possible applications. The translational move, which links basic research with practical applications became particularly interesting for me. Despite the fact that my research still has not translated into any discovery of clinical use, I continue this line of work bearing in mind the importance of tackling the problems of human health. The really exciting part of research began for me when I came across the possibility of making the connection between basic research and basic knowledge, and how to apply it. We have data from human biobanks, and we can see how complex cardiovascular disease is for humans.

I have always been fascinated by the changes that occur in cells during human diseases

This is CNIC's philosophy. Are you thinking of collaborating with CNIC?

We already are; together with Miguel Ángel (Del Pozo) and his group, we have applied for a project. It has a specific approach that is completely new, and my group has available human data resources, so together we make the perfect combination to tackle the matter of protein modifications and how these different protein modifications can play a role in cardiovascular disease. We make a good combination to research a completely new question.

How did your academic career take you from Serbia to Sweden?

That was in 2002, so that's already 20 years. At that time there was hardly any investigative structure in Balkan countries, including Serbia. There was not much investment, and research was not a priority. So, for somebody interested in research, like me, staying in Serbia was not an option. I chose to study molecular biology, which clearly indicated that I would have to leave my country to devote myself to high level research. Initially, I had no specific ambition to go Karolinska University. In fact. I was considering several universities, including Heidelberg in Germany. However, during my interview at Karolinska, their research impressed me, particularly areas like the generation of knockout animals and the study of kidney and cardiovascular diseases. So the decision to move to Sweden was not solely based on scientific reasons, but rather on the need to leave my country to pursue a career as a researcher.

So you did not specifically choose the area you now research?

That's right. It's more as if it chose me. Although my doctorate was on kidney diseases, around ten years ago I made the transition to cardiovascular diseases. As a molecular biologist, my interest resides in understanding the bases of molecular biology behind human diseases in general, instead of focussing on one specific disease.

As a molecular biologist, my interest resides in understanding the bases of molecular biology behind human diseases in general, instead of focussing on one specific disease

You mentioned population data banks. Scandinavian countries are pioneers in this area...

In Sweden, we have a unified system and a personal number, and everything you do ends up registered under your personal number. That is a lot of information. But the information we are interested in refers to medical or hospital registers. Many Scandinavian countries have the same system. We have very high standards. The other aspect is the agreement of the Scandinavian population to contribute information and samples for research. Most people agree to provide their samples for research purposes when they go to hospital or the doctor, with informed consent, of course. These samples are kept in a biobank. Throughout Scandinavia, when patients are asked to donate their samples for research, 99% of them agree to do so. So there is a very high level of agreement to donate your own biological samples and data for research. And that is basically what feeds the whole infrastructure of biobanks.

Mentoring is different to supervision. It's about trust and experience. Mentors need to have lived various professional and personal situations to effectively relate to their mentees

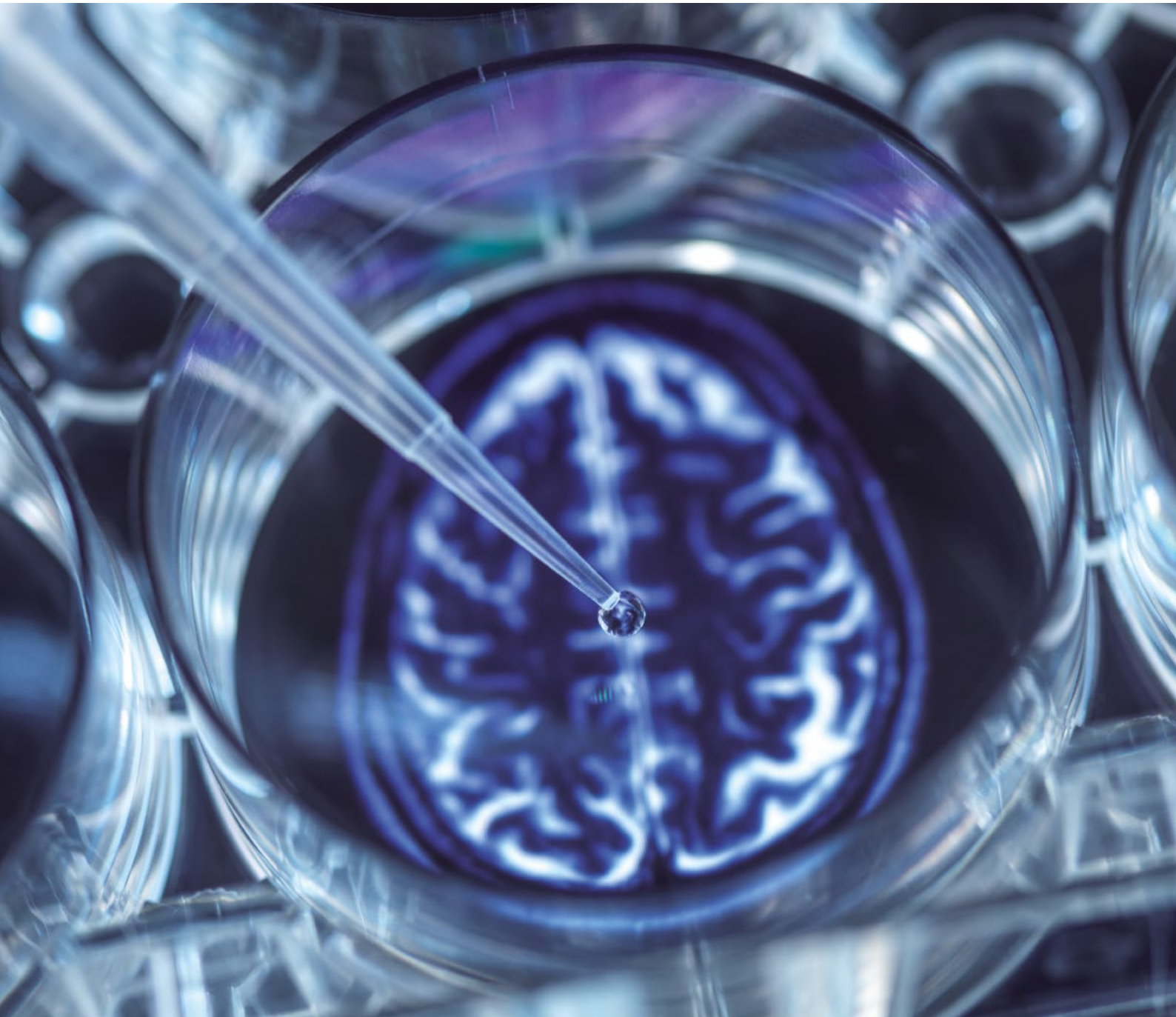
They say that a career in research needs mentors...

Mentoring is different to supervision. It's about trust and experience. Mentors need to have experienced various professional and personal situations to effectively relate to their mentees. Trust is crucial in the mentor-mentee relationship because it often implies sharing intimate thoughts and problems related with a career. Although not all young people can understand the value of mentorship, programmes like the

ones at Karolinska seek to foster tutorial skills equally between students and professionals, acknowledging its importance throughout their careers. At Karolinska we have mentorship programmes. In addition to having their supervisor, each doctoral student at Karolinska has to have a mentor and an external mentor. They can nominate a person from another country, or it may be someone who they have a private connection with. Basically, it is a person of their choice, but they have to choose an external mentor as a part of their personnel. And then, there are also tutor programmes at Karolinska for tutorship. The idea is that even people who are relatively inexpert can try to act as mentors of young students, not only to feel what it is like to be a mentor but also to know the degree of responsibility you have as a mentor and understand the importance of the function. It's like a trial and error mechanism. To foster a new generation in which students realise that a mentor is important and a person to turn to when you have something to talk about, something you can't do with your department or supervisors. What's more, inexpert mentors realise that tutorship is something that they should have throughout their careers. You need mentors at every stage of your career. I have my own mentors: I need to speak to someone with experience I trust, whose advice I will accept, can assimilate and attempt to apply.

You left Serbia 20 years ago, what connections do you have with research in your home country?

I have recently been awarded a grant for an EU project to collaborate in my old institute in Belgrade (Serbia). The aim of the project is to build a research infrastructure and skills in areas like the biobank, as well as support services for research, transferring knowledge from institutions like the Karolinska. It's my way of giving something back to my country, and I'm happy to contribute to the advance of research Serbia. ■



Toronto University's McEwen Stem Cell Institute (Canada)

Michael A. Laflamme:

"SOONER OR LATER WE WILL MANAGE TO REGENERATE THE HEART"

Michael A Laflamme's research at Toronto University's McEwen Stem Cell Institute (Canada) focusses on the development of new therapies for heart failure after a heart attack, based on human pluripotent stem cells (hPSC) as hPSC are the only stem cell type capable of differentiating into large quantities of phenotypically unambiguous cardiomyocytes. His aim is to restore the electrical and contractile function of injured hearts by "remuscularizing" the infarct scar with hPSC-derived cardiomyocytes

His laboratory has already made a number of important advances in this area, including the development of efficient protocols to guide hPSCs into cardiomyocytes and specialized cardiac subtypes, proof-of-concept transplantation studies with hPSC-derived cardiomyocytes in rodent myocardial infarction models, and the first direct demonstration that hPSC-derived cardiomyocytes can become electrically integrated and activate synchronously with host myocardium in injured hearts. His current work is based on these successes and is bringing us closer to feasible cell therapy.

How near or far are we from being able to regenerate the heart?

I think we are going to manage it sooner or later. It is a challenge but there is a lot of very promising research underway. Our laboratory focusses on administering endogenous cells, heart muscle cells, to treat myocardial infarction. There are other groups following other, more endogenous, lines of work, which are attempting make cardiomyocytes recover their capacity to divide. All of these approaches have their challenges, but I am convinced that we are close. In my opinion, there is no fundamental reason why we can't achieve it.

What exactly is your approach?

We work with heart muscle cells that we are generating from pluripotent stem cells, which are special because they can differentiate into any type of cell found in an adult. There are two types of pluripotent stem cells: embryonic stem cells, derived from surplus in vitro fertilization embryos, and induced pluripotent stem cells (iPS cells), which can reprogramme themselves from ordinary somatic cells, such as skin or blood cells, to become the equivalent of embryonic stem cells.

We have had great success guiding these cells to become useful ones, such as cardiomyocytes. I was one of the first to work on these cells, in 2002. At that time, even obtaining a small percentage of heart muscle cells was an enormous achievement. Now, we can reach a purity higher than 95% and produce thousands of millions of these cells in a month. The challenge facing us now is to transfer these cells to animal myocardial infarction models, ensuring delivery and proper integration into the heart.

Our laboratory focusses on administering endogenous cells, heart muscle cells to treat myocardial infarction

Are these cells the same as the ones in the heart?

Not exactly the same ones as in an adult heart, but similar to the cells found in early foetal development. One challenge is their immature phenotype. We have been working on ways to mature these cells. In addition, the heart is made up of various types of cell, not only cardiomyocytes. There are other types of cell that carry out important functions, such as immune cells, fibroblasts and vascular cells. We can generate all of these cells from iPS or embryonic cells. This allows us to start contemplating co-administration of these cells. During the first 10-15 years in the laboratory, we focussed on obtaining a population of cardiomyocytes that was as pure as possible. Now we are going in the opposite direction, we want to control what types of non-cardiomyocyte cell are present.

Will future transplants include all of these types of cell?

That is the aim. Although cardiomyocytes naturally attract other types of cell, co-delivery could accelerate the process.

What results have you had in experimental models?

The outcomes are promising. Cells can form new myocardium in infarction areas and electrically integrate with the heart, improving contractile function. However, our main challenge are arrhythmias, particularly in large animal models.

How are you approaching the problem of arrhythmias?

We have tried many solutions. An effective approach is to mature the cells before transplantation. This reduces the arrhythmias and improves the general results. We also use conventional antiarrhythmic drugs, which significantly help.

What about long-term risks, like cancer?

Tumorigenesis is always a concern when using products based on pluripotent stem cells, but it isn't our main worry. We have seen tumours in our extensive studies with animals. Our efforts focus on efficiently guiding these cells towards the desired ones, minimising risk.

Does cell transplant the only solution for heart disease?

There are other approaches, such as heart transplant, xenotransplantation, ventricular assistance devices and stimulation of endogenous repair. Different clinical scenarios may require different solutions.

When did your interest in medical science and heart diseases begin?

I've always loved science. At university I followed a combined course of medicine and postgraduate studies at Emory. During that period, you visit different laboratories and do rotations in them. To be quite honest, the reason I probably ended up in heart research is because, when you spend time in those labs, you can be working with neurons, which obviously have important functions, or with epithelial cells, or whatever, in a laboratory that works with cardiomyocytes I discovered what cardiomyocytes do that other types of cell don't: they contract. I remember having felt captivated by the instant gratification, by seeing something in action before my eyes. It grabbed my imagination.

And the same thing happened when I finished medical school and postgraduate studies. I did a residency in anatomical pathology, and I became a pathologist specialized in cardiac pathology. I was working in a laboratory, and I remember the first time we had a plate of beating cardiomyocytes obtained from stem cells. To this day I never tire of seeing them beat. If I have a bad day, I like to go to the lab and look through the microscope to see a beating culture.

The real motivation is that heart disease is obviously very serious. There is an urgent need for therapies. I don't see patients in my clinical role, but in my role as cardiac pathologist, I see the worst results. I see the hearts of people who have had to undergo a heart transplant or, worse yet, I perform autopsies. Many of these people die of heart failure. As I observe these sick hearts, I hope to contribute in some way. ■

Professor of Immunology at Tufts University

Pilar Alcaide:

"MOTIVATION IS KEY FOR A SATISFYING, ENJOYABLE CAREER IN RESEARCH"

Pilar Alcaide is Professor of Immunology at Tufts University. She completed her doctorate in biology at the Autonomous University of Madrid and moved to the USA to continue her scientific career. Her laboratory researches the cell and molecular mechanisms of the traffic of leukocytes in acute and chronic inflammatory settings, with a particular focus on T cells and their role in chronic inflammatory diseases and heart failure. During her doctoral studies, she researched immunosuppression during acute T. cruzi infection, and as an independent researcher, she was a pioneer in the emerging field of T-cell mediated inflammation in heart failure. Her group has made important discoveries in cardio-immunology, particularly related to adaptive immunity in heart failure with a reduced ejection fraction. She also makes significant efforts in mentorship of students and junior professors.

How did you decide to become a scientist?

I was really interested in biology during my teens. But I was also interested in many other things, including sports science and football. So it wouldn't be true to say that I always wanted to be a scientist. At university, I specialized in biology and, in my last two years, in molecular biology. From my first cell biology class, I was fascinated by immune cells and my interest grew when I had my first immunology class and worked on a scientific literature project about the benefits and side effects of nonsteroidal anti-inflammatory drugs. When someone suffers an autoimmune disease, the immune system seemed fascinating to me and that's why I chose immunology for my doctoral research. However, I deliberately avoided studying my autoimmune disease because I didn't want to be thinking about it all the time. When the time came to think about what to do next after finishing the doctorate, I knew I had to do an academic post-doc. It was difficult to decide if I wanted to broaden my training in immunology or apply it to other fields. As immune cells need vasculature to circulate between organs and exercise their effector functions, I felt that the cardiovascular system was the next logical step for my scientific growth. I made the right decision. I love what I have learned and continue to learn about cardiovascular diseases. The integration of immunology and cardiovascular biology has substantially contributed to our understanding of many aetiologies of cardiovascular diseases. Several scientists, me included, have gone from identifying immune cells in unexpected cardiovascular organs to learning that stromal cells are also an important component of our immune response. There is an immense potential to make discoveries at the cardiovascular-immune system intersection that will almost certainly lead to new therapies.

You have just received the Excellence in Science Award for leadership, mentorship and research...

It is awarded by the American Professional Society Federation, which includes over 30 scientific associations from immunology to oncology or the cardiovascular field. It was a pleasant surprise. They give three prizes: one to the most senior people, another to younger researchers who have been in the field of research for less than 8 years and finally, the one they awarded me, which is for consolidated research. They considered that I had impact in the field of immunology in cardiovascular research.

I was the first person to discover that there were immune system cells in the heart.

It had been discovered in people who had had myocardial infarction or with autoimmunity, when there is direct damage to the heart. However, we didn't know whether they were present in patients with heart failure caused by other aetiologies, who had not had damage in the heart. So we were the first.

And why was that discovery important?

It is important because we assume that T cells, the cells of the immune system, have evolved to combat infection or to promote wound healing. That's why it was not surprising that there should be cells in the heart if there was a viral infection that reached the heart or if you have a heart attack, which is also a wound that needs to heal.

But there were a group of patients with heart failure that had not been caused either by infection or by myocardial infarction. In the laboratory, we saw that these patients, when they are waiting to receive a transplant and have an unknown aetiology, also have T cells, which made us think: they are there and since they haven't gone to do any good, they must be doing something bad.

Really, they are doing what they have been trained to do: cause fibrosis, which is necessary if you have a wound or a myocardial infarction. But they do it when there has been no lesion, causing a type of pathological fibrosis, which means that the heart neither contracts nor relaxes correctly. And that causes heart failure.

I had that idea, but before doing it all experimentally, we decided to obtain samples from patients with non-ischaemic heart failure, i.e. who have never had a heart attack or a known viral infection involving the heart. In that group of patients, we saw that there were T cells. The next step, in the laboratory, was to study whether those cells were good or bad. We studied these T cells in animals in the laboratory.

What percentage of patients have this type of heart failure?

It depends on how you categorise heart failure. If your definition depends on reduced or preserved ejection fraction, it would be 50%. There are 50% of patients whose ejection fraction is not compromised, but they suffer heart failure because their heart does not relax and enlarges. Of the other 50%, who have a compromised ejection fraction, meaning their heart does not contract properly, half are due to heart attacks and the other half due to unknown causes, which may be heart valve disease, congenital disease, high blood pressure, the toxicity of chemotherapy agents (anthracyclines)...

Do you think that the position of women in science has changed since you started your career?

From my first cell biology class, I was fascinated by immune cells and my interest grew when I had my first immunology class and worked on a scientific literature project about the benefits and side effects of nonsteroidal anti-inflammatory drugs

For me, the greatest change has been awareness. Awareness about the importance of a better representation of women, of micro-aggression and the importance of speaking out when things are not right. Awareness is the first step towards a positive change and communication is key. I have spent more time in the USA than in my home country, where I began my career, which means I can comment more on the differences in the USA than in Spain. In the USA, the representation of women has increased in comparison to what it was when I began my career in science. Being seen, listened to and the centre of attention as a female scientist can leave a lasting mark on the next generation of women in science, who now have more models to follow than we did. When I look back to my first years in science in Spain and the USA, I also see improvements in other aspects from the creation of facilities for breastfeeding at work, or even changing the system to allow for maternity leave in the 'post-doctoral period' in terms, for instance, of grant applications. However, there is still room for improvement, and we still need to advance a great deal. Achieving these advances will not only benefit female scientists but the whole research community.

At institutional level we are seeing things change. My university has felt a breath of fresh air with the appointment of a female Chancellor. But she is almost the only one. Representation is important, but I believe that representation has to be done properly.

What are you most proud of in your career?

There are so many things I'm proud of. I think we should be proud of each step; however small it may seem. I am very proud of having completed my doctorate at the same time as I was a footballer with Real Madrid, following both of my passions. I am also very happy to have left my comfort zone of Madrid and come to the USA as a person and a scientist. And I am excessively proud that, while I did it, I managed to have three wonderful children who appreciate what I do and are proud of me. Finally, I'm proud that my discoveries in research have attained recognition within the cardiovascular community and of having become part of a network of colleagues and friends with whom I love working and interacting. Remembering when I knew only a few people in my field and felt intimidated when making a presentation or showing my scientific knowledge and comparing that to where I am now is a fantastic feeling.

What advice would you give people who are setting out on their research careers now?

Take heart, follow your passion and enjoy what you do. Motivation is key for a satisfying, enjoyable career in research. Find the thing that keeps you motivated, projects or experiments that enthuse you, and work hard to finish them because it is fun and satisfying. If you don't have motivation, then follow your passion elsewhere. No other job in the world allows you to be creative and attempt experiments with so many possibilities of failure. But, when the experiment "works" and you make a new discovery, it is published and you see it take life as other scientists improve and develop findings, the feeling of being part of something bigger is stimulating. Finally, my advice is to not be afraid to present or discuss your science and meet other scientists who you may only know through their work but not in person, regardless of how "big" their names are. I recommend taking advantage of every opportunity to do just that. Peer review always leads to professional growth, helps build a network and, often, along the way, you meet incredible people you can learn and have fun with.

What do you think of the CNIC?

Internationally, and in the cardiovascular world, it is well known, and its researchers publish well. I sometimes collaborate with Pilar [Martín], although we haven't had any joint projects yet. For two years I was director of the American Heart Association (AHA) Basic Cardiovascular Science Congress and later, for another two years, I was head of Basic Cardiovascular Science during the AHA Scientific Sessions. I always try to give visibility to Spanish scientists. ■

Stanford W. Ascherman Professor of Genetics, Chair of the Genetics Department and Director of the Centre for Genomics and Personalized Medicine at Stanford

Michael P. Snyder:

"THE BENEFITS OF SHARING DATA OUTSTRIP THE POSSIBLE HARM"

Michael P Snyder is Stanford W. Ascherman Professor of Genetics, Chair of the Genetics Department and Director of the Centre for Genomics and Personalized Medicine at Stanford. His laboratory develops and uses diverse omics techniques such as genome sequencing, transcriptomics, proteomics, metabolomics, DNA methylation and microbiome assays to study complex systems. They are pioneers in the use of multi-omic longitudinal profiling to track health and detect presymptomatic diseases with portable sensors. In over 34 years as leader of an independent laboratory, he has trained 170 postdoctoral researchers and 65 postgraduate students, over 95% of whom went on to have successful careers in research. His team established the first omic longitudinal profiling for personalized medicine, predicting risks of disease and detecting their onset using genomic sequencing and continuous monitoring. He pioneered in the field of functional genomics and systems biology with the first prototype for next generation sequencing of genes and proteins. His team was among the first to use portable devices for the early detection of diseases and to monitor heath, including the early detection of infectious diseases and continuous glucose monitoring for glycaemic disorders in pre-diabetes, among others.

Big data, omics...How does all of this technology help biomedicine?

We are in the middle of a big data revolution where omic data and portable devices can characterize health and biological systems. Much of this technology is currently used in research, although only a small part of it is beginning to be employed in the clinical sphere. We now sequence genomes to conduct our research, particularly into cancer. There are many risk genes for cardiovascular diseases, with several hundred genes identified. This means that scientists are already starting to use large panels or to sequence full genomes to predict the risk of cardiovascular disease. So for people with a family history of cardiovascular diseases, using genomics is not a bad idea. Other "omics" are also becoming more centre stage: proteomics and transcriptomics. The genome is excellent to predict risks, but to see how a disease manifests there are other markers that are crucial. Genetics established

We are in the middle of a big data revolution, where omic data and portable devices can characterize health and biological systems. Much of this technology is currently used in research, although only a small part of it is beginning to be employed in the clinical sphere

the broad view of what could happen, but the interpretation comes from how your genome manifests through the transcriptome, proteome and metabolome. These are powerful tools to understand diseases and find useful biomarkers, particularly for cardiovascular diseases. Known biomarkers like troponin are only the start; there are many more to be discovered, like the biomarkers for atherosclerosis and heart failure.

We are in the middle of a big data revolution, where omic data and portable devices can characterize health and biological systems. Much of this technology is currently used in research, although only a small part of it is beginning to be employed in the clinical sphere.

We are on the road to a future where we use predictions of genetic risk and various biomarkers to predict and monitor diseases...

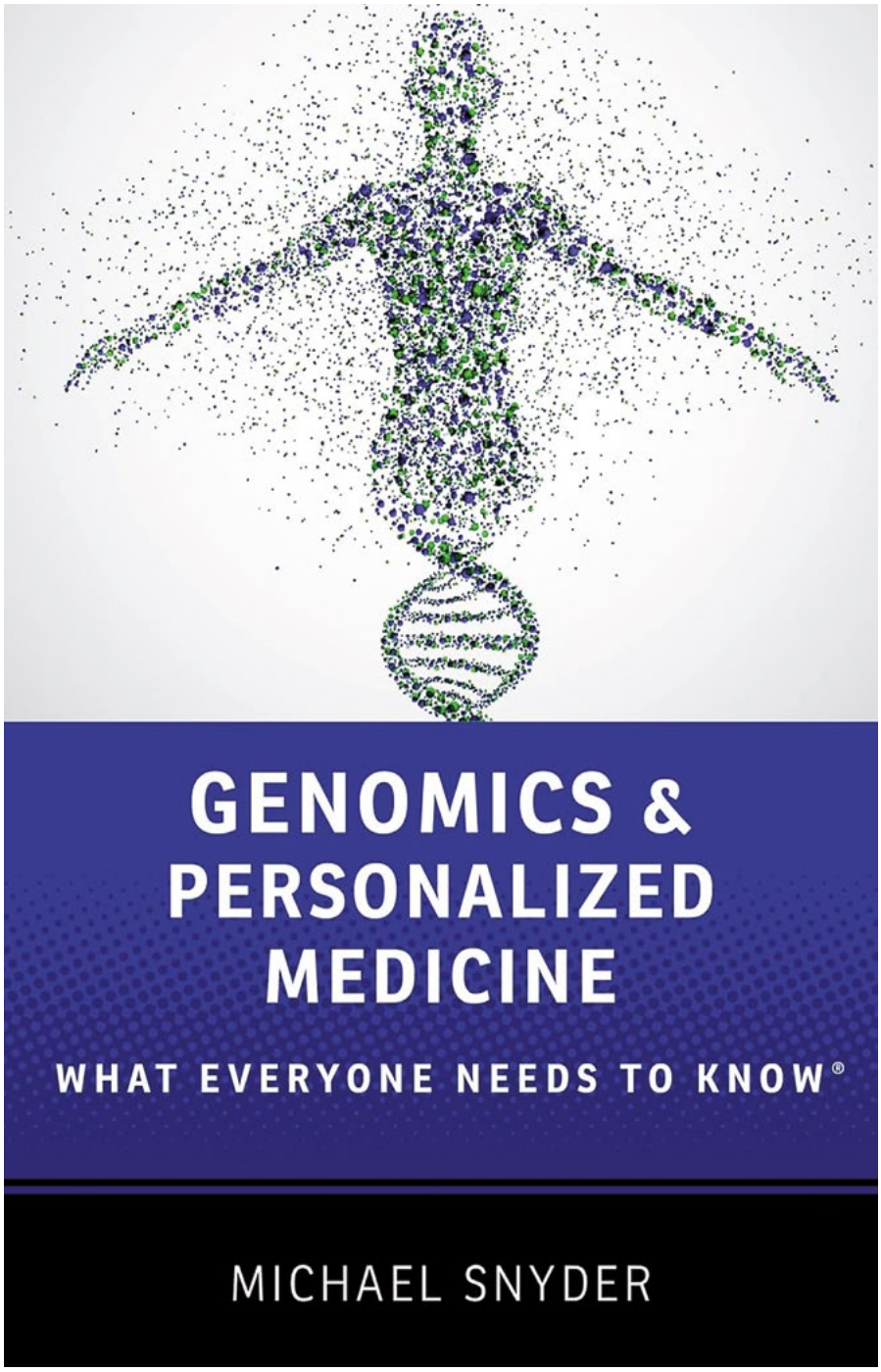
Exactly. We need those markers and genetic risk predictions for different diseases. Big data is essential. We are also starting to understand the important role that portable devices like smart watches can play in monitoring health 24/7. These devices are increasingly powerful in tracking heart diseases and other conditions. For instance, the FDA has approved some of them to track atrial fibrillation (Afib).

Taking into account this technology, is personalized medicine a reality now, or do we still have to wait?

I think we are only seeing the tip of the iceberg: it's only just beginning. Some advances have been made, particularly in the sphere of cancer. Cancer treatment is often based on the specific genetic mutations present. For instance, lung cancer has five different forms, and the type of cancer determines the treatment. The same is true of breast cancer.

In the cardiovascular context, this is an emerging approach. Knowing your specific risk can determine the medication you receive. However, the field is still developing. Tracking people in general requires knowledge of their personal benchmarks in order to detect change. Atrial fibrillation (Afib) is a good example: you need to know the personal benchmark to see changes. This approach is becoming mainstream, particularly with portable devices to predict risk and certain treatments.

Personalized response to medication also plays a role, particularly in dosage. Dosage is very personal and depends on your metabolic rate and the specific genes and enzymes that affect the response to drugs. This was first discovered in the case of warfarin and now many drugs have personalized dosage.



On some level, personalized medicine is already here, for drugs, with portable devices and in other areas. However, there is still much to learn. We should be able to sequence a person's genome and, with a few other measurements, know exactly what is at risk, which treatments should be received and even what diet to follow.

We are moving towards a world where all of our information is shared with physicians and businesses. What about the privacy of information?

I have two answers to the issue of privacy. First, my opinion is that we should get over it: nothing is private anymore. There are cameras on every corner, and a lot of personal information is already accessible from credit cards and other sources. Businesses have had access to this information for a long time and people haven't panicked because it's a convenient way of doing things. We don't walk around with our pockets full of cash because it isn't very safe. So, in one sense, privacy is already a thing of the past.

However, on the other hand, I think that the benefits of sharing data outstrip the potential harm. Sharing data allows us to learn important things about which drugs work for which people, and this type of information can only arise from the exchange of data. If we can share data more effectively, the general good will outstrip the bad, in my opinion.

People are worried about privacy because they are afraid of being abused by the system, like being excluded from health insurance. In Spain, I think there is better access to medical care than we have in the States. In the USA, the system is more fragmented, and you can be excluded from health insurance for pre-existing conditions. I think we should eliminate this. Everyone should have the basic right to medical care in a rich society, like the ones in the West.

So, if everyone had a minimum access to medical care, concerns about privacy would be fewer. If you have a pre-existing condition, you would not be excluded, you would have healthcare. That is what I would like to see, so that privacy would be a lesser consideration in medical care.

But what if there are no treatments for certain conditions? Would it still be important to know your genetic risk?

That decision should depend on each individual. Knowing your risk for certain conditions like Alzheimer's or Huntington's could be important, even if no treatments currently exist. Some people want to know their risks to take preventive actions or participate in clinical trials. Ultimately, it should be a personal choice.

Some advances have been made, particularly in the sphere of cancer. The treatment for cancer is often based on the specific genetic mutations present

Is it also important to interpret this information, not only for patients but also for physicians?

Yes, interpreting genomic data to assess risk is critical. For instance, we discovered a person at high risk of a heart condition from their genomic sequencing and a more thorough examination confirmed the risk. Portable devices have also helped us detect serious conditions before the symptoms appear, potentially saving lives.

So we need a change in the system of "patient care" to a health system focussed on prevention?

Absolutely. Keeping people healthy is the aim of our health system. We are trying to prolong healthy life.

Do you think that humankind will understand the importance of taking care of their health?

Yes, I think a subset of people already understand this. We are trying to spread this awareness to as many people as possible. By monitoring the health of people and detecting problems at an early stage, we can put remedial actions in place. When people measure their levels more frequently, they become more aware of their health. In our study, everyone reported that they improved their lifestyle just because they had participated in it. ■

British Heart Foundation

Paul Riley: "I'M OPTIMISTIC ABOUT THE FUTURE"

Paul Riley is the British Heart Foundation Personal Chair of Regenerative Medicine at the University of Oxford. He is also Director of the BHF Oxbridge Centre for Regenerative Medicine. He was Professor of Molecular Cardiology at the UCL-Institute of Child Health, London, where he was a principal investigator within the Molecular Medicine Unit at UCL-ICH for 12 years. He obtained his PhD from University College London and completed post-doctoral fellowships in Toronto and Oxford. In 2008, Professor Riley was awarded the Outstanding Achievement Award of the European Society of Cardiology in recognition of the discovery that epicardial cells can regenerate the heart of adult mammals, and in 2014 he was named member of the United Kingdom's Academy of Medical Sciences. His research interests cover diverse aspects of cardiovascular development, and the mechanisms involved in restoring embryonic potential in the adult heart with disease or lesions in order to promote optimal repair and regeneration.

Your work focusses on regenerative medicine, particularly in the heart. Could you summarize the current state of your research?

There are currently a combination of approaches in regenerative medicine for the heart. One of them is the transplant of cells or tissue engineering to repair the lesion by introducing new cell types. However, this approach has not met much success because many transplanted cells do not survive or correctly integrate. On the other hand, keeping the patches alive and vascularized is also a challenge. Another focus consists of stimulating endogenous cell types designed to respond to a lesion and promote the growth of the heart muscle from existing muscle that survives the lesion or foster the growth of new blood vessels to support the new muscle. This also includes modulating inflammatory response and fibrosis. These processes can potentially be boosted by activation of cells using molecules or nucleic acid therapeutics such as modified RNA (similar to the COVID vaccine).

Many organs cannot repair themselves.

If you have a heart attack and lose a significant portion of your vasculature and heart muscle, you risk developing heart failure, which is a debilitating disease that affects 65 million people worldwide. Heart failure has an awful prognosis, significantly reduces quality of life and is, ultimately, fatal. The aim of regenerative medicine is to prevent this by restoring new cells and tissues in the heart and tackling heart failure itself with reversion of the fibrosis or promotion of new blood vessels. This is crucial because heart failure is a common problem worldwide, not just in the western world but increasingly in low and middle-income countries.

What are the main challenges in this field?

The challenges include achieving the right balance; for instance, when stimulating the growth of heart muscle it is crucial to ensure sufficient vascularization to support the muscle. When reducing fibrosis, there should be heart muscle to replace the scar tissue, which is formed because the heart muscle cannot renew itself. Another great challenge is heart-specific therapeutic delivery. Methods being explored include invasive injections into the heart muscle or blood vessels, but it would be ideal to have a less invasive, oral drug directed at the heart. Safety is also a concern. These drugs should be safe, controllable

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and specific for the type of heart cells. For instance, large animal studies have shown that stimulating the growth of heart muscle too much can cause arrhythmias and be fatal. So we need therapies that can be turned on and off, which are also safe and effective.

How safe are these therapies?

Studies on animals suggest that they can be safe if they are properly regulated, and the right level of cell regeneration is achieved. However, stem cell transplantation is more difficult to control because many transplanted cells do not survive in the inflammatory, fibrotic environment of a lesioned heart. Patients often need immunosuppressive drugs, which can be toxic. What's more, we don't fully understand what drives these cells to achieve clinically beneficial outcomes; they often die shorty after transplant. So using drugs that can be turned on and off, targeted at the types of resident cell, is a more promising approach. The heart is also one of the organs least susceptible to tumours, which makes it a relatively safe target for such therapies.

Are there animal models that can regenerate their hearts? What can we learn from them?

Yes, there are several models. For instance, adult zebra fish can completely regenerate its heart in approximately 30 days after the loss of a portion or a tissue lesion. Another model is the neonatal mouse, which can completely repair its heart during the day following its birth if there is a lesion. Studying these models helps us understand the mechanisms underlying cardiac regeneration. It has also been seen that human babies regenerate their hearts after an in utero heart attack, showing functional recovery after birth. These models are vital to help understand how to drive the growth of new heart muscle and blood vessels.

Although they are rare, there are also various documented cases of babies that have managed to regenerate their heart after suffering a heart attack. Babies who suffer an in utero heart attack and are then born and treated successfully have shown full regeneration and functional recovery. Although there are few such cases, they show that human babies can regenerate their hearts and studying them can provide valuable information.

This shows that we can renew our hearts when we are very young, but we lose the capacity. Do we know why?

Thanks to study of the neonatal mouse model, we know that between the first and seventh day after birth, the muscle cells of the heart mature, get larger and have more than one nucleus, which makes them less able to divide and form new muscle. Changes in signalling and maturation of the immune system during this period improve heart function but reduce regenerative capacity. The heart, designed to beat thousands of millions of times during a life, develops to have minimal cell renewal to maintain precise functioning. In early development, there are more opportunities for the formation of new cells. Understanding these signals and key targets can potentially help us restore this capacity in adults with heart lesions.

Given your experience, do you think we will achieve the target of cardiac regeneration in the next 10-20 years?

Yes. And studies exist on large animal pre-clinical models that suggest it is possible to boost different aspects of heart regeneration. What we need is a collaborative research centre focussed on the proliferation of heart muscle, new blood vessels, the immune system and fibrosis. This centre should work with industrial partners to develop vectors and controllable, targeted nucleic acid therapies. The centre could achieve a new therapeutic treatment in 7-10 years and take it to clinical trials. I'm optimistic about the future.

Do you have collaborations with the CNIC?

Yes, I have collaborations with Enrique Lara and an EU Marie Curie programme, studying the neonatal mouse model. I am also familiar with the work of Miguel Torres and José Luis de la Pompa, which is very prominent in cardiovascular development and regeneration. ■

CNIC CO-LEADS REACT, AN INTERNATIONAL PRECISION MEDICINE PROJECT TO TRANSFORM CARDIOVASCULAR PREVENTION

Globally, cardiovascular diseases due to atherosclerosis – the build-up of plaque in arteries – are the leading cause of death. A new Danish-Spanish research collaboration aims to develop methods to detect atherosclerosis at earlier ages and encourage prevention. Denmark's Novo Nordisk Foundation has granted up to EUR 23 million to cover the first 2.5 years of the REACT initiative. The initiative is expected to run for 8 years in total.

"Atherosclerosis may develop from an early age and often remains 'silent', that is, without symptoms, for many years until it suddenly hits, for example with a heart attack," says Dr. Henning Bundgaard, Chief Physician and Professor at the Department of Cardiology at Rigshospitalet, Copenhagen, Denmark, and leader of the project. "In REACT, we hope to identify new means to detect atherosclerosis at earlier stages and at a younger age, that is during the 'silent' period."

REACT is a collaboration between Danish hospitals and Centro Nacional de Investigaciones Cardiovasculares (CNIC), a Spanish research center, world-leading in imaging diagnostics for atherosclerosis. CNIC and Rigshospitalet have collaborated for many years on the development of new and better methods for early detection of cardiovascular disease.

"At present, we use factors like blood pressure, cholesterol levels, age, and lifestyle to estimate the risk of atherosclerosis," says Dr. Borja Ibáñez, Scientific Director of CNIC, cardiologist at Fundación Jiménez Díaz hospital, and leader of the Spanish part of the study. "By contrast, REACT will develop – at scale - methods to directly visualize the disease (atherosclerosis)." Today, the treatment of atherosclerosis is largely the same in all cases, but the two professors anticipate a future with far better, individually tailored precision treatment of many more patients and from earlier ages.

A total of 16,000 individuals — 8,000 from each country — aged 20-70 will be included in the first phase of the project. The program includes imaging of arteries in the neck and groin and of the coronary arteries, as well as genetic analysis and blood tests.

The purpose of the first phase of REACT is to establish the prevalence of atherosclerosis in various sites in the body and to identify optimal methods for detection of atherosclerosis – and its risk factors – from an early age and at early stages, with the ultimate goal to enable prevention early in the 'silent' phase. Prevention may be pharmacological or involve lifestyle changes, the exact method being dependent on the individual's risk profile.

"The study represents a shift in paradigm from the traditional treatment of diseases to detection and prevention at early stages, that is, before serious or potentially life-threatening disease presents. At the Novo Nordisk Foundation, we strongly support this development," says Martin Ridderstråle, Senior Vice President at the Foundation.

"A crucial purpose of REACT is to find out who should be recommended which type of treatment and when, or for that matter, who should be advised against treatment: what we call precision medicine."

Depending on the results of the first phase of REACT, the next step – phase 2 – is to expand the collaboration and to investigate if treatment of early-detected atherosclerosis is effective and will prevent the many lives lost. This part of the project would last 5.5 years.

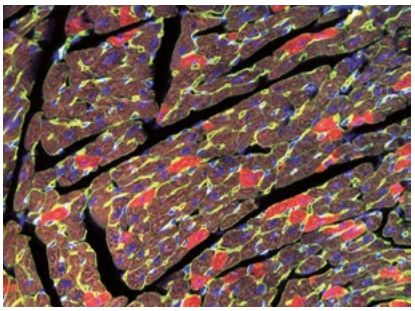
THE REACTIVA PROJECT, LED BY CNIC SCIENTIST DR. MIGUEL TORRES, RECEIVES ERC ADVANCED GRANT FUNDING

The CNIC project will use innovative approaches to investigate cardiac regeneration. The **REACTIVA** project, directed by Dr. Miguel Torres at the CNIC, has been awarded an ERC Advanced Grant to fund innovative approaches to the investigation of cardiac regeneration. The award provides **€2,500,000** in funding over a period of 60 months.

The hearts of newborn mammals have abundant diploid cardiomyocytes, allowing them to efficiently regenerate damaged tissue. However, this ability is lost son after birth, and the hearts of adult mammals are unable to regenerate because the fully differentiated cardiomyocytes they contain have a limited capacity to proliferate.

"Heart failure is a global epidemic. Its impact in terms of avoidable deaths, ill health, and health care costs is immense. Because the adult human heart lacks the ability to regenerate, the loss of myocardial tissue that occurs in many heart conditions is irreversible and often leads to fatal heart failure," said Dr. Torres.

The goal of the REACTIVA project is to establish a new strategy for cardiac regeneration based on the reactivation of the heart's dormant endogenous mechanism. This will represent a major advance in cardiac regenerative biology. Research in mice has shown that the regenerative capacity of the adult heart is related to the proportion of diploid cardiomyocytes; however, so far it has been difficult to characterize the molecular profile of these cells, and this has held back understanding of their role in cardiac regeneration.



Thanks to a new method for sequencing RNA in individual cardiomyocytes, the Genetic Control of Organ Development and Regeneration laboratory at the CNIC, which Dr. Torres leads, has identified a molecular signature of diploid adult cardiomyocytes that is related to the fetal program and is controlled by a transcriptional repressor. Inhibition of this repressor in the hearts of newborn mice increases both the numbers of diploid cardiomyocytes in adulthood and their proliferative activity.

The team propose that diploid adult cardiomyocytes are the vestige of an endogenous regenerative mechanism, and that stimulating these cells could promote cardiac regeneration in the adult mammalian heart. REACTIVA will build on these findings to provide a complete characterization of the regulatory network in diploid adult cardiomyocytes, identify and track these cells in the adult heart, and use this knowledge to induce their activation and promote cardiac regeneration in adulthood.

Together with **Dr. Hesham Sadek**, Dr. Torres coordinates the CNIC Cardiovascular Regeneration Program, whose goal is to identify endogenous mechanisms that stimulate the regenerative capacity of the heart and the vascular system and to use the knowledge gained to design therapies for patients.

Funded by the European Union

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THE IMNOVATH PROJECT, LED BY DR. DAVID SANCHO, HAS BEEN 2W FOR ITS PROOF OF CONCEPT GRANTS

The ImnovAth project, led by Dr. David Sancho, head of the Immunobiology Laboratory at the CNIC, has been selected by the European Research Council (ERC) for its Proof of Concept grants, receiving funding of €150,000. ImnovAth will investigate an alternative therapy for atherosclerosis focused on inhibiting a new therapeutic target. This new target may serve to develop an independent or complementary therapy to current treatments for atherosclerosis, thereby enhancing their effectiveness.

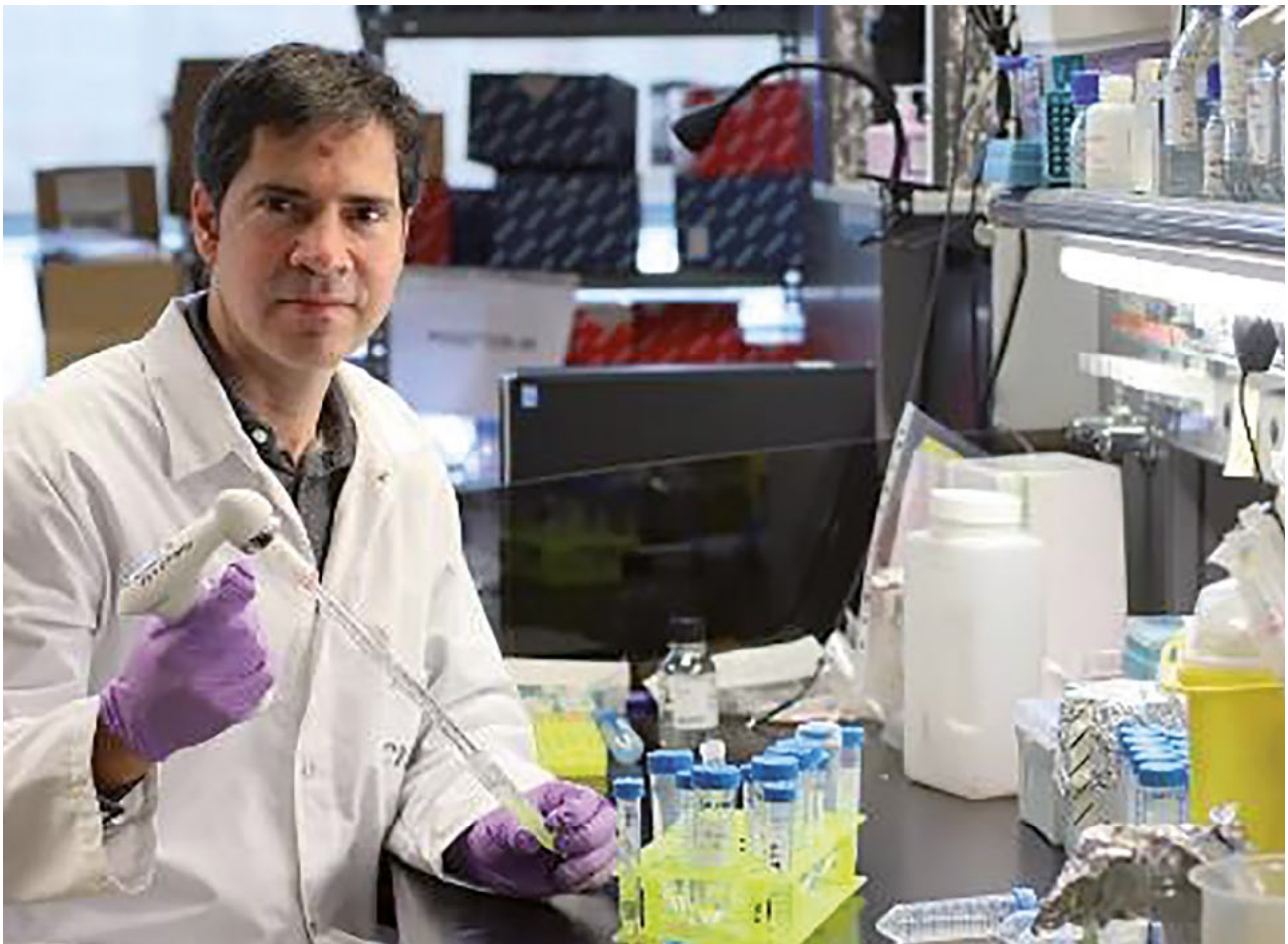
Atherosclerosis is a leading cause of death worldwide, and current treatments are insufficient to address future cardiovascular events. Therefore, there is an urgent need to find new complementary treatments.

ImnovAth is a continuation of Dr. David Sancho's MITOMAD project and is carried out as an individual project at the CNIC. In the context of the MITOMAD project, funded by the ERC, "we found a microbiota-derived metabolite that affects the development of innate and adaptive immunity. Subsequently, we discovered that this metabolite is associated with and causes atherosclerosis, and blocking the interaction of this metabolite with its cellular receptor prevents the progression of atherosclerosis."

Dr. Sancho explains that ImnovAth aims to develop these innovative results "to complement our preclinical findings with an existing pharmacological agent that blocks the interaction pathway of this microbiota-derived metabolite with its cellular receptor. If this proof of concept is successful, the idea is to initiate clinical trials and develop a drug that can be commercialized."

The main objectives of ImnovAth include validating that this blockade is effective in treating atherosclerosis. Dr. Sancho details that the toxicity/tolerability of the existing pharmacological agent and the effect/efficacy of blocking this metabolite/receptor axis with the pharmacological agent alone or in combination with other current standard treatments for atherosclerosis will be studied in a preclinical setting.

The Proof of Concept grants awarded by the ERC help bridge the gap between groundbreaking research results and the early stages of commercialization. "**Courage and skill are needed to take an idea from the laboratory to the business world. These grants are designed to enable researchers to take this step and transform pioneering research into tangible innovations,"** says Iliana Ivanova, European Commissioner for Innovation, Research, Culture, Education, and Youth.



CNIC AND FUNDACIÓN OCCIDENT HOST A VISITING RESEARCHERS PROGRAMME SCIENTIFIC SYMPOSIUM

The Visiting Researchers programme began in 2008 and enjoys great recognition in the area of scientific research thanks to the work undertaken by the Fundación Occident and the support offered by institutions and organizations to enable progress in the programmes being worked on.

Fundación Occident and CNIC hosted a scientific symposium for the presentation of the preliminary outcomes of Dr Mark Hlatky and Dr Carlos Morillo, the two researchers participating in Fundación Occident's Visiting Researchers Programme. The programme has cemented the scientific relationship between the two organizations, as well as attracting the presence of internationally prestigious researchers to CNIC.

On this occasion, Fundación Occident was represented at the symposium by Laura Halpern, its vice-president, and Susana Codina, the deputy director, in addition to the two visiting researchers Dr Hlatky and Dr Morillo. Representatives of CNIC included Dr Valentín Fuster, Alberto Sanz, Dr Vicente Andrés, Antonio Ureña and Beatriz Ferreiro, in addition to Dr Hlatky's CNIC hosts, Dr Borja Ibáñez and Dr Inés García Lunar, and Dr Morillo's hosts Dr David Filgueiras and Dr José Jalife.

To date, eight scientists have participated in this programme at CNIC. In addition to Mark Hlatky and Carlos Morillo, Guillermo

Oliver, Benedetta Izzi and Raffaele Strippoli, Sandeep V. Pandit, Stuart Pocock and Gabriel Núñez are the other scientists who have benefited from the programme.

Dr Carlos A Morillo is Full Professor at the Department of Cardiovascular Sciences and Senior Clinical Researcher at the Libin Cardiovascular Institute, Calgary University.

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His chief areas of research are related with the design of clinical studies in atrial fibrillation, syncope and treatment and management of Chagas disease. Alongside the CNIC researchers, José Jalife and David Filgueiras, they have researched new ways of treating atrial fibrillation, the most common heart rhythm disorder in the world. Dr Morillo has participated in the Fundación Occident and CNIC Visiting Researchers Programme.

How did you find out about the Fundación Occident and CNIC Visiting Researchers Programme?

Almost by chance. I was participating in a conference on atrial fibrillation, and I bumped into Dr José Jalife, who told me about the programme. The truth is that I already had the idea of taking a sabbatical year. After several years as head of the Cardiology Division at the University of Calgary, Canada, I thought the time had come. Through Dr Jalife and Dr Valentín Fuster, we made a connection and that's how I sent an application to participate in the Visiting Researchers Programme.

What is your opinion of CNIC?

I have been in many institutions worldwide, and I can tell you that CNIC ones are the highest level. The staff are highly qualified, and I have had come into contact with very interesting people. The truth is that the facilities are unique and the best that I've seen. I have interacted with David Filgueiras's group and seen an extraordinary infrastructure, particularly on the experimental side and the animal facilities, with state-of-the-art technology that vastly facilitates research.

What differences do you find between the CNIC and other institutions?

The CNIC is very well structured and organized. Here, the different sections are shared within the same centre, which increases efficiency. In many other institutions, each group has its own laboratory and doesn't share much, which reduces efficiency. Here, integration works really well.

What can you tell us about your work in Canada?

I am at the University of Calgary, in a centre that coordinates the cardiology services for the city. It is also a research institute with different groups working on clinical and basic science. Before Calgary I was at McMaster University in the Population Health Research Institute, which is one of the institutes that generates most clinical studies. But I didn't have the infrastructure we have here at CNIC, where there are well equipped rooms with magnetic resonance and CT machines that make work a lot easier.

What areas of cardiology do you work on?

I am an electrophysiologist, and I mainly work in three research areas: atrial fibrillation, where I design clinical studies on ablation and new anticoagulants; autonomic dysfunction, with a focus on cardio-neuroablation; and Chagas disease, researching new drugs for this heart disease, which is prevalent in Latin America. Although Chagas ins an autochthonous disease of Latin America, calculations are that in Spain, due to migration, there are around 150,000 people with the infection.

I began in basic research when I started my career in electrophysiology in 1990. I discovered the first model of atrial fibrillation and performed the first cryoablations. Based on this model, Dr Jalife made other descriptions of how to locate the circuits that produced atrial fibrillation. Afterwards, I devoted myself more to the clinical sphere, but now, I wanted to return to the roots of research and I'm at CNIC with Pepe [Jalife] and David [Filgueiras] conducting various studies. In one of them we are attempting to design an antibody that acts on a specific channel of the atrium to produce an efficient, safe antiarrhythmic agent. In the last 30 years there have been no significant developments in antiarrhythmic agents; atrial fibrillation affects 40 million people worldwide and we can't perform ablations on all of them. We need effective drugs. Part of what I am doing with the experimental model developed at CNIC is testing these new drugs to see if we can prevent atrial fibrillation and, above all, its progression.

Clinical and basic science...

I think the way in which the development of basic sciences can translate most quickly is when one is also a clinician. Sometimes there are many things done in basic research that stay in the laboratory and almost never translate into practical clinical applications. I have always been interested in trying to bridge the gap in order to accelerate the changes and discoveries and bring them to patients.

How did your interest in Chagas come about?

I became involved in Chagas research in a very curious way: due to my interest in the autonomic nervous system. When I was at the University of Virginia, I was working as an electrophysiologist in Richmond (USA) and a researcher from Colombia contacted me, mentioning he had seen my studies. He said, "I am working on a disease called Chagas, which affects the heart and cardiac nerves." Chagas cardiomyopathy, caused by a parasite, consumes cardiac tissue, particularly conducting tissues. This can cause arrhythmias, sudden death and dilated cardiomyopathy. It is

the most frequent cause of heart failure and sudden death in Latin America.

I was in Colombia, in Bucaramanga, where there is a high incidence of the disease, and I worked on the design of studies to treat this heart disease.

At McMaster University, we designed a study called BENEFIT, the largest study on Chagas, in which we randomized 3,000 patients to receive a drug or a placebo in order to see if the drug could stop or revert the development of heart disease. Unfortunately, the study results were not entirely positive, but it did open the door to conduct other studies.

What's more, Chagas disease has always been a "forgotten" disease: the pharmaceutical industry considers it a poor people's disease and was never interested in developing treatments. After the study, we had contacts with other laboratories to develop new molecules, some of which have worked. I also collaborated with a group called Drugs for Neglected Diseases, a foundation based in Geneva and Brazil, to develop new drugs for disregarded diseases.

At the moment, we are conducting a study with the Novartis Foundation to use drugs that have been utilized for heart failure of ischaemic origin in order to see if they prevent heart failure in Chagas patients, if they prevent progression of the disease and sudden death.

Do you already have data?

We've already included 1,000 patients. Now we need a year or so of monitoring, and in all likelihood at the end of this year or the next we will be presenting our results.

This would be the first specific treatment for Chagas cardiomyopathy?

Yes. Currently there is nothing specifically for it. Conventional treatments are used, but no specific studies have ever been made of this heart disease, which accelerates much more than ischaemic heart disease or dilated cardiomyopathy. Patients with Chagas develop heart failure and die much younger, at an average age of 40 to 50 years, whereas ischaemic heart disease affects people who are 60 to 65.

Chagas has a high disease burden in Latin America. Today, estimates are that between 10 and 15 million people are at risk and don't have a specific treatment. Chagas is endemic in Argentina, Colombia. Brazil, Venezuela (to a lesser degree), Boliva (with many cases) Peru and Central America, particularly Nicaragua, El Salvador and Mexico. Autochthonous cases have also been described in the south of the United States, in Texas.

In some way, the aim is not only to repurpose these drugs, but to see if the drugs that are used for other types of heart disease could be effective against Chagas. These drugs are no longer patent protected, which would make them accessible for health systems.

This the principle of drug repurposing or repositioning. We have used drugs that we know work for other conditions but that have never been proven effective against Chagas.

Have you thought of returning to work in Colombia?

I studied medicine in Colombia, in Bogota, and later went to Canada and studied cardiology and electrophysiology again. I returned to Colombia for 6 years with a repatriation programme for researchers of Colciencias (the then Colombian Administrative Department of Science, Technology and Innovation) a bit like the USA's National Institute of Health. I set up a basic and clinical research group on Chagas and other diseases. Although I returned to Canada, I have always included Colombian centres in my clinical studies, and I have trained many researchers from Latin America, some of whom have returned to their countries to continue their research.

And the other thing I have done is train many people from Colombia and Latin America at McMaster and Calgary, where I trained them in research and methodology before they returned to their countries. Some have stayed in different places in the world, but many have returned to their countries to try to generate continuity in the production of science in their countries of origin.

How do you see the support for science in Colombia?

There is an interest in science and technology, although it depends on the political climate. They have managed to pass a law channelling a percentage of the royalties from petroleum and other resources to science and technology, which has been very important for the country's development in this area.

Doctor Valentín Fuster always talks about the importance of having a critical mass.

I believe that it is a combination of factors, which means that many of us, unfortunately, have ended up abroad, some for personal reasons but many others for infrastructure-related reasons. I think most of us who are abroad have tried to pay back, to remain involved with the generation of science in their country. I think the attitude has changed and that critical mass is being created in Bogotá, Bucaramanga, Barranquilla, Cali, Medellín, let's say in the main cities, and some large towns, where there are researchers who are doing important things in Colombia. Important contributions have been made in the field of Chagas, malaria, dengue fever and other infectious diseases. Specifically in cardiovascular diseases, several researchers have been important figures in various clinical studies that have changed the practice of cardiology worldwide. So I think that we are on the right track.

What are the current generation of scientist like?

This generation is looking for a work life balance. But I also see many dedicated young people at CNIC. I think it depends on the mentor and the example one gives. Although

a balance is important, dedication is also crucial to advance in science.

You come from a family of doctors. How did that influence your career?

I come from a family of doctors: my father was a physician; my grandfather was a physician, and I have three siblings who are physicians, as well as 16 first cousins who are physicians. However, my children did not want to devote themselves to medicine.

I remember one summer day, my eldest daughter said to me, "Daddy, do you think we care how many articles you have published in the New England Journal of Medicine? If I asked you how many articles a famous doctor had, would you know the answer? We don't care about that, we want you to spend time with us, but you never have time for us." I thought about it, and it seems to me that the new generation is looking for a balance between their career and their personal lives. But I come to the CNIC laboratory almost every day and I see young people who are here until 7 or 8 pm. It depends on your mentor, on leading by example. If young people see this, some of them will follow suit, whereas others will have different interests, which is also valid.

In terms of generations, things are changing. My father was a neurologist, and he trained at the NIH with people who had won the Nobel prize, they belonged to another generation. Balance is important because someone who only knows science ultimately knows nothing. You need to be like Renaissance men, like Da Vinci, who painted, knew music and philosophy. Bach, for instance, had 22 children, and was able to write a cantata for each day of the year.

Talking about mentoring, how did you learn to be a good mentor?

In my case, I learned from my father. My father was a neurophysiologist, he had an experimental laboratory and was also a clinician. Every Saturday three or four students would come to the house to eat, and he gave seminars where he spoke of science, but also of music and literature. That's how he created a group of students who later became teachers. I always considered him to have an effective way of mentoring.

Not everyone is made to be a mentor. In the academic sphere, we sometimes encounter difficulties because not everyone can be a mentor or a researcher, and that's okay. Some are excellent clinicians and don't need to be researchers. There is a place for everyone: on a chess board a pawn can be as important as a bishop if the right moves are made. Science is not only sitting down and writing protocols; some people recruit patients for clinical studies and that is also crucial.

Mentoring begins by sitting down with young people, reviewing articles, encouraging them or following their experiments. Of one hundred, maybe ten or fifteen will be researchers. Each career is difficult and managing frustration is important. However, if you have a research structure you will also be a better clinician.

Did you want to be a scientist when you were a child?

We are five siblings, four men and one woman. The three eldest are physicians, my sister is a photographer, and my youngest brother is a photographer and film maker. When we were little, my father would take us to his laboratory, where he had cats and rabbits with electrodes, because he studied the brain, He researched the arcuate nucleus, anger and the reticular formation. I was exposed to all of that from a young age.

The atmosphere reminds me of the book "Memories of My Father" by Héctor Abad Faciolince. It wasn't just science, but also music and literature?

Yes, my father was a very special man who instilled a love of music and literature in us. At dinner time he would say things like, "Today is Greek day." At home we had microscopes and books, and our university classmates came to study. They had great respect for him, he was head of the physiology and pharmacology department and also faculty dean. He taught us with conversations and left books or magazines on our pillows for us to read, and months later would ask us about them.

What do you think of the Fundación Occident Visiting Researchers Programmes?

I think they are excellent. It doesn't matter what stage of your career you are at; you always have to reinvent yourself, particularly in academic and scientific fields. For me, the programme has been like coming home to what I did 30 years ago, in the 1990s, and I love it because it is stimulating and gives me new ideas. Thanks to the Foundation and its programme for senior scientists, we have the opportunity to devote a year to things that we haven't done for a long time to which we can still probably make significant contributions.

Dr. Mark Hlatky: Cardiologist and Professor of Health Policy and Medicine at the University of Stanford

"We respond to emergent problems, but chronic problems like heart diseases don't generate the same urgent response."

Dr Mark Hlatky is a cardiologist and Professor of Health Policy and Medicine at the University of Stanford. His main fields of research are clinical trials and methods of clinical research. Dr Hlatky has participated in numerous major large multi-centre randomized clinical trials, including studies on coronary revascularization, the treatment of acute myocardial infarction, hormone therapy to prevent cardiovascular diseases in women, and the treatment of potentially fatal ventricular arrhythmias. He pioneered the compilation of data on economic results and quality of life as a part of randomized trials, which has become a standard tool for researching outcomes. He has also developed decision models to assess the effectiveness and profitability of a wide range of clinical strategies, such as the prevention of sudden cardiac death, the use of tests to guide the preventive treatment of heart diseases, etc. During his period at CNIC, alongside researchers Borja Ibáñez and Inés García, he studied the effects of pregnancy on the cardiovascular health of women.

How did you find out about the Fundación Occident and CNIC Visiting Researchers Programme?

I am Professor at the University of Stanford, and I belong to the Departments of Health Policy and Cardiovascular Medicine. My research focusses on populational clinical studies, assessing whether treatments work, who they work for and if they are worth the investment made. For many years I was associate editor of the Journal of the American College of Cardiology, first with Tony Demaria and then with Dr Valentín Fuster. I attended meetings every week with Dr Fuster and Dr Borja Ibáñez. And my area of research is related with their interests. At Stanford you can take a sabbatical to think about new ideas and meet more people. It isn't obligatory, it is optional. I had accumulated the maximum amount of time: 12 months. And my wife said, Spain, since she has Spanish heritage, and she likes the country. I spoke to Dr Fuster and Dr Ibáñez, and they said yes that they would welcome me.

Had you participated in similar exchange programmes before?

I had taken sabbaticals in Oxford (UK), Bologna (Italy) and Copenhagen (Denmark). Meeting different people, learning new ideas and collaborating in different ways is very valuable. Dr Fuster talked to me about the Fundación Occident programme. I wrote a proposal, and they asked me what I wanted to work on. At Stanford, we are interested in learning the specific reasons why women develop heart diseases. We observed that problems like preeclampsia during pregnancy increase the risk of future heart diseases. This project involves examining the biomarkers of women with and without a history of preeclampsia in Stanford and Denmark.

And, on hearing about the PESA-CNIC-Santander project, we thought of analysing the female participants to see how factors of pregnancy affect their risk of atherosclerosis. We proposed observing complications of pregnancy and other unique reproductive risk factors in women from the PESA group.

Your work also focusses on the cost-effectiveness of treatments...

Financial assessments are not common in Europe. We assess whether the prices of drugs are in consonance with their effectiveness. A new treatment for cardiac amyloidosis, for instance, is very expensive. In the USA, I work on health policies, ensuring that drugs justify their cost. We want businesses to have incentives to develop drugs and obtain a reasonable, but not excessive, financial recompense. Part of the research has been financed with public funds. That is more a political than a scientific problem. We want better treatments, but many new treatments reach only a few people due to the high cost.

Do you think that the pandemic has taught us to work together on developing treatments?

The pandemic showed that governments and the private sector can collaborate during an emergency. However, we don't see the same urgency for heart diseases or cancer.

Cardiovascular diseases are the first cause of death worldwide, isn't that a pandemic?

Although it is a good message, not everyone understands it the same way. We respond to emergent problems, but chronic problems like heart diseases or death from weapons don't generate the same urgent response.

You mention mentoring, how important is it for young societies?

Mentoring is crucial to learn, conduct research and connect with people who can help you in your career. Mentors help you understand what is good for a career and offer valuable connections. They also provide support for personal problems like how to achieve a work-life balance.

A career in research means you have to leave the environment you know. Is there a fear of returning?

I have spoken to many people at CNIC who have spent time in the USA. Training in the USA is a plus because you are a different person when you return. Leaving serves to learn new things. I myself am doing it with the Fundación Jesús Serra Visiting Researchers Programme. Going to study at other institutions and then returning is very positive. In Denmark, there is a programme where medical students go to the USA to work in laboratories with mentors, called DARE. I worked with a couple of its students, and it was a great programme because they had access to things that they would never have seen, like meetings with Silicon Valley professionals. The Danish government and foundations sponsored it because they said it was a good investment for Danish researchers. It is a great opportunity to learn and access unique experiences.

Have you seen differences between a career in research in Spain and the USA?

In Europe, there are fewer positions, especially in universities and academic centres. In the USA, it is more competitive and there is more movement; people study in one place and move to another more easily than in Europe.

Benin University

Beatrice Olatundun Oluwatayo:

RESEARCH AT CNIC IS VERY INCLUSIVE; IT COVERS ALL AREAS

The researcher Beatrice Olatundun Oluwatayo, with a PhD from the University of Benin, and a master's in human physiology from the University of Jos, Nigeria, is the first female scientist from Africa to receive a grant from the Women for Africa Foundation and CNIC (through the Severo Ochoa Project) for a fellowship at CNIC. Dr Olatundun Oluwatayo is an experienced full professor and academic vice-rector at the Federal College of Veterinary and Medical Laboratory Technology (FCVMLT) as well as visiting full professor at the Department of Physiology of Madonna University (MAU) and associate dean of the Faculty of Basic Medical Sciences (MAU). She is also a member of various professional organizations like the Association of Medical Laboratory Scientists of Nigeria and the Physiological Society of Nigeria (PSN) among others. Thanks to the Women for Africa Foundation and the Spanish National Centre for Cardiovascular Research (CNIC) (through the Severo Ochoa Project) she has developed the "Gender difference in cardiovascular health among adolescents" Project at CNIC.

How would you evaluate your experience at CNIC?

My experience at CNIC has been very good. When I applied for the grant at CNIC I knew nothing of the centre's great potential in research. But when I arrived, I was impressed. It isn't just a centre devoted to experimental research; its research seeks solutions to real problems. I also discovered that research at CNIC is very inclusive; it covers all areas. We talk about translational research, biology, genetic engineering, everything is covered, particularly anything related to the heart. For me, as a haematologist, blood is vital, and the heart is the engine that pumps blood around the body. If the heart fails, the whole body stops functioning. That's why I see CNIC as a centre of excellence in cardiovascular research that is vital for human existence.

What is the focus of your project?

The initial focus of my project in the cardiovascular area was analysing the effects of alcohol on the cardiovascular system among the adult population. However, when I joined CNIC I discovered that the group I had joined, led by Dr Rodrigo Fernández Jiménez, was working on adolescents. That is important because many future diseases begin in adolescence, or even in infancy. Since I have

If it weren't for the support of the Women for Africa Foundation, I would not have had the opportunity to come to CNIC and participate in this research, which has opened up many valuable aspects to me that I will replicate with my students and young colleagues in Nigeria

worked with adolescents for much of my career, I thought it a suitable approach. We are currently focussing on gender differences in the cardiovascular health of adolescents. We have already progressed in data analysis, and we are at the phase of writing up the results.

Will you continue with the research and your relationship with CNIC when you return to your country ?

Yes, I'll continue working with the group. Although we won't have published the results yet, we keep in touch. While I was at CNIC, I also organized my team in Nigeria to collect data on my initial objective related with alcohol. Although I don't have the license to use the statistical software in Nigeria yet, I have been able to attend capacity building courses and conferences like that of the European Haematology Association, thanks to the support of the Women for Africa Foundation.

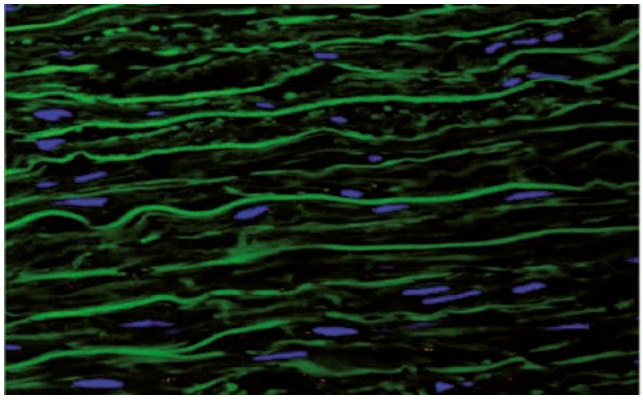
How do you think the experience acquired here will impact on the Nigerian population and the research?

I asked my team in Nigeria to collect data for analysis with the knowledge acquired at CNIC and continue the work when I return. My objective is to replicate the research in Nigeria and find funding to do so. As a researcher, I went into academic management too early. As a university teacher, when I took on administrative roles, I didn't have much time left for research. And also, when I finished my doctorate, I was older, and as I wanted to apply for a post-doc, I realized that age was a hurdle, which discouraged me and took me back to focus on administrative work. However, I have conducted some research, although the lack of funding has always been an obstacle. To advance in research like that being done at CNIC we need funding.

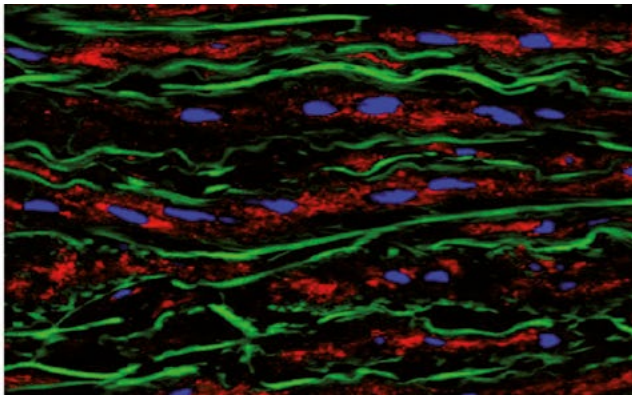
EXCELLENCE IN COMMUNICATION SCIENCE, THE MAIN SCIENTIFIC JOURNALS PUBLISH RESEARCH FROM THE CNIC LABORATORIES.

EMBO Molecular Medicine: Accumulation of the protein versican is the cause of aortic aneurysm in Marfan syndrome

HEALTHY AORTA



PATIENT'S AORTA



A team of Spanish scientists has identified the cause of aortic aneurysm in patients diagnosed with Marfan syndrome, a genetic disorder currently lacking treatment options. The study, published in the journal EMBO Molecular Medicine, was conducted by researchers at the CNIC, in collaboration with partners at the Centro de Biología Molecular Severo Ochoa (CBMSO, CSIC).

The study, led by CBMSO scientists Juan Miguel Redondo and Miguel R. Campanero, reports an accumulation of a proteoglycan called versican—a large protein present in the extracellular matrix between cells—in the aortas of patients with Marfan syndrome and of mice genetically engineered to develop the disease, known as Marfan mice.

The new discovery identifies versican accumulation as a cause of the aortic aneurysms suffered by Marfan syndrome patients. The study also identifies the signaling pathway mediated by protein kinase B, known as AKT, as a possible target for treating aortic disease in Marfan syndrome.

These results represent an important advance in the understanding and of the aortic disease associated with Marfan syndrome. An aortic aneurysm is an enlargement of the aorta caused by a weakening of its wall. Although initially asymptomatic, aortic aneurysm can lead to serious complications such as dissection or rupture of the aortic wall, which can be fatal. "Marfan syndrome is a genetic disorder affecting connective tissue, and thoracic aneurysm and aortic dissection [TAAD] is the main cause of death in these patients," explained Redondo. The study also shows that decreasing versican expression by gene silencing reduces the expression of Nos2 and completely reverses aortic disease in Marfan mice.

The identification of AKT as a possible therapeutic target for the aortic pathology in Marfan syndrome is a very promising finding that could help in the development of new treatments for this disease.

The study was supported by grants from the Marfan Foundation, the MERCK Foundation-Spanish Foundation for Rare Diseases 2022, and the V-Ayudas "Muévete por los que no pueden 2021" program, as well as professional training contracts from the Spanish Ministry of Science and Innovation.

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Science Advances: First therapeutic target for preserving heart function in patients with pulmonary hypertension

A team led by Dr. Guadalupe Sabio at the CNIC has discovered a possible therapeutic target for pulmonary hypertension. The study, published in the journal 'Science Advances', identifies the first therapeutic target that can be modulated to preserve cardiac function in pulmonary hypertension, providing hope in the fight against this rare but fatal disease for which there is currently no cure.

Pulmonary hypertension is a condition of elevated blood pressure in the arteries that carry deoxygenated blood to the lungs. This increased pulmonary blood pressure puts the heart under continuous strain as it has to work harder to pump blood to the lungs.

Pulmonary hypertension affects between 15 and 50 people per million of the world population. In Spain, the estimated prevalence is 1.6 cases per 100,000 inhabitants, and the estimated incidence (new cases diagnosed per year) is 0.3 per 100,000 inhabitants.

Currently available treatments target the lungs, aiming to lower blood pressure. However, these strategies do not improve cardiac function, making heart failure the main cause of death in these patients.

The CNIC researchers found that patients with chronic obstructive pulmonary disease (COPD) have elevated levels of a mitochondrial protein called MCJ.

The study results demonstrate that modulating the levels of MCJ in the heart can preserve cardiac function despite the presence of lung injury.

The study was supported by grants from Ministerio de Ciencia e Innovación (RED2022-134397-T, MINECO-PID2019-104399RB-I00, PGC2018-097019-B-I00), IMPACT-2021 PROJECT (PMP21/00057), Fundación Jesús Serra, EFSD/Lilly European Diabetes Research Programme, Fundación BBVA, Comunidad de Madrid and AECC.

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Circulation Research: APOE genetic variants linked to Alzheimer disease are also associated with the

IScientists at the CNIC have found that one of the most potent genetic risk factors for Alzheimer disease, apolipoprotein E4 (APOE4), is also associated with an increased risk of developing subclinical atherosclerosis in middle age. The study also demonstrates protection against subclinical atherosclerosis in people carrying the variant APOE2, which protects against Alzheimer disease.

The APOE gene encodes apolipoprotein E, which, among other important functions, contributes to the transport of lipids in the blood. There are three main APOE alleles, which give rise to three apolipoprotein isoforms: APOE2, APOE3, and APOE4. "Inheriting one or other of these alleles confers a different risk of developing distinct diseases, among them cardiovascular disease and Alzheimer disease," explained Dr. Cortés Canteli, a neuroscientist at the CNIC and a Miguel Servet fellow at the Fundación Jiménez Díaz University Hospital Health Research Institute.

In the new study, the CNIC team demonstrates that APOE4 carriers among the middle-aged participants in the PESA-CNIC-Santander study (aged 40–54 years) have elevated levels of circulating LDL cholesterol ('bad' cholesterol), which increases their risk of developing subclinical atherosclerosis. This finding provides a window of opportunity for implementing early intervention strategies.

The study also shows that carriers of the APOE2 variant have comparatively less subclinical atherosclerosis in the carotid, femoral, and coronary arteries. This protection

is due to these individuals having normal levels of triglycerides or, in the case of women and individuals in the youngest age category (40–44 years), comparatively low levels of circulating LDL cholesterol. "These findings underline, once more, the importance of a healthy lifestyle," stressed Dr. Fuster, who combines his role at the CNIC with those of President of the Cardiovascular Institute and Physician-in-Chief at Mount Sinai Medical Center in New York. The present study received funding from the European Regional Development Fund (EDRF–A way to build Europe) and the European Social Fund (ESF–Investing in your future).

The PESA study is cofinanced equally by the CNIC and Santander Bank. The study also receives financial support from the ISCIII (PI15/02019, PI17/00590 & PI20/00819) and for the present study in particular has received funding from the BrightFocus Foundation. The present study involved the participation of investigators from the Spanish research networks for cardiovascular biomedicine (CiberCV) and rare diseases (CiberRER).

The research was funded by the European Research Council (No 866240, JFB), the Ministry of Science and Innovation (PID2019-108568RB-I00, JFB), and the Novo Nordisk Foundation in Denmark (NNF17OC0030688, JFB).

Cholesterol lowering depletes atherosclerotic lesions of smooth muscle cell-derived fibromyocytes and chondromyocytes: Laura Carramolino, Julián Albarrán-Juárez, Anton Markov, ..., Ana Dopazo, Fátima Sanchez-Cabo, Carlos Torroja, Jacob F. Bentzon. Nat. CV. Research. https://dx.doi.org/10.1038/s44161-023-00412-w

Nature Cardiovascular Research: New approach to the design of therapies that enhance the effect of cholesterol-lowering drugs

A research team from the CNIC in Madrid, in collaboration with Aarhus University in Denmark, has uncovered a crucial mechanism that leads to the regression, or shrinkage, of atherosclerotic plaques. This discovery, published in Nature Cardiovascular Research, highlights smooth muscle cell-derived cells in the arterial wall as a promising target for future therapies aimed at reducing plaque growth in advanced atherosclerosis.

The mechanism identified involves inflammatory signaling within a subset of smooth muscle cells responsible for the development of atherosclerotic plaques. Jacob F. Bentzon, leader of the research teams at both institutions, pointed out that this discovery could lead to targeted therapies that enhance the effectiveness of cholesterol-lowering drugs and improve plaque regression in patients with advanced cardiovascular disease.

Smooth muscle cells, which are a core part of the arterial wall, play a key role in the progression of cardiovascular diseases such as heart attack and stroke. Their proliferation and transformation during atherosclerosis contribute significantly to these disorders.

High blood cholesterol is the main cause of atherosclerosis, and lifestyle changes or medications like statins are effective ways to prevent the condition. In patients with advanced atherosclerosis, reducing cholesterol levels lowers the risk of irreversible plaque formation, but the precise mechanisms behind this reduction have not been fully understood.

The study demonstrates that, when cholesterol levels are lowered in mice with advanced atherosclerosis, certain harmful smooth muscle-derived cells in the plaques diminish, while beneficial cells that stabilize the plaques remain. This finding, highlighted by Laura Carramolino, the first author, points to the potential for more effective therapeutic strategies targeting these cells to prevent severe outcomes like heart attacks or strokes.

The research was funded by the European Research Council (No 866240, JFB), the Ministry of Science and Innovation (PID2019-108568RB-I00, JFB), and the Novo Nordisk Foundation in Denmark (NNF17OC0030688, JFB).

Cholesterol lowering depletes atherosclerotic lesions of smooth muscle cell-derived fibromyocytes and chondromyocytes: Laura Carramolino, Julián Albarrán-Juárez, Anton Markov, ..., Ana Dopazo, Fátima Sanchez-Cabo, Carlos Torroja, Jacob F. Bentzon. Nat. CV. Research. https://dx.doi.org/10.1038/s44161-023-00412-w

Circulation Research: New mechanism discovered for the life-threatening arrhythmias in Andersen-Tawil syndrome

A team at the CNIC, led by Dr. José Jalife, has made a significant breakthrough in understanding the genetic basis of cardiac arrhythmias, particularly related to the rare Andersen-Tawil syndrome (ATS). Their research, published in Circulation Research, reveals how a specific genetic mutation (C122Y) in the Kir2.1 potassium channel not only disrupts the function of Kir2.1 itself but also impairs the main cardiac sodium channel, NaV1.5. This discovery establishes a direct link between the mutation and the life-threatening arrhythmias characteristic of ATS1. The study shows that the C122Y mutation in the Kir2.1 channel has a dual impact: it causes a reorganization of Kir2.1 that weakens its binding to the phospholipid PIP2, an essential component for cellular signaling in the membrane, while also disrupting the stability and expression of the NaV1.5 protein. Both Kir2.1 and NaV1.5 are critical for maintaining proper heart rhythm, and disturbances in either channel can trigger severe arrhythmias. Although cardiac arrhythmia is a common condition, affecting about 1 in 3 people at some point in their life, ATS is extremely rare, with fewer than 1 in a million affected. ATS1 is caused by mutations in the KCNJ2 gene, which encodes the Kir2.1 channel. Patients with ATS1 experience a unique combination of symptoms, including periodic paralysis, arrhythmias, and distinctive facial features. The disorder is inherited in an autosomal dominant manner.

Using a mouse model that replicates the electrical abnormalities seen in ATS1 patients, the researchers found that the mutation not only impacts the Kir2.1 channel but also interferes with the function of the NaV1.5 channel, essential for cardiac excitability. This disruption of two key ion channels helps explain the severe arrhythmias observed in ATS1 patients.

This discovery represents a critical step forward in improving clinical approaches to arrhythmias, offering hope for more effective, individualized treatments that could benefit millions of people worldwide. The study was funded by the National Heart, Lung, and Blood Institute of the NIH (USA); the la Caixa Foundation; the La Marató de TV3 Foundation; the Spanish cardiovascular research network (CIBERCV); the Horizon 2020 Programme of the European Union; and Program S2022/BMD7229. The imaging studies were performed at the TRIMA@CNIC node of the Distributed Biomedical Imaging Network (ICTS ReDIB).

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JACC: CardioOncology: CNIC scientists identify therapeutic targets for the prevention of heart injury linked to cancer treatment

Scientists at the CNIC have identified the mechanisms through which anthracyclines, a widely used class of anticancer drugs, damage the hearts of patients receiving this treatment. The study, published in the journal JACC: CardioOncology, also identifies possible treatments for this complication, which affects an estimated one third of cancer survivors. Over 4 million Europeans are diagnosed with cancer annually, and while survival rates have improved, treatments like anthracyclines, used in about 3 million patients, pose significant risks. These drugs are cardiotoxic, with one-third of patients experiencing heart damage. In more than 5% of survivors, this leads to chronic heart failure, severely impacting their quality of life. Despite this, no specific treatments to protect the heart have been developed, due to limited understanding of how anthracyclines cause cardiac injury.

Researchers at the CNIC, led by Dr. Borja Ibáñez, have identified how anthracycline chemotherapy damages the heart by disrupting cardiac metabolism, with a focus on mitochondrial dysfunction. Their detailed analysis in an experimental animal model revealed that anthracyclines cause early and irreversible changes in the heart's energy supply from fatty acids and glucose, leading to impaired energy production in the mitochondria. These metabolic alterations occur early in treatment, well before any visible loss of heart contractile function, and result in the atrophy of heart cells as an early sign of irreversible damage. This discovery is crucial because the metabolic changes can be detected long before traditional methods reveal heart damage. By understanding the molecular alterations behind this process, the researchers identified potential points where early intervention could prevent damage. One promising approach under investigation involves a protein-enriched diet to prevent muscle atrophy, including cardiac muscle, caused by anthracycline treatment.

The CNIC is committed to finding solutions to unresolved clinical needs and, within its Programa de Homeostasis Miocárdica y Daño Cardiaco, has set up a research line dedicated to chemotherapy-associated cardiotoxicity, with a particular focus on anthracyclines. The goal is to develop

treatments that maintain the efficacy of the anticancer treatment while minimizing negative impacts on cardiovascular health. Dr. Ibañez's research group also coordinates projects financed by the European Commission (ERC-Consolidator "MATRIX", y Horizon2020-HEALTH "RESILIENCE"), both aimed at reducing the prevalence of heart failure among cancer survivors. Imbued with a translational and multidisciplinary vision, these projects are being conducted through partnerships between the CNIC, Fundación Jiménez Díaz University Hospital, and the CIBERCV.

The current study received support from the European Commission (ERC-CoG 819775 and H2020-HEALTH 945118), the Spanish Ministry of Science, Innovation, and Universities (PID2022-140176OB-I00), and the Community of Madrid regional government through the Madrid Network for Nanomedicine in Molecular Imaging (P2022/BMD-7403 RENIM-CM).

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JACC: A new Spanish study provides the first stratification of the risk of developing dilated cardiomyopathy among symptom-free genetic carriers

Dilated cardiomyopathy is the leading cause of heart failure in young people and a major reason for heart transplants. This condition causes the heart to enlarge and lose its ability to effectively pump blood, putting patients at high risk for arrhythmias and sudden death. In 30%–40% of cases, the disease is linked to genetic mutations, and identifying these mutations allows doctors to screen family members for the altered gene.

Family members who carry the mutation are at risk of developing the disease, making regular check-ups crucial for early detection and treatment. However, it remains unclear whether all carriers will develop the disease, at what age this is more likely, and which factors could predict disease onset in the short term, highlighting the need for more precise monitoring strategies. The new study, led by Dr. Pablo García-Pavía, a researcher at the CNIC, a group leader in the Spanish cardiovascular research network (CIBERCV), and a cardiologist at Hospital Puerta de Hierro, provides the first stratification of the risk of developing dilated cardiomyopathy among symptom-free genetic carriers of the disease.

A total of 25 Spanish hospitals participated in the study, which is published in the Journal of the American College of Cardiology. Data were collected from more than 779 genetic carriers, from 300 families, who had shown no signs of the disease before entering the study. The study also showed that the appearance of the disease was dependent on the specific type of genetic mutation present. The study was supported by the Sociedad Española de Cardiología (a Hereditary Cardiac Disease grant awarded in 2022) and the Instituto de Salud Carlos III through projects PI18/0004 and PI20/0320 (cofounded by the European Regional Development Fund/European Social Fund "A way to build Europe"/"Investing in your Future")

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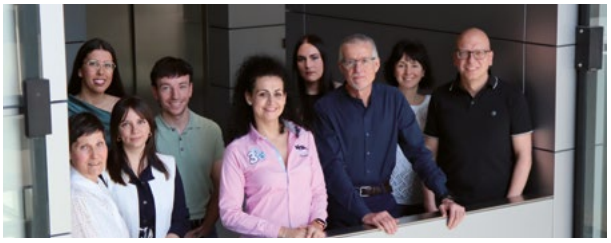
PNAS: CNIC scientists identify the key cell type for strategies to prevent atherosclerosis in progeria syndrome

Hutchinson-Gilford progeria syndrome (HGPS) is an extremely rare genetic disease that causes accelerated aging, severe atherosclerosis, and premature death at an average age of 15 years. Despite the absence of typical cardiovascular risk factors, premature atherosclerosis is the leading cause of death. HGPS is caused by a mutation in the LMNA gene that produces progerin, a harmful version of the lamin A protein.

Recent research has shown that gene editing can correct this mutation, eliminating progerin and restoring lamin A, which improves symptoms and extends life in animal models. A study published in PNAS investigated the effectiveness of removing progerin in endothelial cells and vascular smooth muscle cells, two key cell types in atherosclerosis. The results indicated that removing progerin in endothelial cells did not provide benefits, while its removal in vascular smooth muscle cells significantly reduced atherosclerosis and other complications. These findings suggest that targeting gene therapy to vascular smooth muscle cells could be sufficient to treat HGPS-related atherosclerosis, potentially using lower doses of gene-editing reagents.

The study was funded by the Ministerio de Ciencia, Innovación y Universidades (MICIU)/Agencia Estatal de Investigación (AEI)/10.13039/501100011033 and ERDF/EU (grants



PID2022-141211OB-I00 and PID2022-137111OA-I00); the Comunidad Autónoma de Madrid (grants 2017-T1/BMD-5247 and 2021-5A/BMD-20944) cofinanced with European structural and investment funds; RYC2021-033805-I (MICIU/AEI/10.13039/501100011033 and European Union NextGenerationEU/PRTR); the Ministerio de Educación, Cultura y Deporte; Fundación "la Caixa"; and the Wellcome Trust. The CNIC receives institution-level support from the Instituto de Salud Carlos III (ISCIII), the MICIU, and the Pro-CNIC Foundation, and is a Severo Ochoa Center of Excellence (award CEX2020-001041-S funded by MICIU/AEI/10.13039/501100011033).

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Development Cell: A CNIC study reveals the key role of mitochondrial proteins in cardiac regeneration

A study by CNIC and the University of Bern has revealed new insights into the role of mitochondria in heart regeneration. Published in Development Cell, the research, led by Dr. José Antonio Enríquez and Dr. Nadia Mercader, identifies the cox7a protein family as crucial for the assembly of complex IV (CIV) in the mitochondrial respiratory chain, which is essential for cellular energy production.

The research focused on three members of this family: Cox7a1, Cox7a2, and Cox7a2l (SCAF1). The scientists found that Cox7a1 is key to forming CIV dimers. Using a zebrafish model, they observed that the absence of Cox7a1 negatively affected body weight and swimming ability, but also enhanced the heart's regenerative response after cardiac injury. The study showed that the loss of Cox7a1 in the heart improves its recovery capacity after damage, suggesting that these proteins influence cardiac regeneration. Additionally, significant metabolic changes were identified in the muscles of fish lacking Cox7a1, which could have implications for the treatment of heart and metabolic diseases. This finding represents a major advance in understanding heart regeneration and suggests that mitochondrial assembly proteins may play a key role in controlling cellular metabolism. The study was supported by the European Union Horizon 2020 programme (grants 874764 and 819717), the Human Frontier Science Program (grant RGP0016/2018), and the Swiss National Science Foundation (grant 320030E-164245).

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Nucleic Acids Research: Un equipo del CNIC crea una innovadora herramienta para estudiar la función de los genes de forma más segura y eficaz

ped a new genetic tool called iSuRe-HadCre, which improves the precision and reliability of genetic alterations in tissues or individual cells. Published in Nucleic Acids Research, this technology overcomes the limitations of the Cre-Lox system, which has been traditionally used for gene function analysis.

The Cre-Lox system has been essential in biomedical research due to its ability to manipulate gene expression in a spatial and temporal manner. However, it presents issues such as variability in recombination efficiency and the need for costly controls to ensure proper experimental execution. The new iSuRe-HadCre tool uses an inducible double-recombinase genetic cascade that ensures cells with a fluorescent marker have experienced high Cre activity but no longer maintain it. This allows for precise genetic alterations and eliminates the toxicity and sporadic recombinations associated with constant Cre expression. Additionally, iSuRe-HadCre is more sensitive to induction by CreERT2 and tamoxifen.

Rui Benedito emphasizes that iSuRe-HadCre is a key tool for advanced genetic studies, including high-resolution microscopy, functional analyses, and genetic epistasis studies, allowing for simultaneous genetic modifications with high efficiency. The study was funded by the Ministerio de Ciencia e Innovación, "la Caixa" Foundation, the European Research Council, the Leducq Foundation, the Knut and Alice Wallenberg Foundation, and the Göran Gustafsson Foundation.

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PRIZES

Dr Valentín Fuster receives the AstraZeneca Foundation Honorific Award for Excellence in Scientific Research.

The AstraZeneca Foundation gave its **Honorific Award for Excellence in Scientific Research of the VII Young Researcher Awards to Valentín Fuster**, for his outstanding career as a researcher in the field of cardiology. The award is worth 50,000 euros that will serve to continue contributing to research in the field of cardiovascular medicine.

Rodrigo Fernández Jiménez receives the Gabriella Morreale National Youth Research Award

The CNIC researcher Rodrigo Fernández Jiménez received the Gabriella Morreale National Youth Research Award in the area of Medicine and Health Sciences. The National Research Awards recognise the merit of researchers with Spanish nationality who perform outstanding work in scientific fields of international importance, and who make a significant contribution to the advance of scientific knowledge and the progress of humankind.

Dr José Jalife named Doctor Honoris Causa in Sciences by the Upstate Medical University of Syracuse.

Dr José Jalife, Group Leader of Heart Arrhythmias at the Spanish National Centre for Cardiovascular Research (CNIC) was named Doctor Honoris Causa by the State University of New York, Upstate Medical University of Syracuse, NY (USA).

Dr Valentín Fuster receives the prestigious Lifetime Achievement Award of the World Heart Federation (WHF).

The World Heart Federation (WHF) presented Dr Valentín Fuster with its Lifetime Achievement Award 2024. The award acknowledges his notable contributions in the field of cardiovascular disease and his particular devotion to combating this disease around the world. The prestigious award recognises the international leadership Dr Fuster has displayed over the last four decades and his ground-breaking contributions to cardiovascular medicine, both in the field of research and from the clinical perspective and, more recently as champion of cardiovascular health worldwide.

Dr Cintia Folgueira Cobos receives the Rising Star Award 2024

The European Foundation for the Study of Diabetes (EFST) Rising Star 2024 awarded the CNIC postdoctoral researcher, Dr Cintia Folgueira Cobos a grant of 30.000 euros. Dr Folgueira Cobos had previously obtained the EFSD Lilly Research Fellowship Programme 2022 grant of 50,000 euros. The Fundación IBSA for scientific research also awarded Dr Cintia Folgueira Cobos a grant of

32,000 euros in the area of endocrinology for her project "Exploring new insights into brown adipose tissue mitochondria for protection against endocrine disorders." The aim of the Fundación IBSA is to support talented young researchers under the age of 40 and significant projects in different areas of clinical basic research that could change the treatment of various diseases in the future.

Dr Fuster receives the Medal of the European Society for Clinical Investigation

The European Society for Clinical Investigation (ESCI) awarded the Albert Struyveberg Medal to Dr Valentín Fuster. With this prize the ESCI acknowledges Dr Fuster's valuable contribution to cardiology worldwide.

JACC rewards a CNIC researcher for a PESA-CNIC-SANTANDER study.

The researcher Guiomar Mendieta has received the 2023 William W Parmley Young Author Achievement Award for her work "Determinants of Progression and Regression of Subclinical Atherosclerosis over 6 Years", which was published in the Journal of the American College of Cardiology (JACC) in November 2023 and was led by Doctors Valentín Fuster and Borja Ibáñez. The William W Parmley award, in honour of Dr William W Parmley, ex-editor in chief of the JACC, rewards works published in the JACC whose principal authors are completing their sub-specialization in cardiology and/or are doctoral candidates.

CNIC receives a donation to investigate Hutchinson–Gilford progeria syndrome

The Molecular and Genetic Cardiovascular Pathophysiology Laboratory headed by Dr Vicente Andrés at CNIC received a donation of 11,060 euros from the Alexandra Peraut Progeria Association for its research project into the Hutchinson–Gilford progeria syndrome (HGPS), an ultra-rare genetic disease that affects 1 in every 20 million people.

GRANTS, ACTIVITIES & VISITS

sVisit of the Director of Carlos III Health Institute, Dr Marina Pollán, to CNIC

The Director of Carlos III Health Institute, Dr Marina Pollán, visited CNIC along with Agustín González, Subdirector General of networks and research centres that cooperate with the Carlos III Health Institute. During her visit, Dr Pollán held a meeting with Dr Valentín Fuster, Director General of CNIC; Alberto Sanz, Managing Director of CNIC; Dr Borja Ibáñez, CNIC Scientific Director and Clinical Research Director; Dr Vicente Andrés, CNIC Director of Basic Research, and Icíar Areilza, General Secretary of the Fundación Pro CNIC.

CNIC participates in the Foro Transfiere, the main meeting on Science, Technology and Innovation in the south of Europe

CNIC participated in the 13th European Meeting on Science Technology and Innovation. Known as Foro Transfiere, this is the main meeting for R+D in the south of Europe and its aim is to share scientific and technological knowledge, promote innovation, connect science and business, and facilitate the transfer of knowledge so that scientific and technological developments reach people's daily lives. The Foro Transfiere is co-organized by the Ministry of Science and Innovation, the Andalusian Regional Government and Malaga City Council.

International Women's Day 2024 @ CNIC

CNIC held a symposium on the 8th of March to highlight the inspirational example of our female researchers. The event "Women scientists from around the world at CNIC" was held with the participation of five female international researchers who conduct their investigative work at our centre: Valeria Caiolfa, Italy; Beatrice Oluwatayo, Nigeria; Gillian Dunphy, United Kingdom; Jyothi K C, India and Henar Cuervo, Spain. The researchers talked to the attendees about aspects such as what a career in science is like for women abroad, the differences between countries and cultures, maternity during a career in research and their research at CNIC among other topics.

This activity forms part of funding CEX2020-001041-S given by MCIN/AEI /10.13039/501100011033.

International Day of Women and Girls in Science at CNIC

In Spain, only 16% of STEM professionals are women. On the International Day of Women and Girls in Science, we prepared an activity to attempt to encourage vocation by examples of real women who work at CNIC.

Training Programme for 4-ESO Students

CNIC again participated in the Community of Madrid Programme 4-ESO+Business, opening its doors for educational placements for interested students from public or subsidized schools to bring the educational system closer to the world of work in cardiovascular scientific research and offer them the opportunity to come into contact and collaborate with experts in cardiovascular research. The aim of these placements is to bring science closer to young people, awakening and fostering an investigative spirit among students who may become the next generation of cardiovascular researchers.

Fundación Inocente Gala

The Fundación Inocente, Inocente held its Gala at CNIC headquarters, during which the foundation presented awards of aid to organizations that work with children suffering from rare diseases in Spain.

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