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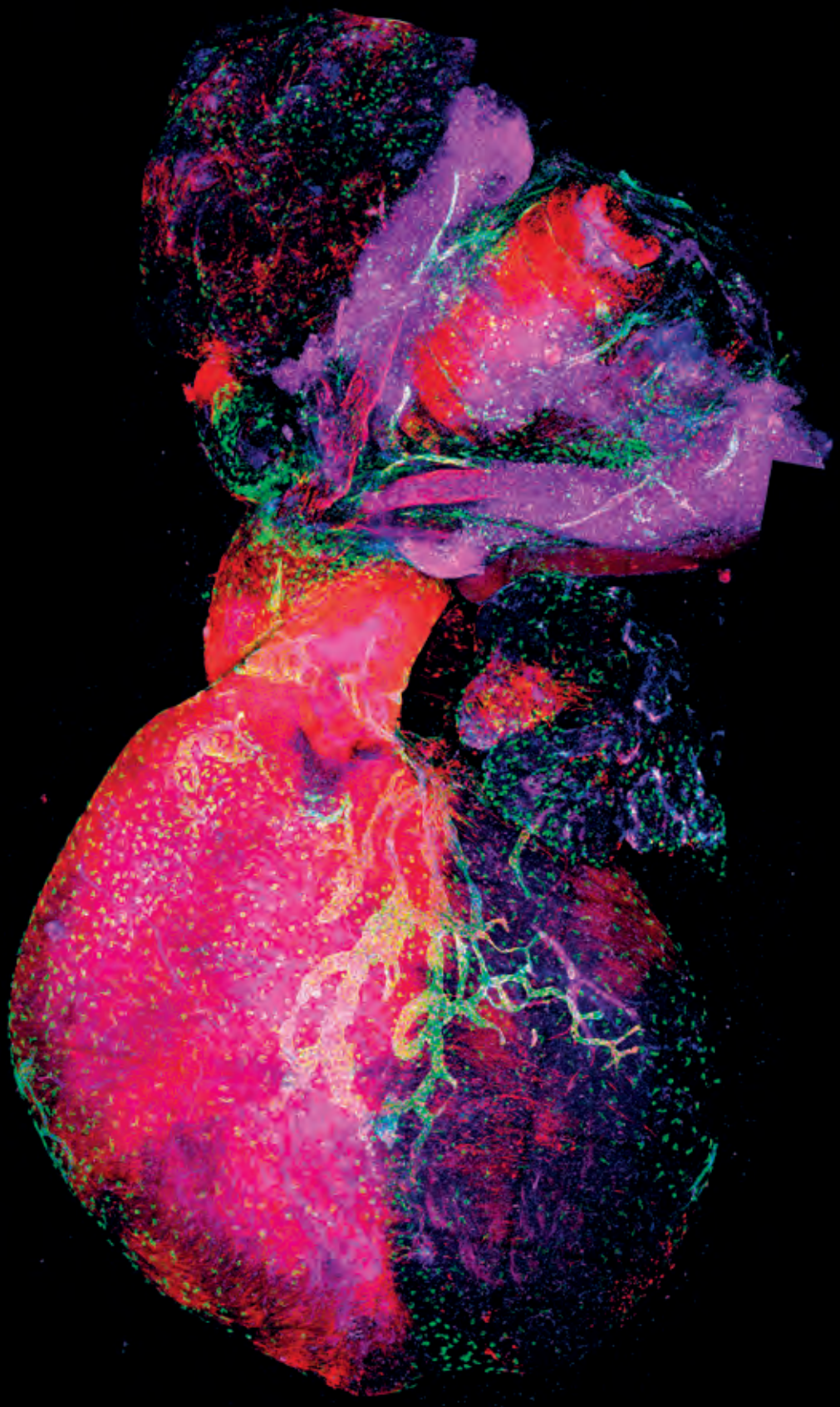

TRAIN2GAIN

WHAT'S ON

INSIDE SCIENCE

CNIC & SOCIETY

SUMMARY

cnic PULSE NUMBER 10

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Dr. Valentín Fuster
General Director of the Carlos III National Center for Cardiovascular Research

Professor Margarita Salas is right

"In order to be lucky you have to be working, even though work doesn't always guarantee luck." This was said by one of the best researchers that science has had in Spain, Professor Margarita Salas, who passed away last year. Professor Salas was an example of what excellent scientific research should be: work, effort and, of course, talent. Because we must not forget that, in Spain, especially at the time she started her career, researchers were like aliens and research something out of this world.

A lot of time has gone by since then and the situation has improved considerably. But right now is the moment, after a few 'complicated' years, to start taking care of the people, the researchers, who are essential to get back on the path of 'excellence'. Dr. Raquel Yotti, Director of the Carlos III Health Institute, is very aware of the relevance of caring for and promoting the scientific network in our country. But not only inside our research centers, but also from the hospitals, something that we have been promoting from the CNIC, since the moment of its creation, through different collaborations and agreements with hospitals throughout Spain and with scientific societies, such as the Spanish Society of Cardiology.

Ensuring that we do not continue losing scientific fabric in health centers of the health care system and that, in addition, we are able to create it is one of the challenges that the Director of ISCIII is addressing. For which she is going to provide the necessary resources through the New Strategic Plan that is being designed.

Promoting research also outside research centers. Thanks to programs such as CARDIOJOVEN, integrated into the Global Training Plan that we have in the center, cardiologists with a research spirit and talent can continue to carry out their medical vocation while progressing in their research career. Something that I myself have been doing for years and to which I am completely committed to as General Director of the CNIC.

As Professor Ángela Nieto points out in this issue: To research, "you have to have resilience, patience and perseverance. These three things together are not easy, they are actually quite hard, but the rewards are obtained after the effort." I cannot express it better myself.

Margarita Salas is, and will continue to be, a benchmark for research in Spain, a country which has high-quality professionals and a lot of talent but does not however, always receive all the necessary support.

"A country without research is a country without development," Professor Salas used to say. Therefore, the best tribute to her would be to follow the path that she marked and provide research with the necessary tools and resources. If the necessary measures are not taken to make it possible, we will not have a future.

Raquel Yotti

Director of the Carlos III Health Institute

"The most important challenge for the ISCIII is **to ensure that we do not continue losing scientific fabric**, and that additionally **we are able to create it**"

Dr. Raquel Yotti, clinical researcher of the National Health System, Doctor in Medicine and Surgery by the Complutense University of Madrid and specialist in cardiology, is the Director of the Carlos III Health Institute since 2018.

Until she was appointed Director, she was head of the Clinical Cardiology Section at the Gregorio Marañón University General Hospital (HGUGM) and taught as an associate professor in the Department of Bioengineering and Aerospace Engineering at the Carlos III University of Madrid.

Her research career has been closely linked to ISCIII since its creation, having benefited from different programs of the Strategic Action in Health. In addition, she has been a member of the Technical Commission for the Evaluation of Cardiovascular Diseases of the General Sub-directorate for the Evaluation and Promotion of Research since 2014 and has participated as an external evaluator for research groups of the Andalusian Knowledge Agency. She is the author of more than 50 scientific articles in journals in the first quartile of her area of specialization.

Dr. Yotti is an expert on genetically based heart disease and multimodal cardiac imaging. Over the last few years, her care activity has been focused on the direct attention of patients and their families in family heart disease consultations, as well as in the performance of complex diagnostic tests, such as cardiac magnetic resonance and interpretation of genetic studies. She has also been chief operating officer for the coordination of the National Reference Centers (CSUR) of Family Heart Disease and Congenital Heart Disease of the HGUGM.

Due to her position, Dr. Yotti also holds the Vice-presidency of the Patronages of the Public Sector Foundations: Carlos III National Center of Cardiovascular Research (CNIC), Carlos III National Center of Oncological Research (CNIO) and Center for Research in Neurological Diseases (CIEN), as well as the Presidency of the Governing Council of the Consortium Center for Biomedical Research Network (CIBER).

You have been in charge of the Carlos III Health Institute for almost two years, the main public institution for biomedical research in Spain. How would you rate this phase?

It has been an exciting year on a personal level. The possibility to see how the state's resources for biomedical research are managed is an extraordinary opportunity, especially in my case that I come from the 'other side' of research in the hospitals, and I know first-hand the difficulties that researchers face every day. To have the opportunity to change, in a way, the manner in which resources are managed and, above all, to build new elements, on what is already established, because the ISCIII has been working in this direction for many years, and to be able to imagine other ways of supporting research that is done not only in research centers, but in hospitals, has been, and is, an exciting challenge that I have faced with great desire and hope, especially so that in the near future we can include elements that change the reality of research in this country.

> *"We are quite aware that we must continue betting on cardiovascular and oncological diseases, but we know we must develop a plan for neurological diseases"*

What is the biggest challenge you'd like to accomplish during your mandate? Which urgent matters have you had to resolve?

There is a fundamental challenge, which are the people, researchers. Over the past 10 years, especially in the last 5, our country has suffered increasing difficulties for researchers who are trying to do science from hospitals. Researchers in research centers have also suffered these, although of a different nature. In my opinion, the most important challenge for ISCIII is to ensure that we do not continue to lose scientific tissue in health care centers and that additionally we are also able to create it.

And when we talk about scientific tissue we are referring to scientists from all areas that are researching in hospitals, but also to clinicians, nurses or health personnel who consider research to be part of their work. For all these people the necessary time and resources must be available, in addition, of course, the recognition of their work.

There are many other challenges, but the fundamental one is to ensure that research can be done in Spain; and for this we need clinical, translational researchers... We need there to be engineers, biologists, etc., in all healthcare centers, all kinds of health researchers who interact with researchers who are at the patients' bedside. And that's why Health Research Institutes were created; but we need to create alliances and exchange programs with the centers of excellence of this country, such as the CNIC; that is fundamental. We need the researchers who are treating patients to be very close to the people who practice science of excellence in these centers. And, also very importantly, we must create bridges beyond the administrative difficulties we have at this moment.

Currently a Strategic Plan for the ISCIII is being developed. Can you give us any information on what it will be like?

We have been working on the new Strategic Plan for some time. We already have a draft that is the result of all the interactions we have carried out from the ISCIII Steering Committee with the scientific community, with the directors of the research centers, the health research institutes, CIBER, the ministries, etc.

The idea is to share it with all of them before. But I can tell you in advance that in it the support for researchers and their research careers will be of extreme relevance to achieve a stable situation for all these people who are dedicated to research. In addition, we will streamline, modernize and facilitate everything related to management.

What are its basic lines going to be?

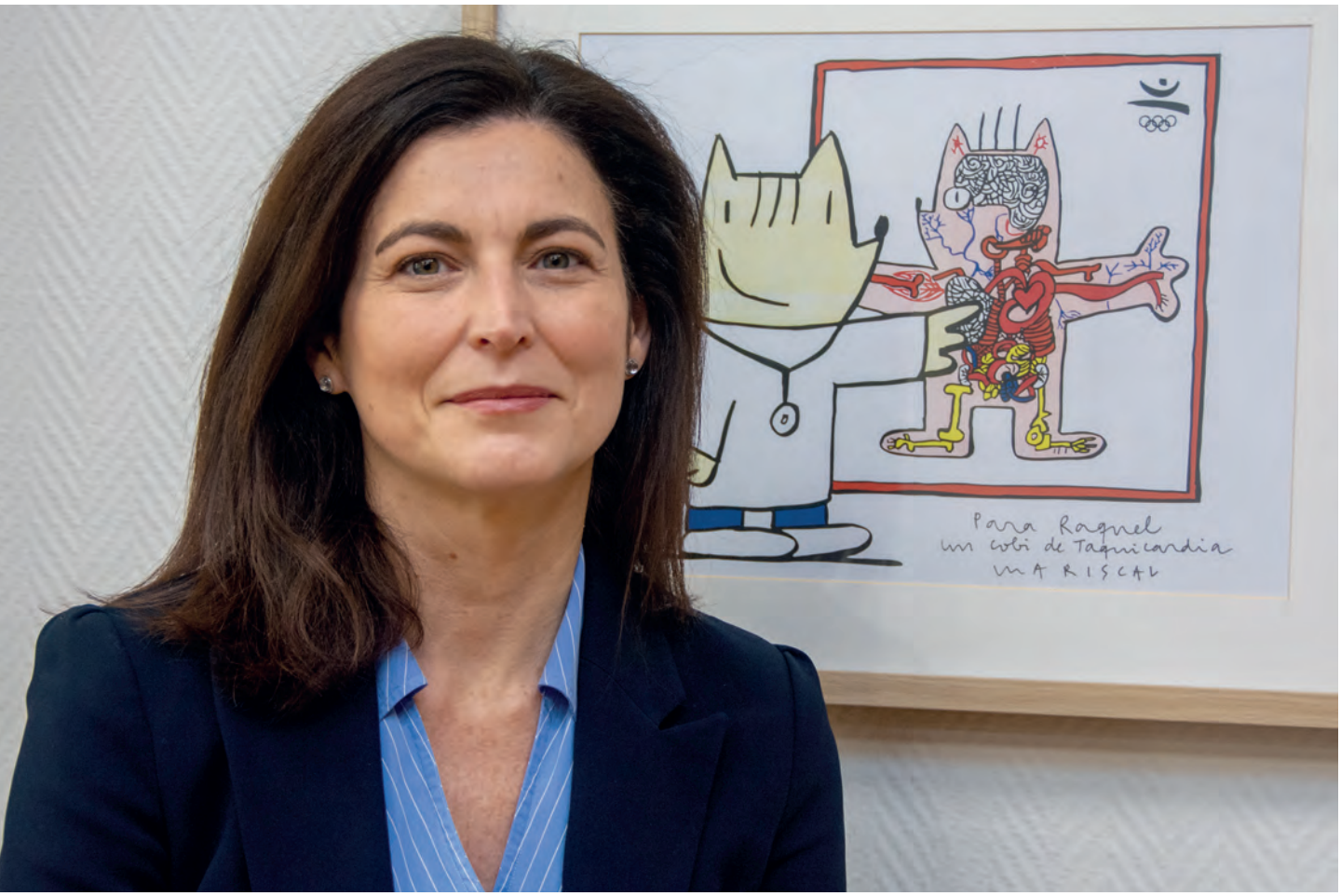
We have identified the functions of ISCIII and designed four vertical strategic blocks and four cross-sectional areas.

The first has to do with our ability to make scientific policy; that is, the function and coordination and backbone of research in the National Health System (SNS).

It is about addressing the careers of scientists in hospitals, the ability to train medical researchers, as is done in centers like the CNIC. Furthermore, we will also address the relevance and strategy that all collaborative structures like REDES, CIBER, etc. need to have. We want to undertake aspects such as generational replacement.

The second block is focused on who we are as a public research organization and goes deeper into research topics. We are quite aware that we must continue betting on cardiovascular and oncological diseases, but we also know that we must develop a plan for neurological diseases. These are currently the three pillars of disease burden.

But additionally, there are a number of areas in which we want to advance: development of advanced therapies, which we are already working on with the Ministry of Health, Consumption and Social Welfare; becoming a very active agent in development, but also in implementing mechanisms so that academic research reverts to health, something that is related to innovation, intellectual property,



> *"It's inexcusable that the ISCIII does not have a Strategic Plan, an external Advisory Committee and long-term objectives"*

personalized medicine, etc. ; digital health and chronicity, that is, how society and medicine are being transformed and new opportunities are being created, which, of course, is very transversal; health and environment or how the influence of external agents determine human health and biological aspects that have to do with the genome and the epigenome, also very transversal; and, finally, global health, better known as public health beyond borders and disciplines of health.

Is it possible for the ISCIII to be more participatory?

There are important aspects that the ISCIII has to develop in line with the principles of Responsible Research and Innovation (RRI), such as more horizontal and more participatory governance. For this we are going to establish stable structures of participation and scientific advice. It is necessary to consider that the ISCIII, as such, does not have an External Scientific Advisory Committee, something which is surprising and extemporaneous. There could be various reasons for this, such as that the ISCIII is many things: a funding agency, a public health institute, a scientific policy agent who makes decisions, etc. So what committee do I create and what for? It is complex, we will dissect the problem and create a series of scientific advisory or strategic advisory committees based on the functions of the ISCIII.

Of course, it is important that there is an External Scientific Advisory Committee to advise us on the research and teaching programs that are developed in the ISCIII as a Public Research Organization. But in addition, we will propose the creation of a strategic committee, in which civil society will also participate, which will help us design the network, collaborative and biomedical research strategy throughout the country and, of course, scientists who look beyond their issues with generosity. Less focused on what

we do as a Public Research Organization (OPI) and more on what we do as coordinators, funders and backbone of biomedical research.

How complex is it to manage a center as special as the ISCIII?

Management is important. First of all, we need to have a sufficient budget. And, we are studying features that will facilitate management: here we are making progress in digital administration, simplification of internal procedures...

In addition, within the Strategic Plan there is an infrastructure plan: scientific, architectural..., we have finished the Majadahonda campus, we are going to build a new National School of Health to which we want to give a new, more modern character, etc.

How can Spanish research contribute to meeting the UN's development goals for 2030?

Another axis of the Plan is responsible research and innovation and sustainable development objectives, which has to do with a way of doing science, oriented towards society so that it provides answers to society's needs, expectations and values. In this section we include gender equality and participation.

When will a final draft be ready?

The draft was presented on December 11th and has been available to the participation of ISCIII professionals, center directors, researchers, faculty, etc., but also externally to Health Research Institutes, Foundations, CIBER, etc. in order to receive contributions. We expect that by the spring of 2020 there will be a draft which we hope will be ratified by the Governing Council. The objective is to present a very legitimate plan, because one of the elements that sometimes makes the operation difficult is that the direction of the ISCIII is subject to changes with the political cycles, however if the plan is very legitimate, it will be above the directors. In other words, a very stable framework that sets milestones and makes it easier to ensure that, if there is a change of direction, there is already a roadmap.

Personally, this is something I have missed. With every change of direction there seems to be a loss of movement, and we cannot allow that. When I took over this job we saw how we could build on what the previous director had done. And, fortunately, it is something that has been done over the years. We have always built on what had already been built before.

At ISCIII, political science is done, something which is very easy to share. I hope that the person who replaces me will already have a stable strategic plan to work with.

In short, we want a plan for 5 years - 2020-2024. We have all of 2020 to share and to shoot. It is inexcusable that ISCIII does not have a Strategic Plan, an external Advisory Committee and long-term objectives.

Transversal Research: the patient as the focus

There has always been a very artificial separation between researchers doing more experimental research and those who are closer to the patients. We need to change this concept and have all researchers working and collaborating towards the same goal, whether it be at the CNIC or at the care centers, and sharing a project. And to do this we need to share language, a space and create trust and an environment in which everyone feels important. And this takes time. Structures and programs need to be created to make collaboration a reality.

Talent: recovering and promoting. How important is human capital for the ISCIII?

We have started a series of meetings, called Forum of Health Research Institutes, which is a space for participation in which the scientific directors and managers of the 31 health research institutes take part, as well as some key players from each organization. We aim to make it a shared work space and to hold two meetings a year. And what concerns us? The first thing we are concerned about is the loss of scientific fabric that is taking place in hospitals and in researchers' careers. We are preparing a document to work on this. There are more issues, which will be presented at the meeting in a course at the Menéndez y Pelayo International University (UIMP) in the summer of 2020.

As part of the stable forum are the patients. We are working on a new evaluation model for the necessary actions in health and one of the most striking things is that patients are going to be part of the technical evaluation commissions.

Women and science. Is breaking the glass ceiling a joint task?

For many years we have believed that the glass ceiling is what each woman had individually, so we left it up to her to break it. But the glass ceiling is not individual, it is a ceiling that we have in society and that is supported by some columns. It has to do with education, co-responsibility, labor aspects, salaries... If we are able to break those columns we are going to eliminate the ceiling not for one woman, but for all of them. Or at least we're going to put it up higher.

Besides, if we don't do it this way we are going to create more distortion by focusing the problem on women when it is a problem of society. We talk about feminism and now we are starting to have a much more inclusive concept of feminism. Today's feminism is equal rights and equal opportunities. It is not about creating a space for women to fight for their rights. Even in the elaboration of Equality Plans in the Institutions, often only women participate. We need this to be a task for everyone: men and women.

> *"Today's feminism is equal rights and equal opportunities. It is not about creating a space for women to fight for their rights"*

CNIC Conference: new concepts in age-related cardiovascular disease

Old age is connected with traditional risk factors: the older we are, the longer we are exposed to them. However, this is not enough to explain why aging increases cardiovascular risk. Cholesterol, a sedentary lifestyle or a poor diet are cardiovascular risk factors; however, in recent years it has been shown that aging, on its own, is one of the main causes.

A new edition of the CNIC Conference, entitled 'New concepts in age-related cardiovascular disease', was held at the National Center for Cardiovascular Research (CNIC) from October 24th to 26th.

Organized by three CNIC researchers, Vicente Andrés, José J. Fuster and Andrés Hidalgo, and a professor at Columbia University (USA), Allan Tall, the meeting hosted world experts in the field of aging related to cardiovascular disease.

The aging of the population is one of the most important demographic phenomena of our time. Its global impact is medical, social and economic. Age is also considered one of the most important risk factors for cardiovascular disease yet the underlying mechanisms are still not fully understood.

One of the diseases most affected by aging is cardiovascular illness. In fact, it is already considered the most important risk factor for this disease

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In recent years, studies have been published on a number of mechanisms specifically linked to ageing that are completely independent from traditional risk factors. These new mechanisms, which are relevant to both cardiovascular and cerebrovascular disease, are completely independent from those known until now and therefore open the door to completely different therapies and prevention strategies.

from the Complutense University of Madrid (UCM), who has just joined the CNIC, and Dr. Manuel Serrano, from the Institute for Research in Biomedicine (IRB) in Barcelona, who was in charge of the EMBO Master Lecture.

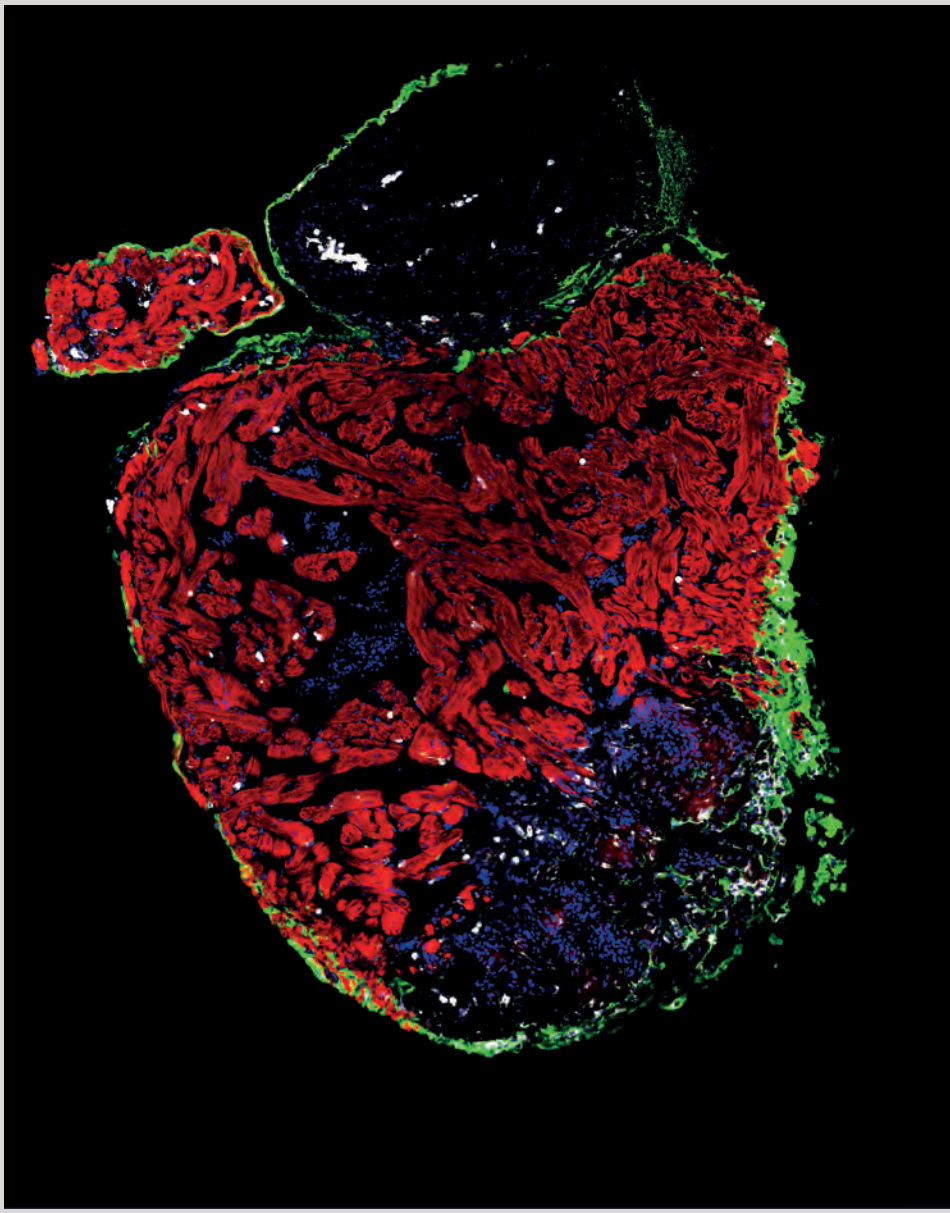
The Company of Biologist (COB) awarded a prize to the best short talk and the best poster. The winners on this occasion were, respectively, Magda Hamczyk and Álvaro Macias,

These mechanisms include: the relationship between cell senescence and cardiovascular disease; alterations between the vascular-neural-immune system as a cause of age-related neurodegenerative diseases; somatic mutations, clonal hematopoiesis and CVD, or alterations in hematopoiesis during aging and its role in CVD.

However, the experts recalled that it is not a question of ignoring the importance of preventing traditional risk factors, which have greatly reduced mortality from these diseases. We must not forget that our lifestyle is something we can change. In addition to Dr. Valentín Fuster, Director of the CNIC, other participants in this scientific forum included Dr. Filip Swirski, from Harvard University, Costantino Iadecola, from the Cornell School of Medicine in New York, and Paul Frennette, from the Albert Einstein College of Medicine, who gave the keynote speech of The Company of Biologist (COB), and the Spanish researchers who are experts in aging and cerebrovascular diseases, Dr. M. Ángeles Moro,

both researchers at the CNIC. The evaluation committees for the awards were made up of speakers with no conflict of interest with the works to be evaluated: Poster Award Committee: Sidd Jaiswal, Hartmut Geiger, Chloé James and Esther Lutgens; Short Talk Committee: Paul Frenette and Andrés Hidalgo.

Cardiac Regeneration: from mechanisms to therapy



The 2020 CNIC the Conference, that should have been held last April (the conference has been postponed due to the Covid-19 pandemic), under the title 'Cardiac Regeneration: from mechanisms to therapy'.

In this Conference, the mechanical and physiological bases of cardiac regenerative capacity will be addressed in depth from an evolutionary and physiological perspective.

The program includes the latest advances in the understanding of the mechanisms underlying cardiac repair in naturally regenerating organisms and how they can be stimulated in non-regenerative mammals. The conference will also review current regenerative strategies, including gene therapy, modified nucleic acid delivery, tissue engineering and cell reprogramming.

The forum will be an ideal setting to critically address recent controversies in the field of cardiac stem cells and the failure, up until now, to successfully translate experimental therapies into clinical benefit.

The conference is organized by Miguel Torres of the CNIC, Hesham Sadek of the University of Texas Southwestern Medical Center (USA), Elly Tanaka of the Research Institute for Molecular Pathology in Vienna (Austria), Nadia Mercader of the University of Bern and Mauro Giacca of the International Centre for Genetic Engineering and Biotechnology (Italy).

Brand Cardiologists CNIC

Training is a principal objective at the CNIC, so the center has developed a comprehensive training plan, called CNIC-Joven, which covers all levels, from secondary education to the training of postdocs and young professionals. One plan is designed to bring biomedical research closer to young people and to create a pool of future researchers of excellence in the cardiovascular area.

The CNIC is making extraordinary efforts to identify and train the brightest young people to create a pool of excellent researchers, present and future, in the cardiovascular field. CNIC-Joven trains around 500 participants per year through programs and courses.

The objectives are to promote scientific vocation, to stimulate young people's scientific careers in cardiovascular biomedicine and to complete the training of doctors in basic and translational research.

And to encourage cardiologists in training to join the CNIC. The CNIC runs training programs in collaboration with the Spanish Society of Cardiology (SEC): res@cnicsec, which offers 2-month stays to first and second-year residents to familiarize themselves with CNIC research projects; and INVESMIR, aimed at final-year residents to carry out a 4-6 month research project. The CNIC's advanced programs for physicians are CARDIOJOVEN, Valentín Fuster and PostMIR SEA / CNIC.

Xavier Rosselló was the first cardiologist to participate in the CARDIOJOVEN program when it was relaunched in 2017. Previously, there was a CARDIOJOVEN program in 2008 and 2009, and in 2017 it was reconvened with co-financing from the Spanish Society of Cardiology (SEC).

"I already knew about the CNIC, because in 2013 I participated in the INVESMIR program, during which I joined the group led by Dr. Borja Ibáñez, director of Clinical Research at the CNIC", says Dr. Roselló.

INVESMIR offers senior resident doctors the opportunity, during their specialization period, to continue their training through a research project in one of the CNIC's laboratories. An important objective is for participants to establish contacts and collaborations with CNIC researchers who will support them, after completing their MIR specialization, in the search of their own research projects in their centers within the National Health System.

After the residency at the Santa Creu i San Pau Hospital in Barcelona, "I spent three years in London with different grants and applied to the 2017 call of CARDIOJOVEN".

CARDIOJOVEN is a course organized in collaboration with the SEC that aims to promote high quality translational research in the cardiovascular area in the centers of the Spanish National Health System. It is specifically aimed at cardiologists who aspire to carry out advanced clinical and research work in any center of the Spanish National Health System. It offers a training period to obtain a Master's degree in Medical Statistics at the London School of Hygiene and Tropical Medicine.

Xavier completed his Master's degree at the London School of Hygiene and Tropical Medicine under the tutelage of Professor Stuart Pocock.

"The CARDIOJOVEN SEC-CNIC Program has enabled me to study a Master's degree in Medical Statistics at the London School of Hygiene and Tropical Medicine and to publish 35 scientific papers since its beginning, 24 of them in the last half year," says Xavier.

He admits that the specialization that he has obtained has allowed him to go deeper in methodological and statistical foundations, as well as to carry out clinical research with high level professionals. "My current professional profile is very specialized, which allows me to participate in many research studies, both basic and clinical".

In fact, Dr. Roselló is a member of the Statistics Committee of the PESA-CNIC-Santander Project and is Coordinator of the REBOOT Study, (TREATment with Beta-blockers after myOcardial infarction withOut reduced ejection fraction (REBOOT), among other performances.

He is currently in his last year of the CARDIOJOVEN SEC-CNIC Program and combines his research work at the CNIC with his on-site work at the Son Espases Hospital in Palma de Mallorca.

"My overall assessment of the SEC-CNIC training programs is very positive: it is a commitment to generate and recover young researchers in an increasingly competitive environment. And he adds: "I am a clear product of the CNIC. My professional career is linked to the center which, in addition, has opened the doors for me to obtain different grants and which, thanks to its programs, has allowed me to return to Spain to do my work, both clinical and research".

Attracting and retaining talent is one of the objectives of these CNIC programs. More than 30% of the participants in the international summer internship program for university students return to the CNIC to complete their master's or doctoral thesis, and more than 70% of the participants in the CNIC's master's program enroll in the CNIC's doctoral program.

About 30% of INVESMIR participants continue to collaborate with CNIC groups on research projects.

More than 100 students take advantage of the CNIC's ACÉRCATE Program

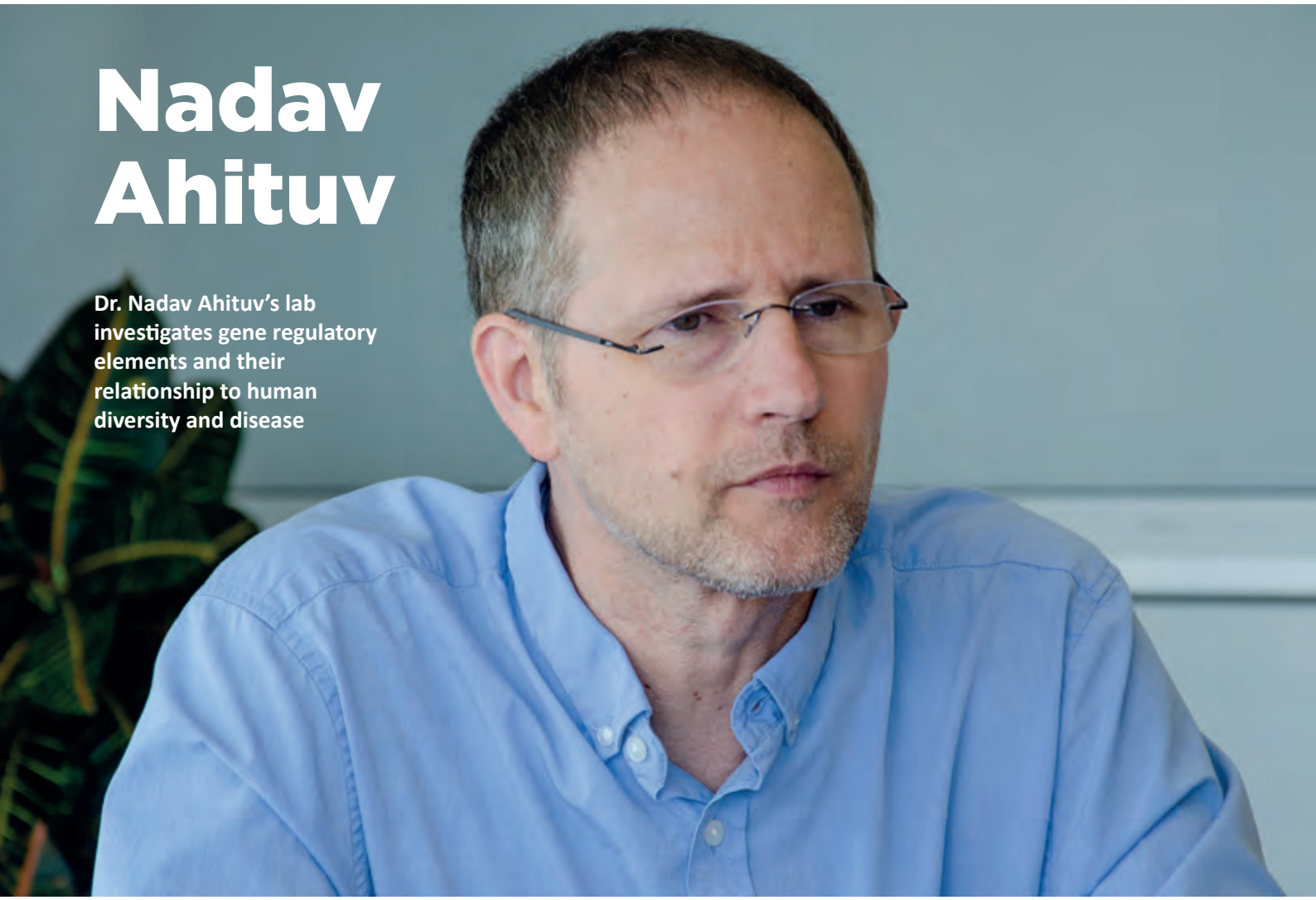
A total of 112 students, 41 men and 71 women, have so far benefited from the ACÉRCATE program, organized by the National Cardiovascular Research Centre (CNIC) as part of its CNIC-Joven Training Plan. The aim of this plan, a personal commitment of the center's General Director, Dr. Valentín Fuster, which began 14 years ago, is to attract and train the brightest young people from the earliest ages in order to create a pool of researchers of excellence in the field of cardiovascular research.

The program is aimed at high school students with a grade point average of 10 in their third and fourth year of high school. The call, open to high school students from all over Spain, was resolved in 2019 in favour of 5 female students and 3 male students from the 50 who met the requirements and applied to participate in the program: the students were from the Community of Valencia, Madrid, Castile and Leon, the Canary Islands, Andalusia and the Basque Country.

On this occasion, the eight young students were: Ismael Gómez Muñoz, Arianna Arbona Amalfitano, Celia Fernández Pérez, Miguel Marijuan Santamaría, María Gutiérrez Peláez, Marina Rodrigo Varela, Guillermo Azcárraga Aranegui and Cleidy De Assis Gallardo.

Dr. Fuster believes that starting the training program at such an early stage is key to attracting the researchers of the future because young people are the "future of research in our country".

This program is the one aimed at attracting the youngest talent of all the training programs at the CNIC. The sustained support of the Pro CNIC Foundation is indispensable so that, year after year, it can continue to celebrate and attract talent from the earliest stage. "We are very satisfied with this concept that we started 14 years ago," adds Dr. Fuster. And, he concludes, "so, if they have that 'research bug' in them, we encourage them to keep going".



Nadav Ahituv

Dr. Nadav Ahituv's lab investigates gene regulatory elements and their relationship to human diversity and disease

"The CRISPR-Cas9 technology has revolutionized the way **we can now modify or modulate DNA**"

Dr. Nadav Ahituv is a geneticist / genomicist who uses advanced computational and genomic tools to characterize how variation in gene regulatory elements leads to human disease. In his laboratory of Bioengineering and Therapeutic Sciences of the Institute for Human Genetics of the University of California in San Francisco-UCSF (USA) he uses different genomic technologies, such as RNA-seq, ChIP-seq, ATAC-seq and CRISPR / Cas9, to characterize the gene regulatory elements. To functionally determine these elements, he works in various model systems, like the zebrafish, mice and cell cultures. In addition, he has created and is developing technologies that allow mass analysis, in parallel, of thousands of sequences. His main lines of research focus, among others, on gene regulatory mutations and their relationship with human limb malformations, obesity, mental illness and response to medication.

> *"I am very optimistic and I think we are going to enter the golden age of gene therapy"*

What is your current area of research?

My work focuses on the search for regulatory elements; that is, sequences that tell genes when and when not to activate. Basically we want to find mutations in the genes that provoke diseases in humans or that cause differences between different species, since diseases are related to these regulators that are responsible for turning the genes on and off.

How did you become interested in genetics and its relation to human illnesses?

It has a lot to do with my own illness. At age 13 I was diagnosed with severe scoliosis. My first treatment was a corset for my spine, something that, for a teenager, is not exactly pleasant. But it didn't work, since my curvature was greater than 50º, so I had to have surgery when I was 16 years old. My younger sister also had this problem. Hence my interest in genes and genetics, genetic diseases, etc.

Do you have any research projects about this disease?

Although I had never worked on scoliosis until now, three years ago we started a line of research on this disease because we think that many of the mutations that lead to scoliosis are caused by regulatory elements that turn the genes on and off. Now we have a big project in this field.

What is the current reality of genetics and what are the actual treatment possibilities offered by the modern techniques of genetic modification?

There are many diseases in which the problem is caused by the dose of the gene; that is, the gene is not expressed at the necessary levels and that generates a series of events that provoke an illness. We work to use these regulatory elements with the aim of reversing this situation and promoting the expression of a gene, by increasing or reducing its expression. We have studies, some recent, in which we have activated these regulatory elements to overcome a deficit of expression in the gene and, thus, increase the expression of RNA or proteins.

There's much talk about genetic modification and its possible risks. What are they?

At first genetic therapy generated a lot of expectations among the scientific community, and in society as well, but over time these expectations were deflated by issues related to their safety or efficiency. But the situation has changed a lot. Call me optimistic if you´d like, but with the current tools, such as CRISPR-Cas9 technology, and even considering that there will be some setbacks, we will be able to move faster and in a safer way.

You currently work in many areas: human limb malformations, obesity, autism, etc. Which is the most promising?

We all know that the transition from the laboratory to the clinic can take years. But fortunately, nowadays we have at our disposal a series of technologies that make this process less slow. For example, gene therapy has benefited from innovative routes of administration through viruses, which

> *"If we are able to use this technique on just one person to treat them, I would be the happiest person in the world"*

are currently much safer than some years ago. CRISPR-Cas9 technology has revolutionized the way we can now modify or modulate DNA, which is what we do at our laboratory. I believe that thanks to all these developments, the current waiting time between the findings in the laboratory and its clinical application is shorter. Because if we look back, for example, years ago we started talking about the modification of RNA, but 20 years passed before the first RNA therapy in the clinic was approved. Things take time, but just by looking at what is currently happening with gene therapy we can see that this time is getting shorter. For example, the FDA has just approved a gene therapy for the treatment of spinal muscular atrophy.

Your team has recently published a study in Science that describes the use of a modified version of the CRISPR gene edition to prevent severe obesity in mice. Could you explain what it is about?

This is the proof of concept that confirms that our therapeutic approach really works. As I said, there are many human diseases that are caused by abnormalities in the expression or dose of the genes and, probably, the most classic are those caused by a deficiency in one of the copies of the gene. It is called haploinsufficiency, and it occurs because a single copy of the normal gene is unable to produce protein in sufficient quantity or quality to ensure normal function. That is, of the two copies of a gene that we inherit, from our mother and our father, one of them does not work, so 50% functionality is produced. And sometimes, a 50% protein production is not enough, and so a disease is generated. Our job is to make the normal copy of the gene increase its

expression and produce more protein and RNA. This way we can treat the disease that causes this insufficiency. Our proof of concept was done with obesity, because it is very easy to see if the therapeutic approach works. You see it very easily: the mouse gets fat or not. The idea is to target obesity-related genes in which only one copy works and increase its expression. And we have seen that, intervening in two different genes, SIM1 and MC4R, both involved in the processes of appetite and satiety regulation, obesity is prevented in these animals. The idea is to move towards people with morbid obesity, who die before the age of 50 usually due to heart problems, diabetes, etc. Obesity in these people is not a consequence of their lifestyle, but of a malfunction of the genes, which makes them never feel satiated and eat without control. Once we have proven that it works, the next step is to address other serious diseases with a high mortality rate in children.

> *"20 years have passed for the first RNA therapy to be approved in the clinic"*

What is that modified version of CRISPR like?

Our CRISPR technique uses the dead Cas9, which does not cut DNA or make any changes in the DNA. Like the conventional **CRISPR-Cas9 technology**, our modification also specifically targets a specific DNA sequence, but once there it doesn't cut anything, but rather enhances the expression of a particular gene. Dead Cas9 has a mutation that eliminates its ability to cut DNA, but not to join it. In this way we get it to work as a distributor, which leads a regulator to where we want it to and tells the gene when, where and at what levels it should be activated. In the case of CRISPRa, this regulator is a protein that provides 'extra transcriptional machinery', so that more messenger RNA is produced, which is the intermediary that translates the information of the protein-encoding DNA. Thus, greater activity of the gene that works correctly is achieved, compensating for the lack of the defective one. By not carrying new copies of the genes possible side effects are avoided.

And when can this research be applied on humans?

That is our goal! If we are able to use this technique on just one person to treat them, I would be the happiest person in the world. But as I said there are many aspects to resolve.

If we are able to use this technique on just one person to treat them, I would be the happiest person in the world.

What are the biggest challenges in the use of gene modification to treat human illnesses?

Of course we have to take into account the ethical aspect. It is most likely that the first approvals will be given for those very serious diseases in which there is no other hope, such as spinal muscular atrophy. But we must not forget other aspects, such as the immugeneicity of CRISPR, which we do not know much about, and must worry about it, and increase our knowledge on it. The administration of therapy is also a challenge, that is, the use of viruses to reach the specific target and not adjacent tissues. But, in any case, as I said before, I am very optimistic and I think we will enter the golden age of gene therapy. The technological tools we currently have, together with the significant investment in gene therapy that the biotechnology industry is carrying out, aware of the value of these techniques and their potential, make me believe that we are very close.

Yes, but it seems it will be a therapy accessible only to very few people, after the FDA approved a therapy that costs 1,5 million dollars.

That is another important challenge. We have to make these treatments accessible to most of the population that needs them. But it is complicated; on one hand, there are pharmaceutical companies that invest billions of dollars in the development of these innovative therapies and expect an economic return on their investment. We cannot forget that these are single-use treatments. It is a complicated situation. In my opinion, it is more likely that, as this field advances, therapies will become more affordable, although of course it will be much more difficult for people living in less developed countries.

However, if we consider that it is just a single dose, then we would save the expenses derived from the illness.

That is exactly what the pharmaceutical companies argue, that in the long term it saves costs. And indeed it is true and it is possible that it is even more economical. But, even agreeing with this point, we're talking about millions for a treatment ... I don't know ... it seems excessive.

Where will we be in 30 or 40 years?

I hope and wish that these techniques will have already reached the clinic.

What do you love most about your job?

Exploring and discovering new things. That is what fascinates me most about my work. I would be happy, as I said, if it serves to treat patients. But we also work on other topics that I love, such as why bats develop wings. That fascinates me too.

"We have to make these treatments accessible to most of the population that needs them"

How important is mentoring in the career of a researcher?

I try, at least. We are the teachers of great scientists and we have a big responsibility. In addition, nobody teaches us how to be a good mentor, you learn on the go and, especially, my case in particular, from mistakes. I try to maintain permanent contact with my researchers and it is my duty to meet with them once a week, for an hour, to talk, not only about their work, but also about aspects more related to their life, their goals, etc.

Is it your first visit to the CNIC?

Although I know many people at the CNIC, it is the first time I have come and it is really impressive. I have collaborated with Miguel Manzanares and currently one of the students from his group is in my laboratory in San Francisco.

Dr. Nadav Ahituv, gave a seminar at the CNIC entitled "Functional characterization and therapeutic targeting of gene regulatory elements" invited by Dr. Miguel Manzanares.

Ángela Nieto

Dr. Angela Nieto is one of the most relevant investigations in the field of Developmental Biology and her career has been worthy of several awards.

Talented people leaving Spain is not a problem as long as they can come back

Professor Ángela Nieto received her PhD in 1987 (Autónoma University, UAM, Madrid) after working on the interactions of nucleic acids in nucleosomes and ribosomes. In 1988, she moved to the Biomedical Research Institute (CSIC-UAM), also in Madrid, to study programmed cell death in lymphocytes. In 1989 she moved to the National Institute of Medical Research in London to work with David Wilkinson, where she isolated a number of genes involved in the morphogenesis of the nervous system. In 1993, she got a position as a Scientist at the Cajal Institute in Madrid. Since then, she has led a research group interested in studying cell movement and plasticity. In particular, her group has studied the transition from epithelium to mesenchyme in development and disease, and her main contribution has been the impact of the reactivation of this embryonic program in adult disease, including tumor progression, fibrosis, bone growth and mineralization. She was elected member of EMBO in 2000 and member of the Academy of Europe in 2009. Among others, she received the "Carmen and Severo Ochoa Award" (2004), "Francisco Cobos Foundation Prize" in Biomedical Research (2005); "Alberto Sols" for the best research career (2008), "Rey Jaime I" in Basic Research (2009), QUO Magazine of the Spanish Science Team (2015), Recognition of Scientific Merit of the Generalitat Valenciana (2015), Prize of Basic Research in Nephrology "Iñigo Alvarez de Toledo" (2016), Mexico Award in Science and Technology (2017) and Lilly Foundation Prize in Preclinical Research (2018).

> *"We have one of the most important schools of Development Biology in the world. It is a pleasure to have such important people in this field in our country"*

What is your current line of research?

For more than 25 years we have been working in the field of cell movements. Starting from Developmental Biology, we want to understand how cell movements occur to form tissues formed by cells that have been born far from their final location. It is what is called, in cellular biology terms, 'mesenchymal epithelium transition'. Initially we have studied it in embryonic development, although the concept that we have developed in the last 15 years is the reactivation of these embryonic programs in adult pathologies. Thus, we have seen that this reactivation brings with it the spread of cancer cells from the primary tumor to subsequently lead to metastasis or secondary tumors. In the same way, we have also observed that this reactivation occurs in other pathologies, such as organ degeneration, specifically in fibrosis.

The CNIC is one of the great research institutes in Spain that also has a very important international recognition.

And in the heart?

Although externally we have bilateral symmetry in the left-right axis, internally there are many asymmetries in this axis, for example, the apex of the heart points to the left, the liver is to the right... The primordium of the heart, that initially is in the center, receives input from cells from both sides of the embryo that are directed to the middle line, and what we have seen is that there are many more cells that come from the right side, exerting a different force, and, therefore, they push the heart to the left side.

When this process does not occur, and the heart stays in the center, a pathology called mesocardia occurs, a condition that is not viable. There are other alterations, such as dextrocardia, in which the heart is located on the right, which in certain cases is viable. The displacement of the heart is essential not only for all organs to be optimally packaged, but also for concordance with the vasculature.

The heart is the first to be placed. Does that determine if the rest are placed correctly?

It does not determine where the other organs are positioned, but it is the first to do so. Now we are studying what is the mechanism that positions the other organs and we are observing that it is something similar, but it is not determined by the heart. In 1 of every 10,000 humans there are alterations of the left-right axis of the embryo, which in many cases produce congenital cardiac malformations. Understanding the mechanism that positions the heart is also important to understand how different malformations occur.

Can these malformations be corrected in humans?

If we know the mechanisms, we will always have more chances to detect it beforehand and, in some way, to stop it.

Your work provides information on metastasis.

The formation of metastasis implies, among other mechanisms, a reactivation of the embryonic program that directs cellular movements. As I mentioned earlier, there are many cells in the embryo that are born far away from their final destination. By activating this program of cellular movements, the cells are able to move until they reach their destination. There, they nest and begin to differentiate themselves in a particular organ; that is the normal process. It is easy to understand that, if this does not work well, the embryo cannot progress. In cancer there is a reactivation of this embryonic program and the cells of the primary tumor detach and nest in different organs where they will form new tumors, which are metastases, the cause of more than 90% of deaths associated with cancer.

You are part of the highly-valued school of Development Biology? How relevant is this in Spain?

Development Biology is a very important subject in Spain. The school in Madrid was essential for this, and it is true that, for a long time, the main model of study was the Drosophila fly. But at the end of the 80s and 90s, some scientists began to work in the biology of the development of vertebrates, especially of mice, but also in chicken, and years later in zebrafish. There is a long tradition of development biology in Spain, thanks to Antonio García Bellido, Ginés Morata or Juan Modollel, etc. We have one of the most important schools of Development Biology in the world. It is a pleasure to have such important people in this field in our country.

In this sense, how important is the mentor figure?

It is very important. Especially, because in the first years of the scientific career you have to make decisions, you have to make them yourself, but with a global knowledge of what happens. And that is transmitted through the mentor.

Do you remember any of your mentors?

I remember my family's support, which I believe is truly fundamental. In my family, there are no scientists. Since I was little I liked chemistry and 'putting things together'. Every week my father brought me the "Investigación y Ciencía" (Science and Research) magazine. I also remember my high school teacher, when I was hesitant to study chemistry or biology. She was the one who piqued my interest in biology, from the cell and biochemistry point of view. And so I decided to study Biology and then Molecular Biology at the Autónoma University of Madrid. And the truth is that I think it was a very good decision.

Are you a mentor too?

I am part of a mentoring program in the Community of Valencia and I also participate in programs especially with young scientists. The important thing is having the possibility to decide what each one really wants to do. In Spain, the scientific career has always been seen as a linear career, at the Academy. But there are many other possibilities, however, in our country unfortunately, many of these options are still missing. It is about finding the niche where one can develop more.

> *"It is essential that from the first moment you enter the university, you know that the performance will determine your chances"*

Why is the scientific career in Spain almost always associated with the Academy?

In addition to lack of information about other options, there is a lack of possibilities in the area. The truth is that we have had some very bad years, which fortunately came after some very good years, which allowed for the system not to be irreversibly lost during the crisis, but we have to keep pushing a lot. Otherwise, we are doomed to lose a generation of scientists.

There is also a lack of information at the universities because the students do not know that, if they do not have a good profile, in the future they will not be able to compete to get predoctoral contracts or do the thesis at a good center. It is essential that from the first moment you enter the university, you know that the performance will determine your chances. And if education in science can be promoted earlier on, it would be even better. For example, our postdocs will give talks to schools to promote science.

You mentioned that there could be a lost generation.

I hope we can recover it. Talented people leaving Spain is not a problem as long as they can come back. Unfortunately, this is not the case on many occasions. In addition to investment, which is important, the management of different institutions within the science and technology system must be flexible, especially universities and public research institutes, where administrative constraint makes us lose competition in comparison with other centers and institutions, both from Spain as well as from other countries.

You have become more of a manager of your team now than a researcher, haven't you?

I don't think it can be separated. What do we call research? To mix things in a test tube or to think and develop projects? You have to do both. It would be great if I had to invest less time in solving administrative problems. But what would not make any sense, at this time when there are 20 people in my laboratory, is that I was in a corner doing an experiment and was not available for what they need or was not thinking about the next project.

The interesting thing about this job is that no day is the same as another. This is a message I give to young people, to children. There are very few jobs in which there is such an important decision capacity only limited by your imagination. It is very enriching from the personal point of view. Although it requires a lot of effort and dedication, it is very rewarding.

What about failures? How do they influence things?

If one is able to overcome difficulties, the rewards can appear. You have to have resilience, patience and perseverance. These three things together are not easy or hard, but the rewards are obtained after the effort. Effortless rewards are not as satisfying. With this I do not mean that you have to suffer but, work, discipline and rigor are important. Together with the freedom and passion that we put into this job, I think they create a mix that, if balanced, is rewarding for the person.

This job is something that has to be done not only as a way of life, but as a way to fulfill oneself. Seeing things for the first time that nobody has ever seen is real, although it is difficult to explain. Great discoveries are not made every day nor every 10 years, but those small advances are fundamental for the progress of science and for that of humanity. That's what we are here for.

Do you think society values scientists?

Society really appreciates scientists: we are highly valued and we have credibility. But it is important to transmit to society that our work has or will have an impact on society. And what is certainly not yet transmitted is that this requires an effort on behalf of the state, and public and private funding, to keep it working. And, even if it were a high amount of funding, it is not an expense, it is an investment. People know that research is the most profitable activity. Now it is up to society to demand more investment from the politicians, and this is not something that usually comes up in the election campaigns, because there are other more visible needs.

It is not your first visit to the CNIC. What is your opinion of the center?

The CNIC is one of the great research institutes in Spain that also has a very important international recognition. Being here is always a pleasure. The CNIC scientists, together with the type of management, make it a very competitive center and I wish other Spanish centers, universities and public research organizations also had a more flexible management that would allow us to be, in global terms, more agile and more competitive.

Do you currently have any collaboration with the CNIC?

Currently, I don't have any collaboration with groups from the CNIC, but in the past I have worked a lot with researchers from this center. For example, Miguel Manzanares was in my laboratory when he returned from England, and we are still in contact, and with Miguel Torres I also have a lot of relation for many years. He is the current president of the Society of Developmental Biology and I was the former president. Also with José Luis de la Pompa and Juan Miguel Redondo, who were my classmates at the Autonomous University.

Dr. Ángela Nieto gave the Seminar"The epithelial to mesenchymal transition in heart laterality" invited by Drs.Miguel Torres y Miguel Manzanares.

María Ángeles Moro

"Various diseases and all very mechanistically different, are included under the name of **vascular dementia**, or better called, cognitive vascular deterioration"

Professor of Pharmacology at the UCM School of Medicine, co-director of the Neurovascular Research Unit of the same university and Director of the CNIC Laboratory of Neurovascular Pathophysiology

María Ángeles Moro is Professor of Pharmacology at the UCM School of Medicine, and co-director of the Neurovascular Research Unit of the same university. Her main lines of research are stroke and vascular dementia, fields in which she has identified new therapeutic and diagnostic targets, among which are nuclear receptors, excitotoxic mechanisms, the contribution of myeloid cells to the inflammatory and resolute response, and mechanisms of physiological and pathological remodeling through neurogenesis and angiogenesis.

She belongs to the "Stroke" Editorial Committees, "British Journal of Pharmacology" and "Journal of Cerebral Blood Flow and Metabolism". She has been a Collaborator of the General Subdirectorate of Research Projects of the State R&D Plan, MINECO (2013-2016), and deputy of the ANEP Biomedicine team (2004-2007). In addition, she has participated / participates as an expert in panels of the Spanish National Plan and, since 2001, as Chair, Vice-Chair or evaluator in more than 40 panels (MSCA, ERC, etc.) of the European Commission (through the Research Executive Agency, European Research Council Executive Agency, and EUCYS) and, more recently, of the Ibero-American Program of Science and Technology for Development (CYTED). She is an ad hoc reviewer for numerous international publications and evaluation agencies (Wellcome Foundation and Alzheimer's Research Trust, UK; ANR, France; CINECA, Italy; NCN, Poland) and External Examiner of Trinity College Dublin (2010-2013). Since 2016 she is "Fellow of the British Pharmacological Society" (FBPhS).

She has participated in the CNIC Conference entitled 'New concepts in cardiovascular diseases related to age' and has joined the National Center for Cardiovascular Research (CNIC) where she leads the Neurovascular Pathophysiology Laboratory.

What is the relationship between neurovascular damage and diseases related to dementia?

The relationship is very direct, and, in fact, although it has been considered that cerebral vascular damage is the second most frequent cause of cognitive deterioration, after Alzheimer's disease, new evidence indicates that mixed type dementias (vascular and Alzheimer) are actually the most numerous. Furthermore, there is increasing evidence that shows that Alzheimer's disease can pass silently and manifest itself clearly after cerebrovascular damage. Therefore, it is surprising the little amount of research that is dedicated to other types of dementia, other than Alzheimer's disease.

We keep living longer and longer.

And with the increase in life expectancy it is logical to increase the prevalence of age-related diseases. We work on vascular dementia, in which cognitive disorders have a vascular cause. It is important to highlight that various diseases, and all very mechanistically different, are included under the name of vascular dementia or, better called, cognitive vascular deterioration. As I said, the fact of living longer also has a downside, which is the increase in the chances of the development of these diseases. And not only is the risk higher, but, in addition, age increases the severity of cardiovascular disease, including cerebrovascular disease. Do not forget that the various types of dementia affect about 40 million people in the world and that by 2050 this figure could reach 150 million or more, which will make this type of disease a major social and health problem.

"Do not forget that the various types of dementia affect about 40 million people in the world and that by 2050 this figure could reach 150 million or more, which will make this type of disease a major social and health problem"

> *"We have demonstrated the role of neurogenesis alterations in the hippocampus in various models of vascular dementia"*

Which is more decisive: age or lifestyle?

Both. Age goes deeper into lifestyle factors. The English physiologist Thomas Sydenham said that "A man is as old as his arteries". At a cardiovascular level it has been observed that many of the problems derived from atherosclerosis or hypertension, such as vascular remodeling or endothelial dysfunction, also occur as a result of aging without any other risk factors. In addition, as we said, age makes these additional risk factors aggravate and thus have more time to develop.

Although in young people the body has resistance mechanisms, the increase in unhealthy habits will cause a greater incidence of cardiovascular disease in the future.

Is it possible to fight against aging?

If we know which mechanisms, possibly yes. Hence the importance of research, such as the one recently published by Dr. Marta Cortés Cantelli and Dr. Valentín Fuster in the Journal of the American Medical Association (JACC) which demonstrates the value of an anticoagulant in a mouse model with Alzheimer's disease. And there are other factors such as senescence, pathological aging, which is of great interest in this context. If we know the mechanisms and act upon them, we have seen that, in animal models, cognitive deficits can be reversed.

We have demonstrated the role of neurogenesis alterations in the hippocampus in various models of vascular dementia. Likewise, in autopsies of people with Alzheimer's disease, brains show a much smaller neurogenesis than in healthy people. This indicates that this is another mechanism that causes dementia, associated with aging, and that it is possible that at some point we can reverse it.

Can we think of neurogenesis as a possible target for future therapies in these diseases?

Yes. Adult hippocampal neurogenesis is a crucial process in memory formation. In Alzheimer's dementia there is a reduction in neurogenesis, although we still don't know if cognitive function would be restored if we reversed this reduction. Our contribution in different models of vascular dementia is proof that neurogenesis is altered, although with differential mechanisms. In the case of post-stroke dementia, aberrant neurogenesis occurs but more importantly, we have shown that if we inhibit the development of this neurogenesis, cognitive function is restored. Interestingly, in other typical models of vascular dementia, such as the one caused by carotid stenosis, the opposite happens: neurogenesis decreases.

In summary, in the models of vascular dementia that we have studied, there is a causal relationship between cognitive deficits and alterations in hippocampal neurogenesis. And in the case of Alzheimer's disease, the data points in the same direction, although there are possibly more causes.

> *"Vascular dementia, despite its high prevalence and consequences, it has received very little attention and its mechanisms still remain very unknown"*

You have just joined the CNIC. Can you tell us what your line of research at the center will be?

Vascular dementia, despite its high prevalence and consequences, it has received very little attention and its mechanisms still remain very unknown. All of this is even more complicated because, as we have said, dementia is not one, but many different pathophysiological entities. Taking advantage of the great critical mass and the avant-garde technology that exists at the CNIC, our objective is to develop innovative approaches and new paradigms to increase our understanding of the molecular and cellular mechanisms involved in vascular dementia, in order to identify therapeutic and diagnostic targets. The establishment and characterization of experimental models that recapitulate these diseases, will also allow us to develop non-invasive, sensitive and specific neuroimaging

markers for each of the different subtypes of vascular dementia. Ultimately, our goal is to transfer our results in order to improve prevention and treatment of affected patients.

In the scenario of cerebrovascular disease, we will also continue our studies on ischemic and hemorrhagic stroke, focusing on its prevention and the development of more effective treatments for both the acute phase and for the more chronic stages of these pathologies.

María Ángeles Moro has participated in the CNIC Conference entitled 'New concepts in cardiovascular diseases related to age'

"In the case of Alzheimer's disease, the data points in the same direction, although there are possibly more causes"

EXCELLENCE in the SCIENCE COMMUNICATION

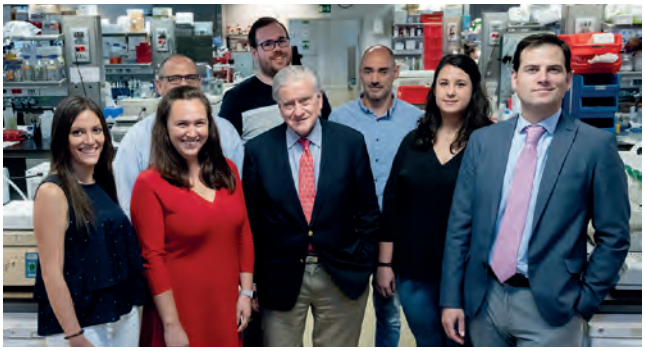
MAJOR SCIENTIFIC JOURNALS PUBLISH CNIC RESEARCH FINDINGS

The excellence of the CNIC is demonstrated year after year with the publication of the research carried out in our center in the most important scientific journals. In 2019, studies were published in prestigious journals such as Nature, Science, Embo Journal, Journal of the American College of Cardiology (JACC), Circulation or Cell Metabolism, among others. Reflecting the translational nature of the CNIC, studies of more basic scientific knowledge have been published, such as that of the new genetic tool (iSuRe-Cre) that allows researchers to ensure the success of genetic modifications made through Cre-lox technology. , the technology used by most biomedical research that aims to understand the function of genes; others with a promising clinical application, such as the identification of a drug, dabigatran, which delays the onset of Alzheimer's in mice, or some with a clear Public Health bias, such as the results of the FAMILY Project that confirm that an early intervention in preschool is a unique opportunity to promote a healthy lifestyle.

PUBLICATIONS

JACC

An oral anticoagulant delays the appearance of Alzheimer disease in mice



Scientists at the CNIC have identified a possible treatment for Alzheimer disease. Working together with a scientific team at The Rockefeller University in New York, the investigators have shown that treatment with the oral anticoagulant dabigatran delays the appearance of Alzheimer disease in mice.

The results, published in the *Journal of the American College of Cardiology*, show that after a year of treatment with dabigatran, mice had no memory loss and no reduction in cerebral circulation. This treatment also reduced typical Alzheimer symptoms, including cerebral inflammation, blood vessel injury, and amyloid protein plaques.

Dabigatran is more effective and has fewer side effects than classical anticoagulants and is approved for the treatment of several diseases. Study coordinator Dr. Marta Cortés Canteli, a CNIC researcher funded through the Miguel Servet program, highlighted the value of the study: "This discovery marks an important advance toward the translation of our results to clinical practice to achieve an effective treatment for Alzheimer disease."

Placing the study in a broader context, Dr. Valentín Fuster, CNIC General Director and a lead author on the study, commented, "neurodegenerative diseases are very closely linked to disease in the cerebral blood vessels. The study of the links between the brain and heart is the major challenge for the next ten years."

Further studies are needed in patients, but the research team believe that dabigatran has the potential to normalize cerebral blood flow in Alzheimer patients. "An individualized treatment strategy such as this will first require the development of a diagnostic tool to identify those Alzheimer patients with a tendency to coagulation. This will be an important line of research in the coming years," indicated Dr. Cortés Canteli.

Cortes-Canteli, M., Kruyer, A., Fernandez-Nueda, I., Marcos-Diaz, A., Ceron, C., Richards, A. T., . . . Fuster, V. (2019). *Long-Term Dabigatran Treatment Delays Alzheimer's Disease Pathogenesis in the TgCRND8 Mouse Model.* ***Journal of the American College of Cardiology***, 74(15), 1910-1923. doi:10.1016/j.jacc.2019.07.081

Cell Metabolism

Cell Metabolism : A new mechanism for the transfer of maternal genetic material

CNIC researchers have defined the dynamics of the transfer of mitochondrial DNA, a type of genetic material, from mothers to their offspring. The study was published in *Cell Metabolism*. Using experimental mouse models, the research team led by Dr José Antonio Enríquez found that when the mother's cells contain more than one mitochondrial DNA variant, this genetic transfer from mother to pup is controlled by two mechanisms: first during the development of the egg (oocyte), and later during the early stages of embryonic development. The scientists explained that "this control is aimed at preventing the co-occurrence of various types of mitochondrial DNA in the new individual," which can lead to the development of mitochondrial diseases.

The information provided in the new study is important for two reasons. Understanding the mechanisms that regulate the segregation of the mitochondrial genome is necessary for the development of strategies to prevent mother-to-child transfer of mutated mitochondrial DNA that cause mitochondrial diseases. The new findings will also help scientists to devise ways to prevent different types of mitochondrial DNA co-occurring in the same cell as an unwanted result of medical interventions; this phenomenon, known as heteroplasmy, is a potential risk of mitochondrial replacement therapy.

The study shows that heteroplasmy can alter the metabolism of embryonic cells, inducing increased mitochondrial production of reactive oxygen species. This produces changes in the morphology of the inner mitochondrial membrane and in the molecular machinery for energy production.

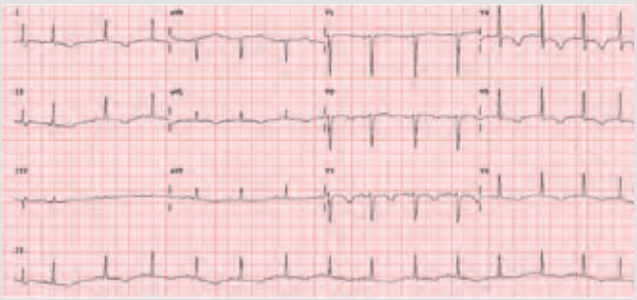
Latorre-Pellicer, A., Lechuga-Vieco, A. V., Johnston, I. G., Hämäläinen, R. H., Pellico, J., Justo-Méndez, R., . . . Enríquez, J. A. *Regulation of Mother-to-Offspring Transmission of mtDNA Heteroplasmy*. ***Cell Metabolism***. doi:10.1016/j.cmet.2019.09.007

JACC

The rate of coronary intervention in coronary-syndrome patients: an index of health system performance linked to survival

CNIC scientists have found that that a higher rate of coronary revascularization during hospitalization for non-ST segment elevation acute coronary syndrome (NSTEACS) is associated with better patient survival 2 years after hospital discharge, whether analyzed at the hospital, national, or supranational level.

The article was published in the *Journal of the American College of Cardiology*, and CNIC researchers Héctor Bueno, Xavier Rosselló, and Stuart Pocock believe that the findings will help to define and update quality-care guidelines for acute myocardial infarction, such as those recommended by the Acute Cardiovascular Care Association of the European Society of Cardiology. The revascularization rate in patients admitted for NSTEACS can serve as an index of health-care quality at the hospital, national, or supranational level.



The CNIC researchers also affirmed that these results highlight "the importance of addressing the mismatch between clinical practice guideline recommendations and common medical practice."

One of the study's main conclusions is that there is a need for more dynamic referral procedures to ensure that NSTEMI patients are rapidly transferred from centers with limited facilities to centers with a catheterization laboratory.

Bueno, H., Rossello, X., Pocock, S. J., Van de Werf, F., Chin, C. T., Danchin, N., . . . Huo, Y. (2019). In-Hospital Coronary Revascularization Rates and Post-Discharge Mortality Risk in Non-ST-Segment Elevation Acute Coronary Syndrome. Journal of the American College of Cardiology, 74(11), 1454-1461. doi:10.1016/j.jacc.2019.06.068

Circulation

Possible treatment breakthrough for arrhythmogenic right ventricular cardiomyopathy type 5

Arrhythmogenic right ventricular cardiomyopathy type 5 (ARVC5) is a fatal genetic disease for which there is unfortunately no cure. Now, scientists at the CNIC and Puerta de Hierro Majadahonda Hospital have discovered a possible treatment for this rare disease. Using a transgenic mouse model that mimics human ARVC5, the research team showed that strategies to inhibit the protein kinase GSK3 ARVC5 reduce fibrosis and improve heart function.

Arrhythmogenic cardiomyopathy can cause sudden cardiac death, especially in young men. Less severely affected men and women with this disease gradually develop heart failure, explained study coordinators Dr. Enrique Lara Pezzi, a group leader at the CNIC, and Dr. Pablo García-Pavía, director of the Familial Cardiomyopathy Unit in the Cardiology Service at Puerta de Hierro University Hospital.

The research team tested several candidate therapeutic approaches in the mouse ARVC5 model. While treatments

directly targeting fibrosis were ineffective, positive results were obtained with two strategies for inhibiting GSK3, one based on pharmacological inhibition and the other on overexpression of the calcineurin subunit CnAβ1.

Having identified a possible route for effective treatment for the disease in mice, the research team is now working to translate the results to patients. Using the mouse model, the scientists are testing drugs used to treat human heart failure to see if they are effective against ARVC5. The team is also investigating gene therapy strategies that could improve heart function or even cure the disease.

Nevertheless, the scientists warn that, although the transgenic mouse model, it does not reproduce all disease characteristics. For example, male and female mice are equally affected, whereas the human disease is much more aggressive in men than in women.

Padrón-Barthe, L., Villalba-Orero, M., Gómez-Salinero, J. M., Domínguez, F., Román, M., Larrasa-Alonso, J., . . . Lara-Pezzi, E. (2019). *Severe Cardiac Dysfunction and Death Caused by ARVC Type 5 is Improved by Inhibition of GSK3beta*. ***Circulation***. doi:doi:10.1161/CIRCULATIONAHA.119.040366

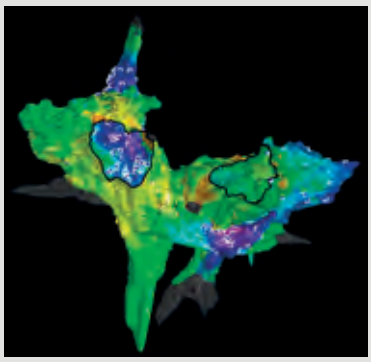
Circulation Research

A new method to improve treatment of atrial fibrillation

Researchers at the CNIC, the Hospital Clínico San Carlos in Madrid, and the Spanish cardiovascular research network (CiberCV) discovered a new method to optimize ablation of atrial fibrillation (AFib), one of the most common forms of irregular heartbeat (arrhythmia). The study featured on the cover of the journal *Circulation Research*.

When a cardiac arrhythmia does not respond to drug therapy, the standard treatment is catheter ablation to isolate the pulmonary veins from the left atrium. However, the results of ablation are disappointing in patients with a complex AFib that is not limited to the pulmonary veins but also involves other atrial regions. “This is especially common in persistent AFib lasting months or years,” explained study coordinator Dr David Filgueiras, who leads a research group at the CNIC and is a cardiologist at the Hospital Clínico San Carlos.

First author Dr Jorge García Quintanilla explained that the new method “allows ablation procedures to be tailored to the specific needs of individual patients with persistent AFib, identifying the key regions to treat with high precision.” Dr Filgueiras added that the new method “costs no more than the conventional procedure and there is thus no obstacle to its use by most centers experienced in AFib ablation.”



To treat persistent AFib, clinical practitioners have begun to use closed systems that guide the ablation to regions with rotational or focal electrical activity. However, these systems are very expensive and, as Dr Filgueiras explained, “often do not establish the spatiotemporal stability of the electrical foci with sufficient rigor and do not take account of the hierarchical organization underlying the arrhythmia.” Moreover, these systems have important technical limitations and require

the use of expensive single-use consumables as well as the purchase of the equipment needed to process the information acquired with these consumables. As Dr García Quintanilla explained, "For the few centers that use these systems, the cost per procedure is very high, making this approach unfeasible for general use with large numbers of AFib patients."

Julián Pérez Villacastín, Director of the Cardiovascular Institute at the Hospital Clínico San Carlos, summarized the importance of the study findings. "Our achievement is a good example of the importance of organizing multidisciplinary teams. This will allow the studies performed at the CNIC to be translated into new treatments for patients with difficult arrhythmias at the Hospital Clínico San Carlos arrhythmia unit and hopefully at many other centers. We are still unable to completely cure these arrhythmias, but this new technology will greatly improve quality of life for our patients."

Quintanilla, J. G., Alfonso-Almazan, J. M., Perez-Castellano, N., Pandit, S. V., Jalife, J., Perez-Villacastin, J., & Filgueiras-Rama, D. (2019). *Instantaneous Amplitude and Frequency Modulations Detect The Footprint of Rotational Activity and Reveal Stable Driver Regions as Targets for Persistent Atrial Fibrillation Ablation*. ***Circulation Research***, 125(6), 609-627. doi:10.1161/CIRCRESAHA.119.314930

JACC

CNIC coordinates an international consensus document on the use of magnetic resonance imaging after a heart attack

The CNIC has coordinated the first international consensus document providing guidelines on the conduct of magnetic resonance imaging studies after a myocardial infarction in clinical trials or experimental models. The document concludes that the main outcome parameter in studies assessing new treatments should be absolute infarct size: the percentage of the left ventricle that is irreversibly damaged. The recommended timing for magnetic resonance imaging is between 3 and 7 days after the infarction.

Recent years have witnessed an exponential growth in the use of magnetic resonance imaging after a heart attack to assess patients' risk of future events, understand the changes taking place in cardiac tissue, and evaluate the benefit of treatments. The colossal technological advances in this area have generated a plethora of new options for studying these parameters. The lead scientists on the consensus document are Dr Borja Ibañez—Clinical Research Director at the CNIC, consultant cardiologist at Fundación Jiménez Díaz hospital, and a member of the CIBERCV cardiovascular research network—and Dr Valentín Fuster—Director of the Cardiovascular Institute and Medical Director at Mount Sinai Hospital in New York. The document addresses the need within the cardiovascular community for guidance on the best protocols, the best techniques, and the most appropriate situations for conducting a magnetic resonance imaging study after a heart attack. The document was published in one of the world-leading cardiovascular research journals, the *Journal of the American College of Cardiology*.

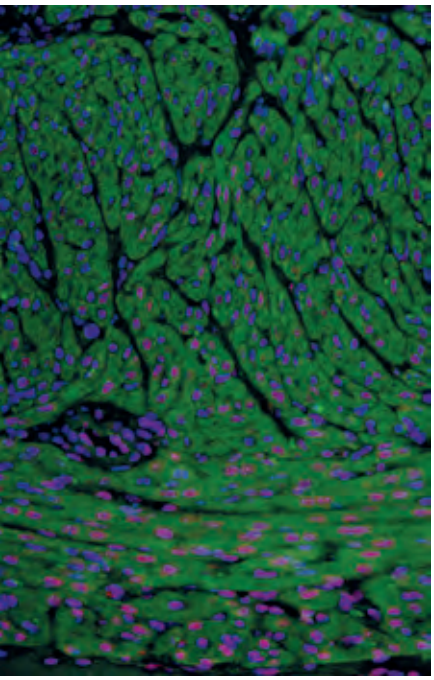
In addition to establishing absolute infarct size as the main outcome measure to assess in studies evaluating new treatments, the document recommends that magnetic resonance scans should be carried out between days 3 and 7 after the infarction. "The scientific evidence indicates that the period between 3 and 7 days after an infarction is when magnetic resonance parameters are more stable and less affected by rapid changes occurring in the heart as it attempts to repair itself. This time window is also practical, since most patients remain in hospital for at least 3 days after having a heart attack. This time window should be used in clinical trials related to myocardial infarction," commented the researchers.

The document's contents were defined during an international meeting held at the CNIC with support from Philips. The meeting brought together a multidisciplinary group of 16 experts in the field from the USA, Canada, the UK, France, Germany, Sweden, the Netherlands, Greece, Switzerland, Singapore, and Spain, including Dr David García-Dorado of the CIBERCV.

Ibanez, B., Aletras, A. H., Arai, A. E., Arheden, H., Bax, J., Berry, C., . . . Fuster, V. (2019). *Cardiac MRI Endpoints in Myocardial Infarction Experimental and Clinical Trials: JACC Scientific Expert Panel*. ***Journal of the American College of Cardiology***, 74(2), 238-256. doi:10.1016/j.jacc.2019.05.024

Circulation Research

An essential protein for correct heart contraction and survival



A team of scientists led by Dr Enrique Lara Pezzi at the CNIC has identified the RNA-binding protein SRSF3 as an essential factor for proper heart contraction and survival. In a study published in *Circulation Research*, the researchers found that loss of cardiac expression of SRSF3 leads to a critical reduction in the expression of genes involved in contraction. Knowledge of the mechanism of action of SRSF3 in the heart could open the way to the design of new therapeutic approaches for the treatment of heart disease.

RNA-binding proteins perform important tasks in the cell. "In this study, we have investigated the role of the RBP SRSF3 in the heart, which was unknown until now," explained Dr Lara Pezzi.

Study first author Dr Paula Ortiz Sánchez, together with the rest of the research team, found that during embryonic development SRFS3 is expressed at high levels in cardiomyocytes and regulates their division. "Embryos lacking SRSF3 in these cells die," said Dr Lara Pezzi. However, in the adult heart, "cardiomyocytes barely divide, and SRSF3 expression is much lower, especially after a heart attack, indicating that the role of SRSF3 in the adult heart must be different."

To investigate the mechanism through which SRSF3 supports heart contraction, the team compared the expression pattern and alternative processing (spicing) of all the mRNAs expressed in the hearts of mice lacking SRSF3 with results from control mice. "We found reduced expression levels of mRNAs encoding protein components of the sarcomere, the physical contractile apparatus within cardiomyocytes," explained Dr Lara Pezzi. "This reduction in the absence of SRSF3 was due to the degradation of these mRNAs, caused by the loss of a chemical modification, called the cap, at the 5' end of mRNAs that, among other functions, protects them against degradation."

The identification of mRNA capping as a mechanism that protects against the development of systolic heart failure could open the way to the development of urgently needed therapeutic tools to combat this disease.

Ortiz-Sanchez, P., Villalba-Orero, M., Lopez-Olaneta, M. M., Larrasa-Alonso, J., Sanchez-Cabo, F., Marti-Gomez, C., . . . Lara-Pezzi, E. (2019). *Loss of SRSF3 in Cardiomyocytes Leads to Decapping of Contraction Related mRNAs and Severe Systolic Dysfunction.* ***Circulation Research***. doi:10.1161/CIRCRESAHA.118.314515

European Journal of Preventive Cardiology

An online tool for predicting cardiovascular risk

There are many online cardiovascular risk calculators, but thanks to a new article in the *European Journal of Preventive Cardiology*, a journal of the European Society of Cardiology (ESC), it is now easy to choose the best one for each individual. CNIC investigator Dr Xavier Rossello, first author on the study, explained: "Risk calculators estimate the possibility that a person will have a heart attack or stroke and indicate the most effective lifestyle changes and medications for reducing that risk."

U-Prevent is an online tool available free to the general population and health care professionals. The platform includes different risk calculators for distinct population categories: patients with established cardiovascular disease (CVD) or type 2 diabetes, people below the age of 70 with neither of these conditions, and people aged 70 or above (with or without CVD or diabetes). U-Prevent allows the estimation of 5 and 10 year CVD risk and the lifetime effect on CVD-free life expectancy of medication with specific drugs.

The article details the free online tools for estimating cardiovascular risk. For each one, the article specifies the specific population group and geographical area for which it is most appropriate and outlines the results it provides.

"Risk calculators evaluate prognosis objectively and impartially," commented. Dr Rossello. "Their use can prevent both excessive and insufficient treatment and allows physicians to optimize resources to obtain better results. Traditional methods are based on clinical judgement, experience, and personal belief, and are therefore inconsistent and can be imprecise."

U-Prevent is the result of the ESC Prevention of CVD Programme, run by the European Association for Preventive Cardiology (EAPC) in partnership with the Association of Cardiovascular Nursing and Allied Professions (ACNAP) and the Acute Cardiovascular Care Association (ACCA). The article was also published in the European Heart Journal – Acute Cardiovascular Care and the European Journal of Cardiovascular Nursing.

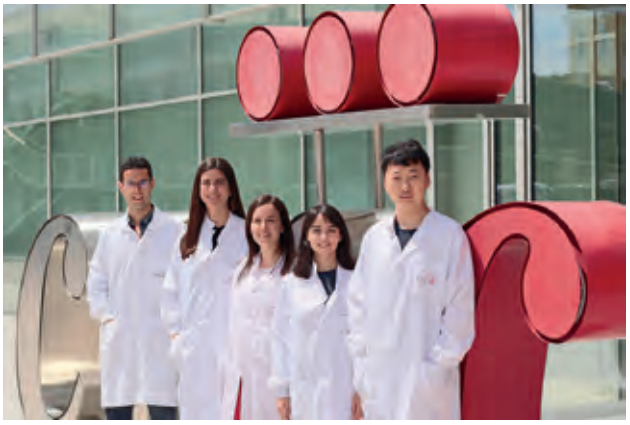
Rossello X, Dorresteijn JAN, Janssen A, et al. *Risk prediction tools in cardiovascular disease prevention*. ***Eur J Prev Cardiol***. 2019. doi:10.1177/2047487319846715.

Nature Communications

A new genetic tool to modify and understand gene function

CNIC scientists led by Rui Benedito have developed a new genetic tool (iSuRe-Cre) that provides certainty in Cre-inducible genetic modifications, a key technique for understanding gene function.

Most analysis of gene function in biomedical research relies on the use of Cre-lox technology. This technology allows scientists to regulate gene expression at any time or in any cell type thanks to the ability of the Cre recombinase protein to recognize and recombine lox sites introduced at specific locations in the mouse genome, leading to the deletion of the genes being studied. Despite the major impact of Cre-loxP technology on biomedical research, numerous studies have demonstrated the need for caution in its use. The main problem is that the Cre activity level is often insufficient to fully recombine and eliminate expression of the target gene, generating uncertainty about whether the desired genetic modification has been achieved.



To overcome this technical hurdle, the CNIC team have developed an innovative method based on a new allele called iSuRe-Cre. iSuRe-Cre is compatible with all existing Cre/CreERT2/lox alleles and guarantees high Cre activity in the cells that express the fluorescent reporter. This ultimately increases the efficiency and reliability of the analysis of Cre-dependent gene function. Moreover, the use of the new iSuRe-Cre mice permits the induction of multiple genetic deletions in the same cell. This important property allows the study of functional genetic interactions or epistasis, or in other words, how the function of one or more genes depends on the function of another.

Rui Benedito believes that the new genetic tool will be of great interest in biomedical research "because it significantly increases the ease, efficiency, and reliability of genetic modification in the mouse, the most widely used animal model in research." The study was published in *Nature Communications*.

Fernández-Chacón, M., Casquero-García, V., Luo, W., Francesca Lunella, F., Ferreira Rocha, S., Del Olmo-Cabrera, S., & Benedito, R. (2019). *iSuRe-Cre is a genetic tool to reliably induce and report Cre-dependent genetic modifications.* ***Nature Communications***, 10(1), 2262. doi:10.1038/s41467-019-10239-4

Nature Communications

A newly identified mechanism can be targeted to boost angiogenesis

CNIC scientists led by Rui Benedito have discovered a cellular and molecular mechanism that can be exploited to induce productive and sustained angiogenesis in tissues that have become ischemic due to reduced blood supply. Until now, tissue regeneration treatments based on vascular growth factors have not succeeded in inducing effective angiogenesis—the process through which the body generates new blood vessels. The results, published in *Nature Communications*, suggest that it might be possible to manipulate the newly discovered mechanism to achieve optimal therapeutic angiogenesis.

Over the last 20 years, scientists have shown that appropriate growth of blood vessels in each tissue depends on a correct balance of several molecular proangiogenic and antiangiogenic mechanisms. Ischemic or hypoxic tissues secrete vascular endothelial growth factors (VEGF), which promote angiogenesis by inducing the proliferation and migration of vascular cells. Previous research by Rui Benedito's group showed that blood vessel cells resist and oppose these external mitogenic cues through an intercellular ligand-receptor signaling mechanism called Notch.

The currently prevailing view is that increases in VEGF concentration or decreases in vascular Notch signaling stimulate both vascular cell proliferation and vessel growth. Therefore, strategies aimed at stimulating mitogenesis and angiogenesis to treat cardiovascular disease are based on drugs that promote VEGF signaling or block natural angiogenesis inhibitors such as Notch.

The results in the *Nature Communications* study indicate that high mitogenic stimulation induced by VEGF (or Notch inhibition) arrests the proliferation of angiogenic vessels while at the same time inducing the proliferation of more mature vessels, which are less important for

effective angiogenesis in the context of disease. "The arrest of angiogenesis is due to a bell-shaped dose-response to the mitogenic stimulation. At high levels of mitogenic stimulus, the endothelial cells migrate and branch, but do not proliferate. Eventually, this affects the sustainable development of the blood vessels and the growth or regeneration of the surrounding tissues," says Rui Benedito.

The newly identified mechanism could also explain the failure of several clinical trials seeking to boost angiogenesis in ischemic hearts after a myocardial infarction.

According to Benedito, the results "significantly increase our understanding of the biology of blood vessels and will enable us to design better therapeutic strategies to induce effective angiogenesis in injured or ischemic tissues."

Pontes-Quero, S., Fernandez-Chacon, M., Luo, W., Lunella, F. F., Casquero-Garcia, V., Garcia-Gonzalez, I., . . . Benedito, R. (2019). High mitogenic stimulation arrests angiogenesis. Nature Communications, 10(1), 2016. doi:10.1038/s41467-019-09875-7

JACC

Early Intervention in preschool is a unique opportunity for promoting a healthy lifestyle

Children may have a better chance of avoiding unhealthy habits linked to obesity and cardiovascular disease later in life if they are taught properly about healthy behaviors in preschool, CNIC researchers have shown in a first-of-its-kind study.

The researchers focused on children living in a socioeconomically disadvantaged community, a situation frequenly linked to higher rates of obesity, heart disease, and other health issues. Valentin Fuster created and led the trial, called the FAMILIA Project at Mount Sinai Heart. The results were published in the **Journal of the American College of Cardiology**.

"Results from this new study prove that early intervention is effective in preschool-age children, but we believe this can also promote healthy behaviors among their caregivers and teachers and have a far-reaching impact", explained Dr. Fuster.

This study follows other successful interventions led by Dr. Fuster in Colombia and Spain, but FAMILIA is unique in being the first time the health promotion curriculum was implemented in a multi-ethnic, underprivileged urban

population. Its precedent is the Comprehensive Health Program (SI!). This intervention program is designed to promote cardiovascular health from pre-school to high school through intervention in four areas: nutrition, body and heart awareness, physical activity, and emotional management.

Fernandez-Jimenez, R., Jaslow, R., Bansilal, S., Santana, M., Diaz-Munoz, R., Latina, J., . . . Fuster, V. (2019). *Child Health Promotion in Underserved Communities*. ***The FAMILIA Trial***, 73(16), 2011-2021. doi:10.1016/j.jacc.2019.01.057

Editorial: *Primordial Prevention of Cardiovascular Disease in Childhood: The Time Is Now*

Nature

The protein p38gamma identified as a new therapeutic target in liver cancer

A research team at the CNIC led by Guadalupe Sabio has discovered that the protein p38g, one of the four types of p38 kinase, is essential for the initiation of cell division in liver cells. This result indicates that "p38g could be a useful therapeutic target for liver cancer," says Sabio, adding, "we are now developing inhibitors of this protein to test in this cancer." The study has been published in Nature.

The four members of the p38 kinase family are so similar that at first they appear to have overlapping or redundant functions. Detailed analysis of their three-dimensional structures revealed that one of the four, p38g, also shares close similarities with another family of proteins called CDKs. These proteins are well-known regulators of cell division and the cell cycle and play a well-established role in the development of cancer.

Study first author Antonia Tomás-Loba examined the outcome of chemically inducing liver cancer in mice that lack the enzyme. The results were truly promising: "in mice lacking p38g or treated with inhibitors to block its

activity, the development of hepatocellular carcinoma was slowed," says Tomás-Loba. These results, says Sabio, "could be extrapolated to human patients."

Indeed, work with colleagues at Salamanca University Hospital shows that the amount of p38g increases with liver fibrosis, a process that precedes cancer, and is much higher in liver cancer patients. These results suggest that in the future it may be possible to treat liver cancer with drugs that specifically target p38g. The advantage of targeting p38g is that this enzyme appears to control the initiation of the cell cycle in response to stress, and therefore inhibiting this process would not affect tissues that are constantly proliferating, like the intestinal lining or hair follicles.

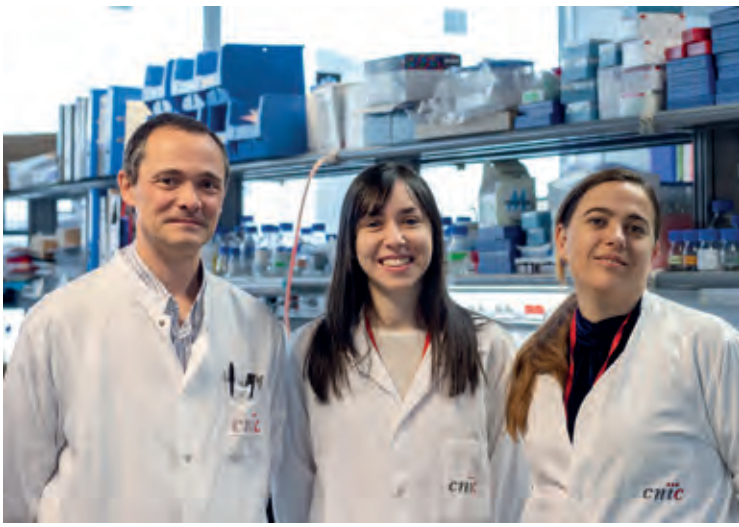
Tomás-Loba, A., Manieri, E., González-Terán, B., Mora, A., Leiva-Vega, L., Santamans, A. M., . . . Sabio, G. (2019). *p38γ is essential for cell cycle progression and liver tumorigenesis*. ***Nature***. doi:10.1038/s41586-019-1112-8

Journal of Experimental Medicine

Adiponectin, the hormone that protects women against liver cancer

A team at the CNIC has found an explanation for the lower rate of liver cancer in women. The answer lies in the hormone adiponectin, which is produced in higher amounts in women than in men and protects the liver against the development of the main form of liver cancer, hepatocellular carcinoma. In their quest to understand why people with obesity have a higher risk of developing liver cancer, the CNIC research group led by Guadalupe Sabio found that adiponectin is more abundant in women and slim people. The study, published in the *Journal of Experimental Medicine*, shows that adiponectin protects the liver against the development of hepatocellular carcinoma.

The research team showed that adiponectin, a hormone produced by adipose tissue, has an anticancer effect in the liver. In a group of healthy individuals, the team found that women produce more adiponectin than men. Describing the study, Dr. Sabio commented, "the circulating levels of adiponectin decline with the development of obesity and after puberty in men, and these are precisely the populations with higher rates of liver cancer. This



observation prompted us to study the phenomenon in depth."

The results "open routes to combating a cancer for which there is currently no specific treatment. One approach would be to use adiponectin itself, while another option is to use metformin, a drug used to treat diabetes that targets the same anticancer protein as adiponectin."

Manieri, E., Herrera-Melle, L., Mora, A., Tomas-Loba, A., Leiva-Vega, L., Fernandez, D. I., . . . Sabio, G. (2019). *Adiponectin accounts for gender differences in hepatocellular carcinoma incidence*. ***Journal of Experimental Medicine***, 216(5), 1108-1119. doi:10.1084/jem.20181288

JACC

Advanced imaging technology predicts cardiovascular risk from inflammation detected in arteries

Using advanced PET/MRI technology, researchers at the CNIC have detected arterial inflammation in regions that have yet to develop atherosclerotic plaques. These results from the PESA-CNIC-Santander study were published in *JACC*. The research team used this innovative technology to analyze the inflammatory process in the arteries of a group of people who had already developed atherosclerotic plaques.

The results show, for the first time, that inflammation is present at early stages of atherosclerosis, above all in regions that have not developed plaques. The study also shows that this arterial atherosclerosis can be an early indication of the later appearance of plaques that underlie cardiovascular disease and events such as heart attack and stroke. The researchers are currently analyzing the role of arterial inflammation in this process; this information will help to establish early diagnosis and develop new anti-inflammatory therapies for this disease.

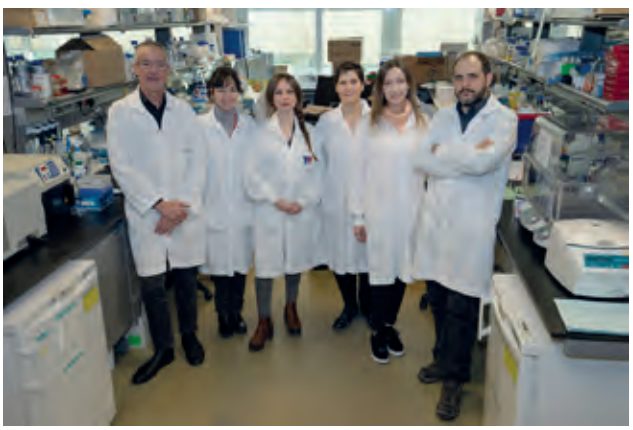
Fernández-Friera, L., Fuster, V., López-Melgar, B., Oliva, B., Sánchez-González, J., Macías, A., . . . Sanz, J. (2019). *Vascular Inflammation in Subclinical Atherosclerosis Detected by Hybrid PET/MRI*. ***Journal of the American College of Cardiology***, 73(12), 1371-1382. doi:10.1016/j.jacc.2018.12.075

EMBO Molecular Medicine

New therapeutic target for blocking early atherosclerosis in progeria

Researchers at the CNIC and the Universidad de Oviedo have discovered a new molecular mechanism involved in the premature development of atherosclerosis in mice with Hutchinson-Gilford progeria syndrome (HGPS). The results, published in *EMBO Molecular Medicine*, identify a potential therapeutic target for this severe genetic disease.

The study was co-directed by Vicente Andrés of the CNIC and the CIBERCV and Carlos López Otín of the Universidad de Oviedo and identifies a molecular mechanism involved in the accelerated development of atherosclerosis in progeria. In addition, the results identify a candidate pharmacological treatment that slows the progression of atherosclerosis and extends the lifespan of progeroid mice.



The study, featured in an editorial in the journal, shows for the first time that "stress in the endoplasmic reticulum (ER stress) and the associated unfolded protein response (UPR) are involved in the death of vascular smooth muscle cells in progeroid mice," explained first author Magda Hamczyk.

The research team used the compound tauroursodeoxycholic acid (TUDCA), which reduces the negative consequences of the activation of the ER stress and UPR pathways. Treatment of progeroid mice with TUDCA inhibited the progression of vascular disease, including vascular smooth cell loss and atherosclerosis. TUDCA also prolonged the lifespan of progeroid mice, which die from the complications of atherosclerosis.

The authors conclude that "these findings open a new research avenue in progeria and suggest that TUDCA could be used to treat vascular disease in HGPS patients and increase their life expectancy."

Hamczyk, M. R., Villa-Bellosta, R., Quesada, V., Gonzalo, P., Vidak, S., Nevado, R. M., . . . Andres, V. (2019). *Progerin accelerates atherosclerosis by inducing endoplasmic reticulum stress in vascular smooth muscle cells*. ***EMBO Molecular Medicine***. doi:10.15252/emmm.201809736

JACC

A very early marker of cardiac damage triggered by cancer treatment

Researchers at the CNIC identified a very early marker of cardiac damage in patients undergoing therapy with anthracyclines, a family of drugs commonly used to treat cancer. This finding will enable the early diagnosis of the cardiotoxicity associated with this group of widely used chemotherapy drugs.

Dr Borja Ibañez coordinated the study, published in the *Journal of the American College of Cardiology* (JACC). As Dr Ibañez explained, the results have important implications for therapy because the detection this drug-induced damage at very early stages will permit "the implementation of treatments to prevent further deterioration in heart function and a clinical management more closely adapted to the needs of each patient." The identified marker is affected much earlier than any of the markers used in current clinical practice.

This valuable discovery was possible thanks to a new pig model of anthracycline-induced cardiotoxicity developed by the CNIC team. In the study, animals received increasing doses of the anthracycline drug doxorubicin over 10 weeks. This strategy allowed the accumulation of the drug in the heart muscle without major exposure in other organs.

The results of the JACC study may help to prevent the severe secondary effects experienced by cancer patients

receiving chemotherapy. Moreover, the study may also open the way to new therapies based on mitochondrial transplantation.

Galán-Arriola, C., Lobo, M., Vílchez-Tschischke, J. P., López, G. J., de Molina-Iracheta, A., Pérez-Martínez, C., . . . Ibanez, B. (2019). Serial Magnetic Resonance Imaging to Identify Early Stages of Anthracycline-Induced Cardiotoxicity. Journal of the American College of Cardiology, 73(7), 779-791. doi:10.1016/j.jacc.2018.11.046

CNIC and SEC promote a study to modify clinical practice after a heart attack

The REBOOT study aims to demonstrate whether it is really necessary to maintain beta-blocker therapy after discharge from hospital for AMI in patients without left ventricular systolic dysfunction. In Spain there could be almost one million people with these characteristics.

Together with the Spanish Society of Cardiology (SEC), the CNIC is leading a pioneering project in Spain: TREeatment with Beta-blockers after myOcardial infarction withOut reduced ejection fracTion (REBOOT), which has the ambitious goal of changing clinical practice guidelines after acute myocardial infarction. "For this, the effect of maintaining treatment with beta-blockers after discharge from hospital for an infarction, will be tested on a total of 8,468 patients", explains Dr. Borja Ibáñez, main researcher of the study and Director of Clinical Research at the CNIC.

Beta-blockers are drugs that reduce heart rate, blood pressure, and contractility (strength of the heart) by promoting cardiac diastole and thereby improving heart function and blood flow to the coronary arteries. Despite the fact that most of the evidence comes from a time when what was done was reperfusion to patients, beta-blockers have been approved in both European and American clinical practice guidelines for decades for the treatment of patients after acute myocardial infarction. "Although there is no evidence of clinical benefit in patients without left ventricular systolic dysfunction, they are very frequently prescribed," says Dr. Manuel Anguita, president of the SEC. "Both prescription and non-prescription of beta-blockers in these patients are currently valid options," he points out.

Each year in Spain, about 100,000 heart attacks occur that do not produce left ventricular systolic dysfunction. These

patients are almost universally discharged from hospital with two antiaggregant drugs (aspirin and a P2Y12 inhibitor), statins, IECAS, beta-blocker and a gastric protector. In many cases other types of medication are associated. Except for the P2Y12 inhibitor and the gastric protector, the rest of the medications are currently prescribed for life.

But one of the main Achilles' heels of heart attack treatment is low adherence, with the number of medications prescribed being one of the main factors contributing to this low adherence. This is why a polypill has been developed that includes aspirin, statin and ACE inhibitors. The use of this polypill has been shown to increase medication adherence. Beta-blockers, despite having a very high safety profile and being very cheap (they are already off patent), are not exempt from possible adverse effects that can limit patients' quality of life and which include asthenia, weakness and in some cases impotence.

Since many patients who suffer a heart attack are middle aged and have many decades ahead of them and quality of life is a very relevant factor to take into account, it is of vital importance to know if these are really necessary in this type of patients. If they were not shown to be effective in this type of post-infarction patient, they would not be prescribed and this could result in an increase in the patients' adherence to medications that have been shown to be effective and also avoid possible adverse effects that could limit the patients' quality of life.

The research will recruit a total of 8,500 patients who will randomly receive treatment with or without beta-blockers and who will be followed-up on for a minimum of two years and a maximum of three. In addition, the study will record the incidence of clinical events as well as adherence to the randomized treatment. In a sub-sample of 1,000 patients the quality of life of these patients will also be assessed during follow-up.

CNIC, with the support of the SEC and the CIBERCV, has finally made it possible for REBOOT to be carried out, thanks to the altruistic collaboration of 55 Spanish and 25 Italian hospitals. Other hospitals that are interested can contact via the trial account reboot@cnic.es. The trial is included in line 2 of the CIBERCV, which seeks to improve the treatment of acute myocardial infarction.

The topic of research is of such clinical relevance that three other clinical trials similar to REBOOT are to be initiated in Europe – in Sweden, Norway and Denmark. In total, more than 20,000 patients with similar characteristics will be randomized to receive beta-blockers or not after a heart attack without ventricular dysfunction. "Running in parallel will not only measure our potential to match countries with a tradition of large clinical trials, but will also allow meta-analyses to be performed by bringing all the cohorts together," concludes Ibáñez.

CNIC and CNIO promote cooperative work to facilitate research excellence

Cancer and cardiovascular disease share many molecular mechanisms. For this reason, scientists from both these fields can collaborate on many projects. This situation also applies to scientists at the National Cancer Research Centre (CNIO) and the National Cardiovascular Research Centre (CNIC), who share similar and complementary technological platforms. With the aim of sharing knowledge and promoting synergies and future collaborations, the two centers of excellence affiliated to the Carlos III Health Institute (ISCIII) organized the CNIO-CNIC Joint Meeting.

With the presence of Raquel Yotti, Director of the ISCIII, and Maria Blasco and Valentin Fuster, Directors of the CNIO and CNIC respectively, they touched upon some of the most innovative lines being carried out in each of their institutions and highlighted the vital importance of collaborative research.

"This is a very important initiative, not only because of the outstanding quality of the scientific program of this meeting, but also because it represents a real effort to share knowledge between disciplines and build bridges between two of the most important research centers in Spain and Europe. This kind of multidisciplinary and collaborative environment can inspire creative interaction, which can lead to new questions and eventually new solutions," said Yotti.

"The CNIO and the CNIC are working to advance treatments for diseases that in many cases have a common origin," said María Blasco. "To do this, it is essential to collaborate and share knowledge between our institutions".

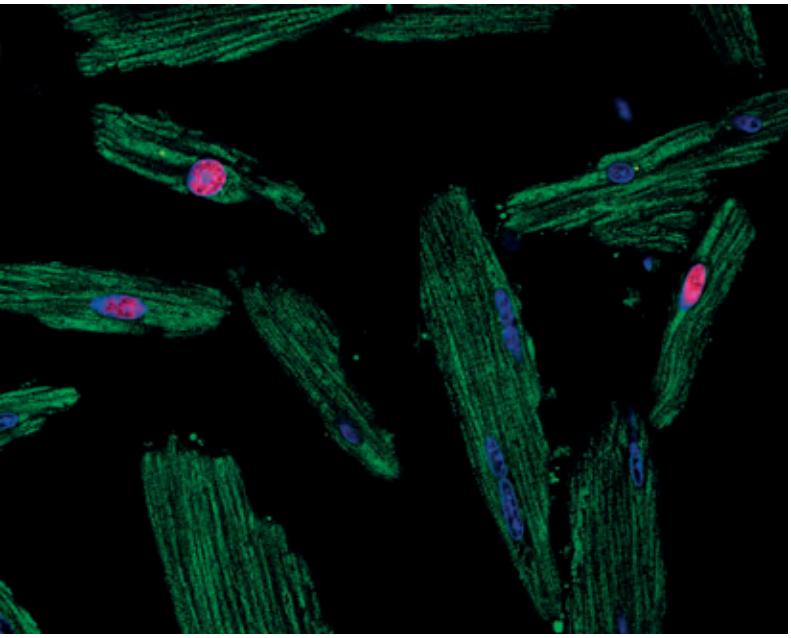
On his part, Valentín Fuster stated that "this meeting reflects the philosophy that the CNIC has followed since its foundation, based on collaborative research with research centers of excellence, as is the case with the CNIO, and oriented towards translation and the benefit to the patient".

The conference was attended by some of the most renowned scientists from each center, who have told us upfront about their lines of research. On behalf of the CNIO, Marisol Soengas, head of the Melanoma Group; Óscar Llorca, head of the Macromolecular Complexes in Response to DNA Damage Group; Ana Losada, head of the Chromosomal Dynamics Group; and Óscar Fernández-Capetillo, head of the Genomic Instability Group, all intervened.

Representing the CNIC were Guadalupe Sabio, head of the Group on the Role of Stress Activated Kinases in the Development of Cardiovascular Disease, Diabetes and Cancer; Andrés Hidalgo, head of the Cardiovascular Inflammation and Immune Response Imaging Group; Jacob Bentzon, head of the Experimental Pathology of Atherosclerosis Group, and Borja Ibáñez, head of the Translational Laboratory for Cardiovascular Imaging and Therapy.

REANIMA: toward a new paradigm in cardiac regeneration

Dr. Miguel Torres, of the Centro Nacional de Investigaciones Cardiovasculares (CNIC), leads a new project that will receive €8 million in funding over 5 years, €1,380,000 of which will be directly managed at the CNIC



Research into new endogenous mechanisms of tissue regeneration is an innovative research avenue in cardiac regeneration. This is the central goal of the **REANIMA** project (New generation cardiac therapeutic strategies directed to the activation of endogenous regenerative mechanisms), a research program coordinated by Dr. Miguel Torres at the *Centro Nacional de Investigaciones Cardiovasculares* (CNIC) and supported by **€8 million funding over 5 years**, of which €1,380,000 will be directly managed at the CNIC. The project was launch in January 2020.

"REANIMA addresses one of the big challenges in biomedicine: how to successfully translate knowledge gleaned from basic research on biological regeneration into medical applications, in this case the regeneration of the heart," said Dr Torres.

Cardiovascular disease is the leading cause of death in the world. The associated heart failure is a worldwide epidemic that imposes a heavy societal burden in death, disease, and escalating economic costs and can only be resolved by heart transplantation.

The inability of the human heart to regenerate myocardium lost during a heart attack is the major factor in a high proportion of cases of heart failure. To resolve this problem, Dr Torres said that "the goal of REANIMA is to provide new therapies for heart regeneration."

Until now, clinical trials based on the introduction of stem cells into the heart have not shown regenerative capacity. However, studies of spontaneous and induced heart regeneration in animal models suggest that the path to progress lies in the reactivation of endogenous regenerative mechanisms. Fish and amphibians are able to regenerate their hearts, and although mammals have historically been considered to lack this capacity, regeneration was recently shown to occur in injured hearts of newborn mice. Unfortunately, in adult mammals, including humans, the heart's residual capacity to regenerate is insufficient to recover function naturally.

REANIMA, said Dr Torres, "will exhaustively analyze knowledge accumulated from research in animal models in order to transform it into new regenerative therapies to resolve heart failure."

The project brings together knowledge obtained from species that can regenerate their hearts (fish and amphibians), animals that cannot (adult mammals), and human heart tissues generated by tissue engineering.

> *"REANIMA addresses one of the greatest challenges in biomedicine: translating knowledge of regenerative biology from the laboratory to clinical applications, in this case regeneration of the heart"*

REANIMA is the first Europe-wide project to integrate basic research findings in an effort to transform them into medical applications in the field of cardiac regeneration. **REANIMA is funded by the European Union's Horizon 2020 research and innovation programme under grant agreement nº 874764**. Project activities range from identifying new targets in animal models to the design of clinical trials. The project is linked to the similarly named 'REANIMA-CM' project funded by the *Comunidad de Madrid*, which is also coordinated by Dr Torres. In addition to the CNIC, another 11 European centers participate in this innovative project: Universitaetsklinikum Hamburg-Eppendorf , UKE (Germany); King's College London (United Kingdom); University of Bern (Switzerland); Research Institute of Molecular Pathology, IMP (Austria); the Weizmann Institute of Science (Israel); Hubrecht Institute (the Netherlands); Ethris GMBH (Germany); ZeClinics SL (Spain); German Primate Center, DPZ (Germany); Scuola Superiore Sant' Anna (Italy), and the Fraunhofer Institute for Cell Therapy and Immunology, IZI (Germany).

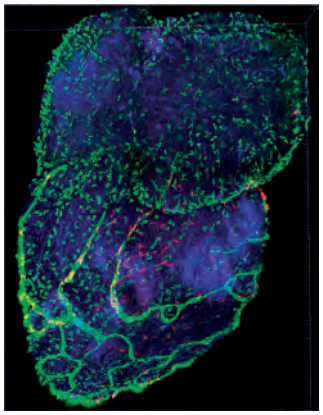
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement nº 874764.

The synergy between the various partners will allow REANIMA to identify new regeneration pathways in animals and use this knowledge to design strategies to reactivate these pathways in animals and human heart tissues generated by tissue engineering.

By bringing together industrial partners and academics specialized in translational and preclinical research, REANIMA will allow the development of new advanced therapies.

"We believe that REANIMA will overturn the paradigms that underlie current clinical research in regenerative cardiology by transforming basic knowledge of endogenous pathways into effective new therapies," said Dr Torres.

> *"In addition to the CNIC, another 11 European research centers are participating in this innovative project"*



REANIMA was selected for funding in the **"Regenerative medicine: from new insights to new applications"** call, published within the "Health demographic change and wellbeing" H2020 Work Programme. This call had a total Budget of €50,000,000 and received 154 project submissions. REANIMA was the second ranked project and received the maximum permitted funding, a total of €8 million for 12 European institutions in several countries and covering a period of 5 years.

Miguel Torres

elected a member of the European Molecular Biology Organization – EMBO

EMBO promotes excellence in scientific research, and one of its major goals is to support talented researchers at all stages of their careers

Dr. Miguel Torres, a group leader at the Centro Nacional de Investigaciones Cardiovasculares (CNIC), has been elected a member of the European Molecular Biology Organization (EMBO). EMBO today named the 56 new members who will form part of this organization of more than 1800 leading scientists from Europe and around the world.

EMBO Director Maria Leptin explained that "EMBO members are expert scientists who carry out pioneering research across all disciplines in the life sciences, from computer models or analysis of individual molecules and cell mechanisms to the study of higher-level systems in development, cognitive neuroscience, and evolution."

Dr. Miguel Torres's scientific research focuses on **the regulation of embryonic development and the formation and regeneration of organs**. His major contributions include the understanding of how gene activities regulate regionalization processes in the developing embryo and the discovery of mechanisms involved in quality control and organ regeneration.

Dr. Torres formed his group at the CNB-CSIC in Madrid in 1996, where he developed his research into vertebrate organ formation, including projects investigating the limbs and the heart. A major focus of his work on organogenesis is homeodomain genes, and his research in this area has contributed to the understanding of the molecular interactions that regulate the correct formation of distinct regions in the embryo.

Dr. Miguel Torres's research centers on understanding the regulation of embryonic development and the formation and regeneration of organs.

In the field of tissue homeostasis, his work has contributed to understanding the conservation of cell death pathways in the animal kingdom and has demonstrated the physiological relevance of 'cell competition' in mammals. His contributions in this area demonstrate the importance of cell competition in maintaining pluripotency in early embryonic development and its possible role in cardiac regeneration.

In the last ten years, his research has extended to the investigation of how tissue morphogenesis and homeostasis are determined by cell behaviour. This line of research has involved the introduction of new techniques, including new genetic and methodological tools for 3-dimensional microscopy of the developing embryo. Dr. Torres described how his group's work has "established the first technique for the in vivo microscopy of the developing heart in mouse embryos, and this has enabled us to propose a new model of the formation of the heart tube."

Among his various projects, Dr. Torres directs the first Spanish-coordinated international project funded by the prestigious Leducq Foundation: 'Redox Regulation of Cardiomyocyte Renewal' and REANIMA project (New-generation cardiac therapeutic strategies directed to the activation of endogenous regenerative mechanisms).

La Caixa Banking Foundation selects 2 CNIC projects in its call "2018 Health Research Projects"

Two CNIC projects were selected by the La Caixa Banking Foundation in its call "2018 Health Research Projects -La Caixa Banking Foundation". The projects selected by the CNIC are: 'Dysfunction of Ion Channel Complexes in Inheritable Cardiac Diseases', led by Dr. José Jalife, and 'Nitric Oxide signaling and proteoglycans in Marfan syndrome's aortopathy: mechanisms and new therapeutic targets', led by Dr. Juan Miguel Redondo.

The project led by Dr. Jalife uses cutting-edge approaches to understanding the mechanisms of sudden cardiac death in hereditary heart disease, and to identify new therapeutic targets and opportunities for more effective prevention. The study uses new techniques such as the transfer of mutant genes mediated by adeno-associated viruses intravenously into the heart cells of mice, or the use of cardiomyocytes derived from induced pluripotent stem cells, as well as proteomic and bioinformatics technology. In total the project will receive 499,895 euros.

The proposal led by Dr. Redondo aims to unravel the physiopathological mechanisms underlying Marfan syndrome and the formation of aneurysms and dissections in the aorta; as well as to identify new molecular targets to develop effective treatments for the disease and to identify biomarkers. In total it will receive 500,000 euros.

Valentín Fuster, 2019 National Research Award

The Ministry of Science, Innovation and Universities awarded Valentín Fuster the 'Gregorio Marañón' 2019 National Research Prize in the category of Medicine. The winners in other categories were: Ángela Nieto, Susana Marcos, Manuel Carreiras and Mercedes García-Arenal.

The jury awarded him this distinction for his enormous contributions to research, prevention and the diagnosis and treatment of the cardiovascular pathology.

The National Research Awards, created in 1982, are Spain's most important recognition in the field of scientific research. Their objective is to distinguish the merit of those Spanish researchers who are doing outstanding work in scientific fields of international importance and who make an exceptional contribution to the advancement of science, technology transfer and the progress of humanity. These awards have a total value of 150,000 euros, (30,000 euros each prize).

Pura Muñoz-Cánoves, Rei Jaume I Medical Research Award

The CNIC researcher, Dr. Pura Muñoz-Cánoves, was awarded in the category of Medical Research, in the 31st edition of the Rei Jaume I Awards.

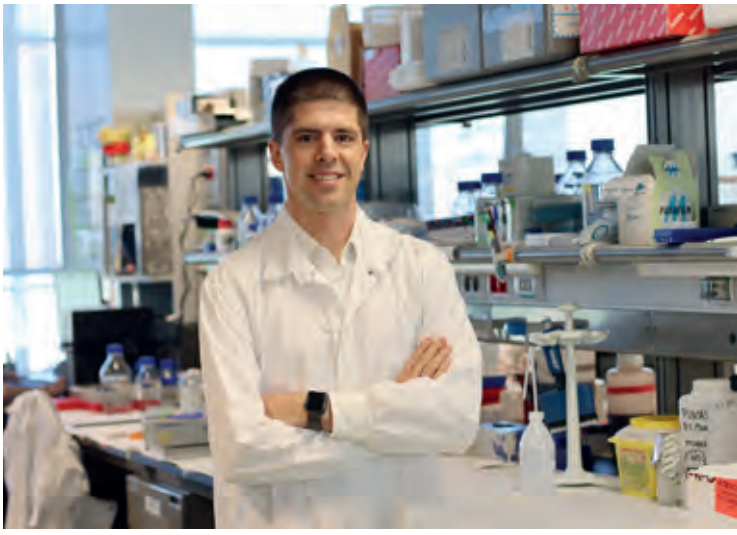
The Rei Jaume I Awards recognize people whose work is highly significant and has been developed mostly in Spain. They are held annually and each one of them is endowed with a gold medal, a diploma and 100,000 euros - with the commitment to reinvest part of the amount in research and entrepreneurship in Spain.

The jury valued her contributions to the molecular mechanisms of aging, especially in the progressive changes of stem cells in aging animals and the possibilities of regenerative medicine.

This year, Dr. Muñoz-Cánoves was also awarded the 2019 Lilly Foundation Preclinical Biomedical Research Award for her pioneering work in the field of tissue regeneration. One of her most innovative advances was the comparative analysis of stem cells in mice of different ages (adult, old and geriatric), and from people of corresponding ages (including very old people, with obvious signs of sarcopenia and fragility) with which Professor Muñoz-Cánoves and her team, have succeeded in changing the prevailing idea that ageing occurs gradually, and have demonstrated that, in the geriatric age, there is an acute and dramatic decline in the regenerative and functional capacity of tissues, attributable to practically irreversible intrinsic alterations in their stem cells.

Rodrigo Fernández wins the 2019 Marie Skłodowska-Curie Actions Award

The researcher Rodrigo Fernández Jiménez received the 2019 Marie Skłodowska-Curie Actions Award, in the category 'Scientific Careers for Policy making' with his project "CLIP" (Comprehensive Lifestyle Intervention Project).



His research addresses new approaches to health promotion and prevention. His ultimate goal is to provide guidance to policy makers to establish effective strategies to promote health in children.

The project aims to convince governments that a low-cost, no-side-effect educational intervention for health promotion has the potential to reduce the epidemic of cardiovascular disease if included as part of the standard national curriculum.

Francisco Sánchez-Madrid awarded Honorary Doctorate by the UCO

Professor Francisco Sánchez Madrid, researcher at the CNIC, Professor of Immunology at the Autónoma University of Madrid and Scientific Director of the IIS-Princesa, was awarded Honorary Doctorate by the University of Córdoba.

His area of research has extended in recent years to the interactions of lymphocytes with the endothelium, activation of lymphocytes and chemokine directed migration, as well as the role of adhesion and activation receptors, and of dendritic cells in the initiation of the immune response, the immune synapse and the regulation of the inflammatory response.

He has been Manager of the National Plan for Biomedicine (2001-2005), President of the Commission on Immunology and Infectious Diseases of the FIS (1998-2000) and Member of the evaluation panel of the ERC (2007-2010). Following an agreement with the Autonomous University and the Princess University Hospital, of which he is Professor and Head of the Immunology Section, in January 2007 he joined the CNIC as head of the Intercellular Communication in Inflammatory Response group.

Dr. José Javier Fuster receives a 2019 Leonardo Scholarship

The project 'Somatic mutations and clonal haematopoiesis in atherosclerotic cardiovascular disease' by Dr. José Javier Fuster, from the CNIC, was one of the 60 projects awarded one of the 2019 Leonardo Grants for Researchers and Cultural Creators. The project aims to study how certain mutations acquired in blood cells and traditionally associated with a high risk of developing leukemia can also contribute to the development of cardiovascular disease and become a new cardiovascular risk factor apart from traditional factors such as cholesterol, diet, hypertension, etc. The project is financed by the BBVA Foundation with 40,000 euros.

Dra. Ivana Nikoli awarded with two projects from the European Diabetes Society

CNIC postdoctoral researcher Ivana Nikolić was awarded with two projects from the European Diabetes Society (EFSD) to study the role of T cells in the development of obesity-related diseases: the "EFSD/Lilly Young Investigator Award" and the "EFSD Rising Star Fellowship". The EFSD/Lilly Young Investigator Award Program consists of a 50,000 euro grant, while the EFSD Rising Star Fellowship Program will be funded with 30,000 euros. Previously, the researcher had been awarded the 2017 EFSD Lilly Research Fellowship Program, with a grant of 50,000 euros.

Dr. Nikolić is one of the examples of the success of the FP7-People Marie Sklodowka - Curie Actions, MSCA - COFUND talent recruitment program which is aimed at attracting important foreign scientists to the CNIC at an intermediate stage of their careers so that they can develop their careers in Spain. So far, she has been awarded three projects from the EFSD to study the molecular mechanisms of obesity.

Cardona hosts the International Cardiovascular Research, led by Dr. Fuster

For the third consecutive year, the town of Cardona in Barcelona hosted the Master Course "Molecular, Clinical & Population Bases of Cardiovascular Disease and Health", directed by Dr. Valentín Fuster - director of the CNIC and the Cardiovascular Institute of Mount Sinai Hospital. The 2019 edition was held thanks to the support of the Icahn School of Medicine at Mount Sinai.

The course is aimed at cardiologists and cardiology residents who are particularly motivated by research and interested in learning about the latest scientific advances.

Since its commencement, this course has been one of the best valued within the entire Summer Courses Program that the International Menéndez y Pelayo University (UIMP) carries out. It counts with the collaboration of the American College of Cardiology and the scientific endorsement of the CNIC. In addition, it is accredited by the Spanish Society of Cardiology and supported by the Network Research Center on Cardiovascular Diseases (CIBERCV).

The course was broadcast in streaming on the websites of the UIMP and the JACC.

Ninth Edition of “Jornada Vive”

For the ninth consecutive year, the Pro CNIC Foundation organized a new edition of its traditional ‘Jornada Vive’, an outreach activity aimed at the part of the population whose hope lies in changing the current situation of the cardiovascular epidemic: the child population. Aimed at children between the ages of 3 and 10, this edition of the ‘Jornada Vive’ was held at the Autónoma University of Madrid where the little ones were able to enjoy numerous heart-healthy activities. This year, more than 500 children participated, children of the employees of the 12 companies and entities that are patrons of the Pro CNIC Foundation.

As part of the program of parallel activities of the 'V National Congress of Scientific Entrepreneurs', the day was organized to get to know the activities and facilities of the CNIC for some of those attending. Among other activities, the scientists visited the Advanced Translational Image Infrastructure (TRIMA) of the ICTS Distributed Biomedical Image Network (ReDIB).

Twelve students from 4 high schools also visited the CNIC as part of the '4ºESO+CNIC 2019 Program'. This program is based on Educational Stays in Companies (EEE) and Observation Sessions in Professional Environment of students from 4th year of Obligatory Secondary Education. The objective is to promote scientific vocations among the youngest students.

The 12 students came from seven different educational centers: IES Fortuny, IES Santa Teresa de Jesús, Colegio Raimundo Lulio and Colegio Santa Francisca Javier Cabrini, in Madrid; Colegio Humanitas in Torrejón de Ardoz, Colegio Gredos San Diego El Escorial, and Colegio Calasanz, in Alcalá de Henares.

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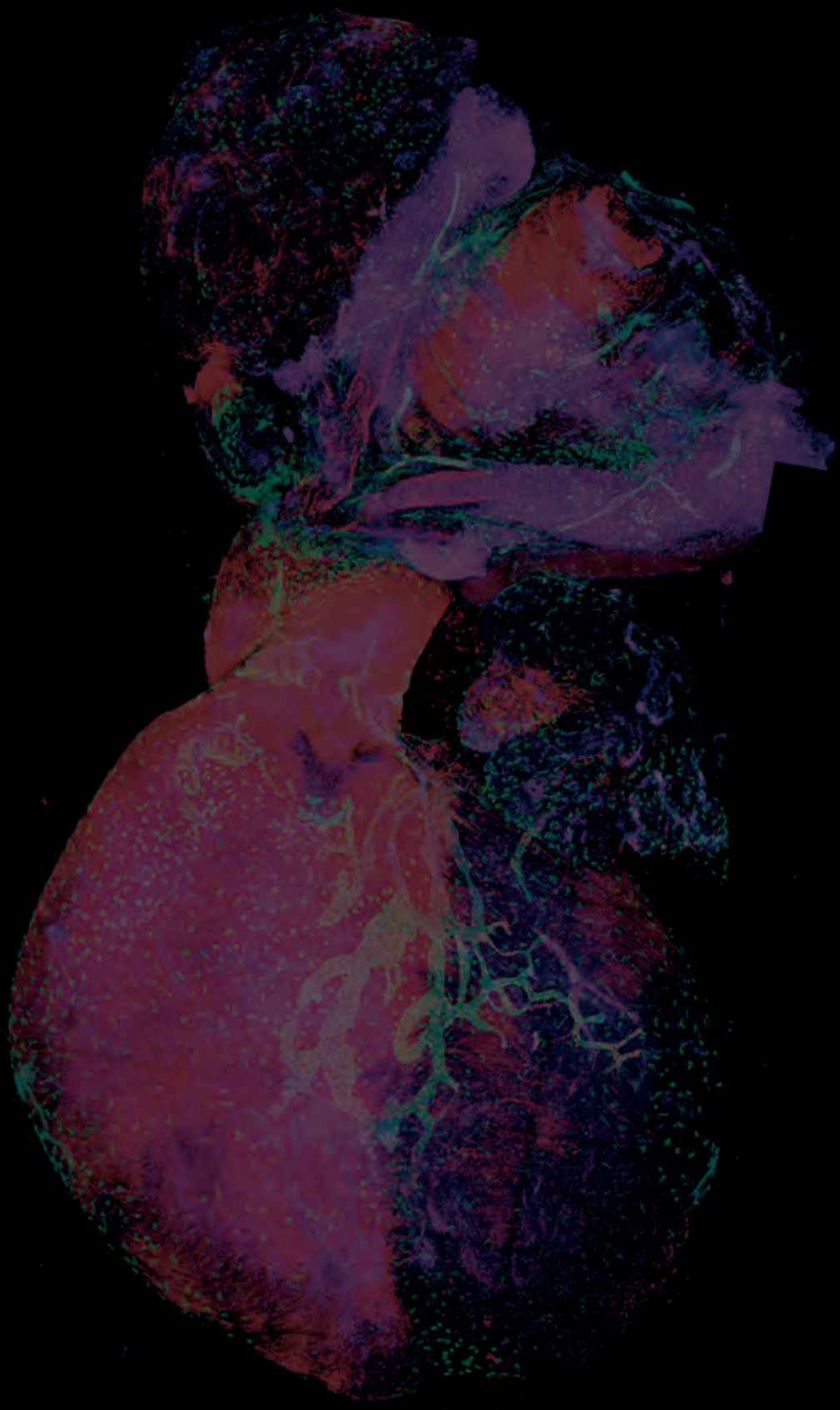

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