CNIC & COVID-19
WHAT'S ON
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contents #11

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

2020, THE YEAR OF SCIENCE

The year 2020 will be remembered as that of COVID-19, a pandemic that many of us had foreseen but for which no one was prepared. Humanity has had to deal with a recurring theme in many disaster movies: a virus. SARS-CoV-2 is a coronavirus that, due to causes yet to be determined, jumped from animals to humans and has caused, and continues to cause today, humanity's worst pandemic since the flu of 1918.

All countries have been affected, from the richest and most powerful, to the least developed and humble.

If we could say that the COVID-19 pandemic has brought about something positive, it would be the general recognition that science is essential to minimize the impact on the health and quality of life for everyone. In less than a year, vaccines have been manufactured that are already alleviating the effects of the infection; and in addition, we have been learning about the characteristics of this virus and the disease and we have understood how some drugs already available, such as anticoagulants, can prevent the most serious cases of COVID-19 and reduce mortality.

After a few days of general confusion, CNIC researchers put all their scientific knowledge at the disposal of society to try to find solutions for this situation, which is estimated to have already caused the death of more than 3 million people around the world and about 80,000 in Spain.

Consequently, **Dr. Borja Ibáñez**'s group analyzes the protective role of the drug metoprolol against the excessive inflammatory reaction of neutrophils in patients with COVID-19.

Furthermore, **Jesús Vázquez**'s team uses proteomics, not only to find markers of the severity of the disease and to make clinical decisions, but also to identify preventive strategies and discover innovative therapeutic targets.

David Sancho and his group have contributed to the development of Professor **Mariano Esteban** and **Juan García Arriaza**'s vaccine at the National Center for Biotechnology (CNB-CSIC) based on the same viral vector that managed to eradicate smallpox, which is known as MVA.

Finally, the CNIC group led by **Dr. Miguel Torres** is working on a project to develop and validate new diagnostic tests for antibodies against coronavirus with proven and improved sensitivity and specificity.

These are just four examples of how science has become involved in protecting humanity from the most harmful pandemic of the 21st century.

The scientific community has given an example of how to work or how the society of the future should be. Without science we would not be vaccinating people right now.

I will end off by saying that I hope this pandemic has been a warning for us to all become more human. ■

CARLOS III NATIONAL CENTER
FOR CARDIOVASCULAR RESEARCH
MADRID (SPAIN)

Valentín Fuster

"THIS PANDEMIC
HAS BEEN A WARNING
FOR US TO ALL BECOME
MORE HUMAN"

According to Dr. Valentín Fuster, General Director of the Carlos III National Center for Cardiovascular Research (CNIC) of Madrid, Director of the Cardiovascular Institute and "Physician-in-Chief" of the Mount Sinai Medical Center in New York, the COVID-19 pandemic has, in some way, caused the world to be changing: "Societies - affirms Dr. Fuster - have realized the disparities that exist in the world and, although there is frustration because the vaccine does not arrive and the pandemic does not end, a greater individual generosity has also emerged, and collective too."

Is this knowledge going to help us prepare for a future pandemic?

Undoubtedly. The second point of the report "Global Health and the Future Role of the United States," in which I was the co-director, already warned in 2017, that the biggest problem, and the one that was most urgent to address, was that we were not prepared for a pandemic. It seems simple, predictable, and obvious. But when the SARS-CoV-2 pandemic hit we all felt out of place; that is, we did not know what was happening. In this report, which identified the challenges and priorities in health, 14 recommendations and priority areas were made for the US Government and the rest of the agents involved in health, and it was pointed out that the second problem was the possibility of viruses mutating. When the plague pandemic struck, the world was not prepared, and unfortunately, with the COVID-19 pandemic it wasn't either. But I think now we are ready for changes in strains, mutations, etc. I think that all this scientific effort is going to be very positive.

How do you think the world responded to this enormous challenge?

The response has been out of step. There are two communities that fluctuate: the public and the government, and the more personal one. They both fluctuate from positive to negative and vice versa. And between them there is a kind of separation; in other words, there is an imbalance: When one is positive the other is negative; there is always the confrontation between society and the individual, and this is a historical thing. And this process has been exciting in the field of health. During the month of March, we found that everyday 5 to 7 patients died at Mount Sinai Medical Center in New York. And the truth is that we did not know what was happening. We were facing a very complex disease; little by little we have advanced in its knowledge and now we already know a lot about it. We analyzed data from a cohort of 7,000 positive COVID-19 patients at Mount Sinai Medical Center hospitals in New York. As a result, we realized that this disease has four stages and that it is vital to determine what stage the patient is in to provide the best response. We learned that the virus enters the upper airways and settles in the lung. In this phase the most common symptom is a cough. The second stage is when the virus passes into the blood and causes fatigue, fever. But, it does not necessarily mean hospital admission. In phase three, the virus passes from the blood to other organs. It is when the individual's fight with the virus occurs. And it is this macrophage fight against SARS-CoV-2 that causes blood clots. And the last phase is the worst. This fight between the virus and the body causes the inflammatory process and the thrombi that form to block the arteries and damage or death occurs in part of the lung, heart or brain segments. These are the patients entering ICUs. And we have learned all of this over time, but at the time it all started, we didn't know anything.

And when do you think that it is important to intervene in this process of thrombus formation with anticoagulants?

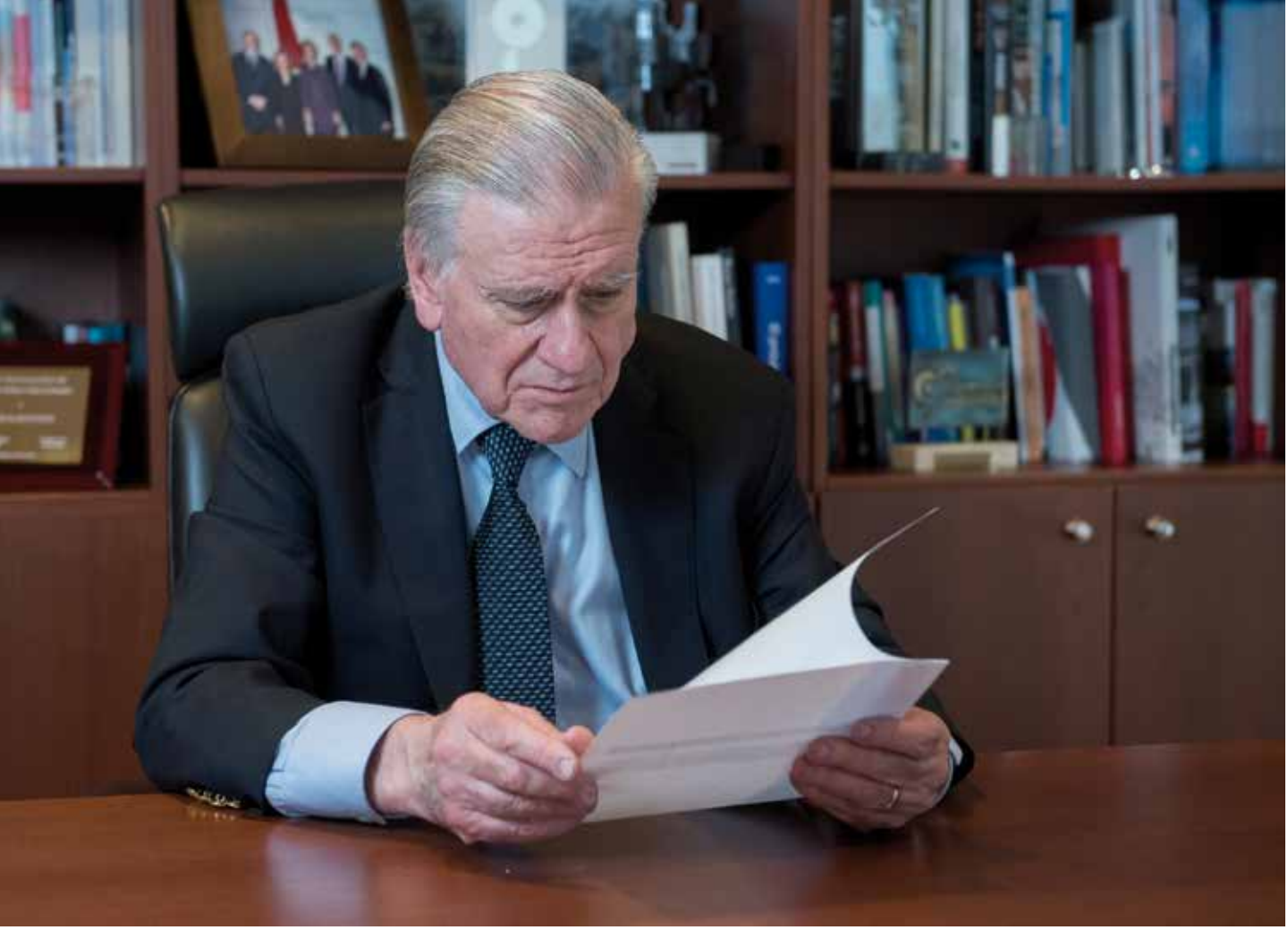
In this struggle in which we are still imbued, society hears words such as drugs, vaccines, plasma, thrombi, inflammation, cytokine storm, etc. At first we saw two cases of patients in the hospital who died with blood clots and I thought that death had occurred due to this fight between the virus and the body and as a consequence of blood obstruction by clots or thrombi. So I decided that all patients admitted to the hospital with COVID-19 had to be treated with blood thinners. But many doctors disagreed. And why do we have to treat them with blood thinners? But we saw that the mortality rates decreased by 50%. It was something observational. And over time we learned that there were actually three blood thinners that were important.

Was it after this observation that you decided to start a clinical trial?

That's right; this led us to an international prospective study. Fellow colleagues suggested that I do it in March 2020, but I did not want to start it then and only decided to start it once we had the results of the observation. In this clinical study, in which more than 100 institutions from all over the world have participated, we have decided not to have a control group, because I do not think it is ethical at this time to give placebo. The objective is to determine the best guidelines to prevent mortality and/or referral to the ICU. We have to recruit 2,500 patients to have impactful results. We have already recruited about 1,500 and each day we include 15 or 25 more patients. This study is unique because the NIH (US National Institutes of Health) did not agree with one of the drugs we wanted to use. So we have resorted to fundraising. Of the 5 million dollars that we need, we already have 4. We have not asked for money from the US Government nor the pharmaceutical companies.

However, for the people, the priorities are different: masks, vaccines, etc.

Exactly. From the social point of view, the important thing is not the complexity of the treatments, but prevention



> "I think the speed with which vaccines have been developed and the way we are now treating patients has shown us how important science truly is. In my opinion, there is going to be a greater awareness of science than there has been until now"

> "The scientific community has given an example of how you have to work or how the society of the future should be. Without science we would not be vaccinating people right now"

thanks to social distance, the use of masks, etc. With the arrival of vaccines, politicians and society believe that they already have the definite answer. Everyone is waiting for a vaccine, but by not reaching everyone as quickly, it generates personal frustration, particularly when observing that the pandemic does not go away. And in the meantime we forget about prevention measures, which are still quite simple.

And is it at this point where you assure that society is starting to change?

On a personal level, however, collective and individual generosity arises: food banks, community support, etc. Thus, in this fluctuation that we are experiencing, from the positive to the negative and vice versa, from a general frustration and a pandemic that affects the entire population that accelerates economic or psychological problems, this personal and collective generosity arises. I hope that this generosity, which is emerging on many levels, is a lasting generosity. But the price is definitely enormous on a personal, psychological and economic level.

Scientists have given a coordinated and effective response to the pandemic. Do you think that society has understood the importance of investing in science?

I think the speed with which vaccines have been developed and the way we are now treating patients has shown us how important science truly is. In my opinion, there is going to be a greater awareness of science than there has been until now. The scientific community has given an example of how you have to work or how the society of the future should be. Without science we would not be vaccinating people right now.

Can any lessons be learned from the pandemic?

This pandemic has been an alarm for us all to become more human. ■

METOPROLOL FOR CRITICAL COVID-19 PATIENTS

BORJA IBÁÑEZ, GROUP HEAD AND CLINICAL RESEARCH DIRECTOR

The most serious manifestation of COVID-19 is severe respiratory failure that requires intubation and is associated with high mortality. SARS-CoV-2 lung infection can lead to the development of acute respiratory distress syndrome (ARDS), in which neutrophil inflammation/hyperactivation plays a central role. Currently, there is a lack of therapies to treat ARDS associated with COVID-19.

The team of **Dr. Borja Ibáñez,** Director of the Translational Imaging and Cardiovascular Laboratory of the National Center for Cardiovascular Research (CNIC) and cardiologist of the Health Research Institute-Jiménez Díaz Foundation (FJD) of Madrid and member of the CIBERCV have recently discovered that Metoprolol, an old beta-blocker drug, has a very selective effect on the hyperactivated neutrophil under acute stress conditions such as myocardial infarction. Due to the central role of neutrophil in ARDS, this team speculated that metoprolol could be repositioned as a therapy in cases of severe COVID-19.

Madrid-COVID is a randomized clinical trial that has been carried out in close collaboration between the CNIC and the cardiology, ICU, pulmonology and biobank services of the FJD Hospital. The main objective of this pilot trial was to study the effect of intravenous metoprolol treatment on pulmonary inflammatory infiltrate and respiratory function in patients with severe COVID-19 who have recently been intubated due to ARDS.

Specifically, explains **Dr. Ibáñez**, "we gave 20 random patients with severe COVID-19 and recently intubated, intravenous metoprolol (15 mg daily for 3 days) or control (without treatment) in 20 patients." **Dr. Ibáñez** emphasizes that "although we must be cautious as this is an initial pilot study, we have observed that treatment with metoprolol in this clinical context is safe, it is associated with a very significant reduction of the pulmonary alveolar inflammatory infiltrate, and this derives in a very rapid improvement of the oxygenation of the patients. Furthermore, we observed that patients who received metoprolol required fewer days of invasive mechanical ventilation."

The main objective of this pilot trial was to study the effect of intravenous metoprolol treatment on pulmonary inflammatory infiltrate and respiratory function in patients with severe COVID-19 who have recently been intubated due to ARDS

Therefore, the researchers consider that intravenous metoprolol appears as a "promising intervention that could improve the prognosis of COVID-19 patients who are in critical condition," and emphasize that metoprolol is a cheap and clinically available drug (daily treatment costs <€2) that can improve results in patients with severe COVID-19.

Although it must be corroborated in a larger sample, the fact that metoprolol has been a drug used in the clinic for more than 40 years with a very high safety profile in well-selected patients (most patients with COVID-19 are), positions this treatment as an alternative that could help many patients today. ■

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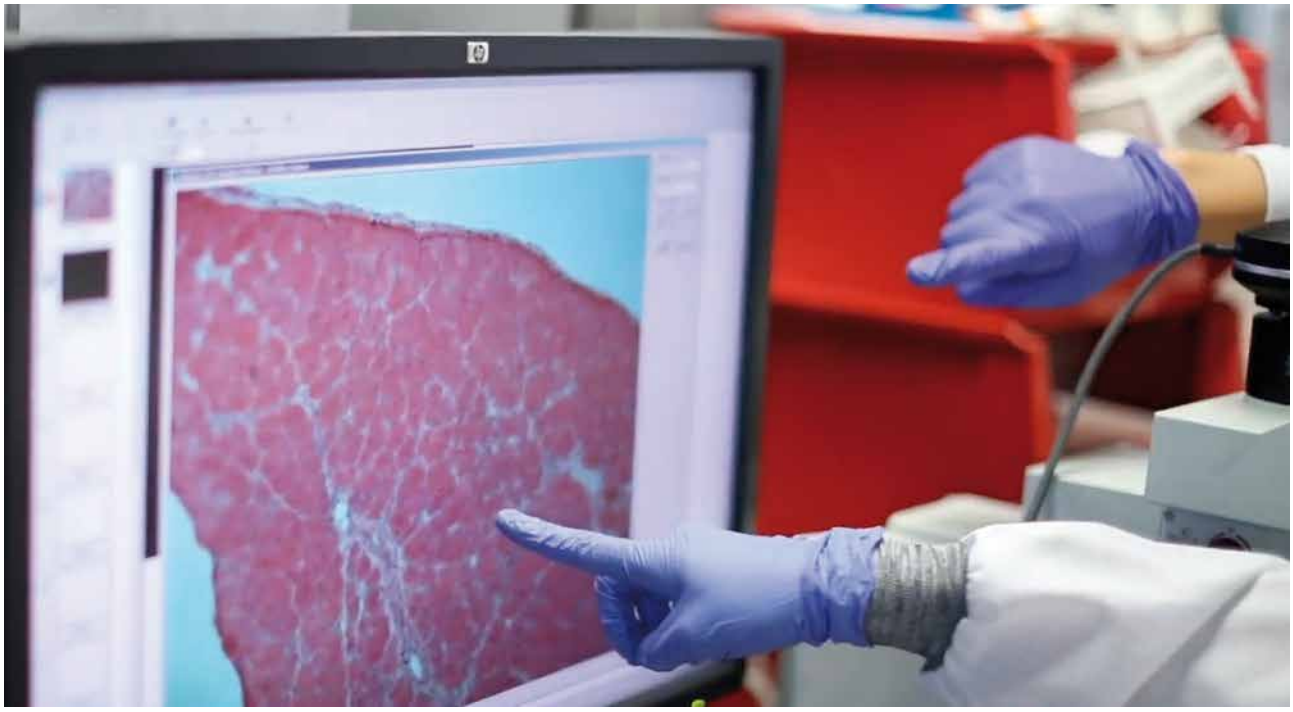

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IMPROVING A VACCINE WITH SARS-COV-2 ANTIGENS

DAVID SANCHO, HEAD OF THE CNIC IMMUNOLOGY GROUP

The response against the COVID-19 pandemic caused by the SARS-CoV-2 coronavirus infection is forcing science to sap its resources as quickly as possible to develop effective vaccines.

In Spain, Professor **Mariano Esteban** and **Juan García Arriaza** at the National Center for Biotechnology (CNB-CSIC) are leading the development of a vaccine prototype based on the same viral vector that managed to eradicate smallpox, which known as MVA. The design of this vaccine is based on the fact that this vector expresses the S protein of the virus, hoping that it will generate protective responses against it. From the CNIC, **David Sancho**'s group, in a collaboration led by **Dr. Carlos del Fresno**, has contributed to this development.

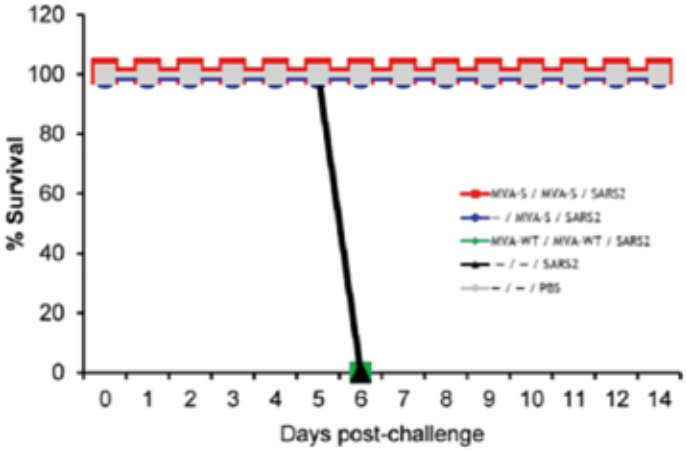
This vaccine has been tested in humanized mice that have the human version of the ACE2 receptor, a molecule that represents the entry point of the SARS-CoV-2 coronavirus into our cells. The results of this vaccine have been spectacular, with 100% efficacy in this mouse model, using different vaccination guidelines.

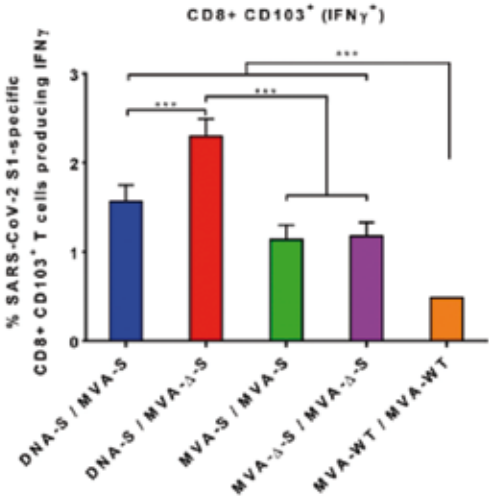
At the CNIC, a part of the study of the response generated by this vaccine has been carried out, analyzing the activation of certain immunological populations in which **Dr. David Sancho**'s laboratory has extensive experience in.

These experiments show that different variants of the vaccine manage to generate protective responses, as long as the vaccine contains the S protein of the coronavirus. The results of this research have been published in the prestigious magazine ***Journal of Virology***.

Vaccines are intended to prepare the immune system against the virus that causes COVID-19. The protective effect of these vaccines is generated thanks to something called immunological memory. Until very few years ago it was believed that specific (adaptive) immunity was the only one that had memory (the ability to 'remember' previous pathogens - bacteria viruses ... - and trigger the response to defend the organism), while innate immunity (not specific for a particular pathogen) did not have it. Today it is known that innate immunity can be 'trained' to achieve a better response against subsequent unrelated infections, such as SARS-CoV-2, and that such training lasts for a long time.

In addition to this collaboration with the CNB-CSIC, **Dr. David Sancho**'s team is studying whether the administration of immune response modulators can improve the effectiveness of various vaccines against the SARS-CoV-2 coronavirus. This project, financed with €100,000 by Banco Santander through the "Together Solidarity Fund," is making it possible to prove that it is possible to optimize the specific responses generated by vaccination.





(Left) Different vaccination schedules with the MVA vaccine are 100% effective against SARS-CoV-2 coronavirus infection in humanized mice. (Right) In these animals, David Sancho's group at the CNIC analyzed the response generated by the vaccine in CD8 + CD103+ immune populations, in which they are specialists. The results show how different vaccination regimens activate these cells as long as the vaccine contains the S protein of the virus, indicating the specificity of the vaccination.

Dr. David Sancho's team is studying whether the administration of immune response modulators can improve the effectiveness of various vaccines against the SARS-CoV-2 coronavirus

CNIC researchers are testing the use of MV130 as an immune booster to enhance the ability of vaccines to generate an immune response against COVID-19. As **Dr. Sancho** explains, MV130 is a preparation that contains several inactivated bacteria that prevents morbidity and mortality in viral respiratory infections, such as influenza, which could boost and improve a vaccine with antigens of the SARS-CoV-2 virus.

In a project pending publication, it has been proven that MV130 protects against viral respiratory infections both by DNA viruses (Vaccinia -virus well known for its role already discussed as a vaccine in the eradication of smallpox disease) and by RNA viruses (Influenza/flu) in preclinical mouse models.

Similarly, "we have collaborated in a clinical trial that demonstrated effectiveness in protecting against recurring respiratory infections in children, which epidemiologically, are of viral etiology," says **Dr. Sancho**. This clinical trial has been accepted for publication in the ***American Journal of Respiratory and Critical Care Medicine***, the most prestigious international magazine of pulmonology and intensive care.

The researchers conclude that these results, would make it possible to improve the efficacy of vaccines, particularly in certain population segments or against variants of the pathogen that may reduce the effectiveness of the vaccine, contributing to better protection of the population against COVID-19. ■

DEVELOPMENT OF TRIALS FOR THE DETECTION OF ANTIBODIES AGAINST SARS-COV-2 IN SERUM

MIGUEL TORRES, HEAD OF THE GENETIC CONTROL OF DEVELOPMENT AND REGENERATION OF ORGANS GROUP

To develop and validate new diagnostic tests for antibodies against coronavirus with proven and improved sensitivity and specificity. That is the project which the CNIC group led by **Dr. Miguel Torres** is working on, in collaboration with other groups at the center, such as **Dr. Jorge Alegre**'s and **Dr. María Montoya**'s groups, as well as with **Dr. Óscar Llorca** of the CNIO.

"We have fine-tuned the Elisa technique so that it is possible to detect immunoreactivity with the spike protein and with the nucleocapsid protein," explains **Dr. Torres**.

The CNIC team has already tested 1,000 samples from volunteers participating in the PESA-CNIC-Santander cohort whose serums were collected before the start of the pandemic.

The PESA-CNIC-Santander is a prospective cohort study in which more than 4,000 middle-aged individuals are controlled long term thanks to the use of the most innovative imaging techniques and whose main purpose is to characterize the prevalence and rate of progression of latent atherosclerotic lesions and to study their association with molecular and environmental factors, including eating habits, physical activity, biorhythms, psychosocial characteristics and exposure to environmental pollutants.

The analyis of these serums, explains **Dr. Torres**, has allowed us to establish the incidence of false positives of this technique, which are very few, "below 1%, which is really very low."

The innovation of the CNIC project is that its test is capable of distinguishing the two immunities when using two proteins; spike, the protein targeted by all the COVID-19 vaccines approved so far, "with which we can detect the immunity generated by these vaccines," and the nucleocapsid protein, which in principle "none of the vaccines immunize you against that protein."

With the test validated at the CNIC, it will be possible to differentiate whether a person, in addition to having been vaccinated, has also passed the infection.

Dr. Torres points out that most of the tests currently used do not distinguish between these two proteins and are made for spike, which would not distinguish one immunity from the other, beforehand, because the natural immunity may be different.

Once established and validated, these Elisa tests will be made available to the public health system and the CNIC is exploring the possibility of their commercial development in collaboration with some national companies.

The next step, says **Dr. Torres**, will be to analyze a sufficient number of samples from those same people obtained during the pandemic. Thus, "what we hope to detect is the number of individuals who are already immunized because they have suffered the infection, so that they can be selected for inclusion in vascular imaging studies with SARS-CoV-2 infection."

It is known that people who are in the acute phase of infection show a greater tendency to atherogenesis. But what is unknown, says **Dr. Torres**, is whether, in the long run, asymptomatic people may have a worse evolution of atherosclerosis, or if, those who have not passed COVID-19, the long-term progression of atherosclerosis differs in

With the test validated at the CNIC, it will be possible to differentiate whether a person, in addition to having been vaccinated, has also passed the infection

The CNIC is exploring the possibility of their commercial development in collaboration with some national companies

people who have had the disease with symptoms and who, during the acute phase, have not had thrombi or any vascular complications."

Thanks to the PESA-CNIC-Santander study, these patients' arteries can be monitored with imaging techniques. "In this way," says the CNIC expert, "we can establish whether such a relation exists or determine that there is no long-term implication and that all the complications that arise are acute and do not compromise long-term health."

The information obtained will be important, says **Dr. Torres**, because, if such relation exists, "then having passed COVID-19 would be an indication to be especially cautious and consider it as a risk factor for atherosclerosis similar to the traditional ones."

Furthermore, **Dr. Torres**'s group is in contact with hospitals and also those responsible for autonomous communities in case they need follow-up collaboration, both for natural immunity and the immunity produced by vaccines.

The project has been carried out with the collaboration of the CNIO, La Princesa Hospital of Madrid and Clínico Hospital of Madrid, which contributed with 100 serums and with which the CNIC has signed an agreement with the approval of the ethics committee.

"Right now we are collecting the samples from these 1,000 people and when we have 500 serums we will conduct a first trial," says **Dr. Torres**, who highlights that since it is the serum from the same person obtained at different times, "we can analyze the reactivity that existed before COVID-19 and the one it has now." ■

RESEARCH ON THE INTERACTION OF SARS-COV-2 AND THE HOST AT THE PROTEOMIC LEVEL

JESÚS VÁZQUEZ, HEAD OF THE CARDIOVASCULAR PROTEOMICS LABORATORY AND THE PROTEOMICS UNIT

One year after the first documented cases of SARS-CoV-2 infection, current knowledge about its pathogenesis still remains limited, so therapies for severe cases are mostly speculative. The pandemic, says **Jesús Vázquez**, has shown that there is an "urgent need for technologies that can accelerate our understanding of this type of new infectious diseases."

One of those tools is proteomics. The proteomic study of circulating proteins in the blood, emphasizes **Dr. Vázquez**, offers a unique opportunity "not only to find markers to measure the severity of the disease and to make clinical decisions, but also to identify preventive strategies and discover therapeutic targets."

The work, that the group led by **Jesús Vázquez** from the CNIC, is carrying out in the Proteomics facilities is included in a macro-project being developed by ProteoRed, a network platform of the Carlos III Health Institute made up of 22 proteomics laboratories distributed throughout Spain. The project, for which **Dr. Fernando Corrales** is responsible, seeks to articulate the full potential of proteomics in our country, optimizing resources and experience to provide the molecular basis for new diagnostic, therapeutic and vaccination strategies necessary to control the epidemic. **Dr. Vázquez**'s group has applied its experience in clinical proteomics in two specific subprojects.

In one of them, in collaboration with basic and clinical researchers from the National Paraplegic Hospital of Toledo, they have demonstrated the key role of heparin, an anticoagulant drug used mainly to prevent and treat venous thrombosis, for patients with spinal cord injury due to SARS-CoV-2 infection, where the clinical characteristics of the infection differ slightly from those observed in the general population.

Cough and asthenia are the most frequent symptoms in this population. Furthermore, patients infected with spinal cord injury rarely have complications that require admission to an Intensive Care Unit, unlike the general population. Therefore, there is a clear need to understand from a molecular perspective how COVID-19 affects patients with spinal cord injury.

The data provided by this project, which has been published in the scientific magazine ***Journal of Personalized Medicine***, shows a significant correlation between the proteins found differentially existing in the bloodstream and the heparin dose, suggesting a key role of this drug in the response to COVID-19 infection in patients with spinal cord injury.

Although the number of patients with spinal cord injury is limited, the data from this study may shed light on new therapeutic options to improve their management and possibly also in the general population.

In the other subproject, the group of **Dr. Vázquez**, in which **Estefanía Núñez**, **Patricia Baena** and **Enrique Calvo** also participate, is comparing the proteome of the blood plasma of those controlled individuals admitted to the hospital with varying degrees of severity and even deaths from the virus in a cohort provided by the Biobank of the Aragonese Institute of Health Sciences, with the idea of elucidating the mechanisms and response to infection. Although they are not published yet, **Dr. Vázquez** acknowl-

This study offers a unique opportunity "not only to find markers to measure the severity of the disease and to make clinical decisions, but also to identify preventive strategies and discover therapeutic targets," emphasizes Dr. Vázquez

edges, the preliminary results support previous studies and demonstrate that COVID-19 has a strong impact on the plasma proteome.

Thus, he assures, "SARS-CoV-2 infection produces a pattern of changes in the plasma proteome very similar to those observed in other cohorts analyzed in China and Germany, although specific differences are also detected."

This early data shows that IL-6-mediated activation of the acute phase response is the most reproducible alteration detected in plasma. In addition, the infection also produces a decrease in the levels of immunoprotective apolipoproteins (HDL) and alterations in the coagulation cascade. On the other hand, changes are also detected in some plasma proteins that reflect lesions in the lung and kidney.

Therefore, the researchers assure that bloodstream proteomics provides objective information about host response and disease progression and also identifies potential targets for therapeutic action.

"Our data," adds **Dr. Vázquez**, "suggest that monitoring of specific proteins can help detect which recently diagnosed COVID-19 cases are more likely to progress to severe disease and assess the specific tissue damage produced by the virus."

Researchers are currently validating these results through targeted analysis of the most relevant plasma proteins in another cohort.

"These experiments suggest that proteomics would be a very useful tool for the diagnosis and monitoring of patients in future pandemics," adds the CNIC researcher. ■

STOWERS INSTITUTE FOR MEDICAL RESEARCH
KANSAS CITY (UNITED STATES)

Alejandro Sánchez Alvarado

"THE REAL MAGIC IS TO IMAGINE THE EXPERIMENT AND EXECUTE IT"

The replacement of differentiated cells is a major challenge for all organisms. Humans, for example, must replace approximately 10 billion cells every day. Despite the importance of regenerative processes for biology and human health, the molecular and cellular mechanisms that drive the restoration of body parts lost to physiological replacement and/or injury remain largely unexplored. This is paradoxical, especially considering that the regeneration of body parts raises important questions about the regulation of polarity, positional identity, and scale and proportion, all of which remain essentially unresolved. Therefore, "the objective of my laboratory is to discover the molecular and cellular mechanisms that support animal regeneration," explained Dr. Alejandro Sánchez Alvarado during his visit to the National Center for Cardiovascular Research to give a seminar. To address this problem, his group is working with the *Schmidtea mediterranea* model. "Planarias are recognized for their regenerative capacity, which is driven by a population of totipotent stem cells," explains the Scientific Director of the Stowers Institute for Medical Research in Kansas City (USA).

Your work focuses on the regeneration mechanisms in animals? In which phase is the research right now?

The problem in regeneration is that it is at a very basic research level because the mechanisms involved, cellular and biological, are almost entirely unknown. Twenty years ago we decided to investigate some animals that do preserve this regeneration process: the planarians. These are tlatworms whose regeneration mechanisms are highly activated: the animal can be amputated into many fragments and each one of them is capable of developing a new complete animal. In our laboratory we use this organism as a vehicle to try to elucidate and dissect the molecular and cellular processes of animal regeneration.

What do these organisms have in common with bigger animals, such as mammals?

We know that regeneration is widely distributed in the animal kingdom, but this distribution seems almost random. In other words, different organisms that are closely related phylogenetically do not have the same capacity to regenerate: one does and the other does not. The big mystery is why the regeneration capacities of animals are so unevenly distributed in the animal kingdom. There are two possibilities. The first suggests that each animal 'invented' its own way of regenerating, therefore each species should be studied independently. The other is that it may be that the process of regeneration is ancestral and, in some way, the processes of adaptation or evolution have enhanced or eliminated these mechanisms in organisms. This conservation allows us to investigate a process that interests us, such as regeneration, in animals that look nothing like us. When we began to observe regeneration in animals, it was not known to what extent these processes existed, for example, in the planaria, these could or could not be shared in more complex animals, such as vertebrates. And it turns out that today we still do not know for sure whether they are related or not, but we do know that the molecules that are executing the regeneration capacity of the planaria are highly conserved throughout the phylogenetic tree. That is to say, our genome has the genes used by the planarians to regenerate. These genes are not specific to these organisms, but rather are very well represented in the animal kingdom.

So, if we have these genes, why don't we have this regeneration mechanism?

This is what we are studying in these animals and we hope to find the answers and be able to manipulate this process to try to activate these processes in non-regenerative animals.

In other words, we have the tools, but not the instructions on how to activate this mechanism?

Our organism does have the capacity to regenerate in the sense that we have tissues that are constantly being reconstructed: the skin, hippocampal neurons, the epithelial tissue of the digestive system... We retain a regenerative capacity at the physiological level, but it is not sufficient to compensate for the level of damage from an extensive injury or degenerative disease. In other words, our body has a limited capacity to regenerate. In my opinion, this implies that we do have these processes, but somehow they have been lost in order to maintain our restorative capacity. Human beings can live about 80 years, while other organisms live shorter periods, so they do not require this type of tissue maintenance that is so important for our health. What we think is that there has been a kind of 'repression' in the evolution of our species that has mitigated our regenerative capacity compared to other animals.

In exchange for the capacity to live longer?

That's one possibility. But there's another, which is that we lost it because it encouraged tumor formation. Regeneration requires cell superproliferation, and when this is abnormal, tumors are generated. It's like a switch: do you want to regenerate or do you want to die? Furthermore, it does not happen in all mammals as it does in man; for example, there are mice, called 'spiny mouse', originating from Africa, that as an adaptation process, when they are attacked by a bird of prey, they are able to detach

themselves from their skin to avoid being captured and, subsequently, they regenerate all their skin in just a few weeks. That is something that human beings cannot do. This is an example of a mammal capable of maintaining its capacity to regenerate and also an example of the irregularity in the distribution of these processes. The question is, if mammals share this ancestral genome, why can some do it and others can't? The difficulty nowadays is to understand why such irregularities in the capacity to regenerate occur.

How does your model serve this purpose?

The model of the planarias allows us to clarify how cellular potentiality is regulated. All of our cells have essentially the same genetic information. Each cell performs a specific task. But they all have the same DNA, which means that they have a fairly specific capacity for differentiation. Stem cells are undifferentiated cells that can be uni, multi or pluripotent. Most species have stem cells that are pluripotent and possibly totipotent, meaning that a specific cell is capable of producing all the cell types that make up the anatomy of the animal. The planarias have an abundance of that type of cells, they are at the surface of the skin. They are not hidden, which allows us to benefit from that abundance of stem cells to try to understand how they are able to regulate their potentiality. Think that if we have a cell that is capable of producing all the tissues, it allows us to know how the chromatin, the chromosomes, and even the genes within those chromosomes are being regulated to activate a choreography of genetic expression that allows it to produce specific lineages of particular cells. That is, that a cell is capable of producing the muscle line, the nerve line, the epithelial line, or the digestive system, etc. These are decisions that are made at the molecular level and that we do not yet understand. We know which transcriptional factors are capable of activating these processes, but it is completely unknown how they are coordinated so that a tumor is not generated, but rather that the appropriate number and type of cells are produced to maintain the form depending on the animal, not only in planarians, but in practically all the organisms that we have studied up until now.

Do these totipotent cells have other organisms?

Yes, they do, but at more specialized levels. We can obtain multipotential cells capable of producing a large number of cell types, but not all of them. We also have very abundant and very important unipotential cells, such as germ line cells that only produce gametes, the cells that are going to perpetuate the species through fertilization. Planarias allow us to dissect these processes of regulation of cellular potentiality in a relatively efficient way. This model system allows us to advance a little more than we would have been able to if we had not studied these little animals.

Can a planaria be created from one of these totipotent cells?

Yes, it is necessary to have a context in which to introduce the cell, but such a cell is capable of restoring the viability and regenerative capacity of the animal. What we have done in the laboratory is to identify technologies that allow us to purify these cells and, by purifying them, we can introduce them into an animal in which all the stem cells have been eliminated, and which are destined to die in two or three weeks because they are not capable of maintaining their tissue. If we inject one of these cells into this animal, that cell begins to proliferate and produce lineages that will generate all the animal's tissues and, in approximately 60 days, the viability and regenerative capacity of the animal is restored. This is the kind of exaggeration that we, as biologists, love to research, because it allows us to attack the problem directly; we don't have to separate layers of complexity to reach the center of the problem, but rather, the nucleus is exposed at the surface of the skin, and that is one of the great advantages of being able to do research on organisms that exacerbate these processes. That is the beauty of being able to study this simpler organism; it allows us to clarify very complex problems. And one of the most profound things that biology has taught us over the last 20, 30 years is the immense genetic and evolutionary conservation that we humans share with all the organisms on the planet. Dozens of genomes have already been sequenced and all of those genomes are highly conserved. In the sense that you can go to the genome of a planaria, which has lived for millions of years, and when you extract the genome and sequence it, you realize that the order of the genes on the chromosomes is preserved in the same way as the

"One of the most profound things that biology has taught us over the last 20, 30 years is the immense genetic and evolutionary conservation that we humans share with all the organisms on the planet"

"I try to instill in the students the notion of reasoning, get them to think that science is not really about discovering the truth, but rather making things a little less false, because our interpretation is always incomplete"

order of genes on the human chromosomes. We're talking about an evolutionary distance of 700 million years. Such deep conservation implies that the scope or space that the genome can occupy to produce phenotypes is limited. Each animal could have evolved with completely different genes or different structures, but no, it turns out that all this genomic sequencing indicates that there was an ancestral organism from which all the organisms that inhabit the planet today supposedly originate. This conservation allows us to investigate a process that interests us, such as regeneration, in animals that look nothing like us. It is not difficult to imagine a situation in which one can do this dissection, organize all the parts, put everything back together and, with that process, think about what is happening in other animals as well. It's much easier to look at a limited number of genes, than at the 20,000 genes that exist in the human genome, and see how they are relating to each other. That is the beauty of being able to study this simpler organism; it allows us to clarify very complex problems.

Why is basic research so important?

Producing knowledge has its own merit. This type of research brings us a little closer to technologies that we have not yet invented, to therapeutic options that we have not interpreted, because it is very difficult to invent without knowing; one can invent on the basis of what one knows, but since we do not know to what extent we have understood the biological processes at the most fundamental level, we have problems in generating technologies that may not have side effects or that are effective enough to cure, or eliminate, any type of pathology. Normally, a large part of our methodologies for attacking diseases, such as cancer, are approaches that have not succeeded in eradicating this type of damage that we humans experience. And the reason is because we do not know, at a very fundamental level, what is the specific and ancestral function of the genes and the genetic processes that keep those tissues viable for so long. I think that basic research is absolutely necessary to get us a little closer to therapeutic applications. We need to work very hard to be able to elucidate that.

Have you always wanted to be a researcher?

Since high school. I had an excellent, excellent biology teacher: **Mr. Maldonado**. I thought I was going to be a physicist or study music, but I had this biology teacher who, although I didn't know it at the time, created a very big impact on the way I saw the world. He taught in a very unorthodox way, instead of forcing things to be memorized, he started the classes with a question. In the first class we had with him, he asked us the following question: "If you had to invent a language, what would be the minimum number of letters you would need?" This is biology, how can it be, I thought. A colleague, who is now a psychiatrist, raised his hand and said: "One, **Mr. Maldonado**." "Good job," the professor said, "explain that." My colleague explained it and **Mr. Maldonado** said: "OK, all right, you are right, but nature uses 4 letters." That's how he introduced us to DNA. I was very impressed that there was such a powerful capacity for synthesis that it allows you to make a metaphor like that. When one looks around and observes what surrounds us, which is very little, but at the same time really impressive, -imagine in Venezuela, in the tropics, where there are birds and plants of all kinds-, and one thinks that this diversity that one can see is all based on 4 letters... well, it knocked me down! Then one begins to think that 95% of all living beings on the planet are microscopic, and that what we are seeing is just the tip of the iceberg and that all this biological activity is based on 4 nucleotides?... "it really fascinated me." All the classes were like that; once he explained to us what the structure of DNA was like, the task was to invent a way for DNA to copy itself. This was before the age of the Internet, so you couldn't go to Google and look it up. So then he explained the Meselson and Stahl experiments [Matthew Meselson and Franklin Stahl explained semiconservative DNA replication], but he did it in a very systematic way. We did the experiment practically on the blackboard and I still haven't forgotten it, so that says it all. Imagine, being in a marine laboratory [Woods Hole Marine Biological Laboratory] in the United States where I go every summer, and realizing that one of the scientists who was walking in the center was Meselson! To me, it's the most beautiful experiment in the history of biology. I didn't know who he was and we started talking, and then I wondered – is he the same person I studied in high school? He and Stahl came up with the experiment, in that same center, under a tree. He showed me how it was all done and I realized that one of the powers of modern Evolutionary Biology is that you can use reasoning to design experiments that take advantage of the experimental vulnerabilities of very complex problems in order to dissect them. That is the power of Evolutionary Biology, of Molecular Biology, which allows us to interpret extremely complex things that, to a certain extent, can be considered magic; but real magic is to imagine the experiment and execute it to demonstrate whether its notions are correct or not. It's marvelous, I was fascinated.

Do you also do that type of teaching work?

I try to, but it's very difficult to copy **Mr. Maldonado**. In the summers I teach a biology course and get together with 24 students. I also do it at my institute, I teach Ph.D. students. I try to instill in them the notion of reasoning, get them to think that science is not really about discovering the truth, but rather making things a little less false, because our interpretation is always incomplete.

It's your first visit to the CNIC, what do you think of the center?

I feel very privileged to be at the CNIC, a center where researchers who are trying to advance in the knowledge of the regeneration process are researching. Of course, it has a very direct association with the capacity of our species to generate therapies and develop processes through which we can mitigate human suffering produced by diseases that we have not yet been able to tame. ■

Alejandro Sánchez Alvarado gave the Seminar 'Understanding the source of regenerative ability in animals' held at the CNIC invited by Dr. Miguel Torres.

HARVARD MEDICAL SCHOOL
AND MASSACHUSETTS GENERAL HOSPITAL
BOSTON (UNITED STATES)

Filip Swirski

"SLEEP HAS BEEN PROVEN TO BE A RISK FACTOR FOR CARDIOVASCULAR DISEASE"

Dr. Filip Swirski is associate professor at Harvard Medical School and Massachusetts General Hospital (USA). In 2004, he obtained his Ph.D. in immunology from McMaster University in Canada, and in 2007 he completed his post-doctoral studies in Vascular Biology at Brigham and Women's Hospital and Massachusetts General Hospital, and joined the Center for Systems Biology at that same hospital. He has received awards from the Canadian Institutes of Health Research and the American Heart Association. His team studies innate immunity and leukocyte communication. Dr. Swirski is the lead author of a study published in Nature magazine that explained the relationship between sleep and heart disease.

Cardiovascular disease is still the first cause of death in the world. Your team studies the relationship between heart disease and sleep. Could you explain to us what you have found out until now?

What we have known for a long time is that sleeping well is very important. No one is going to find that out now; we all know the effects of poor or little sleep, or how jet lag affects us, for example. And we have also known, for years, that poor sleep, with many interruptions, is related to an increased cardiovascular risk. There are many studies in humans, carried out over the years, that show this. That is, we are aware that sleeping well is a protective factor against cardiovascular disease, but in reality, we ignore how sleep keeps us healthier. And that is what we are trying to determine in my laboratory. The question we ask ourselves is how? We know it is important, but how does it happen?

And what have you discovered?

We have seen that there is some biological mechanism in sleep that makes us healthier. And that is what we must identify. In regards to the relationship with heart disease, the most honest answer would be to say that right now we are beginning to understand that such a relationship exists. We know it is important, but we ignore the 'how'. I think we are only beginning to scratch the surface of this knowledge.

You say it's important to sleep well, but do you know why?

We can actually say that we know a lot about this relationship, but also that there is a lot that we don't know. And it is quite fascinating because we spend 30% of our lives sleeping and we are only on the surface of knowing how sleep keeps us healthy or how irregular sleep or interruptions promote the appearance of all kinds of diseases, such as heart failure.

In the last two years there has been a lot of research on how and how much we should sleep in order to improve our health. But, do we actually know what a good night's sleep is?

For this question there are two types of answer: the simple one and the complex one. The simple one, regarding number of hours that it is advisable to sleep, is that it should be between 6 and 9 hours a day. But, in this sense it is necessary to recognize, and this is the complex answer, that we are still learning about it every day. We have to consider our genetic 'fingerprints' that are related to our need for sleep. Some people require more hours of sleep than others. This is what we call chronotypes. And to complicate it even more, not only are the number of hours that one sleeps important, but also, the moment in which one goes to sleep, or if one tends to get up early or not. These habits are, in some way, genetically determined. And, furthermore, there are other factors to consider: do you usually take naps? During the weekends do you make up for lost sleep by binge sleeping? We know that we will never really make up for lost sleep. Therefore, the really important thing is to determine what our chronotype is and in this way find out what our individual sleep needs are and understand if we are doing it correctly or not.

Can you say that sleep is as important a risk factor as tobacco or cholesterol? Should doctors include it as a risk factor?

Of course. Sleep has been proven to be a risk factor in cardiovascular disease and, as such, it should be considered by doctors. But not only the fact of little or poor sleep, but also excessive sleep, which too is unhealthy. We can compare it to tobacco or hypertension as a relevant risk factor. Something that is also becoming increasingly believed among the medical community is the importance of the circadian rhythm to our health, this is our internal biological clock. All organisms have day/night fluctuations throughout the 24-hour cycle and it is not the same for all people. And this rhythm influences the effectiveness of treatments and, therefore, there are more and more voices that affirm that therapies should be synchronized with the circadian rhythm. For example, a study was recently pub-

"Sleep has been proven to be a risk factor in cardiovascular disease and, as such, it should be considered by doctors. But not only the fact of little or poor sleep, but also excessive sleep, which too is unhealthy. We can compare it to tobacco or hypertension as a relevant risk factor"

lished in the ***European Heart Journal*** that showed that the time of day to take a drug can be key in terms of optimizing the drug's effects in treating hypertension ('Bedtime hypertension treatment improves cardiovascular risk reduction: the Hygia Chronotherapy Trial'). And in atherosclerosis it is also known that immune cells migrate at higher levels at certain times of the day. Therefore, the best way to follow a treatment is to adjust it to our biological clock.

And what about aging? You sleep less and less as you get older.

This is a very fascinating phenomenon. Babies sleep almost 23 hours and, as we grow older, we sleep less. There are animals that hibernate for months and others that only sleep a couple of hours. This is related to what we have talked about previously: we do not know the sleep mechanism in detail. It is possible that studies that analyze these animals that sleep for months or others that study and compare the sleep patterns of a baby with that of an 80-year-old person will help us understand this process a little better.

Was sleep one of your priority research areas from the beginning?

Yes, from the beginning we wanted to study this event in the laboratory. Our motivation was the following: What Causes Cardiovascular Disease? Genes, of course, but also a series of modifiable risk factors: hypertension, excess fat, sedentary lifestyle, obesity, diabetes, etc. And when you stop to think about what favors these risk factors, you come to the conclusion that they are all associated with lifestyle: the food we eat, the amount, whether you exercise, the type of stress, what our environment is like, etc. That is why we consider sleep a priority area of research in our laboratory.

How important is it to combine basic and clinical research?

Both are fundamental. In humans, many studies can be carried out: you can analyze blood samples, imaging tests and postmortem analysis... But there are endless tests that are not possible to do. If you want to know something in depth at the molecular, tissue, cellular level, etc. then, there is no alternative but to use animal models. And this most basic information is essential to understand fundamental concepts. It is also true that what is true in a mouse may not be true in humans. The biology is very similar, almost 99% in many cases, but it is not the same. We must not forget this. They are great models, some better than others, but they are models. But it is essential that this data is verified in humans. Now we are at the moment of studying the mechanisms that we have identified in humans.

Do you remember when you became interested in science?

I have always been interested in the natural world. I always thought I was going to be a physicist or a mathematician, but in the end, out of everything that interested me, I decided to focus on this field.

Is there someone in particular that helped you during your research career?

The truth is that I have had a lot of mentors throughout my career and I remember all of them. If you ask me who has been the most important, the answer is easy: my wife. The scientific career is not easy at all and, of course, you are not going to get rich. You have to be passionate and the motivation should be curiosity. Because the path is full of failures.

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

The first time I visited the CNIC was three years ago and I still think that it is a magnificent center. Some of my researchers have done stays at the CNIC. I consider it to be a very diverse research center with great international prestige. ■

Dr. Filip Swirski participated in the CNIC Conference entitled 'New Concepts in Age-related Cardiovascular Disease'.

THE GOETZ LAB FOR TUMOR BIOMECHANICS
STRASBOURG (FRANCE)

Jacky Goetz

"TO DO SCIENCE IT IS ESSENTIAL TO BE PROACTIVE AND NOT WAIT FOR YOUR PROJECT TO PROGRESS ON ITS OWN"

Jacky Goetz graduated in pharmacology and cell biology from the University of Strasbourg in France and moved to Canada to work at Ivan Robert Nabi's laboratory, at the University of Montreal and later at the University of British Columbia. In 2007 he received his doctorate from the University of Montreal and the University of Strasbourg. During his post-doctorate, Jacky Goetz moved to Miguel Ángel del Pozo's laboratory at the National Center for Cardiovascular Research (CNIC) to study the microenvironment of the tumor. Afterwards, he joined Julien Vermot's laboratory at the Institute of Genetics and Molecular and Cellular Biology (IGBMC). In 2012, he won the Young Scientist Award from the French Society for Cell Biology, in 2020 the Grand Prix de Cancérologie de la Fondation Del Duca (Académie des Sciences) and the Prix Ruban Rose Avenir 2020. In 2013, he founded his own research group, "Tumor Biomechanics," in Strasbourg to work on intravital imaging methods and biomechanical forces during the progression of tumors. Currently is the Coordinator of the NanoTumor program (Programme Fédérateur Aviesan, 2020-2022).

Your work is currently directed at digging deeper into the metastasis processes. Can you explain what your main areas of work are?

During the past five or six years, in the laboratory we have been researching the different steps that occur in the process of tumor metastasis in different animal models. In addition, we have developed emerging technologies to analyze metastasis using very high image resolution. In this sense, we have been pioneers in the development of a technique, in collaboration with our colleagues in Heidelberg, called intravital correlative electron microscopy. Thanks to this technique we can observe how tumor cells promote metastasis and, thus, understand how this very harmful process is really happening. In the same way, we are also interested in understanding how the mechanical forces work, which is related to the work I did in Madrid during my first post-doctorate, and how these mechanical forces affect metastasis. However, while at the CNIC I was working primarily on the mechanical forces that come from the extracellular matrix for surrounding tumors, now we are primarily investigating forces generated by fluids, such as blood flow that only affect circulation. In summary, the main project is to understand how blood flow affects tumor metastasis formation, and we know that it does in many different ways. Finally, something that is related to this last question is that tumors generate and share very small vesicles, nanoscale vesicles, in the blood. This is something that happens in many other diseases, especially inflammatory pathologies, but we are interested in the context of cancer progression. And we know that tumors generate vesicles. That's why we are really interested in how they feed themselves so that these vesicles reach distant organs, far from those tumors, and prepare the microenvironment to promote metastasis. And this matters to us in many ways. One angle is microscopy because, when we started the project, there wasn't a good model, no good approach to track these little vesicles, because they are so small. My laboratory is focused on understanding how they behave in the blood flow, because we think that this is the key step in the way in which they diffuse in the body. Furthermore, we have established a new animal model, the zebrafish embryo, which allows us to track these vesicles in the animal at very high speeds in the blood flow. And in doing so, we have understood a little more about how they stop in specific vascular regions and how they can prepare the initiation of subsequent metastases.

This is probably the most important challenge in cancer treatment. How can metastasis be stopped before it starts?

The idea of stopping metastasis before it occurs is something that can be done in animal models, but in patients it will be very difficult because it is very hard to find patients who have a primary tumor with metastasis in very early stages. The main objective of my team is to understand the fundamental mechanisms that are at the base of metastasis. By doing so, we could identify new therapeutic targets that are definitely safe. For example, in the work we did on blood flow and metastasis, we identified on the surface of the tumor cell some receptors that are involved in stabilizing the tumor cell within the blood vessels. And we have identified a new variation that allows them to leave the circulation and form metastases. And this is something we could target to inhibit this metastasis process. And there is another thing that we discovered when we looked at the impact of blood flow on tumor metastasis, which is that the blood flow is actually capable of indoctrinating the blood vessels; that is, it basically makes the endothelial cells that make these blood vessels reactive to blood flow when there is a tumor cell. And, when this happens, we have shown that the vascular microenvironment is involved in a process we call endothelial remodeling. This process expels cells from the vasculature. And when we dissect this a bit more, we identify the molecular mechanism of this endothelial remodeling that is partially driven by a signaling pathway that is very well known, VEGFR, involved in angiogenesis. We have now seen that the early stages of vascular remodeling can be inhibited with the classic drugs available on the market and alter metastasis. However, applying it to a human patient is a very delicate matter in this phenomenon of early metastasis. On a clinical level, we would be more interested in targeting the already established metastasis, in order to find ways to kill the established metastasis, although this is not exactly what we are studying in my laboratory.

In an idealistic scenario, would it be possible to predict if this tumor will suffer metastasis?

Predicting this is very complicated. Of course there are ways to prevent metastasis from starting. For example, one way to do this would be through extracellular vesicles, since they affect the ability of these tumors to share and spread extracellular vesicles, and the amount of metastasis they generate can be considerably reduced. But this is something that is very complex because, although it is true that tumors can metastasize when you do experiments in mouse models, some tumors, even if they are of the same cell lineage, would metastasize and, in other mice, they would not. So there is a combination of many different factors that triggers metastasis.

You currently lead your own group. Do you still have time to do research in the laboratory?

Running a laboratory involves learning to do many things in a short time. If you want to continue researching and doing science, you have to be able to do it in a short and fast way because most of the things that you deal with are not scientific 'per se'. In my opinion, the best option to be able to continue doing science is to identify the people who work with you with whom you can do science and basically, they will be the ones who will research and bring science closer to you. Unfortunately, at least at my level, I can no longer do that research work. And I miss it, like for example when the CNIC was here because I was the person who did the experiment and promoted the project and analyzed the results. That is why, recently, I went to work in Sydney (Australia) for a while to go back to the laboratory a bit and get away from the team a bit. Thankfully I knew it was being run by people I trusted in France. I took a little time to do some experiments. And it was a lot of fun and interesting. In my opinion, it is essential not to be too far away from science for too long because the real science, the one I refer to, is doing experiments.

"The main objective of my team is to understand the fundamental mechanisms that are at the base of metastasis. By doing so, we could identify new therapeutic targets that are definitely safe"

Why did you decide to go back to the laboratory for awhile?
Going back to the laboratory also gives you an idea of what you can ask for and expect from the people who work on your team because, sometimes, being a laboratory manager, all the students of any team in the world will tell you that "my boss is crazy because he asked me to do this and this in one week." And it's not just because we want things to go fast, it's more because we lose track of the reality of what it really means to run an experiment and analyze all the work. So when you go back to the lab you realize that sometimes it is not a good idea to go so fast.

And as a laboratory manager, can you mentor young researchers and students?
I was lucky to have a very good mentor. In a way, she was good because she was always pushing me a lot, in a good way. She always pressured me to find, for example, better and more precise analyses, encouraging me to do more experiments, to make sure everything was correct. She taught and trained me to be able to summarize a set of data, which I had acquired for weeks, basically always trying reconstruct the different pieces of a puzzle and do this work regularly. And I think this is essential. This is what allowed me to come here to Madrid and gain a lot of autonomy. I was working with **Miguel [Del Pozo]**, he was very good at allowing me to work, but I didn't necessarily ask him for so much help in terms of tutoring because I already knew how to work and he gave me the freedom to do it which, in my opinion, was very beneficial for me because later, you reach a different stage and you can create your own project. In that phase you only need help for some parts of the projects, financially or to obtain help from a technician, and basically let the project move forward.

Which qualities should a good mentor have?
One quality that I think I have, and that comes from my own mentoring experience, is how to stimulate people. I'm pretty sure most of my researchers will say just the opposite, which is the worst of me. In my opinion, to do science it is essential to be proactive and not wait for your project to progress on its own. And that's what I try to get my students to do. It's your baby, it's your project, you're working on your specific scientific question, and if you have that little passion that all scientists have, you want your project to move fast and be well done. And, for this, you must make additional efforts. I would like to spend more time on individual discussions with my students. This is one of the main drawbacks of being too busy when you have other responsibilities that take you away from the real world in the lab. If I could change anything, this is something I would have to focus on and would certainly have to make more time for.

Is it possible to identify when a research is "different" from others?
Yes, you definitely can, although I don't have that much experience because I'm still young; but you can definitely distinguish which students have that passion. You can sense it in the way they talk about science and how they listen to your own project because they come up with questions, sometimes very naïve ones, but you can tell they are interested. One of the things I like to ask the students who come to my lab is something very simple: is there something in science, related to our projects that you would love to work on or that you knew about beforehand? I don't find many students who come up with specific questions and say yes, I am really interested in this because I have been reading a lot about this bacterial disease, etc. There are few who have this sensibility. But at the same time, it doesn't mean that the others are not good scientists: some just may be shy or may not have enough experience to know what they could be working on. That is why you must be sensitive to this type of profile because you can find many good students among young people who do not necessarily know where they want to go yet.

Do you remember the moment you decided you wanted to be a scientist?
I recently celebrated my 40th anniversary with many friends and we talked a bit about the past. And even today I can identify exactly when I became interested in science. I was 17 years old and in high school in biology class studying the 3D structures of proteins using software and playing with 3D structures of molecules. When I got home I told my parents "today I have done something that has changed my life." It was that moment. Until that day I didn't know that I was interested in biology, that I knew I wanted to become a scientist. In regards to what you are really interested in doing or what the main scientific question you want to ask is, I think that, in my case at least, it is mainly related to the first laboratory experiment that you enjoyed at the university. And for me it is my work on glioblastoma, on how they evolve, how they form, how they become invasive. I was watching tumor cell migration and this kind of thing. Whatever I do, I always come back to these kinds of questions: how do tumors become invasive, how do they become metastatic.

You also dedicated yourself to scientific dissemination. Why do you think it is important?
When I lived in Vancouver (Canada) I was a columnist for a French monthly newspaper. I had a lot of freedom to choose the topics and I loved that. I chose a topic freely and wrote about it; I really enjoyed doing that. In fact, I still love writing and reading a lot about science. However, when I came back to Europe, to France, I contacted several newspapers, but it was a lot more difficult to do it. ■

Dr. Jacky Goetz taught the 'Multiscale Tracking of Metastasis In Vivo' seminar invited by Dr. Miguel Ángel del Pozo.

EXCELLENCE IN COMMUNICATION SCIENCE

LEADING JOURNALS PUBLISH CNIC SCIENCE

NATURE
A new way to make arteries

A study carried out at the CNIC not only advanced understanding of the biology of blood vessels, but also pointed the way to the design of new therapeutic strategies to induce vascularization and more effective blood perfusion of injured or ischemic tissues.

The study, led by **Rui Benedito** and published in ***Nature***, reveals a new cellular and molecular mechanism essential for the development of arteries from blood capillaries, a process called arterialization. Activation of this mechanism could improve the recovery of heart function after transient or long term reduction in heart blood flow, as occurs after a heart attack.

The results also have important implications for the use of drugs to boost angiogenesis—the formation of new blood vessels—in ischemic cardiovascular disease.

The study suggests that pro-angiogenic drugs that stimulate general blood vessel proliferation will suppress arterialization. "One of our future goals will be to identify new ways to suppress proliferation signals exclusively in pre-arterial cells, thereby promoting effective arterialization without negatively interfering with the induction of capillary angiogenesis," said **Dr. Benedito**.

From a translational standpoint, the authors conclude that the ability to modulate arterial or venous identity of blood vessels is of great interest for the treatment of coronary artery disease and myocardial infarction. The results obtained could lead to novel therapeutic approaches to induce effective arterialization in ischemic cardiovascular disease.

Luo, W., García-González, I., Fernández-Chacón, M. et al. *Arterialization requires the timely suppression of cell growth.* ***Nature*** (2020). https://doi.org/10.1038/s41586-020-3018-x

ELIFE
Neutrophils, the hidden controllers of the liver's internal clock

CNIC scientists have discovered a mechanism underlying the development of steatosis, or fatty liver, one of the main risk factors for liver cancer. The study, published in ***eLife***, for the first time shows that neutrophils act as "circadian messengers" in the liver, controlling its internal clock and lipid metabolism. The study opens a window for potential therapies to treat liver diseases.

The study findings establish that neutrophils are active and crucial circadian regulators of liver metabolism. This could provide a new therapeutic target for the treatment

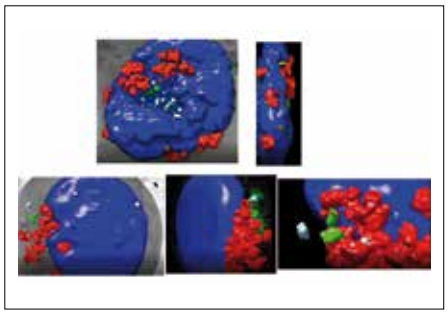
of metabolic diseases such as steatosis, which commonly progresses to certain types of liver cancer.

The study was supported by funding from the Asociación Española Contra el Cáncer.

Crespo, M., González-Terán, B., Nikolic, I., Mora, A., Folgueira, C., Rodríguez, E., ... Sabio, G. (2020). *Neutrophil infiltration regulates clock-gene expression to organize daily hepatic metabolism.* ***Elife****,* 9, e59258. doi:10.7554/eLife.59258

SCIENCE ADVANCES
The role of the CCT protein in the control of immune-synapse formation

A new study published in ***Science Advances*** identifies the role of the cytosolic chaperone protein CCT in the reorganization of the cytoskeleton during the formation of an immune synapse.



The research teams led by **Francisco Sánchez-Madrid** and **Noa Martín** at the CNIC and the IIS Princesa and by **José María Valpuesta** at the CNB-CSIC have shown that CCT controls changes in the arrangement of the centrosome and mitochondria by regulating the production of the cytoskeletal components α- and β-tubulin.

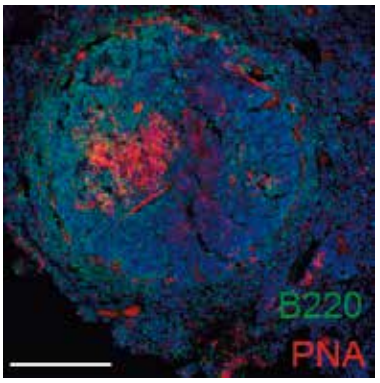
This finding opens the path to the design of strategies aimed at blocking CCT for the treatment of autoimmune diseases that involve hyperactivation of lymphoid cells.

Martín-Cófreces, N. B., Chichón, F. J., Calvo, E., Torralba, D., Bustos-Morán, E., Dosil, S. G., ... Sánchez-Madrid, F. (2020). *The chaperonin CCT controls T cell receptor–driven 3D configuration of centrioles.* ***Sci Adv****,* 6(49), eabb7242. doi:10.1126/sciadv.abb7242

NATURE
A new diagnostic and therapeutic target for cardiovascular disease

A study published in ***Nature*** showed that the mitochondrial protein ALDH4A1 is an autoantigen involved in atherosclerosis. The CNIC research team concluded that ADH4A1 is a potential marker for the diagnosis and treatment of cardiovascular disease (CVD).

Atherosclerosis develops for many years without causing symptoms, and there is therefore a pressing need for new tools for diagnosis and therapy. Study leader **Dr. Almudena Ramiro** explained that, "we know that atherosclerosis includes an immunological component and that the innate and adaptive immune systems are both involved in the origin and progression of this disease." However, little is known about the specific response of B cells in these processes or the repertoire of antibodies these cells produce during atherosclerosis.



Autoantigens are molecules produced by the body that, through a variety of mechanisms, are recognized as foreign and trigger an immune response. "ALDH4A1 is recognized by the protective antibodies produced during atherosclerosis, making it a possible therapeutic target or diagnostic marker for this disease," commented **Ramiro**.

The study shows that ALDH4A1 accumulates in plaques and that its plasma concentration is elevated in the atherosclerosis-prone mice and in human patients with carotid atherosclerosis, establishing ALDH4A1 as a possible biomarker of the disease.

The team also found that infusion of A12 antibodies into the atherosclerosis-prone mice delayed plaque formation and reduced the circulating levels of free cholesterol and LDL, suggesting that anti-ALDH4A1 antibodies have therapeutic potential in the protection against atherosclerosis.

These results broaden knowledge of the humoral response during atherosclerosis and highlight the potential of ALDH4A1 as a new biomarker and of A12 as a therapeutic agent for this disease.

The study was supported by funding from the "la Caixa" Foundation, the Asociación Española Contra el Cáncer, and the Ministerio de Ciencia, Innovación y Universidades.

Lorenzo, C., Delgado, P., Busse, C. E., Sanz-Brazo, A., Martos-Folgado, I., Bonzon-Kulichenko, E., ... Ramiro, A. R. (2020). *ALDH4A1 is an atherosclerosis auto-antigen targeted by protective antibodies.* ***Nature****.* doi:10.1038/s41586-020-2993-2

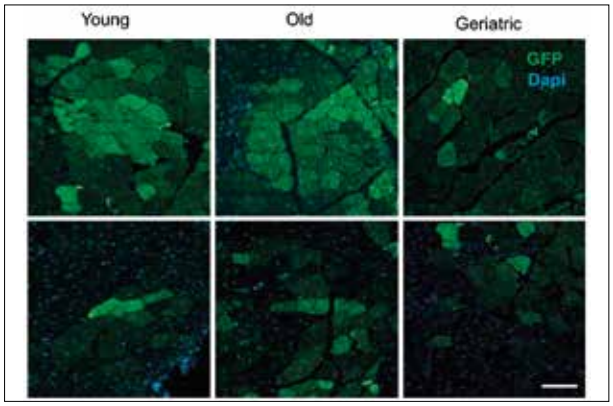
NATURE CELL BIOLOGY

A subgroup of stem cells resists aging and maintains muscle regeneration capacity until geriatric age

Researchers at Pompeu Fabra University, the CNIC, ICREA, and Ciberned have identified a physiological mechanism that maintains the regenerative capacity of muscle stem cells, and surprisingly resists the passage of time far more than expected, until geriatric age.

Skeletal muscle regeneration depends on a muscle stem cell population (satellite cells) in a dormant or quiescent state, a situation that can be triggered by damage or stress to form new muscle fibers and expand in new stem cells.

The regenerative functions of these stem cells are known to decline with aging. **Dr. Pura Muñoz-Cánoves** and colleagues have found in experiments with mice that all muscle stem cells, despite being quiescent, are not equal, and have identified a subgroup that maintains its regenerative capacity over time, declining only at geriatric age.



The researchers have shown that this subgroup of quiescent stem cells has a greater regenerative capacity through the activation of the FoxO signaling pathway (previously associated with longevity), which maintains the expression of a youthful gene program throughout life; however, at geriatric age, FoxO activation in this subgroup of cells is lost, causing their loss of functionality.

The results show that compounds that activate FoxO can have a rejuvenating effect on aged muscle stem cells, opening the way to improving the health of elderly people affected by the loss of muscle mass. The research may also benefit people who have lost muscle mass as a result of neuromuscular diseases or effects associated with cancer or infectious or inflammatory diseases.

The study was supported by funding from the "la Caixa" Foundation, the ERC, and the Ministerio de Ciencia e Innovación y Universidades.

García-Prat, L., Perdiguero, E., Alonso-Martín, S., Dell'Orso, S., Ravichandran, S., Brooks, S. R., ... Muñoz-Cánoves, P. (2020). *FoxO maintains a genuine muscle quiescent state until geriatric age.* ***Nature Cell Biology***. doi:10.1038/s41556-020-00593-7

CELL

The unexpected repair function of neutrophils

The CNIC team lead by **Dr. Andrés Hidalgo** has discovered that neutrophils, the most abundant cells of the innate immune system, have many more functions in the body than previously thought. This finding suggests possible new treatments for many diseases, including cancer.

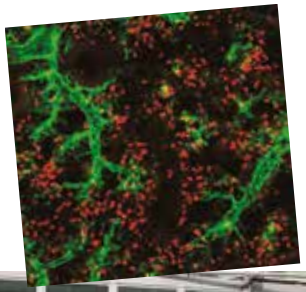
In a study published in the journal ***Cell***, the research team demonstrate that neutrophils acquire new characteristics when they arrive in a tissue and that these specialized functions help to maintain organ health.

Every day, the marrow inside our bones produces immense quantities of neutrophils. These cells then enter the bloodstream and are distributed to almost all tissues of the body. Neutrophils have a short lifespan, living for less than 24 hours. For this reason, scientists believed that these cells had a very limited capacity to adapt to their environment and adopt new functions.

But the authors of the ***Cell*** study found that when neutrophils leave the circulation and migrate into tissues they acquire new, previously unknown properties.

According to **Dr. Hidalgo**, the most fascinating finding is that neutrophils appear to acquire functions useful to the specific tissues in each organ.

This ability to change cell properties was identified in healthy individuals, which suggests that neutrophils participate in a great variety of normal functions in the body and are not limited to combating infection.



Previous studies had already identified neutrophil heterogeneity in several diseases. Indeed, these neutrophil changes are prognostic markers in cancer and help to regenerate blood cells after bone marrow transplantation.

However, the mechanisms that establish neutrophil hyperplasticity are poorly understood, and the new results are a crucial step towards filling this knowledge gap. Essentially, what we have demonstrated is that neutrophils, despite their sort lifespan, can change their function and that they do this when they enter tissues. The identification of these adaptations allows a better understanding of the roles of different immune cells in disease.

The study was supported by funding from the European Regional Development Fund (ERDF), RTI2018-095497-B-I00, the "la Caixa" Foundation, and Leducq Foundation Transatlantic Network of Excellence (TNE-18CVD04).

Ballesteros, I., Rubio-Ponce, A., Genua, M., Lusito, E., Kwok, I., Fernández-Calvo, G., ... Hidalgo, A. (2020). *Co-option of neutrophil fates by tissue environments.* ***Cell***. https://doi.org/10.1016/j.cell.2020.10.003

NATURE REVIEWS ENDOCRINOLOGY
Stress kinases could be the next target in the treatment of obesity-associated diseases

CNIC investigators from the group led by **Dr. Guadalupe Sabio** reviewed the key role played by stress kinases in adjusting metabolism to changing conditions in an article published in ***Nature Reviews Endocrinology***.

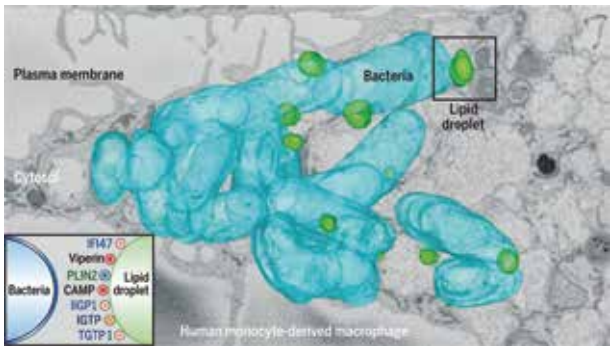
Stress kinases are proteins in the body that are associated with obesity and metabolic alterations such as insulin resistance and diabetes. Understanding their mechanisms and routes of action could be crucial for the design of therapeutic strategies to combat the global epidemic of obesity, which affects millions of people worldwide.

JNK and p38 SAPKs are known to act through diverse signaling pathways and mechanisms that affect metabolic processes such as insulin sensitivity, thermogenesis, and lipolysis. In addition, SAPK activity in immune cells triggers inflammation in several tissues and alters systemic metabolism in obesity. The accumulated evidence also shows that SAPKs have tissue and substrate specific functions and that their activation is involved in disorders related to obesity, steatohepatitis, liver cancer, heart failure, and diabetes mellitus.

The review concludes that the main goal in this field is to identify specific inhibitors for each of the individual p38 and JNK members. These molecules can then be tested for their ability to prevent and treat obesity and associated diseases.

Dr. Sabio's group is supported by funding from the Fundación Científica de la Asociación Española Contra el Cáncer, a BBVA Beca Leonardo para Investigadores y Creadores Culturales (2017), and the European Foundation for the Study of Diabetes.

Nikolic, I., Leiva, M., & Sabio, G. (2020). *The role of stress kinases in metabolic disease.* ***Nature Reviews Endocrinology***. doi:10.1038/s41574-020-00418-5



SCIENCE
A new cellular defense mechanism against viral and bacterial infection

A study published in the journal ***Science*** and coordinated by researchers at the CNIC, IDIBAPS, and the University of Barcelona describes a hitherto unknown immune defense mechanism orchestrated by lipid droplets (LDs), cellular organelles able to attract and eliminate invading pathogens.

LDs accumulate fatty nutrients that provide the energy cells need to perform their functions. For example, LDs provide the energy for the heart to beat, the liver to perform its metabolic functions, and muscles to move.

The newly identified mechanism highlights the intimate relationship between metabolism and immunity, and could stimulate the development of new therapeutic strategies at an especially critical time, when antibiotic resistance is presenting an ever increasing threat to public health.

This study represents a paradigm shift because until now LDs were thought to be at the service of viruses or bacteria during infection. "In light of the widespread resistance to current antibiotics, this study has deciphered an important defense mechanism that could be stimulate the development of new therapeutic strategies to stop infections."

The study was supported by funding from the Human Frontier Science Program Organization.

Bosch, M., Sánchez-Álvarez, M., Fajardo, A., Kapetanovic, R., Steiner, B., Dutra, F., ... Pol, A. (2020). *Mammalian lipid droplets are innate immune hubs integrating cell metabolism and host defense.* ***Science***, 370(6514), eaay8085. doi:10.1126/science.aay8085

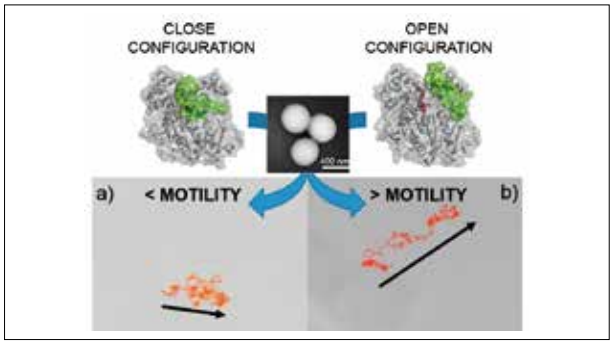
ANGEWANDTE CHEMIE INTERNATIONAL EDITION

Controlling the speed of enzyme motors brings biomedical applications of nanorobots closer

A study by scientists at the CNIC, Universidad de Girona (UdG), and the Institute for Bioengineering of Catalonia (IBEC) has overcome one of the key hurdles to the use of nanorobots powered by lipases.

The study was coordinated by CNIC investigator **Marco Filice** and was published in the journal ***Angewandte Chemie International Edition***. The study describes a tool for modulating motors powered by enzymes.

Microorganisms are able to swim through complex environments, respond to their surroundings, and organize themselves autonomously. Inspired by these abilities, over the past 20 years scientists have managed to artificially replicate these tiny swimmers, first at the macro-micro scale and then at the nano scale, finding applications in environmental remediation and biomedicine.



The speed, load-bearing capacity, and ease of surface functionalization of micro and nanomotors has seen recent research advances convert these devices into promising instruments for solving many biomedical problems. However, a key challenge to the wider use of these nanorobots is choosing an appropriate motor to propel them.

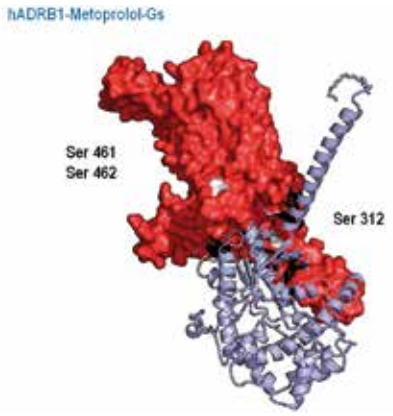
The authors conclude that this new tool for modulating enzyme-powered motors broadens their potential biomedical and environmental applications.

Wang, L., Marciello, M., Estévez-Gay, M., Soto Rodríguez, P. E. D., Luengo Morato, Y., Iglesias-Fernández, J., ... Sánchez, S. (2020). *Enzyme conformation influences the performance of lipase-powered nanomotors.* ***Angewandte Chemie International Edition***. doi:10.1002/anie.202008339

EHJ

Metoprolol: an old drug with unique cardioprotective properties

ICNIC researchers have demonstrated the unique properties of metoprolol, a treatment able to reduce the long term consequences of a heart attack. Metoprolol, a member of the beta-blocker class of drugs that has been in use for more than 40 years, has been found to have unique cardioprotective properties.



This is the conclusion of a study carried out by scientists at the CNIC, Fundación Jiménez Díaz University Hospital, and CIBERcv. The study, performed in sophisticated experimental mouse models, shows that the cardioprotective effect of metoprolol during a heart attack is not shared by other beta-blockers commonly administered by intravenous injection, such as atenolol and propranolol.

The ***European Heart Journal*** study, led by **Dr. Borja Ibáñez**, "demonstrates that metoprolol has unique cardioprotective properties and heralds a paradigm change in cardiology and the treatment of acute myocardial infarction."

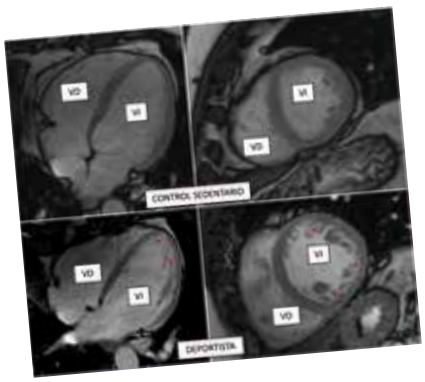
The authors conclude that metoprolol should be the beta-blocker of choice in clinical practice. "If these results are confirmed in future clinical studies, this would herald a change in the clinical guidelines for this devastating disease, placing metoproplol, but not other beta-blockers, as the drug of choice for patients suffering a heart attack," said **Dr. Ibáñez**.

Clemente-Moragón, A., Gómez, M., Villena-Gutiérrez, R., Lalama, D. V., García-Prieto, J., Martínez, F., ... Ibáñez, B. (2020). *Metoprolol exerts a non-class effect against ischaemia–reperfusion injury by abrogating exacerbated inflammation.* ***European Heart Journal***. doi:10.1093/eurheartj/ehaa733

JACC

Vigorous exercise, spongy heart

Scientists at the CNIC and CIBERcv have used cardiac magnetic resonance technology to measure exercise-related hypertrabeculation in a general, non-athlete population. The results of the study have important practical implications because "misdiagnosis of noncompaction cardiomyopathy in people who exercise regularly (whether professional athletes or amateurs) can trigger medical recommendations to stop physical exercise unnecessarily," explained CNIC General Director **Valentín Fuster**.



The authors conclude that cardiac magnetic resonance criteria for diagnosing noncompaction cardiomyopathy should not be interpreted in isolation. Instead, imaging results should be placed in the context of other clinical parameters, genetic tests, and the level of physical activity. This is important even in a population of non-athletes in order to avoid misdiagnosis of the disease. Misdiagnosis can result in the unnecessary cessation of exercise, with all its associated negative physical and psychological consequences.

The study, published in the ***Journal of American College of Cardiology*** (JACC), forms part of the PESA-CNIC-Santander study.

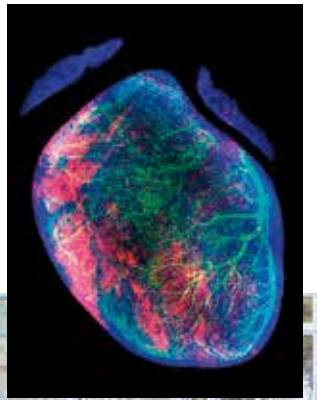
De la Chica, J. A., Gómez-Talavera, S., García-Ruiz, J. M., García-Lunar, I., Oliva, B., Fernández-Alvira, J. M., ... Fuster, V. (2020). *Association between left ventricular noncompaction and vigorous physical activity.* ***Journal of the American College of Cardiology***, 76(15), 1723-1733.
doi:10.1016/j.jacc.2020.08.030

CIRCULATION RESEARCH

An essential factor for the correct formation of the coronary arteries

CNIC scientists have discovered a protein that participates in the maturation of the blood vessels that supply the heart. Loss of this protein during embryonic development leads to an anomalous remodeling of the coronary arteries. The study, published in ***Circulation Research***, provides the basis for further research into clinical applications to promote vascular regeneration after coronary injury.

The study, carried out in a rodent model, focused on the embryonic formation of the coronary tree, the blood vessel system that supplies the heart muscle. The research team used a range of transgenic mouse lines and high-resolution microscopy techniques to obtain an unprecedented visualization of the different phases of coronary vascularization.



The researchers used a range of fluorescent genetic indicators, each one targeting a distinct regulatory element of the gene nestin, to isolate different subtypes of endothelial cells—the cells that line blood vessels—before and during the remodeling of the immature vascular network.

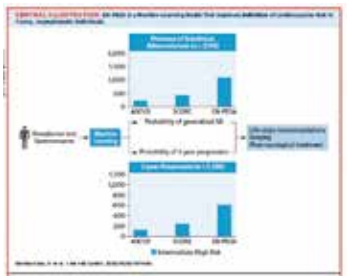
By comparing the molecular profiles of each endothelial cell network, the team identified the restricted presence of the transcription factor Sox17 in vessels undergoing arterial remodeling. Specific elimination of Sox17 from the coronary endothelium produced a severe phenotype characterized principally be defective formation of the left coronary artery.

González-Hernández, S., Gómez, M. J., Sánchez-Cabo, F., Méndez-Ferrer, S., Muñoz-Cánoves, P., & Isern, J. (2020). *Sox17 controls emergence and remodeling of nestin-expressing coronary vessels.* ***Circulation Research***.
doi:10.1161/CIRCRESAHA.120.317121

JACC

A new algorithm for personalized cardiovascular risk estimation in healthy people

CNIC scientists have designed an algorithm that provides a personalized estimate of cardiovascular risk in healthy middle-aged individuals based on a range of variables including age, blood pressure, diet, and blood and urines markers. The EN-PESA algorithm is an affordable tool for estimating the severity of subclinical atherosclerosis—characterized by the deposition of fatty substances in the arterial walls—especially in individuals at higher risk. The researchers conclude that EN-PESA will "help to personalize the estimation of cardiovascular risk, leading to tailored treatments and follow-up plans." The study is published in the ***Journal of American College of Cardiology***.



The success of machine learning algorithms derives from the analysis and systematic processing of huge quantities of data collected from a large number of individuals. One of the pioneering studies in this area is PESA-CNIC-Santander, led by **Dr. Valentín Fuster**.

Sifting through this immense quantity of information, the EN-PESA algorithm identified a small set of variables that are easily measured in primary care centers. These variables accurately predict the extent of subclinical atherosclerosis and disease progression in middle-aged individ-

uals who are classed at low or intermediate risk according to established cardiovascular risk scales.

The parameters include age, blood pressure, data collected in routine blood and urine analysis, and answers to dietary questionnaires.

The authors concluded that "this algorithm will improve the clinical management of apparently healthy individuals with a low cardiovascular risk according to established risk scores but who have a generalized extent of subclinical atherosclerosis or a high short-term risk of significant disease progression."

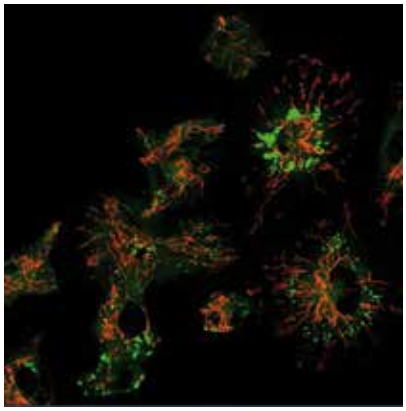
Sánchez-Cabo, F., Rosselló, X., Fuster, V., Benito, F., Manzano, J. P., Silla, J. C., ... Lara-Pezzi, E. (2020). *Machine learning improves cardiovascular risk definition for young, asymptomatic individuals.* ***Journal of the American College of Cardiology***, 76(14), 1674-1685. doi:10.1016/j.jacc.2020.08.017

NATURE METABOLISM
How immune cells regulate obesity

Two CNIC groups have described how macrophages regulate obesity in a study published in ***Nature Metabolism*** that could lead to the design of treatments for obesity and overweight, as well as for related conditions such as fatty liver disease and type 2 diabetes.

The study, led by **Drs José Antonio Enríquez and David Sancho**, explains how fatty tissue inflammation and obesity emerge from the activation of the mitochondrial metabolism in macrophages in response to oxidative stress due to excess nutrients.

The research analyzed how macrophage metabolic changes regulate the inflammatory process underlying obesity and the metabolic syndrome. The new findings reveal how the detection by macrophages of oxidative danger signals—known as reactive oxygen species—leads to mitochondrial metabolism changes in these immune cells essential for their differentiation to the proinflammatory M1 macrophage type. This oxidative stress is found in morbidly obese patients and seems to be related to the high-fat diet typical in developed economies.



A key finding of the study is that a reduction of this oxidative stress ameliorates some of the harmful parameters associated with obesity.

The results support the potential use of specific Fgr protein inhibitors to treat patients with obesity or metabolic syndrome. The goal would be to reduce the inflammation associated with these conditions, reducing impact of associated diseases fatty liver and type 2 diabetes and contributing to increased life expectancy and quality-of-life.

The study was supported by funding from the Human Frontier Science Program Organization (HFSP RGP0016/2018).

Acín-Pérez, R., Iborra, S., Martín-Mateos, Y., Cook, E. C. L., Conde-Garrosa, R., Petcherski, A., ... Enríquez, J. A. (2020). F*gr kinase is required for proinflammatory macrophage activation during diet-induced obesity.* ***Nature Metabolism***.
doi: 10.1038/s42255-020-00273-8

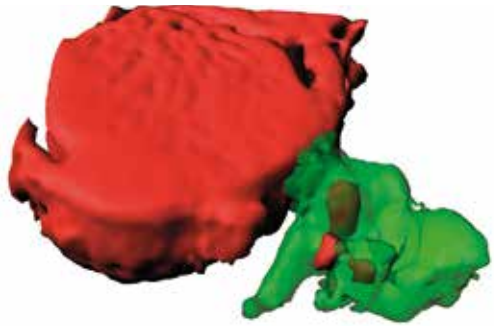
CELL
A cell-cleaning system keeps hearts healthy

Two CNIC groups, led by **Drs Andrés Hidalgo and José Antonio Enríquez**, have discovered a cell-cleaning system that is key to keeping a healthy heart. This mechanism allows the heart's contractile cells (the cardiomyocytes) to release damaged components outside the cell into particles called exophers. These exophers are then taken up by a network of immune cells living inside the heart-the macrophages, which are in charge of removing them before they cause inflammation in the heart.

The study, published in ***Cell***, compiles the results of over five years of research, with collaborations with laboratories in Europe, Asia and the US. The insights that this study provides suggests that cardiac dysfunction can emerge in some instances from defects in resident immune cells, rather than from cardiomyocytes. This finding has important implications for the diagnosis and treatment of heart disease.

The finding that cardiomyocytes surrogate the removal of their waste to macrophages has many implications. "The fact that the heart requires a population of macrophages to do their cleaning work, among other tasks, suggests that many heart diseases of unknown origin can be explained by failure of these macrophages," said **Dr. Enríquez**.

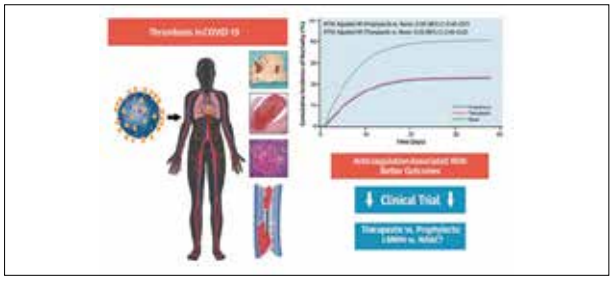
Another potential implication is that there may be similar processes supporting the fitness of specialized cells in oth-



er tissues, including the brain, whose cells share features with cardiomyocytes.

The authors conclude that the identification and elimination of cardiomyocyte-derived mitochondria and other material by resident macrophages establishes a new paradigm of how resident phagocytes contribute to general tissue maintenance.

Nicolás-Ávila, J. A., Lechuga-Vieco, A. V., Esteban-Martínez, L., Sánchez-Díaz, M., Díaz-García, E., Santiago, D. J., ... Hidalgo, A. (2020). *A network of macrophages supports mitochondrial homeostasis in the heart.* ***Cell***. https://doi.org/10.1016/j.cell.2020.08.031



JACC
Additional data on the efficacy of blood thinners in COVID-19 patients

Anticoagulation therapy improves survival among hospitalized COVID-19 patients by helping to prevent fatal events associated with coronavirus, such as infarction and stroke. The study, published in the ***Journal of the American College of Cardiology*** and led by CNIC Director **Dr. Valentín Fuster**, shows that hospitalized COVID-19 patients treated with anticoagulants—drugs that prevent blood clotting—had a better survival rate that those who did not.

At the start of the pandemic, the same research team demonstrated that anticoagulation therapy was associated with superior survival among hospitalized COVID-19 patients. This subsequent observational study showed that patients on both a "therapeutic" or full dose, and those on a "prophylactic" or lower dose, showed about a 50% higher chance of survival, and roughly a 30% lower chance of intubation, than those not on anticoagulants.

The study examined 6 anticoagulant treatment regimens. Among these, the best outcomes were obtained with therapeutic and prophylactic low-molecular weight heparin and therapeutic apixaban.

Nadkarni, G. N., Lala, A., Bagiella, E., Chang, H. L., Moreno, P., Pujadas, E., ... Fuster, V. (2020). *Anticoagulation, mortality, bleeding and pathology among patients hospitalized with COVID-19: A single health system study.* ***Journal of the American College of Cardiology***, 27631. doi:10.1016/j.jacc.2020.08.041

NATURE
A key mechanism in hypoxia

Researchers at the CNIC and the Instituto de Investigación Sanitaria del Hospital Universitario de La Princesa (IIS Princesa) have made a major advance toward deciphering the mechanism through which the production of reactive oxygen species (ROS) increases in the early phases of hypoxia (acute reduction in tissue oxygen). The finding represents an important advance in the understanding of cell physiology and could be exploited in the future to treat a variety of diseases in which hypoxia plays a role, such as stroke and heart attack. The study was published in ***Nature***.

The study shows that sodium ions act as second messengers that regulate mitochondrial function, specifically the function of the mitochondrial electron transport chain (ETC), by inducing the controlled production of ROS

This mechanism of ROS production is fundamental to the ability of the pulmonary circulation to respond to hypoxia by redistributing blood flow to regions with less irrigation, a phenomenon known as hypoxic pulmonary vasoconstriction.

Several of the study findings provide important information about cell physiology. First, the study shows that mitochondrial sodium regulates cell membrane fluidity. This was unknown before and could have major implications for the understanding of a multitude of cellular processes.

A second important discovery is that the mitochondrial supercomplexes of the ETC play an important role in this process by adopting structural conformations that are sensitive or insensitive to sodium, thus ensuring that the action of sodium is nontoxic.

Finally, the study shows that inhibition of the mitochondrial Ca2+/Na+ exchanger NCLX is sufficient to block this pathway, preventing hypoxia adaptation. This finding indicates that NCLX could be a future therapeutic target for diseases in which hypoxia plays a role.

The study results reveal that sodium controls OXPHOS function and cell signaling in hypoxia through an unexpected interaction with phospholipids, with major consequences for cell metabolism.

The study was supported by funding from the International Human Frontier Science Program Organization (HFSP RGP0016/2018).

Hernansanz-Agustín, P., Choya-Foces, C., Carregal-Romero, S., Ramos, E., Oliva, T., Villa-Piña, T., ... Martínez-Ruiz, A. (2020). *Na+ controls hypoxic signalling by the mitochondrial respiratory chain.* ***Nature***. doi:10.1038/s41586-020-2551-y

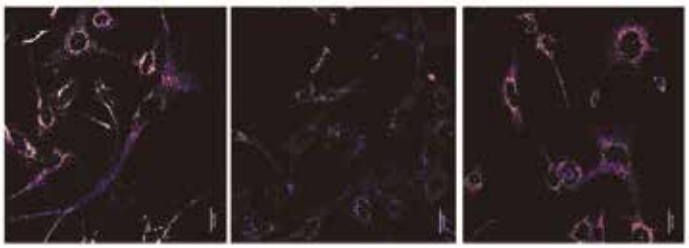
SCIENCE ADVANCES

CNIC scientists discover the mechanism of competition between mitochondrial genomes coexisting in the same cell

Research at the CNIC has identified the mechanism of competition between distinct mitochondrial genomes coexisting in the same cell. The study, published today in ***Science Advances***, examines why the simultaneous presence of more than one variant of mitochondrial DNA (mtDNA) in a cell is rejected in most tissues, which select a single mtDNA variant that differs between different tissues.

The results show that cells are able to detect and select between mitochondria with distinct mtDNA variants that make them more or less efficient for different cell types depending on their metabolic needs. This explains how the preferred mtDNA variant can differ between cell types.

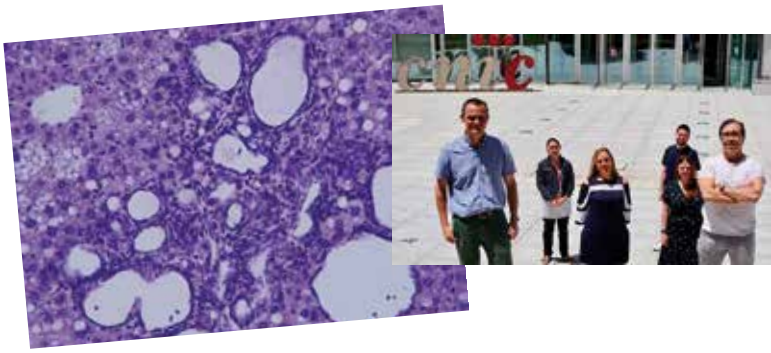
The study establishes that the selection of a mtDNA variant depends on the cell type and not the tissue, as was thought previously.



Moreover, the researchers add, the study has identified molecular targets for the development of tools to control mtDNA selection and cell metabolism in order to prevent the accidental generation of heteroplasmy through new medical procedures. These new technologies include the transplantation of healthy mitochondria to prevent mitochondrial diseases, injection of mitochondria into oocytes to increase fertility, and the proposed transfer of mitochondria in cell therapies to treat diverse diseases, including cardiovascular, lung, and neurological diseases.

The study was supported with funding from the International Human Frontier Science Program Organization (HFSP RGP0016/2018).

Lechuga-Vieco, A. V., Latorre-Pellicer, A., Johnston, I. G., Prota, G., Gileadi, U., Justo-Méndez, R., ... Enríquez, J. A. (2020). *Cell identity and nucleo-mitochondrial genetic context modulate OXPHOS performance and determine somatic heteroplasmy dynamics.* ***Sci Adv***, 6(31), eaba5345. doi:10.1126/sciadv.aba5345



PNAS

A new mechanism controlling liver cancer development

CNIC researchers have discovered a mechanism controlling the development of a type of liver cancer. This study, published in the ***Proceedings of the National Academy of Sciences (PNAS)***, partly funded by the Spanish Association Against Cancer, has identified a protein that, when blocked, dramatically reduces the impact and progression of this type of cancer, called cholangiocarcinoma. This work was possible because CNIC researchers developed an animal model in which alterations in the production of bile acids cause this type of tumor.

In the study, led by **Guadalupe Sabio** and **Alfonso Mora**, mice were bred whose livers do not contain the proteins JNK1 and JNK2. The researchers found that these two proteins control the production in the liver of bile acids, which are essential for proper fat digestion and the absorption of fat-soluble vitamins (A, D, E and K). "A lack of JNK1 and JNK2 in the liver leads to changes in the enzymes responsible for metabolizing cholesterol and bile acids," said **Dr. Mora**. In the analyzed mice, "we observed excess blood levels of bile acids."

This model allowed the CNIC team to show that that a key role in this tumor process is played by the protein PPARα, which regulates the metabolism of bile acids and liver lipids. According to **Dr. Mora**, mice lacking PPARα "have significantly fewer tumors or none at all."

Although it is still unknown if these data can be extrapolated to human patients, the availability of this first animal model will allow the study of a type of tumor that can still only be diagnosed in its very late stages, when metastases have already occurred.

Earlier studies had shown that JNK blockade prevented the development of steatosis in the liver, leading to a variety of clinical trials with inhibitors of these proteins.

The researchers believe that the new findings are a 'wake-up call' for these drugs.

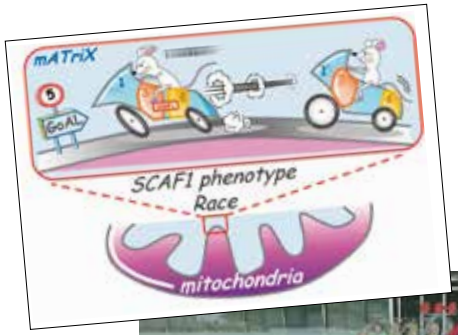
The study was supported by funding from the Asociación Española Contra el Cáncer and a BBVA Beca Leonardo para Investigadores y Creadores Culturales (2017).

Manieri, E., Folgueira, C., Rodríguez, M. E., Leiva-Vega, L., Esteban-Lafuente, L., Chen, C., ... Sabio, G. (2020). *JNK-mediated disruption of bile acid homeostasis promotes intrahepatic cholangiocarcinoma.* ***Proceedings of the National Academy of Sciences****,* 202002672. doi:10.1073/pnas.2002672117

SCIENCE ADVANCES
The mechanism that regulates mitochondrial energy production

CNIC scientists have identified the molecular mechanism by which mitochondria—the main source of the cell's energy supply—regulate their function to optimize energy production in order to meet the body's changing needs. The discovery, published in the journal ***Science Advances***, helps to explain how the body regulates its metabolism.

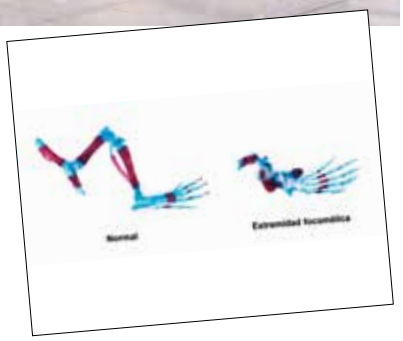
The study, led by CNIC scientists **Jesús Vázquez** and **José Antonio Enríquez**, shows that mitochondria adjust the efficiency of the electron transport chain (ETC) to meet the body's needs by regulating the associations between its component macromolecular structures. The researchers found that the protein SCAF1, discovered by the same team in 2016, plays a key role in this metabolic regulation by optimizing mitochondrial energy efficiency in response to high energy demand.



The research team conclude that SCAF1-mediated physical interaction between CIII and CIV is essential for optimal mitochondrial energy production. SCAF1 is a regulatory factor that allows mitochondria to adapt to the available nutrient sources of sugars, fats, or proteins. This capacity for metabolic adaptation also explains the ability of mitochondria to adapt to stress situations, for example during intense physical exercise.

The study was supported by funding from the International Human Frontier Science Program Organization (HFSP RGP0016/2018), Fundació Marató.TV3, and the "la Caixa" Foundation.

Calvo, E., Cogliati, P., Hernansanz-Agustín, P., Loureiro-López, M., Guaras, A., Casuso, R. A., ... Enríquez, J. A. (2020). *Functional role of respiratory supercomplexes in mice: SCAF1 relevance and segmentation of the Qpool.* ***Sci Adv****,* 6, eaba7509. doi:10.1126/sciadv.eaba7509



SCIENCE ADVANCES
Spanish scientists discover a system essential for limb formation during embryonic development

Researchers at the CNIC have discovered a system that provides cells with information about their position within developing organs. This system, studied in developing limbs, tells cells what anatomical structure they need to form within the organ. The article, published in ***Science Advances***, shows that malfunctioning of this system causes congenital malformations and could in part explain the effect of thalidomide, a drug contraindicated in pregnancy because it induces limb defects.

The CNIC team, working with partners at the National Institutes of Health in the USA, analyzed the molecular basis of limb formation. The scientists discovered how cells obtain information about their position on the proximodistal axis of the limb bud, or primordium (the rudimentary state of a developing organ.)

The study shows that the signal that tells cells where they are is the growth factor FGF. The strength of the signal

received by cells depends on how close they are to the FGF-producing cells at the distal tip of the limb bud.

The researchers demonstrated that the molecule in receptor cells that interprets FGF signals is a transcription factor called Meis. This transcription factor is distributed in a linear abundance gradient, so that it is highly abundant in proximal cells (close to the body trunk) and becomes progressively less abundant in more distal positions.

This system, emphasized **Torres**, "is essential for the correct formation of the limbs." The mechanisms described in the study advance understanding of the origin of phocomelia, a congenital defect in which the embryonic limbs only form hands and feet, with the rest of the limb failing to develop. In the study, experimental elimination of FGF–Meis signaling resulted in all limb-bud cells receiving the incorrect instruction that they were distal, resulting in phocomelia.

The findings establish a new model for the generation of proximodistal identity in the developing vertebrate limb and provide a molecular mechanism for the interpretation of FGF gradients during axial patterning in vertebrate embryos.

Delgado, I., López-Delgado, A. C., Roselló-Díez, A., Giovinazzo, G., Cadenas, V., Fernández-de-Manuel, L., ... Torres, M. (2020). *Proximo-distal positional information encoded by an Fgf-regulated gradient of homeodomain transcription factors in the vertebrate limb.* ***Sci Adv***, 6(23), eaaz0742.
doi:10.1126/sciadv.aaz0742

SCIENCE
Old or stressed immune cells can damage tissues and accelerate age-associated diseases

Scientists at the Instituto de Investigación del Hospital Universitario 12 de Octubre -i+12- and the CBM, in collaboration with researchers at the CNIC, have demonstrated that an aged immune or stressed immune system can attack the body's own tissues and accelerate the appearance of several diseases associated with aging.

Published in ***Science***, the results show that when T lymphocytes age or are subject to stress the release a cytokine storm that can affect a number of different organs and tissue, activating a cell aging program known as senescence. The appearance of senescent cells in these tissues predisposes to several conditions, including cardiovascular, neuroinflammatory, metabolic, and muscle diseases.

The most striking finding was that mice with a stressed immune system began to show signs of premature aging and to develop age-related conditions, most notably cardiovascular changes and weight loss. The animals later lost muscle strength and eventually underwent changes in memory and behavior.

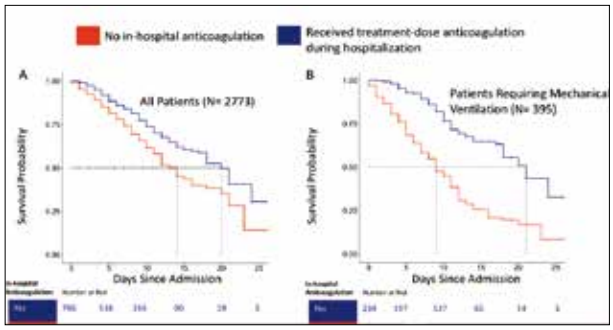
In a second part of the study, the researchers sought to identify treatments able to slow the appearance of these symptoms. They used two strategies, one aimed at blocking the cytokine storm and the other at preventing tissue senescence. Both strategies delayed the appearance of disease symptoms.

Desdín-Micó, G., Soto-Heredero, G., Aranda, J. F., Oller, J., Carrasco, E., Gabandé-Rodríguez, E., ... Mittelbrunn, M. (2020). *T cells with dysfunctional mitochondria induce multimorbidity and premature senescence.* ***Science***, eaax0860.
doi:10.1126/science.aax0860

JACC
Blood thinners may improve survival among hospitalized COVID-19 patients

Anticoagulation therapy improves survival among hospitalized COVID-19 patients by helping to prevent fatal events associated with coronavirus, such as infarction and stroke. The study, led by **Dr. Valentín Fuster**, Director of the CNIC and the Heart Institute and Mount Sinai Hospital in New York, shows that hospitalized COVID-19 patients treated with anticoagulants—drugs that prevent blood clotting—had a better survival rate that those who did not.

The researchers evaluated the electronic medical records of 4389 patients with a confirmed COVID-19 diagnosis, hospitalized at 5 hospitals between March 1 and April 30, 2020. The team analyzed the survival and mortality rates of patients who received therapeutic or prophylactic doses of anticoagulants (oral antiplatelet drugs, subcutaneous low-molecular weight heparin, or intravenous



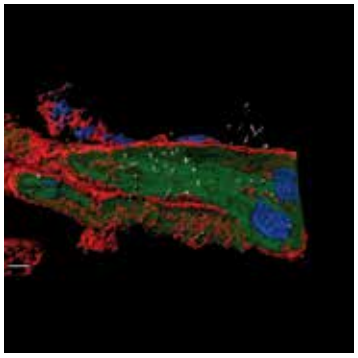
heparin) compared with the rates for patients who did not receive these treatments.

Overall, 467 (10.6%) of the patients required intubation and mechanical ventilation during their hospitalization. Those on therapeutic blood thinners had 31% fewer intubations than those not on blood thinners, while those on prophylactic blood thinners had 28% fewer. The difference between the two anticoagulant groups was not statistically significant.

Paranjpe, I., Fuster, V., Lala, A., Russak, A. J., Glicksberg, B. S., Levin, M. A., Charney, A. W., Narula, J., Fayad, Z. A., Bagiella, E., Zhao, S. & Nadkarni, G. N. (2020). *Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with Covid-19.* ***Journal of the American College of Cardiology***, 76(1), 122-124.
doi:10.1016/j.jacc.2020.05.001

CARDIOVASCULAR RESEARCH

Spanish scientists discover how the flu virus injures the heart



A study by a consortium of Spanish research groups has described the potentially fatal cardiac effects of infection with the influenza virus, especially more virulent forms. The research team showed that the replication of flu virus particles infecting the heart blocks the transmission of cardiac electrical impulses, which can lead to death. The results, published in ***Cardiovascular Research***, highlight the potential value of testing patients with acute cardiac disease for flu infection during seasonal outbreaks of the disease. The study was carried out by scientists at the CNIC, CSIC, CIBERES, CIBERCV and the Hospital Clínico San Carlos together with scientists at the Universities of Michigan and South Florida in the United States.

The investigators assessed the mechanisms of heart injury in mice infected with the flu virus as well as in cardiac muscle cells derived from human pluripotent cells. The results show that the most virulent viral strain persists in the heart for longer and triggers changes, including the modification of ion channels responsible for the transmission of cardiac electrical impulses. These results provide a molecular explanation for the early death of infected mice and suggest that screening for infection in acute cardiac disease patients during seasonal flu outbreaks could enable early diagnosis and treatment.

The authors concluded that "these findings highlight the potential benefit of early detection of the virus in patients with acute heart disease during flu outbreaks."

Filgueiras-Rama, D., Vasilijevic, J., Jalife, J., Noujaim, S. N., Alfonso, J. M., Nicolás-Ávila, J. A., ... Falcón, A. (2020). *Human Influenza A virus causes myocardial and cardiac-specific conduction system infection associated with early inflammation and premature death.* ***Cardiovascular Research***.
doi:10.1093/cvr/cvaa117

NATURE COMMUNICATIONS

CNIC scientists design an experimental mouse model for investigating the mechanical function of proteins in vivo

The CNIC Molecular Mechanics of the Cardiovascular System group, led by **Jorge Alegre Cebollada** in partnership with an international scientific team, has generated the first experimental mouse model that allows direct analysis of the mechanical function of proteins in living organisms.

The model, published in ***Nature Communications***, is based on the insertion of the HaloTag-TEV module into titin, one of the proteins responsible for the elasticity of skeletal and cardiac muscle. The HaloTag-TEV module combines three key properties. **Dr. Alegre** explained: "Thanks to the introduction of this module into the gene, we are able to fluorescently mark the protein, which makes it easy to track the module and see where it has inserted correctly."

The module also includes a target for specific protein lysis, so that the mechanical function of the target protein can be interrupted in a controlled manner at any desired moment, allowing us to study the effect of this interruption. Finally, the module provides a way to anchor the isolated protein to surfaces, enabling the study of its mechanical properties in isolation.

"All of this helps to establish a bridge between the modulation of protein mechanical properties and observing the consequences of this modulation at a cellular level," said **Dr. Alegre**.

The HaloTag-TEV module can be inserted into other proteins with a mechanical function, so that in the future it could be used to study other systems, including those related to diverse muscular and cardiac disorders.

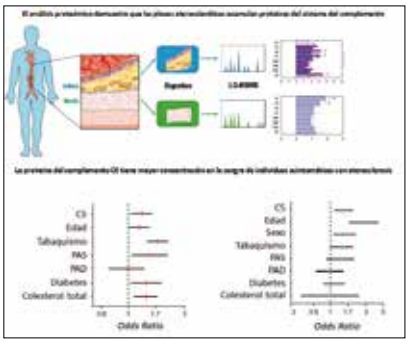
Rivas-Pardo, J. A., Li, Y., Mártonfalvi, Z., Tapia-Rojo, R., Unger, A., Fernández-Trasancos, Á., ... Alegre-Cebollada, J. (2020). *A HaloTag-TEV genetic cassette for mechanical phenotyping of proteins from tissues.* ***Nature Communications***, 11(1), 2060.
doi:10.1038/s41467-020-15465-9

JACC

Spanish scientists identify a biomarker that detects atherosclerosis before the appearance of symptoms

Scientists at the CNIC and the Instituto de Investigación Sanitaria-Fundación Jiménez Díaz (IIS-FJD) in Madrid have demonstrated that a proteins present in early atheroma plaques—accumulations of cholesterol in the walls of arteries—could be used as a biomarker to detect atherosclerosis in the subclinical phase, before the appearance of symptoms.

The study, published in the ***Journal of American College of Cardiology (JACC)***, concludes that activation of the complement system is one of the most characteristic molecular changes taking place in the early development of atherosclerotic plaques. The study shows that plasma levels of the complement system protein C5 could be used to identify individuals with subclinical atherosclerosis in a noninvasive way and at minimal cost.



"This early identification of the disease would help to select individuals who would benefit from more costly noninvasive imaging analysis to get a more precise estimate of their cardiovascular risk," explained **Dr. Jesús Vázquez**, head of the Cardiovascular Proteomics Laboratory at the CNIC and one of the coordinators of the study.

The study was supported by the Comunidad de Madrid (Complemento II-CM, S2017/BMD-3673) and the "la Caixa" Foundation (HR17-00247).

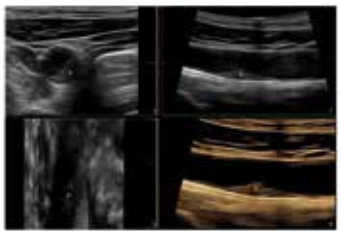
Martínez-López, D., Roldán-Montero, R., García-Marqués, F., Núñez, E., Jorge, I., Camafeita, E., ... Martín-Ventura, J. L. (2020). *Complement C5 protein as a marker of subclinical atherosclerosis.* ***Journal of the American College of Cardiology***, 75(16), 1926. doi:10.1016/j.jacc.2020.02.058

JACC

Atherosclerosis progresses rapidly in healthy people from the age of 40

Almost half of apparently healthy people between the ages of 40 and 50 could be accumulating fatty plaques—atheromas—in their arteries at a much faster rate than was previously thought. the ***Journal of American College of Cardiology (JACC)*** has today published new data from the PESA-CNIC-Santander study demonstrating that atheroma plaques extend rapidly through the arteries of 40% of asymptomatic individuals aged between 40 and 50 years.

Researchers at the CNIC, led by **Dr. Valentín Fuster**, Director of the CNIC and lead investigator on the PESA-CNIC-Santander study, have also found that the progression of atherosclerosis is directly related to classical cardiovascular risk factors: age, sex, hypertension, cholesterol, smoking, and diabetes.



The researchers conclude that the findings, although they await validation from future events in the PESA cohort, will be of great value for identifying strategies to stall the cardiovascular disease epidemic.

López-Melgar, B., Fernández-Friera, L., Oliva, B., García-Ruiz, J. M., Sánchez-Cabo, F., Bueno, H., ... Fuster, V. (2020). *Short-term progression of multiterritorial subclinical atherosclerosis.* ***Journal of the American College of Cardiology***, 75(14), 1617-1627. https://doi.org/10.1016/j.jacc.2020.02.026

NATURE COMMUNICATIONS

CNIC scientists discover a new molecular mechanism that regulates the sentinel cells of the immune system

A team at the CNIC, working in partnership with researchers at Mount Sinai Hospital in New York, has discovered a new molecular mechanism mediated by nuclear receptors that determines the identity and expansion of macrophages—one of the cell types that act as immune sentinels in the body. The newly discovered mechanism specifically affects the macrophages resident in the serous cavities, the membrane-surrounded cavities that enclose and protect many organs. The findings, published today in ***Nature Communications***, could have important implications for the treatment of diseases that affect the serous cavities and the organs they contain, including many cancers and myocardial infarction.

There are three serous membranes: the peritoneum, which covers the abdominal cavity; the pleura, surrounding the lungs; and the pericardium, which covers the heart. "One of the main functions of the macrophages residing in these cavities is to maintain homeostasis by removing dead cells," explained study coordinator **Dr. Mercedes Ricote**. In addition, recent studies have demonstrated that these macrophages can infiltrate adjacent injured organs, "generating an effective rapid repair response that is independent of the recruitment of macrophage precursors via the blood supply."

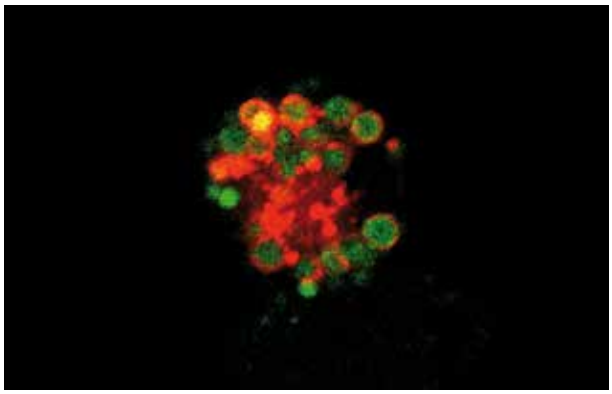
The study demonstrates that the expansion of peritoneal macrophages after birth and their maintenance during adult life are controlled by retinoid X receptor (RXR), a member of the nuclear receptor family.

Using models of ovarian cancer in mice, the study shows that peritoneal macrophages can infiltrate ovarian tumors

and act as 'tumor-associated macrophages' that "support tumor growth," explained **Dr. Ricote**.

The findings demonstrate that loss of RXR function leads to a decrease in the number of macrophages in the peritoneal cavity, resulting in a decreased contribution of these macrophages to growing ovarian tumors, slowing the progression of the disease.

The researchers are especially interested in the possibility of modulating RXR with drugs, including some that are currently used to treat cutaneous lymphomas. "Our research could have implications for the treatment of diseases in which serous cavity macrophages contribute to disease progression, such as cancer, or to the repair of damaged tissue, as in myocardial infarction."



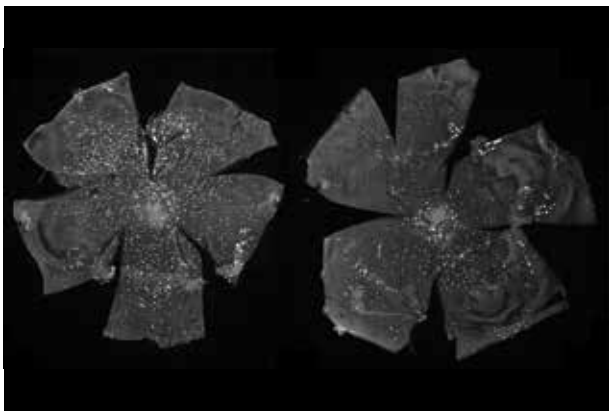
Casanova-Acebes, M., Menéndez-Gutiérrez, M. P., Porcuna, J., Álvarez-Errico, D., Lavin, Y., García, A., ... Ricote, M. (2020). *RXRs control serous macrophage neonatal expansion and identity and contribute to ovarian cancer progression.* ***Nature Communications***, 11(1), 1655. doi:10.1038/s41467-020-15371-0

JOURNAL OF EXPERIMENTAL MEDICINE

An immunological regulatory circuit may play a central role in ocular inflammatory disorders

CNIC scientists have identified an inflammatory regulatory circuit in the eye controlled by a subtype of endothelial cells, the cells that line the interior of blood vessels. The discovery was made by analyzing gene expression in 8,000 cells of the choroid—the vascular layer at the rear of the eye between the retina and the sclera. The results, published today in the ***Journal of Experimental Medicine***, open new perspectives on the study and treatment of retinal vascular disease and inflammatory disorders that affect the choroid.

The study provides valuable information about how the endothelial cells in the choroid regulate the development of inflammatory and vascular diseases in the retina. The authors analyzed the choroids of adult mice using the 'single cell RNAseq' technique, which allows analysis of gene expression simultaneously in thousands of individual cells.



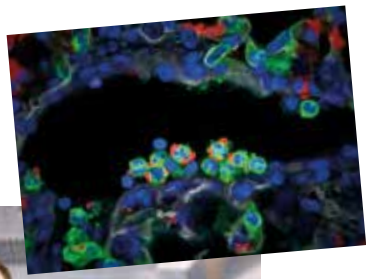
Lehmann, G. L., Hanke-Gogokhia, C., Hu, Y., Bareja, R., Salfati, Z., Ginsberg, M., ... Benedicto, I. (2020). *Single-cell profiling reveals an endothelium-mediated immunomodulatory pathway in the eye choroid.* ***Journal of Experimental Medicine***, 217(6), e20190730. doi:10.1084/jem.20190730

NATURE IMMUNOLOGY

Neutrophils are equipped with a 'disarmament' program that prevents the immune system going 'out of control'

Scientists at the CNIC have discovered a 'disarmament' mechanism that protects our bodies against uncontrolled activity of the immune system. This newly identified immune control system is located in one of the most important cell types of the immune system, the neutrophil. The findings, published in ***Nature Immunology***, could have major implications for the understanding and treatment of conditions such as myocardial infarction, stroke, and acute inflammation.

The study identifies an intrinsic cell mechanism that modifies the protein content of circulating neutrophils, leading to the progressive loss of the toxic contents of the granules and therefore a reduced capacity to form NETs. This program thus undermines the main offensive mechanism of



neutrophils. The study shows that this disarmament program is driven by the receptor CXCR2 and regulators of circadian rhythms.

The findings show that neutrophils possess "an innate system that gradually reduces their capacity to mount a toxic attack, so that as they age, neutrophils disarm themselves before they can damage healthy tissues. There are many diseases that cause more or less damage according to the time of day, and this disarmament program helps to explain the origin of these clinical differences," explained the researchers.

Adrover, J. M., Aroca-Crevillén, A., Crainiciuc, G., Ostos, F., Rojas-Vega, Y., Rubio-Ponce, A., ... Hidalgo, A. (2020). *Programmed 'disarming' of the neutrophil proteome reduces the magnitude of inflammation.* ***Nature Immunology***.
doi:10.1038/s41590-019-0571-2

DEVELOPMENT CELL
A CNIC-led international study discovers a new origin of lymphatic vessels in the heart

The study, published in ***Development Cell***, has identified and characterized a new vasculogenic niche that contributes to the development of the cardiac lymphatic system. The study shows that the coronary lymphatic vessels have varied origins and functions: the results of the study reveal that the coronary lymphatic vasculature does not have a single origin, but instead forms through the participation of cells from different tissues.

This study opens the way to future research into the mechanism underlying lymphatic vasculogenesis in this new niche and the functional diversity of coronary lymphatics.

This international study, led by **Dr. Miguel Torres**'s group at the CNIC, examined the origin of the coronary lymphatic system during the formation of the heart in the mouse embryo. The study shows that the heart contains a second population of lymphatic cells that is recruited later during development and is derived not from veins, but from a region called the second heart field.

The second heart field is composed of multipotent cells "able to generate different types of heart cells, including cardiomyocytes (the cells of the cardiac muscle), smooth muscle cells, and the endothelial cells of the arteries and veins."

One of the more surprising findings was that lymphatic cells generated in the second heart field mix with lymphatic cells with a different, likely venous, origin; the two populations together form the lymphatic vessels in the ventral part of the heart.

This result indicates that the newly discovered cell population not only contributes a large proportion of the cells of the coronary lymphatic system, but also leads a specific and irreplaceable process in the formation of the coronary lymphatic vasculature. "This function reveals, for the first time, the specialization of endothelial subpopulations in the formation of the coronary vasculature and opens the way toward a better understanding of the formation of lymphatic vessels, a process essential not only for embryonic heart development but also for the response of the heart to stress and disease in adulthood."

Lioux, G., Liu, X., Temiño, S., Oxendine, M., Ayala, E., Ortega, S., ... Torres, M. (2020). *A second heart field-derived vasculogenic niche contributes to cardiac lymphatics.* ***Developmental Cell***.
doi: 10.1016/j.devcel.2019.12.006

NATURE COMMUNICATIONS
The 'airbag' that protects cells against stress

CNIC scientists have identified the molecular mechanisms that allow our cells to adapt to, protect themselves against, and survive mechanical stress. The results, published in ***Nature Communications***, show that our cells produce molecules that act as a type of 'airbag' in response to mechanical stress. Without this protective and adaptive system, the heart, an organ subject to continuous mechanical forces, "would be unable to correctly perform its blood-pumping role," explained lead author **Miguel Ángel del Pozo**.

Human cells are able to perceive, adapt to and respond to mechanical forces. As **Dr. Del Pozo** explained, "these

forces can sometimes be excessive, placing cells under a mechanical stress that can rupture the cell membrane and result in the death of affected cells. To avoid this rupture and thus prevent cell death, nature has evolved molecular sensors that 'switch on' in response to these forces and initiate adaptive and protective processes. The purpose of this response is to adapt cells to these forces before they cause tissue or organ damage."

The ***Nature Communications*** study identified relatively large folded or wrinkled structures surrounding cells that can unfold or flatten when the cell is stretched, thus giving cells an extra coating that prevents breakage upon excessive stretching. "It can be likened to an accordion, which unfolds as it is stretched, thus preventing it from breaking when pulled," explained the researchers. These folds thus function as a kind of 'airbag', cushioning cells against excessive mechanical stress.

The team also identified molecules that participate in this mechanism, permitting cells to perceive mechanical force and initiate the biochemical changes needed to adapt to mechanical stress.

Through partnership with CNIC scientist **Jorge Alegre-Cebollada**, the team identified molecules with opposing functions; "one of the molecules (FBP17) protects the cell against mechanical stress, whereas another (ABL) makes the cell more sensitive to these forces," explained the scientists.

Both molecules, working in an ordered fashion, coordinate changes in the cell envelope that protect the cell and the cell skeleton, giving it the structure and solidity needed to resist mechanical stress.

The authors also managed to alter the amount or activity of these molecules in human cells; inhibiting the action of ABL increased protection against mechanical stress, whereas inhibition of FBP17 made cells more sensitive.

The findings are important because knowledge about how cells are protected against mechanical stress "will give us a better understanding of the molecular basis of diseases such as some forms of muscular dystrophy, cardiomyopathies, and lung or vascular diseases characterized by sensitivity to physical activity. The findings will also shed light on the mechanisms of injury to organs with a high level of mechanical activity, such as the heart, lungs, muscles, and blood vessels." The authors concluded that "this study opens the way to future therapies in patients with these conditions."

Echarri, A., Pavón, D. M., Sánchez, S., García-García, M., Calvo, E., Huerta-López, C., ... Del Pozo, M. A. (2019). *An Abl-FBP17 mechanosensing system couples local plasma membrane curvature and stress fiber remodeling during mechanoadaptation.* ***Nature Communications***, 10(1), 5828.
doi:10.1038/s41467-019-13782-2

EUROPACE
Personalized medicine for atrial fibrillation

Patients with atrial fibrillation, the most frequent cardiac arrhythmia, are closer to accessing personalized medicine. This is the claim of a new study led by **Dr. David Filgueiras**, of the CNIC, the Hospital Clínico San Carlos de Madrid, and the Centro de Investigación en Red de Enfermedades Cardiovasculares (CIBERcv). The study results show that it is possible to monitor and predict individual progression of atrial fibrillation from cardiac electrical signals obtained from implantable devices (pacemakers or defibrillators).

The study, published in the latest edition of ***Europace***, involved the participation of 51 Spanish hospitals and the Fundación Interhospitalaria para la Investigación Cardiovascular. The results show that cardiac electrical signals from patients fitted with pacemakers or implantable cardioverter–defibrillators can be used to monitor and predict the progression of the arrhythmia in a personalized and specific manner. This is achieved with standard data transmission technology installed in implantable devices such as pacemakers. This technology can be used to monitor cardiac electrical activity during episodes of atrial fibrillation, thus establishing disease status and the rate of progression.

According to **Dr. Filgueiras**, "this technology opens up enormous possibilities in personalized medicine for atrial fibrillation patients because it allows us to determine the progression rate of the arrhythmia in each individual and to optimize the timing of medical intervention with current treatment options."

In addition, **Dr. Julián Villacastín**, director of the Instituto Cardiovascular del Hospital Clínico San Carlos and an author on the study, this new approach to atrial fibrillation diagnosis will allow physicians "to monitor the influence of different interventions on disease progression."

Lillo-Castellano, J. M., González-Ferrer, J. J., Marina-Breysse, M., Martínez-Ferrer, J. B., Pérez-Álvarez, L., Alzueta, J., ... Filgueiras-Rama, D. (2019). *Personalized monitoring of electrical remodelling during atrial fibrillation progression via remote transmissions from implantable devices.* ***EP Europace***.
doi:10.1093/europace/euz331

EMBO MOLECULAR MEDICINE
Inhibiting a protease could improve the treatment of inflammatory bowel disease

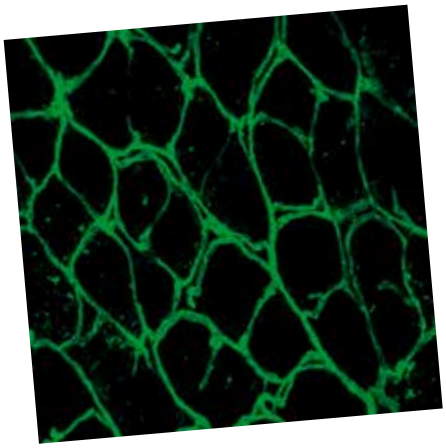
Scientists at the CNIC and the CSIC have identified the protease MT1-MMP as a possible future target for drugs to treat inflammatory bowel disease (IBD). The study, led by **Dr. Alicia G. Arroyo** and published in ***EMBO Molecular Medicine***, shows that inhibition of this protease could improve the treatment of IBD.

During colitis, the intestinal blood vessels duplicate through mechanisms that are poorly understood. In the new study, **Dr. Arroyo**'s team used microscopy techniques and 3D image analysis to characterize these duplication events in a mouse model of colitis. These tools enabled the scientists to demonstrate that MT1-MMP expressed on endothelial cells lining the blood vessels impedes their duplication in the inflamed gut, reducing the severity of colitis.

This finding has potential clinical implications. "The study shows that patients with mild IBD have higher than normal circulating levels of TSP1, which could be a useful biomarker of the disease," commented **Arroyo**.

In addition, the team managed to reduce vessel duplication in mice with colitis by administering either an antibody that inhibits MT1-MMP protease action or a TSP1 peptide that blocks TSP1-αvβ3 binding. This result establishes the MT1-MMP-TSP1-αvβ3 integrin pathway as a new therapeutic target, particularly for less severe forms of IBD.

The authors concluded that "the study presents a new opportunity to develop personalized treatments not only for patients with IBD, but also for patients with other diseases that progress through vessel duplication, like cancer." ■



Esteban, S., Clemente, C., Koziol, A., Gonzalo, P., Rius, C., Martínez, F., ... Arroyo, A. G. (2019). *Endothelial MT1-MMP targeting limits intussusceptive angiogenesis and colitis via TSP1/nitric oxide axis.* ***EMBO Molecular Medicine***, e10862.
doi:10.15252/emmm.201910862

TWO CNIC PROJECTS AWARDED ERC CONSOLIDATOR FUNDING IN THE ERC-2020-COG CALL FOR PROPOSALS

ProtMechanics-Live is based on Dr. Alegre's unique experience in protein mechanics and engineering, biophysics, biochemistry, and cardiovascular biology and will for the first time permit investigation of protein mechanics in a physiologically relevant context

Dr. Rui Benedito's project, AngioUnrestUHD, will develop and apply new research tools and methods to advance knowledge about the biology of blood vessels in distinct physiological and pathological contexts

Two projects from groups at the Centro Nacional de Investigaciones Cardiovasculares (CNIC) have been selected in the European Research Council Consolidator Grant awards for 2020 (ERC-2020-COG). The projects are ProtMechanics-Live: Uncovering Protein Mechanics in Physiology and Disease, led by **Dr. Jorge Alegre**, and AngioUnrestUHD: Understanding and modulating vascular arrest with ultra-high definition, coordinated by **Dr. Rui Benedito**. Each will receive €2 million in ERC funding over the next 5 years.

The ERC supports pioneering projects that promise to revolutionize health and society. The ERC's touchstone for project funding is research excellence. The 2 CNIC projects have been selected within the ERC Consolidator Grant program, which supports young investigators with an established record of leadership but who are still consolidating their research group. The ERC is the first Europe-wide organization to fund basic research projects on the sole basis of a researcher's scientific excellence and the innovative strength of her or his ideas, independently of nationality or research field.

UNDERSTANDING PROTEIN MECHANICS IN CONTEXT

The CNIC Molecular Mechanics of the Cardiovascular System group, led by **Dr. Jorge Alegre**, investigates the fundamental influence of protein mechanics on heart form and function. "ProtMechanics-Live builds on our unique experience in protein mechanics and engineering, biophysics, biochemistry, and cardiovascular biology and will for the first time permit investigation of protein mechanics in a functionally relevant physiological context," said **Dr. Alegre**.

While it is no secret that cells and living organisms in general respond to changes in their environment, in the past relatively little attention has been devoted to understanding how living beings respond to the mechanical forces they are continuously exposed to. "This relationship between cells and the mechanical forces acting upon them is immensely important and can explain multiple disease processes, including cancer metastasis, atherosclerosis, and cardiomyopathies currently lacking a defined underlying molecular mechanism," explained **Dr. Alegre**.

Indirect approaches have indicated an important role for protein mechanics in these processes. However, the mechanisms involved remain elusive, largely due to the absence of methods to modulate protein mechanics in living systems.

The ProtMechanics-Live project aims to "overcome these technical barriers to scientific progress by establishing the manipulation of proteins in living cells and animals as a new research field," said **Dr. Alegre**.

Advances over the past decades have produced new technologies that permit the study of the mechanical behavior of proteins that determines the ability of cells to sense and generate force. These techniques have enabled the characterization of the mechanical properties of individual proteins in isolation. While this has transformed understanding of the relationship between force and biological molecules, these pioneering methods are limited to the study of simplified systems in the laboratory that do

not reflect the real situation in living cells and organisms. ProtMechanics-Live will translate this analysis to proteins' natural environment, the living cell, thus generating knowledge about how protein mechanics integrates with other systems essential for life. This approach has been impossible until now.

This innovative project has three goals. "To overcome the limitations of current methods," commented **Dr. Alegre**, "we will first generate genetic loss- and gain-of-function models based on protein engineering to manipulate mechanical function. We will apply these new tools to the giant protein titin, an important node for the generation and detection of force in cardiomyocytes that is implicated in several cardiovascular disorders."

"Once we have generated these tools, we will use them to define how perturbations in titin mechanics affect the function of healthy and diseased cardiomyocytes," **Dr. Alegre** continued. The third project goal is for these studies to "shed light on the contribution of titin mechanics to the initiation and progression of cardiomyopathies, both those with a genetic cause and those arising after an event such as a myocardial infarction."

In the ERC evaluation report on ProtMechanics-Live, the international panel of experts emphasized that they were "impressed by the quality of the proposal, which was considered to be highly original."

THE BIOLOGY OF BLOOD VESSELS

Dr. Rui Benedito's project is called "AngioUnrestUHD: Understanding and modulating vascular arrest with ultra-high definition." The project will use new research tools and methods developed by **Dr. Benedito**s' group to advance understanding of the biology of blood vessels in different physiological and pathological contexts. "This knowledge will help to identify improved strategies to promote vessel development in ischemic heart disease, cure vascular malformations, and inhibit angiogenesis in tumors," explained **Dr. Benedito**, head of the Molecular Genetics of Angiogenesis group at the CNIC.

Therapeutic modulation of the proliferation and migration of vascular cells is essential for the efficient blockade of angiogenesis in cancer and for its induction to treat cardiovascular disease.

The previously accepted view was that increased levels of growth factors or mitogenic stimuli will promote angiogenesis by increasing both the proliferation and migration of endothelial cells.

"Through innovative genetic and imaging studies, we have identified a previously unknown mechanism whereby a highly mitogenic environment (stimulating cell division) can lead to the inhibition of angiogenesis and the arrest of the cell cycle in endothelial cells, thus reducing the efficiency of angiogenesis," said **Dr. Benedito**.

This context-dependent mechanism "can explain the failure of growth factor therapy to promote functional angiogenesis in ischemic heart disease."

The new project aims to define how hypermitogenic stimulation arrests angiogenesis and to identify ways to intervene in this process to efficiently stimulate the formation of new blood vessels.

Dr. Benedito's group has exploited recent advances in DNA synthesis, CRSPR gene editing, microscopy, and cell-lineage tracking technologies to develop new genetic tools, animal models, and methods of wide applicability that are enabling a more precise and high resolution study of gene function. ■

CNIC TO COORDINATE A EUROPEAN PROJECT INVESTIGATING HOW CANCER THERAPIES PROMOTE ATHEROSCLEROSIS AND CARDIOVASCULAR DISEASE

THE PROJECT WILL INVESTIGATE THE ROLE OF **CLONAL HEMATOPOIESIS**—THE FORMATION OF MUTATED HEMATOPOIETIC STEM-CELL CLONES PROMOTED BY **ANTI-CANCER THERAPIES**—IN THE DEVELOPMENT OF **ATHEROSCLEROSIS** AND ASSOCIATED **CARDIOVASCULAR DISEASE**

The international consortium "Cancer Therapy-Related Clonal Hematopoiesis as a Driver of Accelerated Atherosclerosis," coordinated by **Dr. José Javier Fuster** of the Centro Nacional de Investigaciones Cardiovasculares (CNIC), has been awarded €624,000 by the ERA-CVD network (European Research Area Network on Cardiovascular Diseases) financed by the European Commission within the framework of the H2020 program. The award includes €167,000 in direct funding to the CNIC capitalized through the ISCIII. The consortium will investigate the role of clonal hematopoiesis—the formation of clones from mutated hematopoietic stem cells promoted by anti-cancer therapies—in the development of atherosclerosis and associated cardiovascular disease.

Consortium members include international experts in hematology and cardiovascular disease, such as the research groups led by INSERM investigator **Chloé James** at the Université de Bordeaux, France, and by **Carolina Greco** at the Istituto Clinico Humanitas, Italy. These research scientists will collaborate in the analysis of several innovative models of clonal hematopoiesis and exposure to anti-cancer treatments.

Every day, explained **Fuster**, the body generates in the region of "200,000 million blood cells," equivalent to the number of cells present in "100 human hearts."

"The high cell proliferation rate needed to generate blood cells inevitably produces DNA copying errors. Most of the resulting mutations have no effect, but some give a competitive advantage to the mutant cell, leading to its expansion in the blood cell population."

This process, called clonal hematopoiesis, has been known about for many years and is an essential element in the development of leukemias and other blood cancers. However, new studies suggest that clonal hematopoiesis is also a risk factor for cardiovascular disease.

"Clonal hematopoiesis is especially frequent in patients and survivors of non-blood cancers, which are independent of mutations acquired in blood cells. This suggests that the phenomenon is related to the exposure to anti-cancer treatments," said **Fuster**.

Although the mortality rate among cancer patients has declined significantly in recent years, many survivors face health problems. An especially important problem is an elevated risk of death from cardiovascular disease. The causes of this increased risk are largely unknown.

Recent evidence suggests that mutations in blood stem cells can contribute to the development of heart disease, constituting a hitherto unknown cardiovascular risk factor.

One of the consortium's goals is to determine which specific mutations play a role in the development of cardiovascular disease.

The new project thus promises to describe "a possible new mechanism linking cancer, anti-cancer therapies, and the development of cardiovascular disease," said **Fuster**.

Continuing, **Fuster** explained that the knowledge acquired during the project will be "important for the design of personalized prevention and treatment strategies specifically aimed at blocking the effects of blood-cell mutations linked to clonal hematopoiesis triggered by cancer treatments."

The research program will also deepen knowledge about the possible causes underlying the high rate of infarction in the general population, which affects approximately 10% of individuals who have received optimal cardiovascular prevention therapy. "We think that clonal hematopoiesis may contribute to persistent cardiovascular risk in individuals who have received optimal treatment for traditional cardiovascular risk factors. Clonal hematopoiesis is totally independent of established cardiovascular risk factors (cholesterol, high blood pressure, etc.) and acts through distinct mechanisms. This will enable the design of new treatments and prevention strategies for cardiovascular disease," said **Fuster**.

Fuster concluded: "The development of these strategies would be of great value for the prevention of cardiovascular disease in many of the 32 million cancer survivors in the world, a number that is expected to grow still larger in the coming years." ■

A CONSORTIUM LED BY THE CNIC RECEIVES FUNDING FROM THE "LA CAIXA" FOUNDATION TO DISCOVER NEW THERAPEUTIC TARGETS IN ATHEROSCLEROSIS

Atherosclerosis (accumulation of cholesterol and inflammation of the arterial walls) is the leading cause of death in the world, compromising blood flow and causing, among others, heart or brain infarcts due to the deprivation of blood and oxygen to the tissues.

Although most risk factors (high-fat diet, hypertension, diabetes, smoking, aging, sedentary lifestyle) act throughout the body, these lesions develop in places where blood flow is irregular (i.e. arterial bifurcations), which causes inflammation and makes the vessel sensitive to other risk factors, promoting the development of atherosclerosis. Current therapies (anti-inflammatory, cholesterol reduction) slow the progression of the disease, but do not reverse it. It is necessary to understand how the different mechanisms cooperate to maintain the progression of the disease, even when a specific factor is nullified.

To respond to this problem, the "la Caixa" Foundation, within the 2020 Health Research Call, has funded the AtheroConvergencia project with €999,988, which will be carried out by a consortium led by the CNIC researcher **Miguel Ángel del Pozo**.

In the consortium, the following researchers' groups will also participate:

- **Martin A. Schwartz**, Yale University, New Haven, CT USA
- **Jacob Fog Bentzon**, Aarhus University, Denmark
- **Jesús Ruiz-Cabello**, Center for Cooperative Research in Biomaterials Association, Spain

Through AtheroConvergence (Flow-driven inflammation and arterial wall remodeling in atherosclerosis: mechanisms and

therapeutic potential) the consortium will try to find new markers and therapeutic targets in atherosclerosis. This initiative combines multidisciplinary experience and the latest technologies to obtain a global understanding of the disease, identify new opportunities for precision medicine to intervene in advanced atherosclerosis, and find new predictive genetic markers of the potential risk of developing atherosclerosis.

Other researchers from the CNIC also participated in this project, like **Fátima Sánchez**, **Héctor Bueno** or **Carlos del Fresno**. ■

CNIC SCIENTISTS COORDINATE A EUROPEAN PROJECT TO DEVELOP A BIOMARKER FOR THE EARLY IDENTIFICATION OF THE VASCULAR COMPONENT IN ALZHEIMER DISEASE

THE BIOCLOTAD PROJECT, COORDINATED BY CNIC SCIENTIST **DR. MARTA CORTÉS CANTELI**, HAS BEEN SELECTED BY THE EU JOINT PROGRAMME – NEURODEGENERATIVE DISEASE RESEARCH (JPND)

The BioClotAD project, coordinated by Centro Nacional de Investigaciones Cardiovasculares (CNIC) scientist **Dr. Marta Cortés Canteli**, who is supported by Spain's Miguel Servet Program, has been selected by the JPND transnational call for multinational research on novel imaging and brain stimulation methods and technologies for neurodegenerative diseases. BioClotAD will receive €771,430 over the next 3 years, including €227,480 in direct funding to **Dr. Cortés Canteli**'s group at the CNIC.

The JPND (EU Joint Programme – Neurodegenerative Disease Research) is the largest global research initiative aimed at tackling the challenge of neurodegenerative diseases. The JPND aims to increase coordinated investment between participating countries in research aimed at finding causes, developing cures, and identifying appropriate ways to care for those with neurodegenerative diseases (www.jpnd.eu).

The goal of BioClotAD is to develop a neuroimaging biomarker to detect the procoagulant state in the brains of patients with Alzheimer disease (AD).

The BioClotAD consortium brings together 4 research groups at the forefront of European research in the areas of neuroscience, biochemistry, preclinical imaging, radiochemistry, and translational medicine. As well as the CNIC group, the consortium includes the groups led by **Dr. Manuel Desco** of the Instituto de Investigación Sanitaria del Hospital Gregorio Marañón de Madrid in Madrid (IiSGM); **Dr. Dag Sehlin** of the Public Health and Caring Sciences at the University of Uppsala, Sweden; and **Dr. Susanne Kossatz** of the Klinikum rechts der Isar der Technischen at the University of Munich, Germany.

AD is the most frequent form of dementia and probably also the most devastating in terms of its societal impact. Unfortunately, most treatments for AD have failed, in part due to the multifactorial nature of the disease.

In response to the disappointing results of "one target, one treatment" strategies, current AD research seeks to develop personalized therapies that combine several drugs directed at the multiple mechanisms that contribute to the disease.

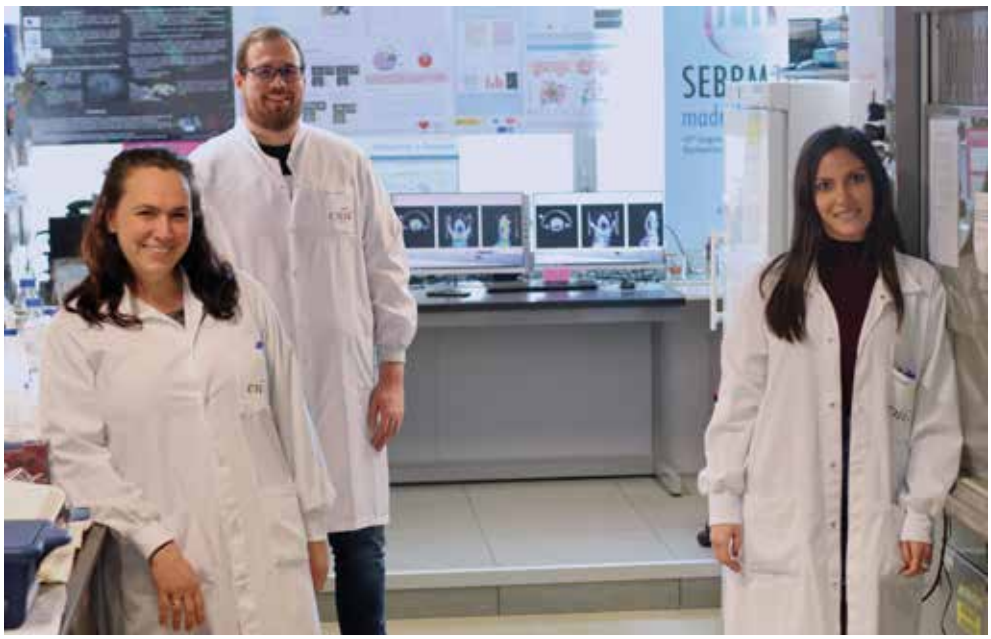
However, the success of personalized therapy requires the development of accurate diagnostic tools to monitor the various factors that contribute to AD. One of the promising targets for diagnosis and treatment is a patient's procoagulant status.

The aim of our project is to design a new non-invasive imaging biomarker to identify the procoagulant state in Alzheimer

AD includes a vascular component characterized by severe cerebral hypo-perfusion. Reduced cerebral blood flow is also a feature of mild cognitive impairment and even occurs in cognitively unimpaired individuals at high risk of developing AD. This cerebral hypo-perfusion is in part due to a chronic dysregulation of hemostasis in AD.

Accumulating evidence indicates that AD is characterized by a prothrombotic state. This favors the formation of persistent fibrin clots that contribute to the initiation and progression of the disease.

In experiments with the thrombin inhibitor dabigatran in a mouse model of AD, **Dr. Cortés Canteli**'s group at the CNIC has already shown that long-term anticoagulation blocks fibrin deposition; preserves cognitive function, cerebral blood perfusion, and the function of the blood-brain barrier; and reduces neuroinflammation and amyloid deposition (***Journal of the American College of Cardiology***).



Accumulating evidence indicates that Alzheimer disease is characterized by a prothrombotic state. This favors the formation of persistent fibrin clots that contribute to the initiation and progression of the disease

These results have opened the way to future research into the potential of approved oral anticoagulants for the treatment of AD. However, consistent with the multifactorial nature of the disease, this prothrombotic state is not present in all AD patients. It is therefore important to identify those patients who would benefit from anticoagulant therapy.

"The aim of our project is to design a new non-invasive imaging biomarker to identify the procoagulant state in AD," said **Dr. Cortés Canteli**.

Explaining the strategy, **Dr. Cortés Canteli** continued: "In animal models of Alzheimer disease, we will combine molecular biology approaches with molecular imaging tools to develop a probe to detect fibrin clots both in the cerebral blood vessels and in the brain parenchyma."

Dr. Susanne Kossatz from the University Hospital Klinikum rechts der Isar (TU München) in Munich, Germany, says that she and her team are very excited to be part of this international consortium. **Dr. Kossatz**' team will investigate how the novel molecular imaging probes operate on the cellular level. She will conduct tissue-based analyses to confirm the selective and specific nature of the molecular imaging approach of the prothrombotic state under investigation.

Researchers from Uppsala University, led by **Dr. Sehlin**, will contribute to the project with their expertise in the delivering drugs across the blood-brain barrier, which restricts the passage of molecules between blood and brain. Using a molecular 'Trojan horse' strategy, the probe will be modified to interact with receptors in the blood-brain barrier. This will facilitate transport of the probe into the brain parenchyma, where it can find and interact with fibrin clots.

The Uppsala group has previously used a similar approach to transport radiolabeled antibodies into the brain of mice for PET imaging of Alzheimer pathology.

"We see great opportunities in this collaborative project that we believe will open new avenues for Alzheimer diagnosis and therapy," said **Dr. Sehlin**.

This probe will be used to preselect Alzheimer patients with a prothrombotic state for inclusion in clinical trials or for antithrombotic therapy. Crucially, the biomarker will also prevent inappropriate prescription of oral anticoagulants to patients lacking this prothrombotic state.

Although the risk of intracranial hemorrhage with direct oral anticoagulants is low, it is not inexistent. It is therefore important to carefully evaluate each patient's case in a precise and personalized way. The biomarker developed in this project will play a fundamental role in this process.

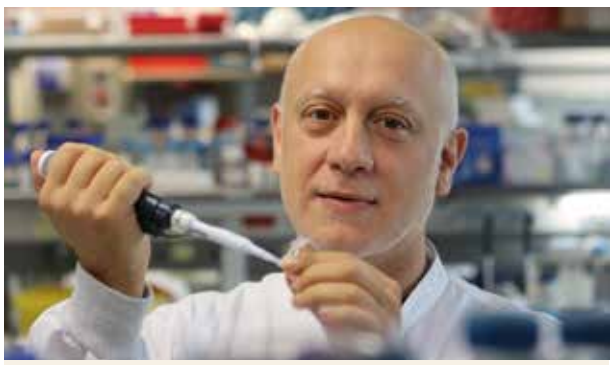
According to **Dr. Manuel Desco**, from the Gregorio Marañón Health Research Institute and head of the CNIC's Advanced Imaging Unit, "The paradigm of personalized and precision Medicine will be applied in numerous pathological processes, undoubtedly including Alzheimer's disease. The so-called molecular imaging can be a tool of extraordinary value in many aspects of the disease, including diagnosis, the selection of effective treatments or the establishment of a precise prognosis. In this line, our group collaborates in the development of new imaging probes that allow characterizing the pathophysiology of the disease in a non-invasive way ." ■

NEUTROCURE: EXPLOITING THE DUAL NATURE OF NEUTROPHILS TO CURE INFLAMMATORY DISEASES

Curing disease with neutrophils; this is the goal of the NeutroCure project. How will that work? "Neutrophils have a yin yang character," explained **Andrés Hidalgo**, whose team at the Centro Nacional de Investigaciones Cardiovasculares (CNIC) is one of six member groups participating in this project coordinated by **Andriy Mokhir** from Friedrich-Alexander University, Germany. "Neutrophils are 'good' cells because they destroy bacteria and other microbes that enter the organism, but they are also 'bad' cells because they are unspecific, meaning they can also destroy neighbouring healthy cells."

NeutroCure focuses on reactive oxygen species (ROS) produced by neutrophils. In healthy organisms, ROS play crucial roles, such as signaling to regulate cell growth, providing the trigger for the formation of neutrophil extracellular traps (NET), and modulation of inflammation. However, high ROS concentrations damage tissues, and nature has therefore evolved precise mechanisms to control ROS duration and concentration and to ensure that these molecules remain confined to locations close to their targets.

Disruption of these mechanisms causes aberrant ROS production, leading to uncontrolled inflammation. This occurs for example during myeloablation triggered by radiotherapy or chemotherapy, and is a key characteristic of the phenotype of cancer cells and autoimmunity.



- Proyect: NeutroCure: Development of "smart" amplifiers of reactive oxygen species specific to aberrant polymorphonuclear neutrophils for treatment of inflammatory and autoimmune diseases, cancer and myeloablation.
- This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 861878.
- Call: FETOPEN-2018-2020: Fet-Open Challenging Current Thinking.
- Coordinador: Friedrich-Alexander Universitaet, Germany
- Start: 2020. €3 million for 5 years.
- CNIC: Andrés Hidalgo - €400,000.

The project has received European funding of €3 million for 5 years in the category H2020-FETOPEN-2018-2020 – FET Open – Novel ideas for radically new technologie.

Despite the damaging properties of ROS, drugs that amplify ROS production can revert ('cure') many features of disease. **Hidalgo** described how this paradox underlies the ability of ROS to "inhibit tumor growth by inducing cancer-cell death, contribute to the resolution of inflammation by disactivating T cells and NET formation, and alleviate myeloablation by increasing hematopoiesis."

According to the coordinator of the project, **Andriy Mokhir**, "the NeutroCure project will be the first attempt to find an innovative solution to this problem. The consortium will develop safe ROS amplifiers that can increase ROS levels specifically near neutrophils associated with cancer or pathogenic inflammation without affecting healthy cells. The technology may also be applicable to the treatment of myeloablation."

Neutrophils act like 'chemical bombs' because, among other properties, they produce highly reactive substances that, when they enter a microbe, destroy it. "These bombs act like a kind of bleach: nonspecific but very effective," said **Andrés Hidalgo**.

The goal of NeutroCure is to ensure that these substances are selective and controlled. To achieve this, the consortium members focus on the protein elastase, which is specific to neutrophils. The team has designed a 'chemical cage' that opens to 'release' ROS only when elastase is in highly defined anatomical locations and contexts.

The CNIC team led by **Andrés Hidalgo** will receive €400,000 as one of the six member groups of the NeutroCure consortium. The project will assess this approach in models of inflammatory disease, such as arthritis, multiple sclerosis, autoimmune neuritis, lupus, and psoriasis.

The NeutroCure consortium includes six academic member groups and a private company that will steer the commercialization of new medication developed in the project. The consortium members anticipate that NeutroCure will have a major societal impact by providing new treatments for severe disorders caused by the dysregulated production of ROS. ■

JACOB FOG BENTZON RECEIVES 2 M EUROS FROM THE EUROPEAN RESEARCH COUNCIL FOR A GROUND-BREAKING RESEARCH PROJECT ON ATHEROSCLEROSIS

Although atherosclerosis is one of the most common diseases in the world, researchers studying it still have much work to do to uncover and understand exactly what happens when fat and cholesterol are deposited in the arteries, leading to arteriosclerosis and the risk of blood clots in the heart and the brain.

They have only recently discovered that many of the cells seen in atherosclerosis are in reality what are known as vascular smooth muscle cells which alter their appearance and function. A research group led by professor of experimental atherosclerosis **Jacob Fog Bentzon**, will now work to uncover the significance of these mysterious cells.

The professor has just received a Consolidator Grant of 2 M euros from the European Research Council towards a five-year research project in Aarhus and Madrid.

"When you look at atherosclerosis in the microscope, what you see is a complex disease with many types of cells. But we now know that although the cells may look different, the majority of them originate from the arteries' own vascular smooth muscle cells," says **Jacob Fog Bentzon**, who divides his time as professor between the Department of Clinical Medicine (Cardiology) at Aarhus University and the CNIC in Madrid. He is also affiliated with the Steno Diabetes Center Aarhus.

"The background for the project is our discovery that atherosclerosis in mice is driven by very few of these vascular smooth muscle cells that alter their function and proliferate massively. In our coming research we will try to uncover whether the same is true in humans and – very importantly – whether we can affect the altered vascular smooth muscle cells in a way that ameliorates the disease," says **Jacob Fog Bentzon**.

"Ultimately, the goal is to find new ways of treating late atherosclerosis in humans. And the path to doing this is paved with a wide range of studies in genetically modified mice and pigs," he adds.

The 2 M euros will, among other things, be used to bring together a team of young researchers who, like Jacob Fog Bentzon, will move between Aarhus and Madrid

The 2 M euros will, among other things, be used to bring together a team of young researchers who, like **Jacob Fog Bentzon**, will move between Aarhus and Madrid and in this way utilise the research facilities in both locations – all in the spirit of the EU funding.

Grants from the European Research Council are given for free and independent research that has the potential to lead to ground-breaking discoveries. The Consolidator Grant which **Jacob Fog Bentzon** has received is for researchers with 7-12 years of experience since the completion of their Ph.D. ■

cnic AWARDS AND SCHOLARSHIPS

FRANCISCO SÁNCHEZ MADRID AWARDED THE SANTIAGO RAMÓN Y CAJAL NATIONAL PRIZE

Francisco Sánchez Madrid received the Santiago Ramón y Cajal National Prize in the area of Biology. **Dr. Sánchez Madrid** is a group leader at the CNIC and a Full Professor in Immunology at the Universidad Autónoma de Madrid (UAM) and heads the Immunology Service at Hospital Universitario La Princesa. The committee awarded the prize to **Sánchez Madrid** in recognition of his contributions to biomedicine in the field of leukocyte intercellular communication, adhesion, migration, and activation and the impact his work has had on the study of chronic inflammatory diseases. These achievements, together with his high international profile throughout his scientific career, his outstanding record of training and mentoring young Spanish scientists, and the biotechnological applications of his discoveries, amply justify this award. The National Prizes for Research, created in 1982, are the highest award in Spain for scientific research.

DR. VALENTÍN FUSTER RECEIVES THE PRESTIGIOUS PREMIO PRÍNCIPE MAHIDOL FOR HIS SCIENTIFIC CONTRIBUTIONS TO MEDICINE

CNIC General Director **Dr. Valentín Fuster** received the 29th Premio Anual Prince Mahidol in the area of Medicine. This prestigious award from the Prince Mahidol Foundation recognizes the international leadership shown by **Dr. Fuster** over the past 40 years through his innovative contributions to cardiovascular medicine, spanning basic research to clinical care, and more recently his tireless promotion of cardiovascular health throughout the world. The committee noted the "value of **Dr. Fuster**'s research in unifying and extending knowledge gained through basic research to bring new benefits to patients, especially regarding antiplatelet therapy. His exceptional contribution has saved millions of lives throughout the world." Five previous winners of this prize later went on to win the Nobel Prize.

Dr. Fuster is also the first Spanish scientist with a Webometrics classification. This measure, established by the cybermetrics group at the Consejo Superior de Investigaciones Científicas (CSIC), is based on the h index, one of the most widely used tools to determine the influence of discoveries over a scientist's professional career. This parameter was defined by the physicist **Jorge Hirsch** to provide a single measure of the quality of an investigator's findings.

GUADALUPE SABIO RECEIVES THE 'YOUNG INVESTIGATOR AWARD' FROM THE EUROPEAN SOCIETY FOR CLINICAL INVESTIGATION

The European Society for Clinical Investigation awarded CNIC scientist **Guadalupe Sabio** its 'Young Investigator Award', which recognizes the achievements of young research scientists who have made an outstanding contribution to basic, translational, or clinical biomedical research in Europe.

BORJA IBÁÑEZ WINS THE 'YOUNG TALENT' PRIZE IN THE PREMIOS CONSTANTES Y VITALES FOR BIOMEDICAL RESEARCH

Dr. Borja Ibáñez Cabeza, Director of Clinical Research at the CNIC, was awarded the 'Young Talent' Prize in the 6th edition of the Premios Constantes y Vitales for biomedical research and disease prevention, an initiative of the laSexta television channel and the Fundación AXA. These prestigious awards aim to recognize, support, and strengthen the achievements of Spanish scientists working in the areas of biomedical research and disease prevention during 2020, an especially challenging year that demonstrated the importance of this work more than ever. The prize comes with a financial award of €100,000 to support ongoing research projects.

DR. MIGUEL TORRES NAMED AN HONORARY MEMBER OF THE LATIN AMERICAN ACADEMY OF SCIENCES

The Latin American Academy of Sciences (ACAL) has named **Dr. Miguel Torres** an honorary member in recognition of the alignment of his work with the Academy's goals. These goals are high-quality research, scientific progress, and the integration of Latin America and the Caribbean through cooperation in research. **Dr. Torres** and fellow honorary member **Dr. Ángela Nieto** are the first Spanish investigators to join ACAL, whose mission is to promote and contribute to the progress of the mathematical, physical, chemical, life, and earth sciences and their use to support the human, cultural, and social integration of Latin America and the Caribbean.

DR. VALENTÍN FUSTER AWARDED THE MUJERHOY 'PREMIO AL COMPROMISO MASCULINO' (MEN'S COMMITMENT PRIZE) FOR THE 'MUJERES POR EL CORAZÓN' (WOMEN FOR THE HEART) CAMPAIGN

Dr. Valentín Fuster received the Mujerhoy 'Premio al Compromiso Masculino' for his health promotion work to raise awareness among women of their vulnerability to cardiovascular disease. Since 2014, **Dr. Fuster** has led the 'Mujeres por el corazón' campaign, a joint effort of Fundación Mapfre, the Pro-CNIC Foundation, the Community of Madrid, and the Spanish Heart Foundation. The campaign aims to raise awareness of women's cardiovascular risk so that symptoms can be recognized early and to promote healthy lifestyle habits.

THE SEC ANNUAL MEETING HOLDS ITS FIRST SESSIONS DEDICATED TO BASIC AND TRANSLATIONAL CARDIOVASCULAR RESEARCH

In its 2020 congress, the Spanish Society of Cardiology for the first time included sessions dedicated to basic and translational cardiovascular research. Several CNIC scientists were among the participants, including **Héctor Bueno**, **Miguel Ángel del Pozo**, **Fátima Sánchez-Cabo**, **José Javier Fuster**, **Andrés Hidalgo**, **Miguel Torres**, **Guadalupe Sabio**, **David Filgueiras**, and **José Jalife**.

CNIC NAMED ONE OF THE 4 LEADING CARDIOVASCULAR RESEARCH CENTERS IN EUROPE AT THE 2020 EUROPEAN SOCIETY OF CARDIOLOGY CONGRESS

The CNIC was one of only 4 leading centers in cardiovascular research to be invited to showcase itself in a live session at the European Society of Cardiology (ESC) annual meeting, which in 2020 set a new record of more than 115,000 participants from 211 countries. The CNIC joined in the 'Leading Cardiovascular Research Centres in Europe' session by Oxford University, the Stockholm Karolinska Institute, and the University Medical Center Hamburg-Eppendorf.

SCIENCE WEEK 2020: A TALK ON COVID-19 FOR CHILDREN AND THEIR FAMILIES

As part of Semana de la Ciencia (Science Week) 2020, the CNIC organized an event for children at which **Dr. Miguel Ángel del Pozo** spoke about the science behind SARS-CoV-2 infection and the body's immune response to it.

LALIGA JOINS THE PRO-CNIC FOUNDATION IN THE FIGHT AGAINST CARDIOVASCULAR DISEASE

LaLiga and the Pro-CNIC Foundation have joined forces to promote awareness among football fans about the importance of cardiovascular disease prevention, taking care of one's heart, and avoiding bad habits like physical inactivity and smoking, which are major causes of diseases that affect the heart. The 2 organizations have launched the Cuida tus latidos campaign (Take care of your heartbeats; www.cuidatuslatidos.com), which provides soccer fans with information on how to prevent serious cardiovascular conditions like a heart attack.

VISITING RESEARCHERS PROGRAM: THE JESÚS SIERRA FOUNDATION FINANCES DR. GABRIEL NÚÑEZ' STAY AT THE CNIC

The Jesús Serra Foundation, part of the Catalana Occidente Group, financed **Dr. Gabriel Núñez**' stay at the CNIC during 2020. **Dr. Núñez** is professor in the Department of Pathology at the University of Michigan (USA). This scholarship is part of its Visiting Researchers program and aims to promote interaction in the field of research to contribute to advances in science.

Promoted by the Jesús Serra Foundation with different Spanish institutions since 2009, the Visiting Researchers program finances the stay of renowned scientists of international prestige so that they can travel to Spanish research centers and stay several months. Its purpose is that the visiting researcher can, on the one hand, deepen the scientific relationship of the host research group with that of the researcher's own center of origin, and, on the other, start new lines of action based on innovative scientific interests.

Dr. Núñez is recognized as one of the leading experts in gastrointestinal and systemic inflammation, host-microbe interactions, and mucosal immunology. ■

CNIC & COVID-19
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#11