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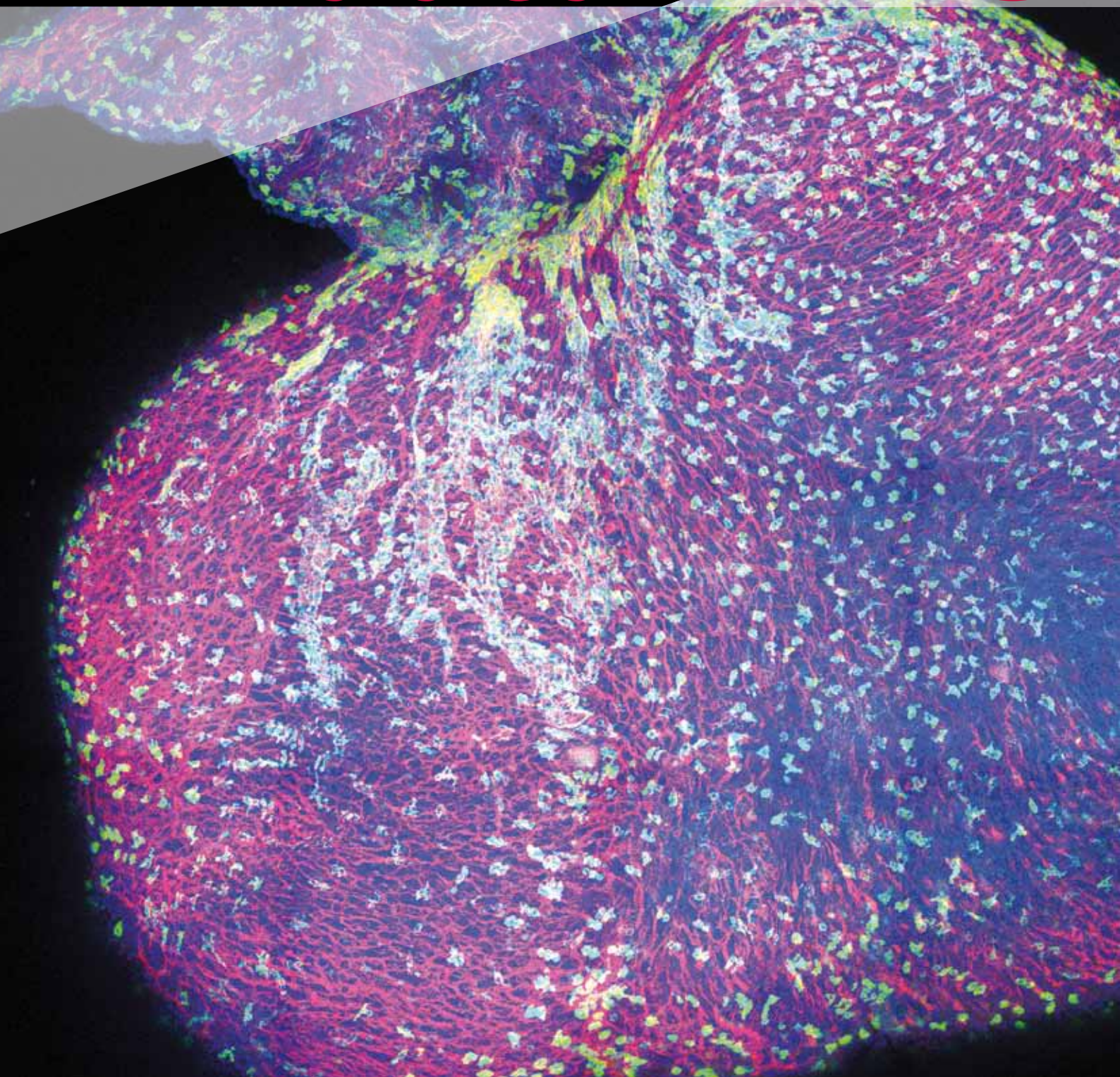

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Dr. Valentín Fuster, General Director of the Carlos III National Center for Cardiovascular Research (CNIC)

TALENT, EFFORT, WORK AND OF COURSE, FINANCIAL RESOURCES

Excellence in research requires talent, effort and work. But we cannot forget the obvious: financial resources are also required. The innovative financing formula of the CNIC, public-private, has allowed the center to maintain its level of excellence since its creation also allowing it to become a world leader in cardiovascular research. And, thanks to the center's class, its researchers and its projects, the CNIC also obtains resources through International Programs, such as the Leducq Foundation, The International Human Frontier Science Program Organization or the E-Rare joint transnational call 2017: 'Transnational Research Projects for Innovative Therapeutic Approaches for Rare Diseases',

Thus, two CNIC projects, led by **Dr. Miguel Torres** and **Dr. Vicente Andrés**, have been selected by the Leducq Foundation. Each of them will receive $6,000,000 during five years through its Transatlantic Network of Excellence Program. In both cases, the CNIC will be the coordinator in Europe, a responsibility shared with two other centers in the USA, and in the case of **Dr. Torres** it is the first time that a Spanish center coordinates a project of the Leducq Foundation.

In addition, **Dr. José Antonio Enríquez** is in charge of coordinating an international research project that will receive $ 1,350,000 (1,100,062 euros) over the next three years thanks to a grant from The International Human Frontier Science Program Organization. The research addresses a fundamental biological issue and the evaluation committee itself considers the proposal "experimentally challenging".

Finally, the project 'Identifying new treatments for Hutchinson-Gilford progeria syndrome' (HGPS) TREAT-HGPS, coordinated by **Dr. Vicente Andrés**, has been funded in the E-Rare joint transnational call 2017 with 797,744 euros over the next three years (2018-2020), with the aim of researching possible new treatments for progeria.

These are only three examples of how the research we do at the CNIC has been consolidated over these years, but they also establish a paradigm of how research gives back to society. To these we could also add the awards obtained by **Dr. Guadalupe Sabio**, **Dr. David Sancho** or **Dr. Xavier Roselló**.

We can assert that the harvest of the CNIC has been fruitful and, in addition, this year we have a proven fact: the research we carry out is being transferred to the patient and benefiting society. Undoubtedly, we can say that 2017 has been a fundamental year for the CNIC in the translation of knowledge.

That is, the research we do at the CNIC not only affects the health care of the general population, but also produces an economic return that allows us to continue investing in projects and, in short, to mobilize the country's economy. All this means that, today, we can affirm that we are doing translational research of excellence for the benefit of the patient and the Spanish society.

TWO LEDUCQ PROJECTS DEMONSTRATE THE CNIC'S LEADERSHIP IN CARDIOVASCULAR RESEARCH

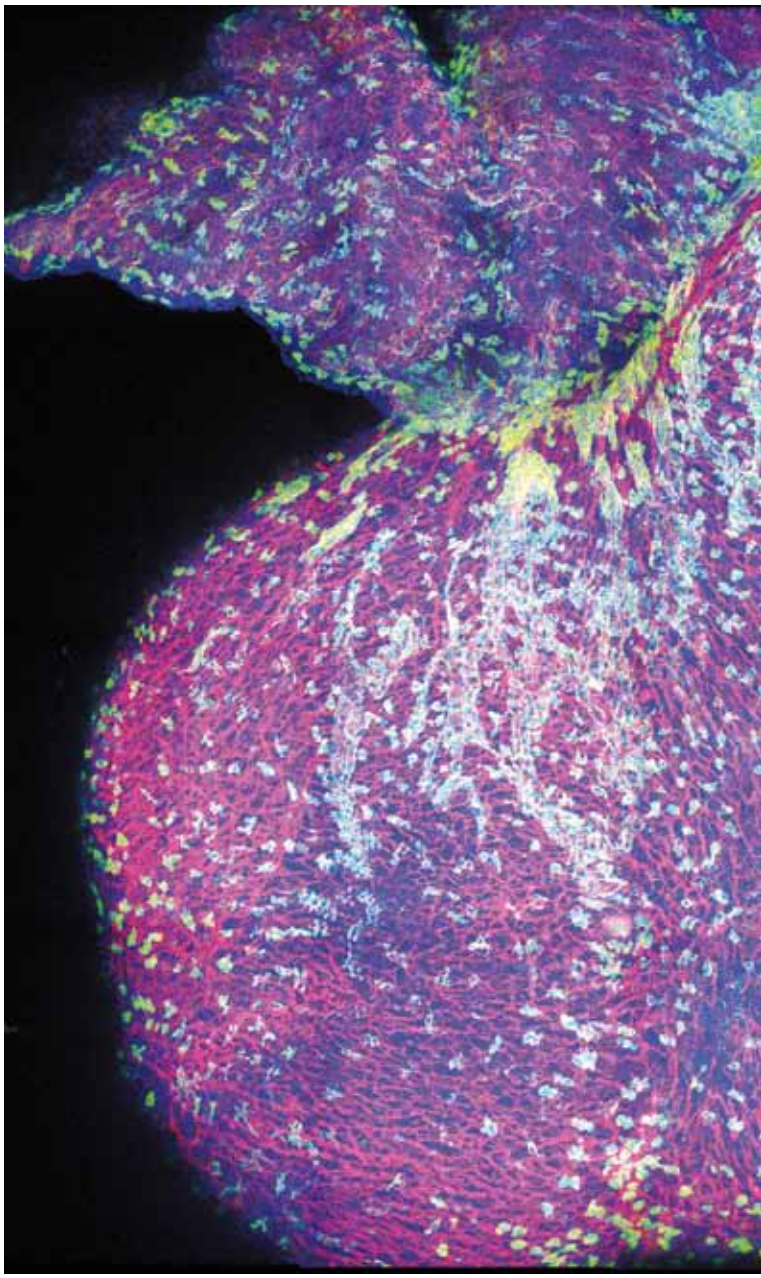
The Leducq Foundation has selected two projects from the Carlos III National Center for Cardiovascular Research (CNIC) which will receive funding of $6,000,000 during five years through its Transatlantic Network of Excellence Program. The CNIC will be the coordinator in Europe, a responsibility shared with two other centers in the USA.

The Leducq Transatlantic Network of Excellence Program funds teams of scientists who collaborate in the research of cardiovascular and neurovascular diseases. Since 2014, the Foundation has supported 57 networks, which represent more than 400 researchers in 130 institutions in 21 countries. **Dr. Miguel Torres** and **Dr. Andrés Hidalgo**, both from the CNIC, will be the European coordinators of these two projects.

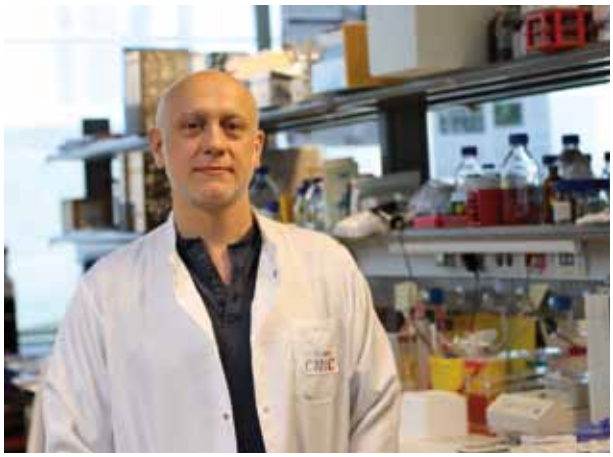
The project "Redox Regulation of Cardiomyocyte Renewal", coordinated by **Dr. Miguel Torres**, of the CNIC, and **Dr. Hesham A. Sadek**, of the University of Texas Southwestern-Dallas Medical Center (USA), is one of the five projects selected by the Transatlantic Network of Excellence Program of this prestigious Foundation and it is the first time a Spanish institution coordinates a project of this type, which "gives an idea of the CNIC's leadership capacity in cardiovascular research", points out **Dr. Torres**.

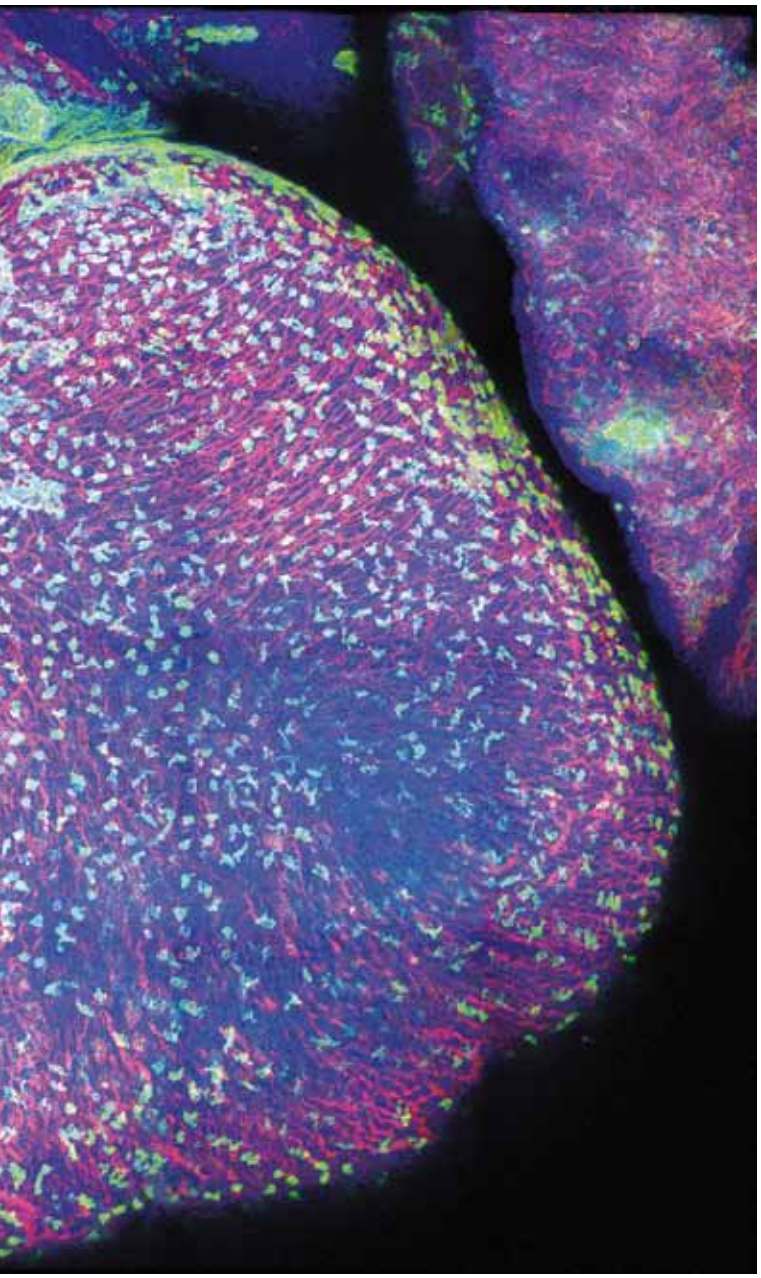
Specifically, the "Redox Regulation of Cardiomyocyte Renewal" project will receive global funding of $6,000,000, $800,000 of which corresponds to the CNIC. The project began in January 2018 with an international launch meeting.

In the event of a heart injury, animals such as fish or amphibians are able to regenerate the heart muscle, producing new cells from the undamaged heart cells. However, adult mammals, including humans, lack this regenerative capacity and, in the event of a heart injury, develop heart failure. However, it has recently been shown that newborn mammals do have the ability to develop new cardiac cells and repair the heart after an acute injury, although they lose it soon after birth.



In addition, **Dr. Torres** points out, in this specific aspect, there will be additional funding from the Community of Madrid through a project that will explore the validity of the Leducq project research in children, conducted in animal models. The Community of Madrid's project, which will be carried out in collaboration with **Dr. Ignacio Flores** and **Dr. Silvia Martín Puig**, with La Paz Hospital and the Complutense University of Madrid, will provide an endowment for the CNIC of approximately 600,000 euros over the next four years.





CLONAL HEMATOPOIESIS

A very relevant finding in the last two years has been to identify that mutations that cause cancer are also responsible for the formation of atheromatous plaques. The project 'Clonal hematopoiesis and atherosclerosis,' coordinated by **Dr. Andrés Hidalgo**, of the CNIC, and **Dr. Alan Tall**, of Columbia University Medical Center, New York (USA), seeks to understand how these mutations alter the behavior of the cells that make up the atheromatous plaque and that are, ultimately, responsible for cerebral and myocardial infarctions.

The project will receive a total funding of $6,000,000 during five years and is one of the five projects selected by the 2018 Transatlantic Network of Excellence Program of this prestigious Foundation. Of the $6,000,000 that the project "Clonal hematopiesis and atherosclerosis" receives, $712,500 correspond to the CNIC. In addition to the CNIC and Columbia University, this project also involves several other prestigious centers, including the prestigious universities of Harvard and Stanford in the USA and Ludwig Maximilians in Germany.

The production of blood cells is a process called hematopoiesis. Hematopoietic stem cells are the precursor or progenitor cells of the bone marrow that, ultimately, give rise to the blood cells that circulate in the blood. When a single mutation occurs in the DNA of a stem cell, a higher than normal amount of blood cells is generated from that single stem cell. It is believed that the resulting subpopulation of blood cells is "clonally" derived from a single founder cell and, therefore, is composed of genetic "clones" of the founder. Clonal hematopoiesis can occur in completely healthy people, but also in those with hematological diseases. In addition, it has been shown that the incidence of clonal hematopoiesis increases dramatically with age - recent studies have shown that less than 1% of the population under 40 years of age, but approximately 10-20% of the population over 70 years of age, has clonal hematopoiesis. Clonal hematopoiesis does not usually show obvious symptoms, but it does increase the risk of cardiovascular disease and can explain the increased occurrence of these with age.

This Leducq Network will investigate the genetic and environmental factors that promote the development of clonal hematopoiesis. It will also explore how clonal hematopoiesis increases the development of atherosclerosis and subsequent heart disease and will determine how to modify the impact of these clones on cardiovascular diseases in humans. ■

AN INTERNATIONAL PROJECT COORDINATED BY THE CNIC RECEIVES MORE THAN 1 MILLION EUROS OVER THE NEXT THREE YEARS

RESEARCH ADDRESSES A FUNDAMENTAL BIOLOGICAL QUESTION: IF DIPLOID ORGANISMS HAVE DEVELOPED **MECHANISMS TO ENSURE MONOALLEIC EXPRESSION OF DEFINED GROUPS OF GENES** AND THUS AVERT FUNCTIONAL CONFLICT BETWEEN ALTERNATIVE PROTEIN VARIANTS

An international research effort led by the CNIC will receive 1.350.000 $ (1.100.062 euros) over the next 3 years thanks to a grant from The International Human Frontier Science Program Organization (HFSPO), and entity which funds frontier research projects in life sciences, fostering collaboration among scientists from different countries (and even different continents) and with different specialties.

This international program finances only risky and pioneering projects, and is the only one that sponsors scientific teams across the globe, "without borders". The grants appeal to the innovative and creative potential of the applicants.

This year's call is endowed with more than $34 million over the next 3 years. The 31 winning teams of the 2018 call have gone through a rigorous selection process which lasted one year. Among the winners are 8 scholarships for young researchers and 23 grants for international programs.

The project coordinated by CNIC research scientist **José Antonio Enríquez**, titled 'Handling OXPHOS structural heterogeneity and metabolic plasticity', addresses a fundamental biological question: whether the fact of having two copies of each gene (alleles), not necessarily identical, can cause functional conflicts when forming the OXPHOS system. And if this were the case, how are such problems avoided.

All the members of the team possess distinct skills for the project and have clearly defined tasks within it: functional and genetic profiling of mitochondria corresponds to the CNIC's group led by **Dr. José Antonio Enríquez**. Individual cell transcriptomic analysis will be led by **Dr. James Eberwine** of the Perelman School at the University of Pennsylvania (USA). Functional and dynamic analysis will be carried out by **Dr. Karin Busch**'s team, of the Cell and Molecular Biology Institute at the University of Münster (Germany), while the analysis in mouse and in the zebrafish will be carried out, respectively, by the teams of **Dr. Enríquez** and **Dr. Nadia Mercader**, of the Institute of Anatomy from the University of Bern (Switzerland).

The researchers want to examine the oxidative phosphorylation system (OXPHOS), the only process in animal cells that requires components encoded by 2 genomes: the mitocondrial DNA (mtDNA) inherited from the mother and the nuclear DNA (nDNA) inherited from both the mother and father. The assembly of functional respiratory complexes involves the physical association of protein products from both genomes within the same macromolecular structures.

Researchers explain that, the OXPHOS protein components therefore need to fit together physically and functionally, and this limits their variability. This, they add, requires the coevolution of both genomes, which is hindered because the mechanisms that generate variability for nuclear DNA (by sexual reproduction, mutation and coexistence of paired alleles) differ for the OXPHOS genes encoded by mtDNA (by mutation, polyploidy and segregation).

Researchers will study two different regulatory mechanisms through which this process operates, and to identify

The International Human Frontier Science Program Organization (HFSPO), funds frontier research projects in the life sciences, fostering collaboration among scientists from different countries and with different specialties

them they propose: 1) RNA sequencing and gene expression analysis in individual cells to determine if one or other allele is expressed; 2) fluorescence microscopy in zebrafish to monitor tagged proteins produced by one or other allele; and 3) analysis of how these findings relate to mitochondrial function in specific mouse and zebrafish lines.

The evaluation committee considered this an "experimentally challenging" proposal and said that it promises to develop "advanced methods that are of general utility; it has the potential to generate results that may have truly transformative power and regardless of whether the answer to the posed question is positive or negative, the knowledge gained will significantly improve our understanding of basic biological mechanisms." ■

CAROLINA FOUNDATION-BBVA SCHOLARSHIPS: EDUCATING FUTURE SCIENTISTS

One of the main objectives of the CNIC is to contribute to the training of young people in cardiovascular research. Hence the creation of the CNIC Youth Training Plan, which includes university internship programs and the completion of the final master projects (FMP).

The Carolina Foundation scholarships are included in this framework. In 2017, through a new collaboration agreement (promoted by the Pro CNIC Foundation), BBVA funded six of these master degrees scholarships in biomedicine in different Spanish public universities, with the commitment to carry out the Final Master's Project at the CNIC. The Carolina Foundation scholarships make it easier for university graduates from Latin American countries and Portugal to expand their studies.

This synergistic collaboration in the Carolina Foundation-BBVA-University-CNIC scholarship maters program therefore allows the incorporation of international students into a CNIC research group in order to contribute to their training in the field of cardiovascular research and the essential collaboration with the master's programs of biomedicine of the universities. The development of a Final Master Project (FMP) can be the beginning of a longer term research to complete a PhD.

The Brazilian student **Nayane Pastoriza**, the Ecuadorian students **Ana Claudia Samaniego Villacís** and **Paul Morocho Jaramillo**, and the Mexican student **Lilian Gutiérrez Espinosa de los Monteros**, were the four students that participated in this year's call and that have been integrated into the groups of **Mercedes Ricote**, **Pilar Martín**, **Rui Benedito**, **David Filgueiras** and **José Luis de la Pompa**. "The Carolina Foundation scholarships make it easier for university graduates from Latin American countries and Portugal to expand their studies. This synergistic collaboration in the Carolina Foundation-BBVA-University-CNIC scholarship masters programs allows students from other countries to join a CNIC research group", highlights **Dr. Mercedes Ricote**.

For example, **Nayane Pastoriza**, integrated in the groups of **Mercedes Ricote** and **Pilar Martín**, has worked on a project oriented toward the investigation of new biomarkers for the diagnosis of cardiovascular diseases, such as acute myocardial infarction and myocarditis. "We use state-of-the-art tools that allow us to discover small RNA molecules in the blood of patients with these diseases."

For **Dr. Pilar Martín**, incorporating students in a CNIC research group aims to contribute to the training of students in the field of cardiovascular research. "As mentors, we contribute to the education of future scientists", adds the researcher. ■

THE CALL 2017 E-RARE FUNDS A PROJECT THAT RESEARCHES NEW TREATMENTS FOR PROGERIA

The project 'Identifying new treatments for Hutchinson-Gilford progeria syndrome' (HGPS) TREAT-HGPS, coordinated by **Dr. Vicente Andrés**, researcher at the Carlos III National Center of Cardiovascular Research (CNIC) and also associated to the Research Networking Center for Cardiovascular Diseases (CIBER-CV), has received funding in the 2017 E-Rare joint transnational call: 'Transnational Research Projects for Innovative Therapeutic Approaches for Rare Diseases' and will receive funding of 797,744€ over the next three years (2018-2020).

The objective of the call for this European Union (EU) program is the collaboration between scientists from different countries in a common interdisciplinary research project based on complementarity and the exchange of experiences, with a clear focus on translational research in rare diseases. Unfortunately, research on rare diseases is not only scarce; it is also dispersed in different laboratories all over the EU. This shortage of experience results in a late diagnosis, few medications and difficult access to medical attention. That is why rare diseases are an excellent example of an area of research that would greatly benefit from European and international coordination. In this context, the EU E-Rare call was created, which aims to provide an international model platform for the implementation of research on rare diseases.

The project, coordinated by **Dr. Andrés** –which also involves other participants like **Dr. David Filgueiras**, from the San Carlos Clinical Hospital of Madrid; **Dr. Karima Djabali**, from the Technical University Munich in Germany; **Dr. Ryszard Rzepecki**, of the University Wroclaw of Poland, and **Dr. Giovanna Lattanzi**, of the CNR Institute of Molecular Genetics of Italy–, is based on the hypothesis that existing drugs that have shown some efficacy in preclinical models of progeria can cause synergistic effects when administered jointly. The TREAT-HGPS consortium will use available models of cells and HGPS mice to develop new therapies using "cocktails" of medications. The consortium will also evaluate the reversibility of progerin-induced damage by suppressing its expression, either in the whole body or just in target tissues, at different stages during the progression of HGPS in mice. This project will lay the foundations for more efficient therapies to combat HGPS. ■

The objective of the call for this European Union program is the collaboration between scientists from different countries in a common interdisciplinary research project based on complementarity and the exchange of experiences, with a clear focus on translational research in rare diseases

STANFORD UNIVERSITY, STANFORD (USA)

Sanjiv Narayan

"WE NEED TRANSLATIONAL MENTORS"

The dual training of Dr. Sanjiv Narayan, professor of medicine and cardiologist at Stanford University (USA) and biomedical engineer, allows him to have a global vision of medicine and research. Therefore, for years, he has been trying to integrate the computational and analytical methods in clinical practice to improve the results in terms of prevention and treatment for the patients' benefit. Dr. Narayan is co-founder and director of the Stanford Arrhythmia Center, a center whose mission is to develop a leading therapy for heart rhythm disorders based on patient-centered research. In addition, as Director of the Computational Arrhythmia Research Laboratory, Dr. Narayan has developed an extramural program for atrial fibrillation (AF) and ventricular fibrillation (VF), applying analytical methods and automatic learning models to define the mechanisms of arrhythmias. His work allowed for the identification of rotational activity (rotors) responsible for the maintenance of human cardiac fibrillation. His studies have shown that ablation based on the removal of these rotors improves the results of therapy in patients with AF. Thus, the understanding of the factors favoring AF and VF has become an important clinical and research area. Furthermore, Dr. Narayan is a passionate mentor and has tutored numerous graduate students in bioengineering, residents and medical students. Dr. Narayan, participated in the CNIC Conference 'Atrial fibrillation: from Mechanisms to Population Science' held at the CNIC in November of 2017.

What is your current area of research?

For two decades I have been investigating the mechanisms of atrial fibrillation (AF) and how this knowledge can allow us to give patients suffering from this heart disease a better treatment. The work that we have developed in recent years has been based on seminal work by **Professor José Jalife** and others, and we were able to demonstrate that rotational activity (rotors) can drive the disorganized activity of AF and many patients with ventricular fibrillation. Between 2000 and 2011 we tried to map the AF with the objective of establishing whether or not there is rotational activity, using bioengineering signal processing methods, computational biology and novel hardware design. In 2010 we began working on a translational application program in patients with AF. Through sophisticated and innovative computational biology systems we have mapped and identified those regions that could be responsible for AF and, in clinical studies, we have demonstrated that it is possible to improve the results of ablation when compared to the traditional techniques that have been used until now. At this time, our objective, among others, is to try to understand why there are differences in terms of results when using different mapping systems. That is to say, in some cases the methods show these rotors as 'engines' of AF, but in others they do not. In addition, we also want to determine the underpinnings of AF drivers and their interplay with disorganized activity at the cellular level in humans, as we have already seen in animal models.

Does that mean that these 'engines' of AF are a target for therapy, present of future?

We believe that they can be a present target for therapy via ablation. But that is not the only goal of our investigation; our idea is that, thanks to a deeper knowledge of rotors and other drivers, we can facilitate many forms of AF therapy. But for this we need a greater knowledge of the characteristics of the tissue of these drivers control. In the future, this may enable the design of preventive strategies or genetic therapies based on the individual phenotype of each patient.

How do you see the treatment of AF in the next 10 years?

My hope is that in the next 10 years we will have more sophisticated systems to phenotype individual patients and personalize therapy. I expect that we will have continuous sensor systems that will provide us with precise and detailed information about AF as well as other conditions, enabling us to 'profile' a patient, discern different diseases that make up AF, and make more accurate decisions. Advances in imaging techniques and biochemical sensors will allow, without doubt, a more specific approach to AF.

How did you become interested in science?

Actually, ever since I can remember I have always liked science. My passion for computer science started when I was 14 years old, but at that time there were limited options to combine computer methods with medicine. I thus studied medicine directly, but always with the idea of going back to computational research. During my residency and fellowship as a cardiologist I discovered

that electrophysiology was an ideal avenue to combine my interests in medicine and computer science to treat patients.

You have always emphasized the figure of the mentor and, as such, practice in your center. What advice or recommendations do you give young researchers?

First of all: follow your passion! You'll always be better if you do something you really like. Second, find a good mentor: it is advisable to be in permanent contact with him or her and take time to develop the work. One is not aware of how important it is to have a good mentor until you do or do not have one! I try to be a good mentor to my students in the laboratory. In my opinion, one of the major challenges in clinical science is the lack of training of the next generation of clinician-investigators by current senior figures. Another challenge is the gap between basic and clinical researchers. This is an área that we try to bridge in our laboratory. It seems that at the CNIC this problem has been resolved very well.

What is the most passionate thing about your job?

From a personal point of view, I believe it's fascinating to have the opportunity to apply bioengineering to a field as complicated as biology to treat patients. In the 90s I was already trying to apply artificial intelligence to medicine, but the problem appeared too complicated. The tools may now be emerging, and I think we are at the beginning of the next era in using computational methods to advance systems biology and translational medicine. It is possible that this will define scientific research in coming decades.

What's your opinion of the CNIC?

All institutions should aspire to be leaders in their field. This requires visionary leadership, interdisciplinary science and relevant sources of financing. The CNIC achieved this model exceptionally well, without a doubt. I learned about the CNIC through **Dr. Fuster** and **Dr. Jalife**. A center with these characteristics, which uses the latest advances in computational technology, image, genomics, focused on translational research and directed at patients is really something unique in this world and is present here at CNIC. ■

"Advances in imaging techniques and biochemical sensors will allow, without doubt, a more specific approach to atrial fibrillation"

"We are at the beginning of the next era in using computational methods to advance systems biology and translational medicine"

Dr. Narayan, participated in the CNIC Conference 'Atrial fibrillation: from Mechanisms to Population Science' held at the CNIC in November of 2017 and organized by David Filgueiras, José Jalife and Miguel Manzanares, from the CNIC, and Stephane Hatem, from the University of Sorbonne, Paris.

STANFORD UNIVERSITY SCHOOL OF MEDICINE
(INSTITUTE FOR STEM CELL BIOLOGY AND REGENERATIVE MEDICINE)
STANFORD (USA)

Hiro Nakauchi

"MAKING ORGANS FROM PIGS IS PROBABLY NOT THE BEST SOLUTION, BUT RIGHT NOW IT'S THE ONLY ONE HAVE"

Dr. Hiro Nakauchi is one of the most important scientists in the field of Regenerative Medicine and Cell Therapy and his research explores the use of chimeric animals as receptors for the culture of human organs. Recent advances, particularly those related to the identification and generation of various types of stem cells, have broadened the repertoire and usefulness of the interspecies chimeras of mammals and have traced new paths towards the understanding of biology, as well as its possible clinical applications. In 2010, his team succeeded for the first time in the creation of rat pancreas in mouse. However, the rat pancreas generated was mouse sized and too small to perform transplantation. So his team tried a reverse experiment to generate mouse pancreas in rats. This time, the generated mouse pancreas was rat-sized and was able to supply sufficient number of islets to treat diabetic mice. In early 2017, his team reported that upon transplantation of islets isolated from the mouse pancreata generated in rats cured diabetes without immunosuppression (*Nature:* Interspecies organogenesis generates autologous functional islets). In addition, his group was also the first to cultivate an embryo that was part sheep, part human (human-sheep hybrid), which was the first step for the development of animal embryos with functional human organs. His studies show how the organs of one species can grow inside another's body, a method that could one day help toward the production of human tissues and organs for transplants. Dr. Hiro Nakauchi, of the Stanford University School of Medicine, Institute for Stem Cell Biology and Regenerative Medicine (USA), participated in the 2017 seminar cycle organized by the CNIC with the conference "From Stem Cells to Organs: Exploiting the Organ Niche for Interspecies Organogenesis".

At the beginning of this year, your group reported, for the first time the creation of a rat pancreas grown in mice that can help reverse diabetes. What is the status of that research?

We genetically modified rat embryos so that they lacked the Pdx1l gene, a key regulator in the development of the pancreas. During the first days of embryonic life, we grafted pluripotent stem cells of mice, both induced or iPS and embryonic, into a rat embryo without Pdx1. And as a result, we obtained rats whose tissues and organs maintained cell lines of both organisms, except in the case of the pancreas that only contained mouse cells. Our final goal was to reverse diabetes and we saw that the pancreatic islets that grew in the rats were functional when transplanted into a diabetic mouse. Upon receiving the transplant, the blood glucose levels of diabetic mice were normalized long-term without immunosuppression except for the first 5 days after the procedure. These data indicates that the autologous organs generated in different species are functional and they can be transplanted without rejection. During the course of these studies, we noticed that there is a xenobarrier when we generate interspecies chimeras. We need to understand and get over this barrier to produce human organs in large animals.

Are animals the future in the development of organs that can be used in transplants?

When we started this project, a decade ago, nobody, including myself, thought it would work this well. However, in the last few years we have been able to show proof-of-concept data in rodents and which we are now applying in sheep and pigs that could in the future house a human pancreas.

When you think about the future, do you believe there will be animal farms that produce organs to transplant in humans?

The truth is that when you hear what you have just asked, it sounds a bit "surreal". But, on the other hand, we have to think that it is "crazy" to produce human organs on a Petri dish. Making organs utilizing a developmental environment of large animals is probably not the best solution, but right now it's the only practical one available. And, right now we think that the pigs are the most appropriate animals to cultivate human organs, although, if we see that sheep work better, there's no problem in changing that.

These organoids, how far are they from being used in humans?

Far; that's why we call them organoids. They are still not completely functional.

You work on the generation of the kidney, lung, liver, thymus, and blood vessels. What about the heart?

Although it seems to be a simple organ structure-wise, we still don't really know which genes intervene in its development at the embryonic stage and that complicates the process.

One of your lines of research is the development of platelets for their use in humans. What is the state of that research?

We are about to complete a pre-clinical study of iPSC-derived platelets. We can generate other blood cell types in vitro, but we chose platelets because they are the most difficult blood cells to supply. Because they can only be maintained for three to four days, we constantly need freshly donated blood. We investigated pluripotent stem cells as a source of blood cells and finally, we developed a system to derive platelets from ES or iPS cells. In principle, if we have one ES cell line that is type-O and Rh-minus, we should be able to replace all the donated blood. Platelets derived from a patient-derived iPS cells are aimed at those who require repetitive transfusions due to congenital platelet deficiency. After repetitive platelet transfusion, they tend to develop antibodies which reduce the therapeutic efficacy. It is best to use platelets derived from patient's own iPSCs. Other targets are hematopoietic diseases, such as myelodysplastic syndrome. We are planning clinical trials with platelets obtained from iPS cells in Boston and Kyoto, which will hopefully start sometime next year. It is possible that in the future the donation of blood and organs will be very different from what we now know.

What are the main obstacles of this research?

From an ethical point of view, we have the reluctance to the concept of endowing an animal with human genetic material. In the USA the moratorium for which federal public funds are not allocated to this type of experiment when human cells are used is still in effect. And in Japan, it is directly forbidden, although I trust that this situation will soon change. In addition, we still have to resolve the genomic distance between species, but I am optimistic in this sense and I believe that it will be overcome. ■

Seminar: "From Stem Cells to Organs: Exploiting the organ niche for interspecies organogenesis".

Invited by Miguel Manzanares.

"We think that the pigs are the most appropriate animals to cultivate human organs, although, if we see that sheep work better, there's no problem in changing that"

"In the USA the moratorium for which federal public funds are not allocated to this type of experiment when human cells are used is still in effect. And in Japan, it is directly forbidden"

MASSACHUSETTS GENERAL HOSPITAL
(CARDIOVASCULAR RESEARCH CENTER)
AND HARVARD MEDICAL SCHOOL
BOSTON (USA)

Juan Manuel González-Rosa

Juan Manuel González-Rosa currently works at the Cardiovascular Research Center of the Massachusetts General Hospital and Harvard Medical School (USA), but knows the Carlos III National Center for Cardiovascular Research (CNIC) quite well because he worked there from 2008 to 2013. Juan Manuel researches in the field of genetics, molecular biology and cellular biology, especially with the zebrafish model.

When did you decide to become a researcher?
I have always wanted to be a researcher; since I was little I was quite sure of it. My high school teachers tried to talk me out of studying Biology... For some it was frustrating that I didn't want to study Medicine. But, since all of us have to work, the best is to work in something that we are passionate about. And, that is what I try to do, despite the big obstacles that us researchers must sometimes face.

You have been one of the researchers that has benefited from the CNIC's training programs, like Cicerone. What do you think about these types of programs?
I think they are very useful. In my case, it was my chance to get to know the center. I worked at a laboratory at the University of Malaga and thanks to this summer scholarship I was able to come and research at the CNIC, where I ended up staying and starting my career as a researcher.

Did you know right from the beginning which line of research you wanted to follow?
From the beginning I started working on the zebrafish. In the summer of 2008 I joined **Alicia García Arroyo**'s team with a Cicerone scholarship and, later, I joined **Nadia Mercader**'s team, who at that time was forming her

"AT THIS RATE OF FUNDING, GETTING A POSITION IN AN ACADEMY WILL BE THE 'ALTERNATIVE CAREER'"

laboratory; I was her first intern. Since then I have been working on cardiac regeneration in the zebrafish model. I have changed my line of research a little, but I still continue in this field.

In this sense, what is the current situation of cardiac regeneration research?

We still know very little about it. It is very difficult to study the regeneration in mouse or in humans because, in fact, we do not even fully understand how it is produced in the zebrafish, which is a much simpler model. The regeneration of the zebrafish was discovered only 15 years ago and, thanks to this, we now know something more about the cellular and molecular mechanisms that are involved in this process. But, realistically, we are still a long way from understanding how it works. In any case, I think basic research in animals, like the zebrafish, is extremely important in order to understand and design new therapies. Without this work in the field of basic science, we will not get anywhere.

What are the main challenges that cardiac regeneration research poses?

It is an extremely complex task. The heart is one of the organs that, like the brain, does not regenerate after an injury. We know that the heart, which is continuously working, does not have the necessary resources to regenerate after a heart attack. Unlike other tissues, such as the musculoskeletal system, the heart does not have specialized cells for repair and maintenance. What we have learned in the zebrafish is that there are no stem cells in the heart that take care of the regeneration; it is the cardiomyocytes themselves that carry out this process. They enter the cell cycle, divide and regenerate damaged tissue. And why doesn't this happen in humans? What we found out about the zebrafish in the lab in Boston, where I work, gives us some insight. One of the factors that doesn't allow the heart of mammals to regenerate lies in the differences in the cardiomyocytes between both models. Those of mammals are polyploid, that is, they have either two nuclei or a very large nucleus that contains four or more copies of each chromosome. The zebrafish cardiomyocytes are very simple, with a single nucleus and are diploid; they have two copies of each chromosome. If we transform the zebrafish cells into polyploids, the capacity to regenerate is lost. Understanding that this is really very important we can start designing new therapies.

How would these therapies be designed?

What is very interesting is that humans, and mice, have a very small percentage of diploid cardiomyocytes, similar to those of the zebrafish. And if we know that these are the only cells that have regeneration capacity, we will have to expand them somehow. How? It is possible that there are drugs that favor the growth of these cells after a heart attack, or that we can transplant these cells to infarcted hearts.

Cardiac regeneration has created many expectations that unfortunately have not been fulfilled. What have been the causes?

It is true that many expectations have been created in the general population about the potential applications of regenerative medicine, and it is true that they are unfulfilled expectations that only generate frustration. And it is also true that us scientists are partially responsible for this. As professionals we must take responsibility for this situation. It is essential that we convey the idea that biomedical research is slow and that we need to invest in basic knowledge before moving on to therapies. When I started my thesis there were many studies focused on the transplantation of stem cells from the bone marrow to the infarcted heart of patients. Obviously it is very important to do this type of studies, in my opinion, but first they must be done in animal models. When they have been done systematically, it has been discovered that the marrow stem cells have a small beneficial effect on the heart, but not the expected one: the cells do not differentiate in muscle, they secrete some signals that attenuate the effects of the infarction, but they do not regenerate the heart.

Are you going to continue in this line of research?

My idea is to continue working with the zebrafish. But in the future, if I can become an independent researcher, I would like to incorporate other systems. Studying only one model will give us a very partial vision. It is important to compare, for example, what happens in mice with what happens in the zebrafish. I would also like to work with other organs, such as the liver, which is a polyploid organ, and its cells are capable of dividing very efficiently. Understanding how other types of cells do it is a possible way to be able to apply it to the heart. Instead of transplanting cells, the goal should be to stimulate the cells that are already in the heart in order for them to be able to divide themselves. That is, use our own modified cells to do the same as those of the zebrafish.

How complex is it to become an independent researcher?

In my opinion, it is becoming a more and more complex process. In principle, those researchers who have completed years of postdoctoral research and who have published several articles in high-impact scientific journals will seek independence. But the truth is that there are a very few number of vacancies and the level of demand is very high. It is a stage of maximum vulnerability for the researcher and, unfortunately, there is very little support for young talent.

You've spoken about the people at the CNIC that have supported your research. What is the role of the mentor?

The mentor's role is critical. And it does not necessarily have to be your director or thesis director, but rather someone with whom you can speak to about the next steps in your career. **Nadia Mercader** has helped me a lot, but also **Miguel Torres** and, especially, **Miguel Manzanares**, all of whom have been a great help to me when making career decisions. Although I have not worked directly with them, they have always had time to talk to me and advise me. Mentors are people who are already settled and are generous enough with their time to support the younger researchers.

> "I think basic research in animals, like the zebrafish, is extremely important in order to understand and design new therapies"

You currently work in Boston. Would you like to come back to Spain?

I would love to work in my country. Besides, I feel Spain has invested in me, through scholarships, for many years and I would like to give back everything it has given me. I would also like to transmit all the knowledge I have acquired in the USA. However, the economic situation is what it is.

What advice can you give researchers who are just starting their career?

When I was studying Biology I was told what a "traditional research career" was: thesis, post doctorate, and at some point you have your own independent research group. In my opinion, this is a very academic and, nowadays, unrealistic view, which only takes into consideration a part of current research. What were once called 'alternative careers' that is, non-academic, should not continue to be called that. The problem is that in universities and research centers there is a great lack of information about what can be done outside the academic world. Scientists can also work in the industry or serve as intermediaries between industry and basic science. If I could give some advice to students, I would tell them to explore different alternatives well and to ask themselves without inhibitions what they really want to do. Many people do a postdoc after the thesis because it is what 'must be done' and they do not know that they could do other jobs which they are better suited for. It is at this moment that the role of the mentor is key, because the mentor can guide with knowledge.

The general impression is that if you do not do a "traditional" career you are not a good researcher.

It may be that the academy itself generates that kind of stigma. Some of my fellow thesis students, who now work in the industry, tell me that other researchers refer to them as "those who have gone to work for the enemy". And it is a very outdated vision. Not all researchers want to have their own line of research. In the USA, most of us postdocs that continue at the Academy are foreigners. In one of Harvard's doctoral programs, 90% of doctoral candidates opt for positions in industry because they know they have better salaries, better working conditions and that they are really going to work with fantastic equipment. There is much less stigma than in other countries, like in Spain. In my opinion, we should not promote the idea that the academy is the only option, but rather that there are multiple career prospects. As mentors to younger people we must be very respectful of the choices that each one makes. At this rate of funding, getting a position in an academy will be the "alternative career".

And going back to the academy from the industry, is it possible?

I have little experience in this regard, but I have the impression that, in biomedical research, that return is really infrequent. When this conversation comes up in training talks, I have come to understand that this return is very limited to those researchers who during their time in the industry have acquired really unique technical knowledge that makes them very appealing for certain academic research centers.

What differences do you find between researching in the USA and Europe?

Yes, it is different; neither better, nor worse, but very different. There they are focused on 'selling' their story in the scientific field as if it were unique and the most relevant. Europeans, in general, are more conservative and timid when it comes to 'selling ideas' and 'selling' ourselves. And what is completely different are the resources. Philanthropy does exist in the USA: it is very prestigious to create a chair or a research center with your name. And in Spain, this is very rare. Another important difference that I have found is the emphasis that is given in the USA to scientific communication, in the transmission of ideas. In the Spanish universities we have a great technical level, but we do not know how to express ourselves very well. Any first-year student from an American university is able to teach a seminar with much more confidence than a Spanish student who is finishing the degree or the thesis. Simply, they are very aware of how important it is to know how to communicate. And that is something they are trained to do. ■

Juan Manuel González-Rosa gave the Seminar "Humanizing the zebrafish heart: exploring the role of elevated cardiomyocyte ploidy as a barrier to heart regeneration", at the CNIC, and was invited by Miguel Manzanares.

CAMBRIDGE UNIVERSITY
(CAMBRIDGE STEM CELL INSTITUTE)
CAMBRIDGE (UNITED KINGDOM)

Bertie Göttgens

"COMMUNICATION BETWEEN BASIC AND CLINICAL RESEARCH IS COMPLEX"

Bertie Göttgens' group, of the Cambridge Stem Cell Institute at the University of Cambridge (United Kingdom) uses a combination of experimental and computational approaches to study how networks of transcription factors control the function of blood stem cells, and how the mutations that disrupt these networks cause leukemia. This integrated approach has facilitated the discovery of new combinatorial interactions between key regulators of blood stem cells, as well as experimentally validated computational models for these cells.

What is the main field of your research?

In our group we are trying to reveal how the blood cells are produced and what goes wrong in the process that causes these cells to be transformed into leukemia cells. Actually, we are trying to discover how the cells make their decisions: the cells in the most embryonic states transform into different types of cells, but they also do it in adult phases and make decisions to maintain a good functioning of the blood –homeostasis–. However, when there are mutations, they are capable of transforming into leukemia cells. That is what we are investigating: which mutations interfere in these decision-making processes that end up producing blood cancers.

And if we know what happens in these processes in their earliest stages could we, in some way, prevent the development of these tumours?

I don't think so; I think that this information is most likely to be very useful in managing or treating this type of cancers. The idea is that the balance between normal differentiation and abnormal proliferation is damaged and, if we can find out what controls this balance, we could have a variety of innovative ways to attack the leukaemia tumour cells. Preventing, however, would not be feasible because, in some way, it is a matter of 'bad luck'. How to prevent bad luck? It is very complicated, and in reality, you only have the certainty that you have had bad luck when you have been diagnosed with cancer. But it's true that this information will be useful to improve the treatments. If we know exactly how regulation occurs normally and how it gets out of control, then we will have different routes of therapeutic approach.

Would it be possible to identify these mutations in the earliest phases and in this way apply a direct treatment as soon as possible?

Like in the rest of the tumours, in leukemias there are a variety of mutations that promote the formation of cancer. That's why it is very important to determine which individual mutations affect this cellular decision-making process and which are the most suitable to be used as targets in a future treatment. In this sense, we are currently carrying out preclinical trials in a very basic model in order to be able to expand our knowledge in these cellular networks and their interconnections. At the moment we have obtained financing from a pharmaceutical laboratory. This is of course a good sign, because they think that our approach may reach the clinic in the future and have selected it from hundreds of other projects. It is an example of something that has been discovered in my laboratory but that may have clinical implications, especially in the field of diagnosis. And if we finally discover mutations that disrupt cell behaviour, we could screen these mutations and classify patients in different groups. This way, patients could be treated more specifically.

Do you think there is a "gap" between basic and clinical research?

More than a "gap", I think that basic-clinical communication is complex. I would classify it as a very narrow "bridge". Partly because clinical research, especially if a clinical trial

is conducted, is very expensive, and requires public funding or funding from a pharmaceutical company. This is part of the problem. But it is also a 'cultural' issue that divides basic researchers from clinical ones. The good thing is that there is a lot of room for improvement. For example, integrating clinical researchers in the basic research groups. That is, make a round trip: 'bench to bedside' and 'bedside to bench'. But in the end, in most cases, it depends on the people. In my case in particular, I collaborate with three different pharmaceutical companies and all of them do it because one of my postdoctoral researchers works in some of them or because I know someone who has put me in contact with someone in their company so that we can work together. What I want to say is that, I am not really convinced that a scientific meeting organized with researchers and industry personnel will be useful to develop joint projects. I think it's more of a personal issue, of friendship. It is not by any means the only way to

"It is very important to determine which individual mutations affect this cellular decision-making process and which are the most suitable to be used as targets in a future treatment"

"It is increasingly important that the people who design the experiments, in addition to having knowledge of biology, should be good in the field of computer science and in the analysis of results, because, otherwise, they will not make any relevant discovery"

transfer basic science to the clinic, but in the end, you have to trust the people with whom you are going to collaborate with and, from my experience, this is the way it works best.

How important is mentoring for the younger researchers?

I see mentoring as part of my work. But I understand the mentoring of young researchers as something that senior researchers do automatically, and not just on issues related to science. That is, we can provide them with very valuable information on various topics: what types of projects can you request? How to advance in the professional career with the difficulties posed by the PhD? ... It is not only about answering scientific doubts, but something more global, more integral. In my case specifically, I go for lunch every Wednesday with two of my junior researchers to discuss aspects related or not to science. We can talk about anything else that they consider relevant (economic aspects, related to the doctorate, etc.). There are many other topics (leading groups, how to organize a budget, how to manage in the academic world ...) that no one usually talks or asks about. And of course, we talk about scientific aspects. I think the best way to be a good mentor is to consider all these aspects, and not just the scientific ones. Otherwise, mentoring would be incomplete.

As Director of a lab, do you have any time to do research?

If I worked 37 hours a week, then no. But no scientist works just those hours, and we try to find time to continue researching. In reality, I don't have time to do experiments, but I am involved in the process. If I had to take samples, I wouldn't be able to, because I'd have to leave behind my other obligations, like attending meetings, answering phone calls, creating budgets, etc. But, I am involved in the discussion processes. It is the interesting part of science, the other, writing a job offer, etc. is more boring.

How have the new technologies changed scientific research?

One of the biggest changes in the field of science has been the incorporation of information technology. You can spend a lot of time with cell cultures, but the interpretation of the results requires bioinformatics. New discoveries in the field of biology are produced with computer science. With genomic technologies it is possible to make great advances. It is increasingly important that the people who design the experiments, in addition to having knowledge of biology, should be good in the field of computer science and in the analysis of results, because, otherwise, they will not make any relevant discovery. Discovering something new is the exciting part of my job. Of course, science has changed, and it will continue to do so, because it is becoming easier and cheaper to perform genomic and proteomic analyses.

Do you remember when you decided to be a scientist?

I was 19 years old I think. I was in the army, doing my military service. At school I was good at science and mathematics, but I was also good at playing the violin. I was between two possible career options. But I realized that my talent in violin wasn't exceptional, just normal, so I thought, ok, I'll do the science career then. My older brother was studying an engineering degree and I went to see him at the university and attended some classes, and quickly decided that I wasn't going to study engineering. I chose Biology. But, I continue to play the violin.

What is your opinion of the CNIC?

Before coming to the CNIC the first time, I asked some of my colleagues about it and they all told me it was a centre of excellence in research. And, I've been collaborating with Dr. Miguel Torres for a long time. ■

Göttgens gave the conference "Cellular States, Differentiation Trajectories and Regulatory Networks of Blood Cell Development" at the CNIC Seminar cycle, invited by Dr. Miguel Manzanares.

UNIVERSITY OF MICHIGAN
(CENTER FOR ARRHYTHMIA RESEARCH)
ANN ARBOR (USA)

Omer Berenfeld

THE TUTORING CAPACITY IS DIRECTLY RELATED TO THE POSSIBILITY OF OBTAINING REAL ANSWERS TO SCIENTIFIC PROBLEMS

Dr. Omer Berenfeld is Professor of Internal Medicine and Biomedical Engineering at the Arrhythmia Research Center of the University of Michigan (USA). His research focuses on the principles and mechanisms of propagation of electrical impulses in the heart using. His research uses a combination of experimental, clinical and numerical approaches in order to better understand acute and chronic atrial fibrillation.

How would you define the current research situation in atrial fibrillation (AF)?

We find ourselves in an exciting moment now. Although there are still many issues to resolve, we have made great progress in characterizing the events that lead to AF. Thanks to the use of optical and electronic systems, it has managed to characterize what happens during AF in order to improve treatments. In my opinion, I think it is fundamental to understand what happens during AF. Not long ago there were many aspects of AF that were a real mystery for researchers, but now we have made important progress in aspects as relevant as the genetic base of AF or the propagation of electrical impulses in the heart.

How far away are we from determining and knowing all the events that lead to AF?

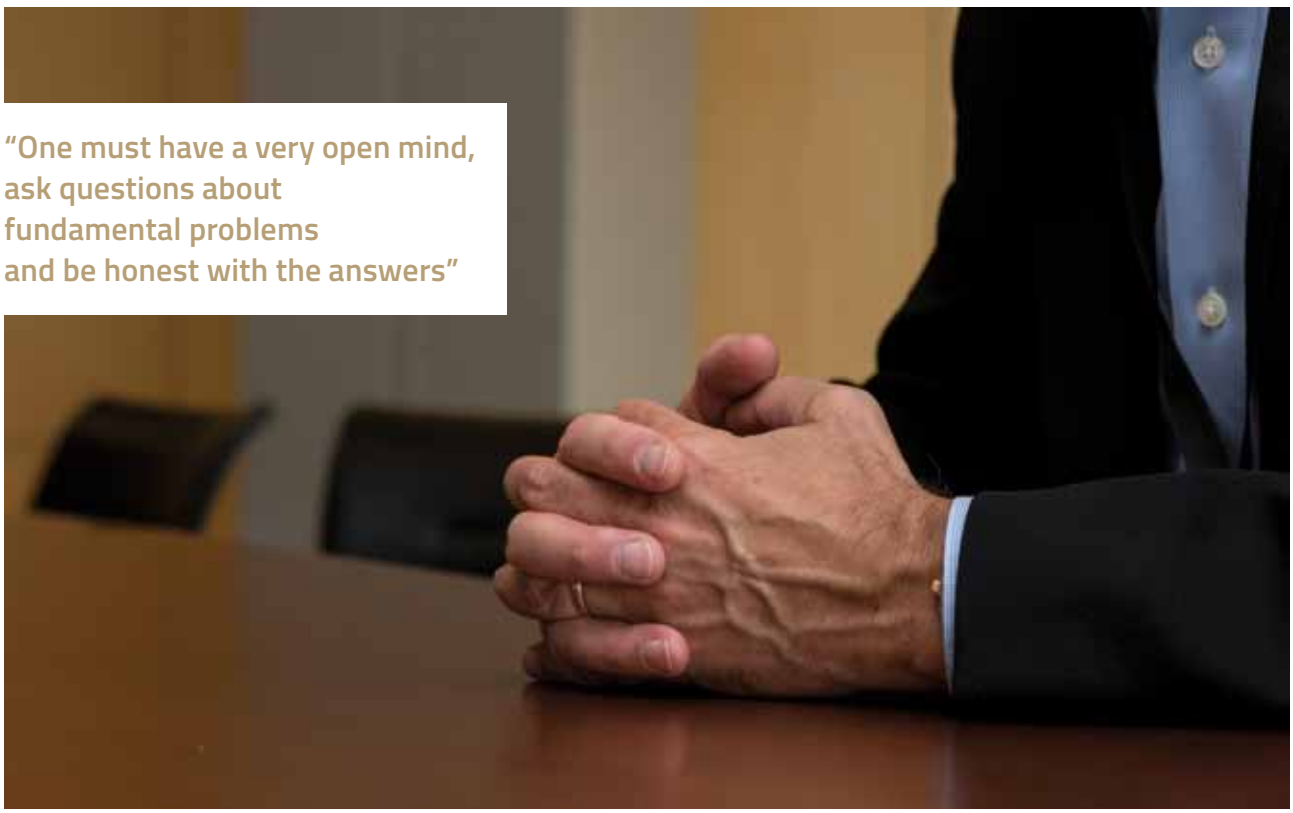
In reality, we still don't know exactly what happens in this disease, which is why it is risky to say how far away we are from having a complete vision of AF. What we have recently found is that the more we research, the more events we discover; that is to say, in my case, when we research pulse propagation, as technology gets more sophisticated and allows for a better resolution, we get more detailed information. Unfortunately, we still don't know what happens at the beginning, in the early stages of AF. We still don't have the technology with enough resolution in order to be able to answer this question; at this moment we are defining what type of precision is necessary to identify the key characteristics of AF.

What are the areas of research that you are focusing on right now?

We are currently working on the mechanisms of pulse propagation. There are many aspects related to the mechanisms of pulse propagation, but the main ones are the mechanisms of the rotors (rotational activity). The evidence we have obtained is that there are some small anomalies in the heart that are enough to start those rotors and, in this way, trigger AF. My research focuses on the factors that affect the dynamics of the rotors, how they behave and how to stop this process and restore the normal heart rate.

Does that mean that these "rotors" could be a possible target for new treatments of AF?

Exactly. We must avoid alterations that promote induction in the rotors, whether it be with the use of medication,



"One must have a very open mind, ask questions about fundamental problems and be honest with the answers"

> "The most important thing one must do when starting a career in research is to focus on something that one really wishes to discover and put all of one's effort in that"

through techniques such as ablation or through any other method. Additionally, we need special technologies for the study of these rotors, because we are not talking about regular patterns like those that occur in a tachycardia, but rather an activity that generates extremely complex patterns of pulse propagation. We probably need technology with much greater precision.

What advice would you give to young researchers?

In my opinion, the most important thing one must do when starting a career in research is to focus on something that one really wishes to discover and put all of one's effort in that. Additionally, one must have a very open mind, ask questions about fundamental problems and be honest with the answers.

In this sense, how important is the mentor figure for you?

It is a critical facet of development in science. It is part of the scientific speech and discussion, of the research machinery itself to solve problems. In my opinion, it is key. The tutoring capacity is directly related to the possibility of obtaining real answers to scientific problems.

It's not your first visit to the CNIC. What do you think about the center?

I was here a few years ago and they showed me what this center and its laboratories would be like. And now I see it and it's impressive. A very serious and rigorous system has been created that includes the facilities, researchers and workers of the center. It is not only the building, but the way in which the CNIC articulates, is financed, works, interacts with other centers, regulatory agencies, researchers, etc. The feeling that it transmits is that someone has given the CNIC a very special priority. It is probably a model of success. Time will tell. ■

Dr. Omer Berenfel participated in the CNIC Conference 'Atrial fibrillation: from Mechanisms to Population Science' held at the CNIC in November of 2017 and organized by David Filgueiras, José Jalife and Miguel Manzanares, of the CNIC, and Stephane Hatem, of the Sobornne University, Paris.

EXCELLENCE IN COMMUNICATION SCIENCE

LEADING JOURNALS PUBLISH CNIC SCIENCE

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 2017 alone, more than 250 studies were published in prestigious journals such as ***Nature***, ***Science***, ***Embo Journal***, ***Journal of the American College of Cardiology (JACC)*** or ***Cell Metabolism***, among others. In that semester, several sub-analyzes of the PESA study have been reflected in publications of scientific articles in ***JACC*** and the CNIC's researchers have made valuable contributions in fields like the treatment of heart failure, cardiac regeneration, the treatment of obesity or in the knowledge of Hutchinson-Gilford syndrome (HGPS) or progeria.

DEVELOPMENTAL CELL
A 'social control' system guarantees embryonic stem cell purity

A sophisticated system of 'social control' operating between neighboring cells allows embryos to protect the purity of their population of pluripotent cells, which are able to generate all body tissues. This system works through the elimination of cells that begin to differentiate prematurely. The control system is important for pluripotency during the development of mammalian embryos and is described for the first time in ***Developmental Cell*** by CNIC researchers led by **Miguel Torres**. The process involves a phenomenon known as cell competition, in which cells compare their levels of a factor encoded by the gene Myc, which plays important roles in embryonic development and pluripotency. The results also reveal the 'yin and yang' action of genes such as Myc. The ability of Myc to regulate cell growth and proliferation is essential for embryonic development, but this same capacity means that excessive Myc expression in the cells of adults is one of the main causes of cancer.

Díaz-Díaz, C., Fernández de Manuel, L., Jiménez-Carretero, D., Montoya, M. C., Clavería, C., & Torres, M. *Pluripotency Surveillance by Myc-Driven Competitive Elimination of Differentiating Cells.* ***Developmental Cell***. doi:10.1016/j.devcel.2017.08.011

JACC

Spanish research confirms the importance of breakfast in the prevention of cardiovascular disease

Skipping breakfast or eating very little at the start of the day doubles the risk of atherosclerosis. This is the latest finding from the Progression and Early Detection of Atherosclerosis study (PESA), led by the CNIC in partnership with Banco Santander. The study is published in the ***Journal of the American College of Cardiology (JACC)***. The report shows that people whose breakfast contains less than 5% of the recommended daily calorie intake (100 calories for a daily intake of 2000) have on average twice the number of atherosclerotic lesions as those who eat a high-energy breakfast. This increased risk is independent of classical risk factors such as smoking, high cholesterol, and physical inactivity. The report not only confirms the importance of eating breakfast for cardiovascular health, but also suggests that skipping breakfast could indicate more generally unhealthy eating and lifestyle habits.

Uzhova, I., Fuster, V., Fernández-Ortiz, A., Ordovás, J. M., Sanz, J., Fernández-Friera, L., ... Peñalvo, J. L. (2017). *The Importance of Breakfast in Atherosclerosis Disease: Insights From the PESA Study.* ***Journal of the American College of Cardiology***, 70(15), 1833-1842. doi:10.1016/j.jacc.2017.08.027

NATURE COMMUNICATIONS

A specific protein regulates the burning of body fat to generate heat

Scientists at the CNIC have identified a protein that holds promise as a target for therapies to reduce obesity. **Drs. Guadalupe Sabio** and **Nuria Matesanz** have demonstrated that MKK6 controls the conversion of fat stores, known as white fat, into brown fat, in which lipids are burned to maintain body temperature and reduce obesity. The study is published in ***Nature Communications***. The research demonstrates that eliminating MKK6 after mice have become obese stops the further development of obesity and leads to a drop in body weight. These findings all point to the potential of MKK6 as a therapeutic target in the fight against obesity.

Matesanz, N., Bernardo, E., Acín-Pérez, R., Manieri, E., Pérez-Sieira, S., Hernández-Cosido, L., ... Sabio, G. (2017). *MKK6 controls T3-mediated browning of white adipose tissue.* ***Nature Communications***. doi:10.1038/s41467-017-00948-z

JACC

Five health indicators are enough to predict cardiovascular risk in healthy people

Just five indicators of cardiovascular health—blood pressure, physical activity, body-mass index (BMI), fruit and vegetable intake, and smoking status—accurately predict cardiovascular risk in healthy individuals. This is the conclusion of a CNIC study published in the ***Journal of the American College of Cardiology (JACC)***. The study demonstrates that the Fuster-BEWAT score, which is based on these five cardiovascular health indicators, effectively predicts the presence and extent of subclinical (asymptomatic) atherosclerosis in healthy middle-aged individuals with no known history of cardiovascular disease. Fuster-BEWAT predictions are as accurate as those obtained with the widely used Ideal Cardiovascular Health Index (ICHS), the score currently recommended by the American Heart Association, which additionally

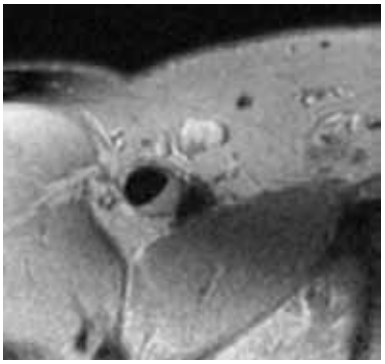
includes blood analysis cholesterol and glucose. The new study forms part of the Progression and Early Detection of Atherosclerosis project (PESA) study, a CNIC initiative conducted in partnership with Banco Santander. The results demonstrate the usefulness of the Fuster-BEWAT score for evaluating cardiovascular risk.

Fernández-Alvira, J. M., Fuster, V., Pocock, S., Sanz, J., Fernández-Friera, L., Laclaustra, M., ... Bueno, H. (2017) *Predicting Subclinical Atherosclerosis in Low-Risk Individuals Ideal Cardiovascular Health Score and Fuster-BEWAT Score.* ***Journal of the American College of Cardiology,*** 70(20), 2463-2473.
doi: 10.1016/j.jacc.2017.09.032

JACC

LDL cholesterol is the main modifiable predictor of atherosclerosis in individuals with no risk factors

A high level of LDL cholesterol (LDL-C) is the underlying reason why many apparently healthy individuals have a heart attack or stroke during middle age despite not having cardiovascular risk factors such as hypertension, smoking, obesity, dyslipidemia, and diabetes. Even at levels considered normal, LDL-C, after age and male gender, is the main predictor of the presence of atherosclerotic plaques in the arteries. This is the finding of research conducted at the CNIC and published in ***JACC***. The results of the new study support the use of more aggressive strategies to reduce LDL-C, even in individuals considered at minimum risk according to traditional risk estimates. Fortunately, LDL-C is the main risk factor that can be modified in order to prevent the appearance of atherosclerotic plaques. The new findings have important societal and clinical implications because they demonstrate the importance of aggressively reducing LDL-C, both for individuals and in the general population. The research is a subanalysis of the PESA study, a shared project of the CNIC and Banco Santander that uses the latest noninvasive vascular imaging technology (magnetic resonance, PET, CT, and 2D and 3D ultrasound) to answer key unresolved questions: when and how cardiovascular it begins and what has to happen for it to manifest clinically.



Fernández-Friera, L., Fuster, V., López-Melgar, B., Oliva, B., García-Ruiz, J. M., Mendiguren, J., ... Sanz, J. (2017). *Normal LDL-Cholesterol Levels Are Associated With Subclinical Atherosclerosis in the Absence of Risk Factors.* ***Journal of the American College of Cardiology***, 70(24), 2979-2991.
doi:10.1016/j.jacc.2017.10.024

NATURE COMMUNICATIONS

Scientists identify a key mechanism regulating a protein required for muscle and heart function

Scientists at the CNIC and Columbia University in New York have discovered an important mechanism in the regulation of a protein that plays an essential role in the function of skeletal muscle and the heart. The study, published in ***Nature Communications*** and coordinated by CNIC researcher **Jorge Alegre-Cebollada**, describes a new mechanism in the regulation of the elasticity of the giant protein titin, a key protein in the function of striated muscles throughout the body, particularly the heart. In the words of Alegre-Cebollada, "the proof of this is that mutations in the titin gene are a common cause of diseases affecting the muscles of the body and the heart."

One of the many mechanisms that determine titin elasticity is the unfolding of specific regions in its structure called immunoglobulin domains. In all, titin elasticity is determined by the concerted action of more than 100 immunoglobulin domains within the protein. Using bioinformatic and structural biology approaches, the research team found that the immunoglobulin domains have a high content of the amino acid cysteine, which confers special properties. When 2 cyteines in a protein come close to one another, they can form a chemical link between different parts of the polypeptide chain, called a disulfide bond. The formation of disulfide bonds is an example of a broader class of biochemical transformations known as reduction-oxidation (redox). Sharp changes in the redox state of the heart muscle are involved in many disease processes affecting the heart, including myocardial infarction. The latest findings show that the formation and isomerization of disulfide bonds causes major changes in the elastic properties of titin.

The research group is currently investigating how our cells modify the titin redox state as a mechanism to modulate skeletal and heart muscle activity and how different diseases can interfere with the mechanical action of the protein, resulting in loss of functionality.

Giganti, D., Yan, K., Badilla, C. L., Fernández, J. M., & Alegre-Cebollada, J. (2018). *Disulfide isomerization reactions in titin immunoglobulin domains enable a mode of protein elasticity.* ***Nature Communications***, 9(1), 185.
doi:10.1038/s41467-017-02528-7

JOURNAL OF EXPERIMENTAL MEDICINE

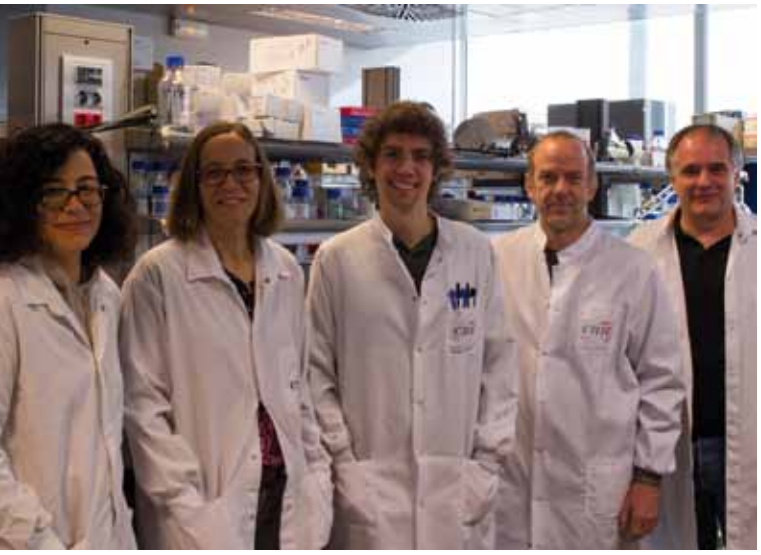
CNIC scientists produce an atlas of genes mutated by an immune-system protein and linked to lymphoma

Researchers at the CNIC have identified the largest collection to date of genes mutated by AID, a key protein in the immune response. The study reveals a new link between the mutagenic activity of AID and the generation of lymphomas. The information obtained, published in the ***Journal of Experimental Medicine***, will increase understanding of the molecular mechanisms that control the activity of this enzyme and its possible contribution to the development of cancer.

The research team led by **Dr. Almudena Ramiro** has complied an atlas of the mutations that accumulate in the DNA of B lymphocytes during the immune response. This damage is caused by the activity of the protein AID, an enzyme with a key role in the generation of immunity to various pathogens. The research team developed a new method based on mass sequencing to detect AID-induced DNA mutations, a major goal in the field. Thanks to this technology, the team was able to identify almost 300 genes mutated by AID. The collection includes several genes that are recurrently mutated in human tumors and lymphomas.

The findings will increase understanding of B cell damage during the immune response and how this contributes to the generation of lymphomas, a type of blood cancer. The results constitute the largest collection to date of genes mutated by AID, and the characterization of these genes will increase understanding of the molecular mechanisms that control the activity of this enzyme and its contribution to cancer.

Álvarez-Prado, A. F., Pérez-Durán, P., Pérez-García, A., Benguría, A., Torroja, C., De Yébenes, V. G., & Ramiro, A. R. (2018). *A broad atlas of somatic hypermutation allows prediction of activation-induced deaminase targets.* ***Journal of Experimental Medicine***. doi:10.1084/jem.20171738



JACC

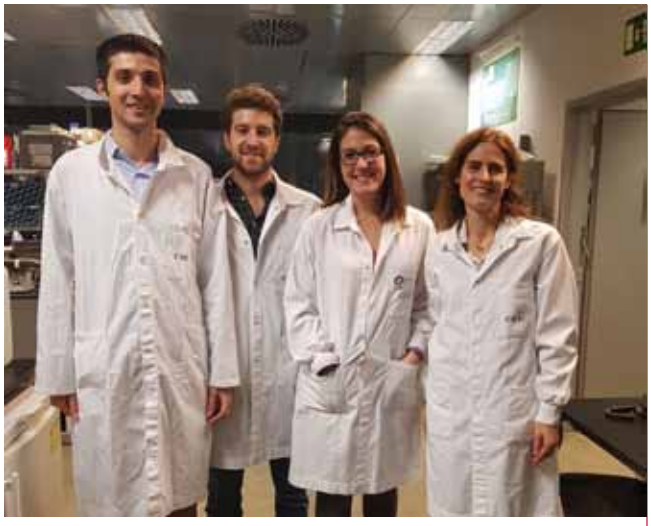
An enzyme variant reduces cardiac hypertrophy and improves heart function

CNIC scientists have identified a variant of the enzyme calcineurin, called CnAβ1, whose action reduces cardiac hypertrophy and improves heart function. The results of the study, published in ***JACC***, are the first to identify the beneficial effects of a CnAβ1-induced metabolic pathway in the hypertrophic heart, and may open the path to new treatment strategies. The findings also show how alternative forms of the same protein, produced from the same gene, can have opposite effects on a biological or pathological process.

Aortic stenosis results in a narrowing of the blood outflow channel from the left ventricle of the heart, increasing the pressure within the ventricle. As study coordinator **Dr. Enrique** Lara explained, "To compensate this pressure overload and maintain efficient pumping action through the narrowed artery, the heart increases the thickness of the ventricular wall." This increase in heart size, called cardiac hypertrophy, is effective initially, but over time problems arise. The sustained high demand for energy in the hypertrophic tissue leads to excessive oxidation of mitochondrial proteins, and this impairs the production of ATP, the "fuel" used by the heart's muscle cells to contract. In this way, "the left ventricle progressively dilates and loses its capacity to contract."

Pathological cardiac hypertrophy is to a large extent mediated by the enzyme calcineurin, which induces a program leading to the production of increased muscle mass in the heart. However, the new study shows that the calcineurin variant CnAβ1 has the opposite effect. The team found that overexpression of CnAβ1 in the hearts of mice prevented the development of cardiac hypertrophy and fibrosis, resulting in improved contractility. In contrast, cardiac hypertrophy and reduced contractile function are induced in knockout mice genetically modified to lack CnAβ1.

Padrón-Barthe, L., Villalba-Orero, M., Gómez-Salinero, J., Acín-Pérez, R., Cogliati, S., López-Olaneta, M., ... Lara-Pezzi, E. (2018). *Activation of Serine One-Carbon Metabolism by Calcineurin Aβ1 Reduces Myocardial Hypertrophy and Improves Ventricular Function.* ***Journal of the American College of Cardiology***, 71(6), 654-667. doi:10.1016/j.jacc.2017.11.067



NATURE COMMUNICATIONS
CNIC scientists describe the mechanism of heart regeneration in the zebrafish

Some animals, including the zebrafish, have a high capacity to regenerate tissues, allowing them to recovery fully after cardiac injury. During this process, the heart muscle cells divide to replace the damaged tissue. However, there has been uncertainty about whether all cells contribute equally to the reconstruction of the heart wall. Now, a team led by **Nadia Mercader** at the CNIC and the University of Bern (Switzerland), working with collaborators at the University of Zurich (Switzerland), has discovered a high level of plasticity among the cells of the zebrafish heart muscle. The study is published in ***Nature Communications***.

After a heart attack, the human heart loses millions of cardiomyocytes, the cells that form the muscle wall. In contrast, other animal species have a high regenerative capacity, enabling them to replace the injured myocardium with new cardiomyocytes. One such species is the zebrafish (Danio rerio). The ability of the zebrafish heart to reestablish its function after injury depends on the capacity of its cardiomyocytes to divide and repopulate the infarcted area, thus eliminating the damaged tissue. Unfortunately, the hearts of most animals, including humans, are unable to activate this process.

In the study, the authors investigated two types of cardiomyocyte, one located in the innermost heart regions, the trabeculae, and the other in the external heart wall. Scientists had presumed that during regeneration each cardiomyocyte population would give rise only to the same specialized cell type. But the CNIC study shows that cardiomyocytes from the trabeculae can contribute to the regeneration of the external heart wall. The results reveal a high level of plasticity among zebrafish cardiomyocytes and that there is more than one way to rebuild a damaged heart.

Sánchez-Iranzo, H., Galardi-Castilla, M., Minguillón, C., Sanz-Morejón, A., González-Rosa, J. M., Felker, A., ... Mercader, N. (2018). *Tbx5a lineage tracing shows cardiomyocyte plasticity during zebrafish heart regeneration.* ***Nature Communications***, 9(1), 428. doi:10.1038/s41467-017-02650-6

NATURE COMUNICATIONS
Blockade of a protease can support the blood vessel 'police patrol' in the fight against infection or cancer

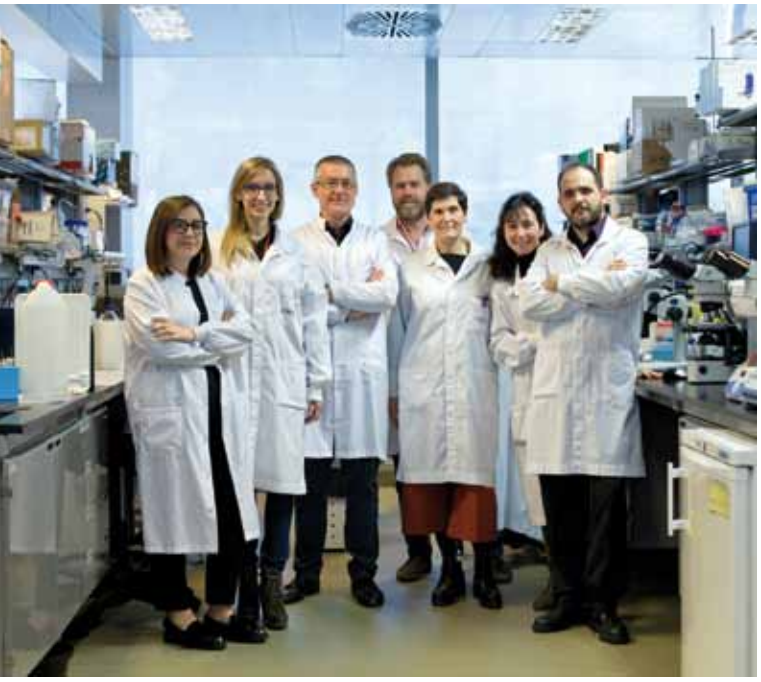
CNIC researchers led by **Dr. Alicia G. Arroyo** have identified a function of a protease that could be targeted for the treatment of some infections and even tumor metastasis. The study, published in ***Nature Communications***, shows that blockade of the protease MT4-MMP increases the surveillance activity of blood-patrolling monocytes, a type of circulating white blood cell. These cells act like 'police patrols' that detect foreign or undesired material in the blood. The findings have possible clinical implications and could contribute to strategies to eliminate foreign or undesired materials from the blood, such as infectious agents or tumor cells. The study suggests new strategies to combat infection or prevent metastasis, which are currently being evaluated for patent protection.

Our immune system involves circulating leukocytes (white blood cells) with specialized functions. One population consists of inflammatory monocytes that are released rapidly to the circulation in response to injury and generate an immune response at the injury site. But there is another monocyte population tasked with "the surveillance of the blood-vessel interior, giving rise to the name blood-patrolling monocytes," explained **Dr. Arroyo**. These monocytes rarely migrate to sites of tissue injury, and therefore their role in inflammation is less known.

Now, the CNIC team has conducted an in-depth analysis of the function of patrolling monocytes in inflammatory disease and the mechanisms that regulate their vascular surveillance activity. As a model, the researchers studied the inflammatory process of atherosclerosis. The first thing the team observed was that early atherosclerotic plaques in mice lacking MT4-MMP (a member of the matrix metalloprotease family) accumulated more macrophages and that atherosclerosis was accelerated when these mice

were fed a high-fat diet. The researchers also observed that early lesions in mice lacking MT4-MMP selectively accumulated more patrolling monocytes, whereas inflammatory monocytes were recruited as normal. When the MT4-MMP-deficient mice were treated with the CCR5 inhibitor Maraviroc, used to treat patients with HIV, the migration of patrolling monocytes to atherosclerotic plaques was blocked, preventing the macrophage accumulation and accelerated atherosclerosis. Thus, while MT4-MMP blockade in early phases promotes atherosclerosis, it could at the same time potentiate the response to treatments aimed at combating infection or preventing metastasis. However, **Dr. Arroyo** stressed that "we don't know if this acceleration of atherosclerosis is maintained at later stages, and this is something that will need to be analyzed."

Clemente, C., Rius, C., Alonso-Herranz, L., Martín-Alonso, M., Pollán, Á., Camafeita, E., ... Arroyo, A. G. (2018). *MT4-MMP deficiency increases patrolling monocyte recruitment to early lesions and accelerates atherosclerosis.* ***Nature Communications***, 9(1), 910. doi:10.1038/s41467-018-03351-4



CIRCULATION
Spanish scientists discover the cause of accelerated atherosclerosis and premature death in progeria

Hutchinson-Gilford syndrome (HGPS, also known as progeria) is a very rare genetic disease that affects fewer than 400 people in the world and for which there is no effective treatment. HGPS is characterized by early aging accompanied by the development of atherosclerosis. Patients die at an average age of 14 years from a heart attack or stroke, events triggered by the rupture of unstable atherosclerotic lesions. Now, scientists at the CNIC and the CIBER de Enfermedades Cardiovasculares (CIBERCV), led by **Dr. Vicente Andrés**, have generated the first genetically modified mice with accelerated atherosclerosis induced by the protein progerin, which causes the development of HGPS. The research team found that the main cause of accelerated atherosclerosis and premature death in these mice was alterations in the smooth muscle cells lining the blood vessels. The results of the study, published in ***Circulation***, identify vascular smooth muscle cells as a possible therapeutic target for combatting the premature atherosclerosis in progeria. The study was conducted in collaboration with **Dr. Carlos López-Otín** of the University of Oviedo and **Dr. Jacob Bentzon** at the CNIC.

There is currently very limited knowledge about the mechanisms underlying the accelerated atherosclerosis in HGPS. This situation is in large part due to the lack of specific animal models. Now, using mice with the disease-causing LMNA mutation and expressing progerin in all tissues, the research team has generated the first animal model of progeria that features premature atherosclerosis, the main cause of death in children with HGPS. The team also analyzed mice that express progerin only in specific tissues implicated in the development of atherosclerosis in order to identify the cells responsible for cardiovascular disease in HGPS.

The results identify the vascular smooth muscle cells as a potential target for treatments to combat premature atherosclerosis in HGPS. According to **Dr. Andrés**, "this new animal model is allowing us to advance knowledge of the molecular and cellular mechanisms that cause cardiovascular disease and accelerated aging in progeria, an indispensable goal for the development of new therapies for patients with this severe disease." Moreover, progerin is detected in cells and tissues of individuals not affected by HGPS as part of normal physiological aging, which shares many features with premature aging in progeria. "Research into progeria can therefore help to identify mechanisms underlying normal aging and promote a healthier old age."

Hamczyk, M. R., Villa-Bellosta, R., Gonzalo, P., Andrés-Manzano, M. J., Nogales, P., Bentzon, J. F., ... Andrés, V. (2018). *Vascular Smooth Muscle-Specific Progerin Expression Accelerates Atherosclerosis and Death in a Mouse Model of Hutchinson-Gilford Progeria Syndrome.* ***Circulation***. doi:10.1161/circulationaha.117.030856

SCIENCE TRANSLATIONAL MEDICINE
CNIC scientists identify a promising target for the treatment of heart failure

A CNIC research team led by **Dr. José Antonio Enríquez** has described a new therapeutic target for the prevention of heart failure, one of the leading causes of death and disability in the world. The new target, a mitochondrial

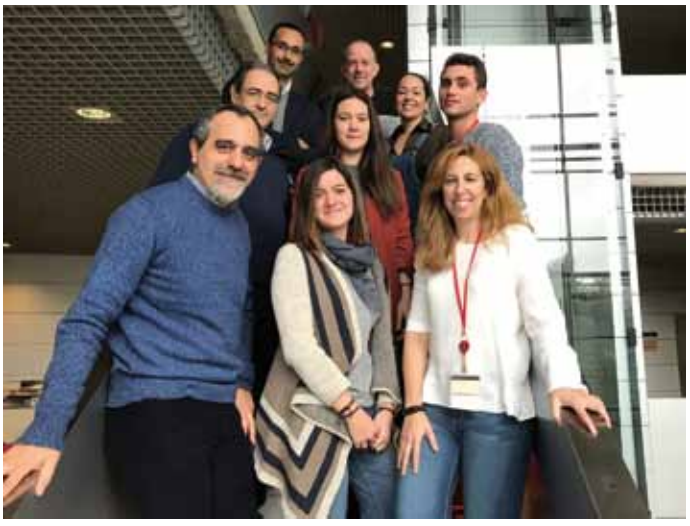
protease called OMA1, is activated when the heart is under stress. Inhibition of OMA1 protects cardiomyocytes (the muscle cells of the heart), preventing their death and stemming the deterioration in heart function. The study is published in ***Science Translational Medicine***.

Correct heart function requires a sufficient contractile capacity and a constant and controlled production of energy to supply all tissues with the oxygen they need. Energy production and the availability of calcium for contraction are coordinated by subcellular organelles called mitochondria. Mitochondria are also the main producer in the cell of reactive oxygen species (ROS), which are toxic when produced in large quantities. To ensure the correct function of the cardiac muscle cells, mitochondria need to maintain a defined internal structure and be able to prevent excessive ROS production during intensive contraction brought on by a high workload, hypertension, or other stress situations.

The study evaluated 3 independent models of heart failure that present distinct symptoms: chronic tachycardia, chronic hypertension, and myocardial ischemia with cardiac hypertrophy. Regardless of the source, stress induced heart injury in all 3 models, triggering key changes in the morphology of the inner mitochondrial membrane.

The research team found that these changes require the activation of the protease OMA1. There is only one OMA1 substrate described to date, OPA1, a mitochondrial protein responsible for maintaining the characteristic folds, or cristae, in the inner membrane. In the study, the elimination of OMA1 prevented heart failure in all 3 models studied, demonstrating a direct role in the protection of cardiomyocytes. The new results identify OMA1 as a promising target for the treatment of heart failure.

Acín-Pérez, R., Lechuga-Vieco, A. V., Del Mar Muñoz, M., Nieto-Arellano, R., Torroja, C., Sánchez-Cabo, F., ... Enríquez, J. A. (2018). *Ablation of the stress protease OMA1 protects against heart failure in mice.* ***Science Translational Medicine***, 10(434), eaan4935. doi:10.1126/scitranslmed.aan4935



NATURE COMMUNICATIONS

Mitochondrial DNA in exosomes is the alarm that triggers the antiviral response

The CNIC research group led by **Professor Francisco Sánchez-Madrid** has provided valuable information about the immune defense mechanisms during the early stages of the response to pathogens such as viruses and bacteria. The research findings, published in ***Nature Communications***, contribute to the understanding of the cellular processes initiated at early stages and explain how the distinct cell populations of the immune system communicate to mount an effective response against pathogens.

The CNIC researchers have shown that mitochondrial DNA contained in nanovesicles triggers a state of alertness in recipient cells that activates an antiviral genetic program. These nanovesicles, known as exosomes, are produced by T lymphocytes and taken up by dendritic cells via intercellular contacts.

Research to date has focused on how the immune synapse activates signaling routes in the T cell; in contrast, the identity and effects of the signals received by dendritic cells have received relatively little attention. In previous work, the CNIC group demonstrated that T cells can transfer exosomes to dendritic cells during the formation of the immune synapse.

In the new study, the research team describe how these nanovesicles transport DNA and proteins of mitochondrial origin. The study reveals that the mitochondrial components are directed to the endosomal system in the T cell, where the exosomes are formed and later secreted, demonstrating the tight relationship between the endosomal and mitochondrial compartments.

These discoveries contribute to the understanding of the cellular processes initiated during the immune synapse and of how components of the innate and adaptive immune systems communicate to mount an effective response to pathogens.

Torralba, D., Baixauli, F., Villarroya-Beltri, C., Fernández-Delgado, I., Latorre-Pellicer, A., Acín-Pérez, R., ... Sánchez-Madrid, F. (2018). *Priming of dendritic cells by DNA-containing extracellular vesicles from activated T cells through antigen-driven contacts.* ***Nature Communications***, 9(1), 2658.
doi:10.1038/s41467-018-05077-9

PLOS BIOLOGY

P38 alpha: the switch controlling obesity and diabetes

One of the research lines targeting the worldwide obesity epidemic is the manipulation of brown fat, a 'good' type of fat tissue that burns lipids to maintain an appropriate body temperature. The CNIC group led by **Dr. Guadalupe Sabio** has now uncovered the mechanism by which brown fat cells are activated to generate heat and eliminate excess fat. The results, published in ***PLoS Biology***, have potential clinical implications for the treatment of obesity and related diseases like diabetes.

The research group has been pursuing a promising research line aimed at understanding how brown adipose tissue can be activated in order to burn the excess fat that accumulates in obese individuals. In more than 150 human samples, the team has now demonstrated that the protein kinase p38 alpha is more abundant in the adipose tissue of obese individuals. The finding suggests that p38 alpha may regulate UCP1, an important protein for brown fat activation and the dissipation of the energy generated from burning excess fat as heat.

In experiments with mice genetically modified to lack p38 alpha, the research team found that the absence of this protein in adipose tissue prevents the mice from becoming obese even when fed a high-fat diet. This protection occurs because the lack of p38 alpha activates brown adipose tissue. Just as important, the study shows that mice lacking p38 alpha are protected against diabetes and fatty liver disease. For **Dr. Sabio**, these results are very promising, as they "suggest that pharmacological inhibition of p38 alpha could offer a route to the treatment of obesity."

The study also reveals another important finding: p38 alpha controls the activation of another protein of the same family, p38 delta. This p38 enzyme is activated by low temperature, so that when mice are exposed to low temperatures, the activity of brown fat is increased. In mice lacking p38, p38 delta is overactivated, resulting in protection against obesity. ■

Matesanz, N., Nikolic, I., Leiva, M., Pulgarín-Alfaro, M., Santamans, A. M., Bernardo, E., ... Sabio, G. (2018). *p38alpha blocks brown adipose tissue thermogenesis through p38delta inhibition.* ***PLoS Biology***, 16(7), e2004455.
doi:10.1371/journal.pbio.2004455

CNIC AGREEMENTS:

COMMITMENT TO ADVANCE IN THE KNOWLEDGE OF CARDIOVASCULAR DISEASES

TWO AGREEMENTS SIGNED THIS YEAR BY THE CNIC CONFIRM THIS RESEARCH CENTER'S COMMITMENT **TO ADVANCE IN THE KNOWLEDGE OF CARDIOVASCULAR DISEASES**, FROM BOTH BASIC AND CLINICAL RESEARCH

Last April the CNIC and the Direction of Integrated Management of A Coruña (XXIAC) - Professor Novoa Santos Foundation (FPNS) signed an agreement for the completion of the project 'Development of large animal models of experimentation in cardiac surgery with extracorporeal circulation and cardiac arrest'. Attending the signature of this agreement were: **Dr. Valentín Fuster**, General Director of the CNIC; **Mr. Alberto Sanz Belmar**, Managing Director of the CNIC; **Mr. Luis Verde Remeseiro**, Manager of the XXIAC and President of the FPNS; **Dr. Borja Ibáñez**, Clinical Research Director of the CNIC, and **Dr. Víctor Bautista Hernández**, of the XXIAC and the FPNS.

The objective of this agreement is to create animal models of experimentation in cardiac surgery with extracorporeal circulation and cardiac arrest. Specifically, a stable and reproducible porcine animal model of severe and calcified aortic valve stenosis will be developed and the possible benefit of a new strategy based on mitochondrial transplantation will be tested.

The present agreement is established with a 4 year duration, from December 15, 2017 to December 14, 2021 and its main researcher is **Dr. Víctor Bautista Hernández**, responsible for Infant and Congenital Cardiac Surgery and Coordinator of the Group of Structural and Congenital Cardiopathy Research, of XXIAC and FPNS.

The project includes four phases, each with their respective specific objectives, which serve to construct a reproducible and stable model of severe and calcified aortic valve stenosis.

FIBAO

Similarly, and with the aim of exchanging the knowledge and experience of professionals of both entities and advance in the prevention and treatment of cardiovascular diseases, the CNIC and the Andalusian Public Foundation for Biosanitary Research of Eastern Andalusia (Fibao) signed an agreement in June 2018. Its main objective is to facilitate cooperation and support for the development of scientific research lines in the field of biomedicine and clinical research, as well as improvement in training in the scientific field. In short, the union is aimed at promoting collaborative activities between both parties to promote research.

Specifically, this collaboration agreement will initially focus on joint participation in common research projects, to join efforts between hospitals and health centers between the CNIC and Fibao; as well as in the collaboration in programs of high specialization of personnel and of the development of scientific activities and of training, dissemination and prevention. ■

THE 2017 CNIC CONFERENCE ON ATRIAL FIBRILLATION UNITED

A GLOBAL PERSPECTIVE FROM THE GENETIC BASIS TO THE NEW ADVANCES IN CLINICAL TREATMENT

On November 3rd and 4th, 2017, the seventh edition of the CNIC Conferences was held at the CNIC. The CNIC Conferences are scientific meetings that are already a reference for cardiovascular researchers from all over the world. This time, the meeting was devoted to atrial fibrillation and was organized by the CNIC researchers **David Filgueiras**, **José Jalife** and **Miguel Manzanares**, and by the researcher at the Sorbonne University in Paris, **Stéphane Hatem**. The meeting, entitled 'Atrial Fibrillation: from Mechanisms to Population Science', brought together 126 world experts in the field of atrial fibrillation in very different areas of expertise: genomics and epigenomics, pathogenesis, gene therapy, animal models and human disease.

The principal objective of the CNIC Conference is to bring together some of the leading experts in atrial fibrillation in Europe and the USA to present and discuss the latest developments in fundamental, translational, clinical and population sciences and technological advances in this field. On this occasion, the experts transferred the latest data and knowledge on the advances in population genetics that have shown that there are genes closely related to the disease, which opens new perspectives in the knowledge of the molecular basis of atrial fibrillation, the most common heart rate disorder in the world, with a great impact on public health.

The researchers also concluded that the interactions of macro-molecular complexes of ion channels at the atrial level are also postulated as potentially effective targets in the prevention and treatment of atrial fibrillation. During the CNIC Conference some clinical area projects were also presented which show that both surface mapping and intracardiac mapping are providing added value to the conventional isolation of pulmonary veins for a more effective treatment of atrial fibrillation in complex cases.

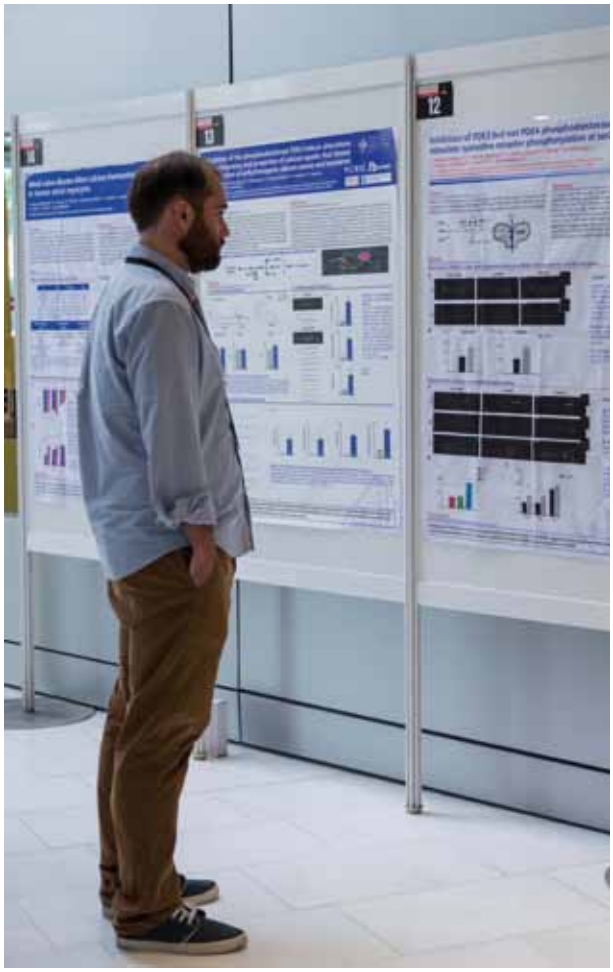
The interactions of macro-molecular complexes of ion channels at the atrial level are also postulated as potentially effective targets in the prevention and treatment of atrial fibrillation.

We must not forget that atrial fibrillation affects more than 30 million people worldwide and, in Spain, it is estimated that there are more than 600,000 people who suffer from this disease. In addition, it is estimated that around 25% of the world's population over the age of 40 will suffer from it in the course of their lives. However, despite more than 100 years of research, the mechanisms that initiate, maintain and perpetuate atrial fibrillation are not fully understood, which probably explains why the therapy has been disappointing up to now. Therefore, the field of arrhythmias and cardiac stimulation, its treatment and improvement of the life expectancy of those who suffer from it is one of the priorities of cardiology research.

The conference also had the support of the Interhospital Foundation for Cardiovascular Research, which awarded two prizes for the best oral communication and the best poster. The prizes, financed with 1,000 euros each, were awarded to:

- **Best short talk:** Raquel Rouco, from the Center for Arrhythmia Research (USA) and the CNIC, for the presentation "Genomic expression during atrial fibrillation progression in a sheep model of persistent AF".
- **Best poster:** David Tinaquero, from the Pharmacology Department of the Complutense University of Madrid, for the presentation of the project entitled "A DLG1 polymorphism shortens the action potential duration and the QT interval".

The 2018 edition of the CNIC Conference entitled "Emerging Concepts in Cardiovascular Biology" will take place on November 16th and 17th and will address the function of blood vessels in cardiac development, function and disease. The conference will bring together the most important scientists in the field of cardiovascular research, to present and discuss their latest findings and will be coordinated by **Dr. Rui Benedito** and **Dr. José Luis de la Pompa** from the CNIC; **Dr. José María Pérez Tomares**, of the Biomedical Research Institute of Málaga, and **Dr. Didier Stainier**, of the Max Planck Institute (Germany). ■



The prize for the best short talk went to Raquel Rouco (Center for Arrhythmia Research and CNIC)

The prize for best poster went to David Tinaquero (Complutense University of Madrid)

PUBLIC-PRIVATE ECONOMIC INVESTMENT WILL BE KEY TO RECOVER TALENT

In order to promote scientific research of excellence in Spain, it will be essential to promote public-private economic investment. During the meeting held at the CNIC between the Minister of Science, Innovation and Universities, **Mr. Pedro Duque**, and the General Director of the CNIC, **Dr. Valentín Fuster**, it was highlighted that governments should promote the conditions to make private investments in these scientific projects profitable, facilitate them through regulations that favor private funding and provide public funds where appropriate. "We are risking a lot, and the longer we take to get to the necessary level, the more it will cost to recover," affirmed the Minister.

Both the Minister and the Director of the CNIC consider that only with an increase in resources can the most talented professionals, that in recent years have been scattered all over the world, be recovered. "Spain has an extraordinary talent and I hope that, with the Ministry of Science, and especially with our current esteemed Minister, we will continue moving forward. We do not have to look at the past, but rather, the future. "

The Minister, during his visit to the CNIC, was accompanied by the Deputy Secretary of Science, **Pablo Martín**, and attended the meeting of the Board of Trustees of the Pro CNIC Foundation, chaired by **Mr. Luis de Carlos**, President of the Pro CNIC Foundation, where he was able to learn about the activities that this Foundation carries out. ■

REPSOL MEETING:
THE FUTURE OF HEALTH, WITH DR. VALENTÍN FUSTER

The General Director of the CNIC, **Dr. Valentín Fuster**, held a meeting with the Repsol shareholders at the CNIC in an act to promote health. In addition, the shareholders were able to learn about the main scientific-medical findings of the center during an informal breakfast where they chatted with **Dr. Fuster** and four CNIC researchers: **Dr. José María Castellano**, **Dr. Antonio Fernández Ortiz**, **Dr. Pilar Martín** and **Dr. Gonzalo Pizarro**.

Also present at the event were **Mr. Arturo Gonzalo de Aizpiri**, Corporate Director of People and Organization of Repsol and Trustee of Repsol Foundation; **Mr. Gonzalo Vázquez Villanueva**, Deputy Director of Institutional and Cultural Programs; **Mr. David Fernández de Heredia Anaya**, Senior Manager of Relationship with Shareholders and Digital Contents; **Mr. Rafael del Portillo García**, Director of Labor Relations, Labor Legal Management and Health in the Workplace; **Ms. Margarita Lozares Villacañas**, Manager of Support and Communication in Health and Welfare; **Ms. Cristina Ordóñez Fernández**, Senior Manager of Health and Welfare, and **Dr. María Jesús Álvarez Vázquez** and **Dr. Javier Sánchez Lores**, of the Medical Department. ■

The shareholders of Repsol shared an informal breakfast with Dr. Fuster and four CNIC researchers: Dr. José María Castellano, Dr. Antonio Fernández Ortiz, Dr. Pilar Martín and Dr. Gonzalo Pizarro

'THE TRIBE OF THE HEART'

The Social Project of Mediaset Spain, together with the Pro CNIC Foundation and **Dr. Valentín Fuster**, have launched 'The tribe of the heart', a community that seeks to raise awareness about cardiovascular diseases. "Having a healthy heart is in your hands" is the motto with which 'The tribe of the heart' takes off. Properly taking care of this organ that moves the world and gives us life is the goal of this new campaign. It seeks to raise awareness through music, art and humor about the need to have healthy lifestyle habits to prevent cardiovascular diseases.

The initiative was applauded by the previous Minister of Health, **Dolors Montserrat**, because it comes from private companies, from Mediaset and Pro CNIC, and because, together with public administrations, it can help raise the population's awareness about the need to take care of ourselves and lead a healthy life to prevent cardiovascular diseases, responsible for the death of 17 million people every year around the world.

The Pro CNIC Foundation, chaired by **Luis de Carlos Beltrán**, demonstrates in this way once again the great commitment of the companies that comprise it to improve the quality of life of citizens, investing in R + D + I and researching cardiovascular diseases, but, also, helping to promote healthy habits as in this occasion.

The precedent of this campaign was launched together with the MAPFRE Foundation, also patron of Pro CNIC, the Spanish Heart Foundation and the Community of Madrid, with 'Women for the Heart'. This campaign began in 2014 in order to raise awareness and facilitate the early recognition of the symptoms of cardiovascular diseases and encourage healthy lifestyle habits, and counts with **Ana Rosa Quintana**, **Mónica Naranjo** and **Ruth Beitia** as prescribers.

In addition, '12 Meses' launched the documentary *The Resilient Heart* of **Doctor Valentín Fuster**. Directed by Oscar nominee for Best Documentary **Susan Froemke**, it shows the preventive and therapeutic work of the doctor in different parts of the world with adaptation and improvement as protagonists. "We have to feel passion for what we do because every day changes, dreams are lost and we are weak, weakness dominates us. The key is how much we can interact. If you are lucky enough to be able to transmit something to someone to improve their life, it is never lost", he assures. ■

cnic AWARDS AND SCHOLARSHIPS

DR. VALENTÍN FUSTER RECEIVES THE GRAND CROSS OF CIVIL ORDER OF ALFONSO X THE WISE

Dr. Valentín Fuster, General Director of the Carlos III National Center for Cardiovascular Research (CNIC), received the Grand Cross of Civil Order of Alfonso X The Wise, an award that rewards individuals and legal entities and both Spanish and foreign entities that have distinguished themselves through their merits in the fields of education, science, culture, teaching and research or that have rendered outstanding services in any of these fields in Spain or abroad.

DAVID SANCHO, YOUNG TALENT AWARD FOR CONSTANT AND VITAL BIOMEDICAL RESEARCH

Dr. David Sancho received the Young Talent Award for Constant and Vital Biomedical Research. Constantes y Vitales (Constant and Vital), the first Corporate Responsibility campaign of La Sexta undertaken together with the AXA Foundation, aims to enhance, give value to, support and strengthen the research work of Spanish scientists in the field of biomedicine, as well as health prevention campaigns.

GUADALUPE SABIO WINS THE FIRST EDITION OF THE JESÚS SERRA FOUNDATION AWARD FOR RESEARCH

Guadalupe Sabio Buzo received, together with **Pablo Pérez Martínez**, of the Maimónides Institute of Biomedical Research of Córdoba (IMIBIC), the first Award for Research given by the Jesús Serra Foundation, aimed at scientists of up to 45 years of age, specialized in nutrition, food and health. The prize, which has an economic endowment of 50,000€ (in this case 25,000€ for each one), aims to encourage research in a fundamental field: the relationship between nutrition and health.

In addition, **Dr. Sabio** has been included in EMBO's network of young researchers, an organization of more than 1,700 leading researchers that promotes excellence in the life sciences. **Dr. Sabio** is one of 28 young researchers who join a network of 47 young researchers and those 417 researchers who have been, and that represent the best leaders of emerging groups in bioscience research in Europe and other parts of the world.

WOMEN FOR THE HEART CAMPAIGN, IWOMAN AWARD IN THE CATEGORY "HEALTHY INITIATIVE"

The Women for the Heart Campaign, an initiative of the MAPFRE Foundation, the Pro CNIC Foundation, the Community of Madrid and the Spanish Heart Foundation (FEC), an entity promoted by the Spanish Society of Cardiology (SEC), was granted the iWoman Award in the Healthy Initiative category. This campaign aims to raise awareness about the importance of early recognition of symptoms and the need to maintain a healthy lifestyle which contributes to reducing the impact of cardiovascular disease in women. The campaign, endorsed by the General Director of the CNIC, **Dr. Valentín Fuster**, includes a 52 page guide called "Take care, Heart", and gives a close-up of the situation of the female heart through the most important statistical data, a review of the main cardiovascular diseases, information on why stress is a risk to the heart - how to identify and manage it, and 11 foods that protect the heart. Also, with the objective of informing the female population about how to help prevent a heart attack, recognize the main symptoms and know how to act if it occurs, the MAPFRE Foundation has set up a bus that travels through the different municipalities in the region, with the goal of conducting rapid and free medical tests.

XAVIER ROSSELLÓ RECEIVES 'ORIOL BONNÍN' AWARD

Dr. Xavier Rosselló, researcher of the CNIC, received the 'Oriol Bonnín' Award for research in cardiocirculatory pathology, convened by the Health Research Institute of the Balearic Islands, the Health Service and the Son Espases University Hospital. The "Oriol Bonnín" Award is sponsored by Obra Social "la Caixa". **Xavier Rosselló**, with his project "Targeting myocardial infarction consequences in the acute and chronic setting using experimental and statistical approaches", will obtain the 3,000 euros with which the award is endowed.

FOUR STUDENTS FROM THE CNIC AWARDED IN THE ARCHIMEDES COMPETITION

Two students from the CNIC, **José Pedro Manzano** and **Agustín Clemente**, have been the winners of the first prize in their respective areas of the Archimedes Competition, and two others, **María Crespo Ruiz-Cabello** and **Antonio Barral Gil**, have been worthy of a second prize. The four students, supervised by CNIC researchers **Dr. Guadalupe Sabio**, **Dr. Eduardo Oliver**, **Dr. Borja Ibáñez** and **Dr. Miguel Manzanares**, will receive an economic endowment: the first prize winners will receive 6,000€, and their tutors 2,000€, while the runners-up and their tutors will each get 2,000€. The contest is organized by the Ministry of Education and has a dual objective: to promote the combination of teaching and researching in Spanish universities, and to favor the incorporation of young students into the research field by awarding them prizes for their original projects of scientific and technological research. On this occasion more than 350 students participated, of which only 25 passed to the final.

JULES HOFFMANN: HOW TO BE A CREATIVE RESEARCHER

Nobel Prize winner, **Professor Jules Hoffmann**, visited the CNIC thanks to the AstraZeneca Foundation, as part of the Nobel Prize Inspiration Initiative (NPII). During the event, attendees had the opportunity to hear him talk about how to be a creative scientist.

THE MADRI+D FOUNDATION VISIT THE CNIC

The Director of the Madri+d Knowledge Foundation, **Jesús Sánchez Martos**, visited the CNIC to learn firsthand about its main lines of research and explore new ways of collaboration.

Accompanied by **Alberto Sanz**, Managing Director; **Borja Ibáñez**, Director of Clinical Research; **Gonzalo Pizarro**, researcher; and **Icíar Areilza**, General Secretary of the ProCNIC Foundation; The Director of the Foundation was given a tour of the center which started off with a presentation of the different projects they develop.

PHDAY 2017: AN EVENT THAT MATCHES UP TO ANY INTERNATIONAL CONGRESS

The last edition of the CNIC PhDay 2017 had the motto 'State of the Art' and developed two main activities: lectures and workshops on topics that include training and motivation, art and science and new frontiers in science; and a poster session with the purpose to promote interaction among attendees. As a novelty, this year seven of the winners of the poster session had a meeting with the professor of the University of Strasbourg and 2011 Nobel Prize winner in Physiology or Medicine, **Jules Hoffmann**.

THE CNIC GETS CLOSER TO THE SCHOOL

Students from 6th of Primary, 1st, 2nd and 3rd of ESO spent a day with CNIC researchers who are at different stages in their research career talking about students' doubts and answering questions about research work. The best projects were awarded with a diploma handed out by **Dr. Valentín Fuster**.

SCIENCE WEEK AT THE CNIC

For the sixth consecutive year, the CNIC participated in Science Week 2017 with two new activities: 'Family day at the CNIC', open to the youngest ones, and the session 'Life in 3D: the latest in microscopy', aimed toward the general public.

'Life in 3D: the latest in microscopy' was an open day session with guided visits to the CNIC that took place on Saturday, November 11th, and showed the latest advances in microscopy in three dimensions of developing organisms.

'Family day at the CNIC' allowed more than 80 children between the ages of 4 and 14, accompanied by their parents, to get closer to science. Through theater, animations and scientific workshops the children had fun, but they also learned from the experiments carried out by the volunteer scientists of the CNIC. The children performed experiments called 'The magic of food: take care of your heart with them', 'Vegetables are fun', 'How many bacteria are in your hands?', and 'Magical antibodies'. They also learned what fermentation is, what cold cuts are made of, what happens when we breathe or the plants breathe, and they purified the DNA of the tomato too. ■

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