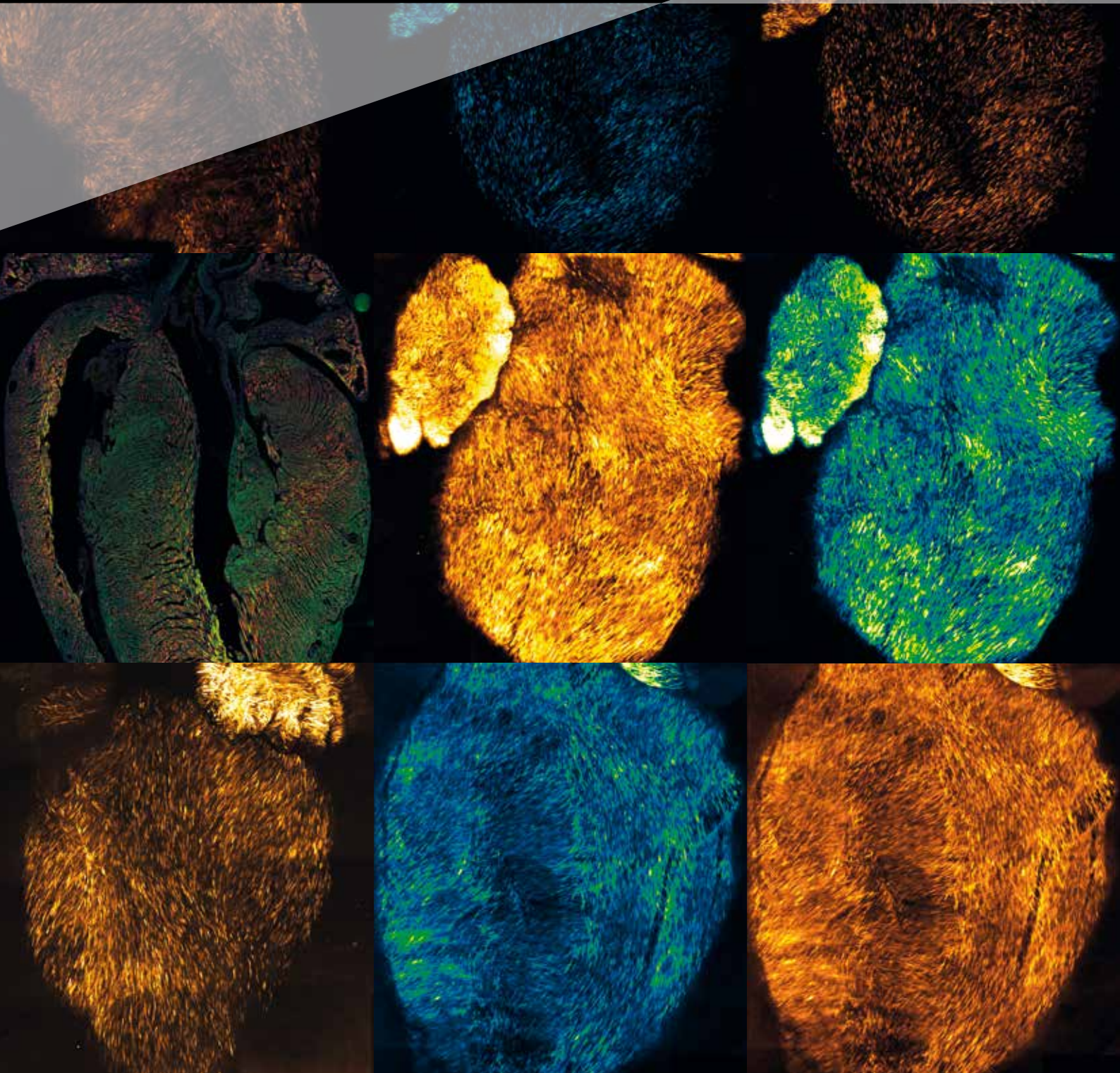


TRAIN2GAIN
WHAT'S ON
INSIDE SCIENCE
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Cardiovascular diseases are the first cause of death worldwide. Recent decades have seen major advances in the diagnosis, treatment and prevention of these diseases. We now know that controlling risk factors, such as tobacco consumption, high blood pressure, diabetes, high levels of cholesterol or a lack of exercise, among other factors, reduce the probabilities of suffering from this disease.

But what happens after the onset of the disease? In these cases, a healthy lifestyle (no smoking, doing exercise, correct diet) can improve prognosis, but it is not enough on its own. We need preventive medication.

The drugs that improve life expectancy after a heart attack are well known: statins to reduce cholesterol, angiotensin-converting-enzyme (ACE) inhibitors, beta blockers and aspirin. The problem is they must be taken every day, which means the patient has to take a large number of pills.

Adhering to this therapy regime is not easy. Almost 50% of patients with chronic conditions do not take their medication in the correct way. There are many reasons that influence treatment adherence, but a major one is the complexity of the therapy. The higher the number of drugs, the lower the adherence.

Moreover, in some countries - generally low or medium income ones - the cost of secondary prevention medica-

tion is prohibitively high for most people. Consequently, this disease continues to spread throughout the world like an epidemic.

It was in 2006, after seeing with my own eyes the grave deficiencies in cardiovascular prevention due to the cost and scarcity of medications in some emerging countries, that I had the idea for a polypill. It was not just a question of simplifying treatment, but of making it more accessible in these emerging countries.

Laboratorios Ferrer took up the challenge, and in September 2006 we began collaboration on an exciting project. Many meetings, consultations with national and international agencies, hours in the laboratory and clinical trials brought the final result: the polypill, a single pill that includes aspirin, an ACE inhibitor and a statin.

The polypill has been proven to reduce cardiovascular mortality 33% in patients treated after suffering a heart attack. The results of the SECURE study, published in **The**



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

New England Journal of Medicine presented at the European Society of Cardiology Congress in Barcelona confirmed our suspicions: a polypill could become an integral part of strategies to prevent cardiovascular events in people who have suffered myocardial infarction. As treatment is simplified and adherence improves, this approach has the potential to reduce the risk of recurrent cardiovascular diseases and death

Even more complex is the challenge of regenerating the heart, as this edition of **CNIC Pulse** thoroughly explains. Regeneration of the heart is currently one of the

greatest challenges facing scientific investigation. At last year's CNIC Conference 2022, over one hundred international experts spent two days debating the current possibilities that exist to overcome this scientific challenge, achieve regeneration of the human heart and prevent heart failure.

International experts, such as **Dr. Elly Tanaka**, **Dr. Hesham Sadek** and **Dr. Mauro Giacca**, among others, provided a critical insight into current controversies in the field of cardiac stem cells and other aspects like the failure, to date, of successfully translating experimental therapies into clinical benefits. The good news is that most of the speakers expect to see cardiac regeneration within their lifetimes.

This is also the work, for instance, of CNIC's Molecular Genetics of Angiogenesis group, led by **Dr. Rui Benedito**, whose project "New approaches to heart tissue regeneration after heart attack" was selected by "La Caixa" Foundation for its Health Research Projects 2022, alongside another three CNIC projects.

CONTROLLING CARDIOVASCULAR DISEASE

POLYPILL: THREE DRUGS IN ONE PILL TO PREVENT A SECOND INFARCTION

Simplifying the treatment for cardiovascular disease and making it accessible to everyone. The polypill, developed by CNIC and Laboratorios Ferrer, has shown that taking a single pill daily after myocardial infarction is not only the most convenient option, but also saves lives. The effectiveness of the polypill to prevent cardiovascular events after a heart attack has been confirmed, with a 24% decrease in cardiovascular events and a 33% decrease in cardiovascular death among patients who had previously suffered a myocardial infarction.

These were the conclusions of the SECURE study, presented in the Hot Line session at the last European Society of Cardiology Conference (ESC 2022), held in Barcelona, with findings published in *The New England Journal of Medicine (NEJM)*. "For the first time, the

The data of the SECURE study show for the first time that the polypill achieves clinically relevant reductions in recurrent cardiovascular events among patients who have suffered a myocardial infarction

SECURE data show that the polypill, which contains aspirin, atorvastatin and ramipril, achieves clinically relevant reductions in recurrent cardiovascular events among people who have suffered a previous heart attack," highlights the SECURE study's principal investigator, **Dr. Valentín Fuster**, Director General of CNIC, Director of Mount Sinai Heart, and Medical Director of Mount Sinai Hospital.



The American Heart Association (AHA) also selected SECURE as one of the most relevant scientific studies in the field of cardiology in 2022.

DR. VALENTÍN FUSTER:

“The polypill could form an integral part of strategies to prevent cardiovascular events among patients who have suffered an infarction. As the treatment is simplified and adherence improves this approach has the potential to reduce the risk of recurrent disease and cardiovascular death on a worldwide scale”

of cardiovascular diseases, which are the most lethal worldwide.

He later joined forces with Ferrer, and the heart polypill project began. “In Ferrer we are committed to generating a positive impact on society and, in our mission to improve people’s the health and quality of life, we firmly believe that private-public collaboration is one of the main motors of innovation. So, when we came across this project with such profound social importance as improving the prevention of cardiovascular disease, our response was firm and resolute,” remembers Óscar Pérez.

Now, after three years of research, the new study vindicates **Dr. Valentín Fuster**.

Despite emphasis on preventive factors against cardiovascular diseases, many people suffer a heart attack, which means they have to follow a treatment for life.

Dr. Fuster explains that the medications to improve life expectancy after a heart attack are well known: “All patients who have suffered myocardial infarction and do not have contraindications must take a statin to reduce cholesterol, ACE inhibitors, a beta blocker and aspirin. The problem is that this medication has to be taken every day, which means the patient has to take a large number of pills.”

Although this patient group is very aware, following this therapeutic regimen is no easy task. We know that 50% of patients with chronic conditions do not take their medication correctly. This lack of treatment adherence determines lower protection and an increase in complications.

There are many reasons that influence treatment adherence, but one of the major ones is the complexity of the therapy the patient receives. The higher the number of drugs or the greater the complexity, the lower the adherence. Moreover, secondary prevention medication (for people who have already suffered a heart attack) in some countries, generally low to middle income ones, has a cost that is prohibitive for most of the population. Consequently, the disease continues to spread throughout the world like an epidemic.

“The SECURE findings suggest that the polypill could form an integral part of the strategies to prevent cardiovascular events in people who have suffered an infarction,” highlights **Dr. Fuster**. “As treatment is simplified and adherence improves, this approach has the potential to reduce the risk of recurrent cardiovascular disease and death on a worldwide scale.” For **Fuster**, “these new results have a great impact both for patients and healthcare systems.”

The cardiovascular polypill is currently available in 25 countries. ■

“Cardiovascular disease is often termed the epidemic of the 20th century,” says Óscar Pérez, Ferrer’s Chief Marketing, Market Access and Business Development Officer. And despite the solid evidence showing the high prevalence of cardiovascular risk factors in the population, he adds, “it is frequently true that preventive strategies do not achieve the desired results, partly due to low adherence on the part of the patient, which is to say they do not fully comply with taking their prescribed medications.”

The idea for this project arose in 2006, during a trip to Russia. While he was there, **Dr. Fuster** noticed the low level of treatment adherence. Not only because of the inconvenience of taking all of the pills, but also due to the high price of the medications. It was then that he had the idea that a formula originally envisioned for HIV treatment could be used to combat the pandemic



cnic CONFERENCE

Cardiac regeneration is currently one of the greatest challenges facing scientific research. Unlike other animals, such as the salamander or the zebra fish, human beings are incapable of regenerating their tissues and organs, but scientists do not know why.

The CNIC Conference 2022 discussed this topic in a scientific congress that tackled the latest advances in understanding the cardiac repair mechanisms of naturally regenerating organisms, and how to stimulate such mechanisms in mammals that do not regenerate.

CNIC brought together over a hundred international experts, who spent two days debating the current possibilities to overcome this scientific challenge and achieve regeneration of the human heart for the prevention of heart failure.

In the conference - organised by CNIC researchers **Miguel Torres** and **Nadia Mercader** - **Elly Tanaka**, **Hesham**

Sadek and **Mauro Giacca** dealt with aspects ranging from metabolism and cardiac regeneration, the micro-environment of cardiomyocytes in this regeneration, cellular crosstalk and the translational road to cardiac regeneration from approaches involving genetics and tissue engineering.

There are animals with a high capacity to regenerate and repair myocardial damage with new cardiomyocytes - the muscle cells that are capable of contracting and are responsible for heart beats. This is the case, for instance, of the zebra fish; however, the same is not true of the human heart, which cannot naturally repair itself.

Experts critically discussed the current controversies surrounding the field of cardiac stem cells alongside other aspects such as the failure, to date, of a successful translation of experimental therapies to the clinical context. ■



Elly Tanaka

"SALAMANDERS ARE EXTRAORDINARY CREATURES"

Cardiac regeneration is currently one of the greatest challenges facing scientific investigation. Unlike other animals, such as the salamander or the zebra fish, human beings are incapable of regenerating their tissues and organs, but scientists do not know why. Elly Tanaka, of the Research Institute of Molecular Pathology in Vienna (Austria), spoke on this subject during the CNIC Conference, 2022. For years, Tanaka has been fascinated by the highly regenerative capacity of *Ambystoma mexicanum*, commonly called the axolotl. "All species of salamander that have been studied appear to be capable of regenerating their limbs," she affirms.

In the future, will it be possible to regenerate the heart after a heart attack?

Making predictions is always tricky, but we are on the right track.

Are humans so different from salamanders?

I have always been fascinated by salamanders because of their capacity to regenerate. Salamanders are extraor-

dinary creatures. If they lose a digit, they can regenerate it. Likewise, if a piece of their heart or their spinal cord is cut, they can regenerate it. Specifically, my laboratory is working on axolotls, salamanders that live in the lakes of Mexico City. At first, we observed that they were able to regenerate their limbs, but recently, as we published in *Nature*, we have seen that they also regenerate their internal organs like the heart and brain.



How can the information provided by your group serve to advance in the regeneration of tissues and organs in humans?

The data we obtained are really important for ongoing research into organ regeneration in humans. Recently, we have seen that stem cells from axolotl brains are similar to the stem cells we encounter in the brains of mammals. We have also identified special genes that are activated in the stem cells of axolotl brains. In future, we're going to investigate whether we can activate these genes in mice, and -why not?- in humans, and inactivate genes that are not related with regeneration. Humans and mice have these genes; now we have to see which genes are active or not in humans.

Whereas the skin and many other tissues of the human body retain the capacity to repair themselves after a lesion, the same is not true of the heart. What can be learned from these other tissues?

That is a difficult question to answer. We are studying, and it is possible that humans have a larger number of cells that block regeneration than axolotls do. The point is that we don't know why. One hypothesis is that the axo-

"In the last 10 to 15 years, we have been able to understand that rat and human muscle cells regenerate in a similar way to those of salamanders and now, the specific factors that make these cells able to proliferate have been identified"

lotl and other salamanders have a different regeneration mechanism to humans, whereas in mammals the mechanism is more related with survival. One of the ways would be to identify and characterise the cells involved in regeneration and attempt to modify them.

Cell therapy and gene therapy are two approaches to the regeneration of the heart that have been tried for some time without successful outcomes. Why?

In the 1970s, the then President of the United States, Nixon, declared war on cancer in the USA and now, more than 50 years later, we have therapies that are very effective against cancer. I hope that within the next 10 or 20 years something similar will have happened in cardiac regeneration which will revolutionise the field in the same way, for instance, as has occurred in immunotherapy for cancer. Of course, the immune system is very important in this aspect, and we see that in animals that are capable of regeneration, in some way the immune system cells help regeneration, whereas in mammals these cells do not seem to help. We have to understand this balance between immune cells.

Although the possibility of a person regenerating an arm or a leg belongs in the realm of science fiction, do you think that salamanders can offer us a new perspective to improve the treatment of human lesions?

We hope so. There are laboratories devoted to studying the spinal cord. My team is working with cultures of mammalian cells to analyse regeneration patterns. I think that the results we are obtaining with salamanders are going to be of great use, not only for spinal cord regeneration.

Is the salamander the most important animal in the field of regeneration?

These amphibians fascinate me. For instance, in the field of heart regeneration, over 50 years ago, the salamander was the first animal in which it was proved that cardiac muscle cells have the capacity to regenerate the heart. For years, investigators have searched for cardiac stem cells, but the results have been very confusing. Recently, in the last 10-15 years, we have been able to understand that the muscle cells of mice and humans regenerate in a similar way to those of salamanders and now, certain factors have been identified that allow these cells to proliferate. And all of these ideas come from studies on salamanders. What we are learning from the salamander is key information to understand what might happen in humans. It is a model that shows us the right path to follow.

You group participates in REANIMA (New-generation cardiac therapeutic strategies directed to the activation of endogenous regenerative mechanisms), the project coordinated by CNIC's Miguel Torres. What is the purpose of this project?

REANIMA is a group of research scientists working on cardiac regeneration from different approaches. The idea is to identify the molecules in different models and be able to compare them between the various research groups.

Soon we will have results, with publication in the medium term. The good thing about this group is that we work on different models, from the smallest, like the zebra fish or the salamander through to mice, pigs and humans.

The European-funded RegGeneMems project ends in 2023. What could the results be?

If we want to progress in the bioengineering of human tissues in the future, we have to try to regenerate a larger limb; I mean, when we regenerate limbs in an embryo, they are very small, but if there is an amputation, we need to do it with something larger. This project is about understanding how an adult salamander is capable of regenerating one of its limbs. We know that it uses the same components as an embryo and that the cells need to communicate with each other. The difference is that,

“What we are learning from the salamander is key information to understand what might happen in humans. It is a model that tells us what the right path is”

in an embryo, the distance between cells is very small; however, in the case of adults, the distance between cells is much greater. What we have seen is that somehow, in larger animals, the factors that these cells use to communicate with each other are able to do it over greater distances. Animals have the capacity to use these factors, even at longer distances. And that is what we are trying to ascertain. How does this happen? The idea is to understand how these factors are capable of communicating over long distances.

But humans have this capacity to generate during their first days of life. So, do we lose the capacity for communication between cells and factors?

Yes, distance is clearly one problem that makes communication difficult, but there are other hurdles. For instance, mammalian cells do not have the capacity to activate these communication molecules because after the first moments of life they are not necessary, therefore the factors deactivate. So, whereas axolotls can reactivate it, this does not happen in mammals. ■

KING'S COLLEGE LONDON
United Kingdom

Mauro Giacca

“THERE IS
A TREMENDOUS NEED
TO ACHIEVE CARDIAC
REGENERATION”

Dr. Giacca is Head of the School of Cardiovascular and Metabolic Medicine and Sciences, Professor of Cardiovascular Sciences at the Faculty of Medicine and Life Sciences, King's College London, and President of the International Society for Heart Research (ISHR) European Section. He is also a founder of Forcefield Therapeutics and Heqet Therapeutics, two recent start-ups that are developing biological cardiovascular devices, and co-founder of Purespring Therapeutics.

A physician by training, **Dr. Giacca** is considered an expert in the generation of viral vectors for cardiovascular applications and in the development of novel biologics for cardiac repair and regeneration after myocardial infarction and heart failure. His group has achieved the regeneration of cardiac tissue after damage caused by a myocardial infarction. He also has a great interest in the molecular biology of HIV-1 infection.

Your group managed to regenerate cardiac tissue after damage caused by a myocardial infarction. What was the key?

What we did was conduct a high throughput screening with molecules that seem to work, although we have not been able to understand what really happens. We started by trying out multiple treatments on cardiomyocytes to see which worked. We have different treatments that were



have to kill all of the tumour cells because if you leave one, the cancer will reproduce. In the heart, although therapy is not completely effective, there is a clinical benefit.

In the future, will it be possible to regenerate the heart after a heart attack?

Of course; we are not far away from achieving it. There is a tremendous need to achieve cardiac regeneration. The way I see it, it is very simple. We know that cardiac cells, cardiomyocytes, lose their capacity to proliferate after birth. Data shows that a 70-year-old person has at least 50% of their cardiac cells with the capacity to regenerate themselves that they had when they were born. Which is to say that the capacity to regenerate the heart throughout life is minimal, and clinically irrelevant. This means that when a person suffers a heart problem, like a heart attack, when part of their heart suffers necrosis or dies, there is no way to recover the lost cardiac cells. And this occurs due to the inability of cells to regenerate. This situation is not dissimilar to what occurs in other organs, like the brain. We are born with a certain amount of neurons, but the capacity of these cells to proliferate is inexistent. And we lose neurons throughout our life, so it is hardly surprising to see a rise in diseases associated with dementia as life expectancy increases. The same thing happens with sight or hearing; the cells of these organs don't proliferate either.

We find ourselves without a treatment for these problems of dementia or cardiovascular disease, but we don't have a cure for diabetes, loss of vision or hearing either, because we do not know how to regenerate cells.

I tell physicians they should tell their patients that when we are born, we are given these cells as a gift, and the better we look after this gift, the better our lives will be. But in my opinion, cardiac regeneration is less complicated than regeneration of the brain. For the brain, not only is it necessary to generate new neurons, but they themselves must manufacture new connections in the brain. And that is very complicated because neurons are highly specialised to perform specific functions, like controlling movement. It is highly complex.

Nevertheless, things are easier in the case of the heart. And different. Cardiac cells are a lot simpler than neurons. They are mechanical cells that integrate in a relatively simple way with residual cells of the cardiac muscle to regenerate the heart. The problem we find is that the heart does not have stem cells that can be activated.

What are the current approaches?

There are two ways of attempting this regeneration. The first is to produce cells in the laboratory and later implant them into the patient, whereas the second is to convince the cardiac cells of the heart to proliferate. Both options are front-line.

able to promote cardiac proliferation, the most promising of which were microRNA. And it worked in mice and pigs! The problem is that our ideas cannot be applied to patients due to the form of delivery. Now, we are using viral particles that contain RNA as vectors, which is the same technology that Moderna and Pfizer used in their COVID vaccines. And we are still looking for the perfect particle for the heart.

The way we see our approach is: a patient with a heart attack is treated with catheterisation in a hospital to unblock an arterial occlusion (the cause of the infarction) allowing the blood to flow. The idea is, at the same time or a few days later, to inject these lipid particles with RNA into the coronary artery to promote the proliferation of existing cardiomyocytes, thus achieving regeneration.

We know that regeneration will not be complete, because that depends on the size of the lesion, but although it only works 30%, 40% or 50% there will always be a clinical benefit.

So, we should talk about partial heart regeneration?

That's not our idea, because what we want is complete regeneration. But this isn't like cancer, where you

We know how to produce cardiac cells from stem cells. After a myocardial infarction we lose at least 1,000 million cardiac cells. There are three clinical trials that are generating close to this figure of 1,000 million cardiac cells in the laboratory for implantation at the site of the heart lesion. The problem with these approaches is that the cells generated are at a very embryonic stage and have difficulties communicating with the patient's cells. They do not have the same connections.

Currently there are attempts to mature the cells so that they can communicate better. But laboratory tests show that within the first three weeks this treatment produces fatal arrhythmias.

The other possibility, based on stem cells is, instead of implanting them directly in the patient, to create a type of cardiac tissue in the laboratory that has contractility and can later be surgically implanted in the heart. This is being done in two laboratories in Germany and is being tested in 8 patients in Göttingen. But this is a very complicated, expensive procedure, as well being very difficult to transfer to a routine clinical setting.

The most attractive idea is to convince residual cardiac cells to regenerate themselves. We know that some animals, like the salamander or zebra fish, or even newborn mice or pigs, are able to regenerate their hearts. This means that it is possible.

There is an anecdotal case of a child in Vienna who had a heart attack shortly after birth, something that is extremely uncommon. The child was treated with the latest technology to deal with the thrombus, but the damage to the heart was already done. Nevertheless, he underwent follow-up for years with MRI imaging tests and, amazingly, the tests showed that his heart was completely healthy. It had completely regenerated, something that had never been seen before. (The study was published in ***Circulation Research***).

So, there is a reason why this does not happen in adults. In mice, we know that the window for regeneration to occur is two or three days. In humans, we think the window is longer, probably months.

Do we know what happens to cause this cell reprogramming?

This is one of the most fascinating mysteries, although we do have some hypotheses. For instance, we know that birth is one of the most traumatic moments for a living organism. Before, inside the mother, everything is easy. The heart of a newborn, outside the mother, has to begin to pump blood and make it circulate to all of the organs without the help of the mother's heart. Also, unlike before birth, when the heart is very far from the lungs and receives blood with a small amount of oxygen, on birth, the heart connects to the lungs, so the blood contains a lot more oxygen.

Evidence exists of hormonal changes. There is probably

a combination of events that tells the heart to stop dividing and make itself bigger because it has to start to work. The idea is to understand these signals in order to revert them.

As well as regeneration after a heart attack, your group is also working on preventing the damage produced by a heart attack. How?

Another of our approaches is to prevent damage, rather than regenerate cardiomyocytes. We have discovered three proteins capable of detaining the death of cardiac cells after a myocardial infarction. We believe that their use within the first 24 to 48 hours, or even in the ambulance, in a patient who has suffered a heart attack, could prevent the death of cardiomyocytes. The protein is injected into the vein to block the death of cardiomyocytes. So, in an ideal situation, we would have different alternatives: first, the use of proteins to prevent the death of

“There are two ways of attempting this regeneration of the heart. The first is to produce the cells in the laboratory and later implant them in the patient and the second is to convince the cardiac cells of the heart to proliferate”

cardiac cells and, subsequently, attempting to regenerate the heart with microRNA. Prevent death and regenerate. It is very ambitious.

You are a physician by training. Do you think that a good biomedical researcher should have a vocation to serve the patient?

Honestly, I have to say that when I decided to study medicine, I did it with the intention of going into research, although at that time I didn't really know what a career in science was, and the image I had was a bit romantic. In fact, I haven't done much clinical work with patients, but I think it is very beneficial for researchers to share a common language with clinicians. Having a solid basis of clinical practice makes it much easier to translate basic research to the patient. Of course, we want to know many things, mechanisms, regulatory genes, proteins, but we also want to develop therapies that benefit patients. ■

FOUR CNIC PROJECTS SELECTED "HEALTH RESEARCH PROJECTS 2022" BY FUNDACIÓN "LA CAIXA"

Four CNIC (Centro Nacional de Investigaciones Cardiovasculares) projects have been selected by "La Caixa" Foundation in the 2022 edition of its Health Research Projects.

The selected projects were:

- "Identifying new immune targets to treat cardiovascular disease," whose principal investigator is **Dr. Almudena R. Ramiro**.
- "New approaches to heart tissue regeneration after a heart attack," led by **Dr. Rui Benedito**.
- "Identifying new biomarkers for the progression of heart failure," whose principal investigator is **Dr. José Javier Fuster**.

The fourth project is "Prompt diagnosis of coronary heart disease to prevent early mortality," a consortium project whose principal investigator is **Teresa Correia** of the Centro de Ciências do Mar do Algarve (CCMAR) (Portugal), in which CNIC's **Dr. Borja Ibáñez Cabeza** participates.



IDENTIFYING NEW IMMUNE TARGETS TO TREAT CARDIOVASCULAR DISEASES

Principal investigator: Almudena R. Ramiro. B cell Biology Lab

Funding: €750,042.40

Consortium project with: Dr. José Luis Martín Ventura, of the Fundación Jiménez Díaz's Instituto de Investigación Sanitaria

Cardiovascular diseases are the main cause of death in the world, and the WHO estimates that they cause the

death of 17.9 million people each year. These deaths mainly originate in atherosclerosis and abdominal aortic aneurysms, the two most common diseases affecting arterial vessels. The immune system plays a key role in both diseases. This is because they are associated with a chronic inflammatory immune response involving both innate and adaptive immunity. Due to this key role in causing the diseases, the immune system is an interesting target for the development of early diagnostic tools and new treatments. However, to date, this approach has faced a hurdle: limited knowledge about which antigens trigger immune response.

This team has already described one antigen of atherosclerosis, and this project will identify new immune targets for both atherosclerosis and abdominal aortic aneurysm. The investigations will pave the way for implementation of new strategies that restrict or boost a specific immune response.

NEW APPROACHES TO HEART TISSUE REGENERATION AFTER A HEART ATTACK

Principal investigator: Rui Benedito. Molecular Genetics of Angiogenesis

Funding: €999,948.04

Consortium project with: Mariona Graupera, of the Fundació Institut de Recerca contra la Leucèmia Josep Carreras; Holger Heyn, of the Centro de Regulación Genómica (CRG); and Rafael Kramann, of University Hospital RWTH Aachen (Germany)

Myocardial infarction is the leading cause of death in developed countries and the third cause of death in



developing countries. Most heart attacks are caused either by myocardial ischaemia or coronary artery occlusion. Seven of every ten people who suffer a heart attack survive.

In common with current therapies, heart tissue has little regenerative capacity, which leads to high morbidity and an associated cost in healthcare. To a large extent, the low regenerative capacity of cardiac tissue is related with the restricted activity of vascular cells in the area of the infarction. This means that an insufficient amount of blood reaches this area and limits the capacity to heal and regenerate.

The group will endeavour to characterise and identify genetic pathways and pharmacological compounds that might activate vascular cells in the infarct area, so that their growth is effectively promoted, stimulating the regenerative capacity of the tissue, which could open the door to discovering new strategies to prevent heart failure.



IDENTIFYING NEW BIOMARKERS FOR THE PROGRESSION OF HEART FAILURE

Principal investigator: José Javier Fuster. Hemato-vascular Pathophysiology

Funding: €998,043.28

Consortium project with: Núria López-Bigas, ICREA-Institut de Recerca Biomèdica (IRB Barcelona); Antoni Bayès Genís, of the Fundació Institut d'Investigació en Ciències de la Salut Germans Trias i Pujol (IGTP); Domingo Andrés Pascual Figal, of the Fundación para la Formación e Investigación Sanitarias de la Región de Murcia; and Manel Esteller Badosa, of the Fundació Institut de Recerca contra la Leucèmia Josep Carreras (Institut Josep Carreras)

Until recently, the acquisition of mutations in blood-forming stem cells was only considered of interest for cancer. Nevertheless, there is an increasing body of evidence to suggest that it is also a distinctive marker of ageing. In fact, several studies on humans have shown that people who have certain mutations in their blood cells, a phenomenon called clonal haematopoiesis, present high mortality rates, essentially due to cardiovascular disease.

A relationship exists between these mutations and the development of heart failure, a disease in which the heart does not pump blood efficiently.

The MyoClonal collaborative project will combine studies in humans and mice with the aim of better understanding the importance of clonal haematopoiesis in cardiovascular disease. The researchers will undertake an in-depth study of the effects of different acquired mutations in blood cells on heart failure. The knowledge generated will enable better treatment for heart failure patients, who usually require frequent hospital admissions and present a high risk of death.

PROMPT DIAGNOSIS OF CORONARY HEART DISEASE TO PREVENT EARLY MORTALITY

Principal investigator: Teresa Correia, of the Centro de Ciências do Mar do Algarve (CCMAR) (Portugal)

Consortium project with: Borja Ibáñez Cabeza. Translational Laboratory for Cardiovascular Imaging and Therapy

Coronary heart disease (CHD), the leading cause of death worldwide, occurs when the flow of blood to the heart becomes restricted. Early detection of this disease is of vital importance to prevent potentially life-threatening events.

Currently, the most frequently used method for early detection of CHD is coronary angiography. This test provides images of blood flow through the coronary arteries to the heart. The drawback is that this invasive procedure requires hospital admission and exposes the patient to radiation. So, in addition to the expense, it is impractical for routine screening.

There is an alternative to angiography: cardiac magnetic resonance imaging perfusion (CMRI perfusion). Unlike angiography, it is a safe, non-invasive procedure. However, it has two drawbacks: the low quality of the image and incomplete coverage of the heart. On the other hand, interpreting the data is complex and requires highly trained staff. These factors have hampered the widespread adoption of CMRI perfusion.

To overcome these problems, the researchers in this project will combine mathematical models of cardiac blood flow, CMRI perfusion and reconstruction of images to obtain unprecedented data about the health of the heart.

The project outcomes will contribute to improving the diagnosis and treatment of CHD and eventually enable an increase in survival rates, quality of life and patient safety. ■

Alejo Rodríguez-Fraticelli

“THE RISK OF CELL
THERAPIES IS
NOT BEING ABLE
TO DO THEM
FAST ENOUGH
IN A SCALABLE WAY”

Alejo E. Rodríguez-Fraticelli was born in Argentina. In 2008, he moved to Madrid, where he studied biochemistry, and obtained his doctorate in developmental and cell biology from the Universidad Autónoma de Madrid in 2014. He subsequently moved to Boston (USA) to pursue work on cell fate determination in haematopoiesis at Harvard University and Boston Children's Hospital. During his post-doctoral fellowship, Alejo Rodríguez-Fraticelli worked on developing methods for single cell lineage tracing in the haematopoietic system. His research has enabled him to establish a revolutionary way of connecting cellular states with cellular fates through clonal analysis to determine how variations in cellular states contribute to cell phenotypic heterogeneity. Since 2021, Alejo Rodríguez-Fraticelli has been group leader at the Instituto de Investigación Biomédica (IRB Barcelona) where he heads the Quantitative Stem Cell Dynamics laboratory. The staff on his team represent a diverse group with different ethnic backgrounds and philosophical approaches who have a passion for sharing resources and knowledge.

Where does your interest in science come from?

I studied in Argentina. I moved to Spain to pursue my scientific career. Before I completed my thesis, I had already done a couple of internships in the United States, and eventually I spent seven years there working at the University of Harvard campus and in Boston Children's Hospital.

I worked in the Hospital's scientific area, which is internationally recognised for having started the treat-

ment of paediatric cancer over 60 years ago. It is one of the best scientific environments to study something that seems fascinating to me, the origin of tumours and blood stem cells.

There are many cancers that originate in the blood cells but, when we began to study and understand the heterogeneity in haematopoietic cells, we realised that, in essence, this heterogeneity not only plays a role in cancer, but also has a part in all diseases: different types of

immune and inflammatory diseases and even in cardiovascular diseases.

I believe that the work I did, which is what made it possible for me to set up my own research group, really highlights the fact that we need to understand biology from a new perspective: Instead of treating tissues, the cells of the tissues, as uniformly homogeneous populations that behave in a more or less uniform way, we have seen that this apparent uniformity is composed of a multiplicity of cellular behaviours that are highly defined and dominated by the origins of the cells themselves. This means that the cells that gave rise to these populations during their development have a great influence on their behaviour, response and, in many contexts, on disease.

This has opened our eyes, and now we are starting to understand this variation, which we all knew was there, but had put to one side. But now we have hit on one of the keys, which is that there is a highly intrinsic component to each of these cells, which is heritable and therefore propagates through cellular generations. When a cell divides, for instance, when we develop, and in the maintenance of our tissues, the daughter cells inherit characteristics that we have not fully determined, but which greatly define their functioning.

And although we have discovered it in blood, we believe this is probably valid for all of the cells in our organism, from the heart to the brain, liver, bones, etc. But due to the available tools, it is easier to apply to blood cells.

So, the probability of having a disease is inherited through cell lineage?

It is completely possible that the only reason that a cell of mutates and causes a cancer in you, whereas for me it does not, is due to cell lineage. Obviously, there is a very strong component of other factors: environmental, genetic, etc... We know that there are many processes, but we had never thought of this as a defining factor. I think this will help explain many things about biology that we haven't been able to explain so far. This is a growth field; at the moment there are 20 groups worldwide studying these things in this way, but there will be 100 of us by the end of the year, and thousands by the end of the decade.

So, the €1.5 million of European Research Council (ERC) funding you were awarded is for research along these lines?

We want to understand a very important process: ageing. Right now, we see ageing as something relatively stochastic, and we wonder whether there is something intrinsic in the process that defines which cells will age worst. If this is the case, we could eliminate them before, we could cut off the problem at the root and not wait until we get old to tackle ageing. This is very interesting for many reasons: first, because it should be a more or less specific therapy, not one aimed at all of the cells in the body, but only at those which are predetermined to age. And also, because -as we all know- prevention is always easier than a cure.

We want to study whether ageing is really something we can foresee at cellular level and, therefore, treat.



What treatment options would be possible?

There are several possibilities. The first is to find routes, mechanisms that are present in these cells that age, which would allow us to minimise the impact of their impaired function so that, for instance, they don't spread. In the end, one of the great problems we face with ageing is that certain cell populations accumulate in our organism. We know that in haematopoiesis this type of maintaining populations that are not functional increases over time, and we want to see whether we can in fact identify the mechanisms that could avert this expansion.

And the other is with cell therapy, which means finding a way of modifying "aged" cells, maybe by extracting them from the organism and remodelling them, for instance, using gene or epigenetic therapy.

And, of course, the possibility also exists of not directly using haematopoietic cells but having cell therapy based on immunotherapy.

Immunotherapy has had great success in certain cancers; however, the main bottleneck when it comes to gaining approval for drugs is the risk that they may have for the patients who undergo treatment. The fact that so many cancer patients have been successfully treated with cell immunotherapy opens the door to applying these therapies as safe and tolerable for other types of disease.

Many studies already exist, and in the coming years we will see therapies with modified immune cells to treat diseases from Alzheimer's to heart or kidney diseases. There will be an explosion of immunotherapies precisely because they are well tolerated by our body.

But maybe what companies and governments see is the cost of treatment for each patient?

That is the risk of cell therapies: not being able to achieve them fast enough in a scalable way. The main hurdle we need to overcome with cell therapies is that they are the patient's own cells. And that brings problems: it is a slow process and more costly. If we could, like any other product, make them universal, they would be more accessible.

Public hospitals already exist, like Barcelona's Hospital Clínic, which have their own line of cell therapy. Can that make things easier?

But the cells are still from the patients themselves. At the Hospital Clinic de Barcelona they realised that things can be done more quickly if they are all done in-house. That means they have the whole pipeline centralised. And pharmaceutical companies know this, because before, they had a distributed assembly line, whereas now they are integrating them in a single production line. Universal cells are going to be the key, but that cell will be much stronger if it has more applications and will even be cheaper. We need to find the way to use cell therapies in a more ubiquitous way. And that day will come, especially due to their biosafety.

I'm certain that within the next decade or two there will be many developments in this field, and in the delivery of drugs to specific sites. We tend to think that it has to be lymphocytes, the immune cells, which perform this function, but we can also reach other cells to secrete drugs that are useful wherever they are necessary. A lot of attention is being paid to this field, but obviously there is still a lot of science to do.

Your work as a scientist is very aimed at clinical practice...

I have always like research more than the medical part. I have always been fascinated by the technological part, and when I was little, I was a fan of science fiction; I adored Isaac Asimov and Michael Crichton stories. I loved them! And I've always really liked that biotechnology aspect. I think that I'm a child of the genome generation; what I mean is that I'm from the generation that began to choose what course to do at the exact moment the genome was published and suddenly, biology changed forever. A discipline that was less objective than it is today changed radically with the advent of sequencing technologies. We went from an era, I think of it as the dark ages of biology, when nobody knew what there is and we were blindly stumbling around finding functions, mechanisms and genes based on mutations, and suddenly, the human genome was published. Everything is there to see, everything that makes us what we are. So, if everything is there, we must be able to decipher it.

And for many of us, who lived this revolution at a time when we had to decide what we wanted to do, this caused a great impact, and my decision was very clear to me: this is the next great challenge for humanity for the next 100 years.

Why biology?

Like many other people, obviously, I had a couple of key moments, which were interactions with scientists that opened my eyes. In my case, from quite early on I began to be passionate about cell biology, the mechanisms related with development; I mean, how cells change their form or function. We go from being a single cell that has practically no identity to the diversity of trillions of cells that compose our organism. This has always fascinated me. At first, I was really attracted by the world of *Drosophila* (fruit flies). And I began to be fascinated by certain questions: development patterns, segmentation genes, and so on. Later, the most important question for me was knowing how these processes are regulated through the genome. And I knew that I wanted to do post-doctoral

"In coming years, we will see therapies with modified immune cells to treat diseases from Alzheimer's to heart or kidney diseases. There will be an explosion of immunotherapies precisely because they are well tolerated by our body"

research to learn sequencing techniques, understand the functions and expression of genes, and work more closely in that field. I chose a laboratory to pursue my studies, collaborating with **Fernando Camargo** in the Children's Hospital of Boston, which at that time was starting to develop this new way of analysing cell histories, cell by cell, something that had not been technologically possible before. I really liked the idea of developing new technologies, of getting my teeth into topics of gene dynamics and expression.

From that time on, and for me when I set up my own laboratory, it was essential to understand the consequences of those processes. Now we have more information, the objective is to find new treatments.

You talk about the clinical application of your research. Do you think it is important to have worked in a hospital to understand the idea of translating basic science?

For certain, because it didn't happen for me at university when I was doing my thesis in a much more academic environment. Working in a hospital, being in contact with patients, receiving funding from foundations, many

of which are also formed of families or patients, changed my perspective on many things. For instance, I discovered that scientific enterprise is not only to do with scientists, rather it's a social undertaking of all the individuals in a society, who are the people that drive progress in a society. I was profoundly affected by the time I spent working at the Cystic Fibrosis Foundation on the development of the first therapies. There was practically no solution for patients with this disease, and there I saw how they, through the Foundation and with the creation of scientific projects funded by the Foundation, generated a billion dollar business, or financed a large part of it, and treated thousands of patients with cystic fibrosis all over the world. Having lived that, and seeing how supporting a scientific idea can create something so spectacular, profoundly changed my life.

Until that time, I saw things in isolation, as if they were not part of a whole; there was academic science, and then there was translational science, which were two distinct things. And that experience made me see that it wasn't like that; the patients were almost as involved as

“We have to create a much stronger theoretical basis because the science being practised is increasingly multidisciplinary. You can't hope to reach a solution focusing exclusively on your microworld... things don't work that way”

you, or even more so, in the molecular mechanisms, the biological bases, etc. and wanted to know exactly what was happening to their son, daughter, sister or mother. And that really opened my mind; there were not two different worlds, only a single continuum.

I think it is everybody's obligation, but we need to explain it well. For a person like me, who never had a biomedical vocation, having taken that decision helped me refine my message, to know how to explain things to patients and tell them how what we are doing may someday be a solution.

What's more, lots of these people don't seek solutions just for themselves or their families, they don't want it to happen to anyone else. At the end of the day, that is the hope behind everything we do.

And does that in some way define the people that make up your group?

There are people who have a very strong translational vocation complemented with a theoretical basis, but they are few. This, I think, reflects an educational problem that we have nowadays, which is too specialised and doesn't

provide the strong theoretical basis that serves as an anchor, providing the academic knowledge necessary to face multidisciplinary problems. In the end, you are a specialist in a specific subject. This is a serious problem that we need to tackle from an educational point of view. We have to create a much stronger theoretical basis, because increasingly the science we practise is very multidisciplinary. One day you are a physicist, the next a mathematician or a physician. And you have to work on everything, you have to be able to, at least, integrate that knowledge. You can't hope to reach a solution to a problem focusing exclusively on your microworld of knowledge, because things don't work that way.

In my group, we try to compensate the disadvantages of the educational and academic system by contracting people from different disciplines to create a diverse, dynamic group. In my opinion, science is better that way, more productive in all aspects. And I'm not just talking about diversity of academic training, I mean different origins, cultures, nations and sexes. All of this generates a more diverse group that is more productive, has ideas that are more original and provides more exciting interactions that produce unexpected results.

One of the aspects that some researchers who have visited CNIC mention is the very small number of foreign post-docs in Spain...

We have a big problem in this country, which is that no system exists to recruit talent. We don't have a legal system that protects and promotes the attraction of talent. There should be a system of protection, as there is in other European countries, with mechanisms that are much more flexible for recruiting talent.

We have an immense population crisis; in 20 or 30 years more than half of the population will practically be at retirement age. There is an absolutely terrible crisis and if we don't bring in international talent we will pay dearly.

Is the new Science Law any help?

No, it is a terribly national law, and I understand that. There is a brain drain crisis that has to be mitigated and contained, because the dramatic truth is that the most talented people in the country are pursuing their careers abroad. But, in my opinion, the problem of attracting foreign talent is possibly even more serious. There are a great many jobs for talented people from abroad who want to come here, but they don't come due to bureaucratic obstacles. It is senseless.

We need to bear in mind that before, science went more slowly. But now it is a race, a brutal race. Having, or not having, a patent worth multiple billions may entirely depend on whether that new machine on the market can be purchased next month or not until next year. This is what is completely changing the rules of the game. There is a lot of competition, and we need rules to be competitive. ■

Alejo Rodríguez-Fraticelli participated in the CNIC Seminar “Clonal determinants of blood stem cell heterogeneity,” at the invitation of Rui Benedito.

Mark Febbraio

“IT WILL NEVER
BE POSSIBLE TO GET
ALL OF THE **BENEFITS**
OF EXERCISE
IN ONE PILL”

Mark Febbraio is principal investigator of the National Health and Medical Research Council and Head of the Cellular and Molecular Metabolism Laboratory within the Drug Discovery Program at Monash Institute of Pharmaceutical Sciences, Monash University, Australia.

Mark Febbraio's team focuses on identifying genes, proteins and pathways that are important in metabolic diseases and in certain types of cancer related with obesity,

in order to develop therapies that activate or block the pathway of interest. Currently some candidate drugs are already being researched.



Mark Febbraio is also CSO of N-Gene Research Laboratories Inc., a bio-technology company based in the United States, and founder and CSO of the company Kinomedica. His research focuses on understanding the mechanisms associated with exercise, obesity, type 2 diabetes and cancer, and he aims to develop novel drugs to treat lifestyle-related diseases. He is author of over 260 papers and has won both national and international awards. Before devoting himself full-time to research, Mark Febbraio was a professional athlete and winner of several triathlons.

What led a professional athlete to devote himself to research?

I was a professional athlete and spent many years competing in triathlons all over the world. Based on my own experience, I have always been fascinated by performance and human resistance. I completed my doctorate at the University of Victoria (Australia) on how extreme environmental temperatures can affect muscular metabolism during exercise.

Is your research about reproducing the effects of exercise on the human body?

My investigations focus on the benefits that exercise has for health, particularly in the case of diseases like diabetes, cardiovascular diseases, and some types of cancer.

The idea is to develop drugs that in some way imitate exercise. We are working with a drug that is a peptide very similar to interleukin 6, because many years ago we discovered that during exercise, the muscle releases IL-6, which improves metabolic health.

We have developed a drug, but there are some aspects of interleukin 6 that are also prejudicial for our health since IL-6 can be pro-inflammatory under certain circumstances. In this case, we have modified the molecule so that it only has the benefits and to eliminate the negative qualities. The results were published in **Nature**.

We hope to undertake clinical trials with this drug. We have already passed on to the phase of non-human primates. The problem that may arise is that the molecule could be immunogenic; we don't know, but now we are working with a company that develops artificial intelligence models to ensure that there is no immunogenicity in the molecule. Then we will be able to move on to phase 1 trials.

You know that if it works, you'll be a millionaire?

Yes, I know. We have created a company set up by a venture capital fund from New York to try and market the drug and, if we are lucky, sell it to a large pharmaceutical company. That is the aim.

Aren't you worried that people will become lazy with a pill that imitates the beneficial effects of doing exercise?

No. It will never be possible to get all the benefits of exercise from just a pill. It won't happen; exercise is a great antidepressant, it is good for your bones, for your mental and physical health... You can't get all of that from a pill. But many people opt not to do exercise and get ill, so what we are trying to do is develop drugs that help people who are overweight, sedentary, etc.

In my opinion, society needs to be educated and one of the things I think we must do in the future is to be careful about how cities are planned, because if we look at a city like, for instance, Copenhagen -where it is very difficult to drive and there are lots of cycle lanes- people do exercise and there is very little obesity. But if we leave the city and go to other areas of Denmark where this type of infrastructure doesn't exist, we see obesity. So I believe this is one of the things that we have to do to develop.

But the other thing we need to tackle is how we can modify behaviour so that lifestyle-related diseases are reduced to a minimum; because right now these diseases are on the increase and obesity has not stabilised, it is still growing. We know that obesity is related with 60% of cancers so it is not only about cardiovascular diseases or dementia. It is about all diseases that are not transmissible.

How can we tackle this pandemic?

One of the things that we haven't been able to do is design a pharmacological intervention that suppresses appetite or hunger. This is a great challenge for science because the area of the brain, the hypothalamus, which regulates hunger, is also the same area of the brain that regulates mood. In the past, drugs that were aimed at the brain receptors that modify hunger and the need to eat had negative side effects, such as psychosis and depression. So, it is a great challenge for scientists to develop a drug that can regulate hunger.

What we are trying to do now is develop a drug that slightly increases energy expenditure. For instance, drugs directed at brown fat could become very important in the future because the metabolism of a person could slightly increase and, although they eat the same amount of food, lose weight.

The other challenges, apart from scientific ones, are in having good public health messages so that people try to eat more healthily and do exercise. Because we know that it is people with a lower socioeconomic or educational level who are most at risk of obesity.

But that's not the only problem, the problem we have is that there are people from minority groups who are under-represented in western societies, and they are affected by all of the problems. The majority of these people have changed their lifestyles, including their food intake.

In this context, what is the responsibility of the food industry?

The food industry is always going to try to exploit society because they are private organisations with shareholders who demand profits. But if you think about the role of governments, we see that a lot of work can be

done to reduce the consumption of sugar in the population. Countries like Australia have forbidden some additives such as high-fructose corn syrup. But others, like the USA, have not. Why? You only have to look and see how powerful the maize industry is in that country. Governments have the responsibility to protect their citizens.

We are finding out things about sugar; we knew that it was bad for diabetes or obesity, but now we have seen that it is related with cancer. So, the responsibility of the food industry and governments is to educate people about what to eat and how to ensure that fresh fruit and vegetables are accessible and not a luxury.

“My research focuses on the benefits of exercise for health, particularly on diseases like diabetes, cardiovascular diseases and some types of cancer. The idea is to develop drugs that imitate exercise in some ways”

“We knew that sugar was bad for diabetes or obesity, but now we have seen that it is related with cancer. The responsibility of the food industry and governments is to educate people about what to eat and ensure that fresh fruit and vegetables are accessible and not a luxury”

Does it make any sense that it is more expensive to buy fresh produce than the processed foods of large fast food chains?

In some countries, inflation means that many people cannot access fresh foods. Scenarios like the war in Ukraine are making products more expensive. In Australia, for instance, we have another problem: before the pandemic, many people came to work on farms, but now not so many visas are granted, which has meant that the prices of these foods have increased. And that means that you have to pay more for the same, which has caused higher inflation. ■

Mark Febbraio presented the seminar “Role of gp130 receptor activation in metabolic disease, cancer and atherosclerosis,” at the invitation of Dr. Guadalupe Sabio and Dr. M. Ángeles Moro.

Esteban Hoijman

"I SWAPPED ARCHITECTURE AND ANTHROPOLOGY FOR SCIENCE"

Esteban Hoijman is a developmental cell mechanics biologist thanks to a philosophy teacher who spoke to him about HIV, the virus that causes AIDS. Hoijman obtained his degree and doctorate in biological sciences at the University of Buenos Aires (Argentina) and specialised in advanced microscopy, research into the zebra fish and mechanobiology at the University of Buenos Aires' Centro de Microscopía Avanzada and in the Hubrecht Institute (Netherlands). He undertook his first post-doctorate at Barcelona's Pompeu Fabra University, where he developed a system to obtain images of cellular dynamics during the morphogenesis of tissues in live embryos. For his second post-doctorate, in 2017, he joined Verena Ruprecht's group at the Centre for Genomic Regulation, where he brought his previous experience in images of individual cells within live embryos and his knowledge of epithelial biology and cell death. While there, he discovered a phagocyte capable of eliminating defective stem cells of embryos at an early stage before development of the immune system, revealing an earlier protective function of a tissue during ontogenesis (Hoijman et al. *Nature* 2021; featured in *Nature Reviews Molecular Cell Biology*). In 2021 he joined the University of Barcelona as Serra Hunter Lecturer Professor and head of group and was recently awarded a grant from the Spanish Ministry of Science and Innovation.



You were going to be an architect or an anthropologist. What happened?

It was thanks to a philosophy teacher who one day decided to explain some things about biology that I found incredible. He explained how HIV works, how it affected the organism, its mechanisms to infect a cell and so on. I was hooked! I swapped architecture and anthropology for science. Those talks about the mechanisms of biology in general, and HIV in particular, awoke an interest in biology that I have never lost.

Now you have your own group at the University of Barcelona-IBIDELL...

We started off studying embryonic development and how embryos and tissues in general can defend themselves from problematic situations like stress, independently of the immune system's function; how they are able to protect themselves from different types of disturbance. Although we focus on the embryo, we are also interested in other tissues and adult organs.

What differences are there between being in a group and having your own group?

It is a difficult situation that depends on several factors, like the available funding. Being the head of a group implies taking on a lot of tasks that are almost entrepreneurial, for which we do not have much training, but if you

are in an institution with resources, it is easier to delegate to other people. If, on the other hand, those resources are not available, you have to do that type of task yourself, which is a difficult challenge. However, that challenge motivates you to continue, to develop more ideas.

What qualities do you look for in a researcher?

The only essential requirement is, of course, that they have a great interest in what they are going to do, and by that, I mean passion. And that they have it for any task they are going to carry out, whether it is research or something more technical. Passion for science is undebatable.

I give my all, but not only for the objectives we are going to achieve, which are important, but for the work in itself. What motivates me is the task of discovering, researching. So, anyone who is very capable and gets the top marks but is not interested in what they do, is never going to fit into my group. However, for a person who is really motivated, although they find some things more difficult, I personally will find a way to get the best out of them. Of course, we need the best people in my group, but the indispensable requirement is that they have to come with a passion for what they do. In most cases, research is not an activity where you earn a lot of money. It is not where people are going to get fame or anything like it; it is a very vocational task.

This vocational task is something I see in all of the researchers I admire: they have that great passion for research itself.

Regeneration, how it works and how to promote it. How long have you wanted to study this field?

I always had it clear that I was interested in embryonic development, how structures are formed. At first, I was attracted by the idea of building houses, but I changed that for building biological structures. The field of regeneration is also highly related with early development, which is no other than forming structures from the zero of embryonic development.

What similarities are there between embryo development and the processes of regeneration in adults?

They are not dissimilar, although there are some differences that are so important, they mean that, as adults, we are not capable of regenerating and producing tissues or parts of organs as well as we did during the embryonic development phase. However, they share many structures, and that is basically why advances in regeneration mechanisms are based on the knowledge of embryonic development mechanisms. We know that signalling molecules, the genes that determine processes, are the same, but there are small differences that change everything. Animal regeneration models are very important. There are animals that can regenerate their hearts, like a fish, and even others that can regenerate a head, like worms. This animal, as an adult, retains the capacity of embryonic development.

From a functional perspective, although they have some differences, the heart of a fish and the heart of a human share many similarities. The question is to find out why humans cannot regenerate like a fish. If we find out what these small differences are, we can try to bridge the gap and determine how to regenerate ourselves.

Is it true that the more complex an organism, the less the regenerative capacity?

A bit. There is a lot of evidence to suggest that complexity is what hinders the capacity to regenerate, although I think that it is not the only explanation. We are missing some links that we still don't understand. Of course, as we find out more and see that there are genes that are silenced, genes that stop being expressed in an adult, the fact of expressing them again would require reactivating programmes that we don't want to activate because, for instance, they could be dangerous and produce differentiation or pathological proliferation in tissues.

What other lines of research are you pursuing in your laboratory?

My laboratory basically focuses on trying to study how one type of tissue, the epithelial, is able to carry out immune functions. The immune system has different functions; not only to defend us against infectious agents, but also, for instance, to combat carcinogenic cells, eliminate them, etc. It also destroys the cells that die in a tissue, whether due to normal replacement that occurs in all tissues or due to occasional damage. And we have known

for some time that epithelial tissues are capable of participating in this function of elimination.

What we discovered is that at a very primigenious phase the embryo has an epithelium that carries out a protective role, because it is able to eliminate the cells that die in its interior. This happens at a stage in which the embryo does not have any immune cells and apparently no cellular differentiation. In the embryonic context, what we are asking is whether this epithelium is capable of protecting the embryo when there is no immune system. It would be something like an immune system. In fact, it is the first tissue formed in all vertebrates, including humans. And among other functions it has the capacity to protect the embryo in some way. That means, the first thing formed is a tissue that protects the embryo itself.

We are now attempting to analyse whether this function of epithelial cells is also present in adult organs. We were interested to study how the embryo can respond to stress and whether it can defend itself, and what we were able to observe, because we filmed the dynamics, is how this process changes over time.

“From a functional perspective, although they have some differences, the heart of a fish and the heart of a human share many similarities. The question is to find out why humans cannot regenerate like a fish. If we find out what the small differences are, we can try to bridge the gap and determine how to regenerate ourselves”

Do you think there is a generational gap between today's researchers and your generation?

I notice a change that is related to several factors. On the one hand, it seems that opportunities in the world of science have become limited in recent years because the number of people who are devoted to research has increased a lot; what I mean is that there has been an increase in the number of researchers, but not in the number of group leaders. There are also a lot of regulations related to very high requirements, not only to be successful, if by being successful we understand being able to do relevant research, but simply to survive in the field of science.

There is a science policy, not only in Spain, but in general, which decides that there has to be a very limited number of research groups, which reduces the space for all people who want to research. Not only that, but there also has to be a limited number of research groups.

But, in contrast, many researchers see that their future is too difficult because they have to work, without rest, seven days a week, including weekends, for a very low salary, and that doesn't even guarantee that you'll necessarily be able to remain in the world of science, because it depends on chance as well as, of course, on capacity and effort. But there are times that capacity and effort are not enough.

Likewise, there is the historical perception that a researcher has to suffer, that it is a part of their lives. Before, it was something that was acceptable, but I think it is right that younger generations question their working conditions, which should be better, and demand a code of ethics, something that is respected in other areas but in the field of science, sometimes, not so much.

Regardless of the reasons I have just mentioned, there may be other reasons, such as it being a generation that wants things more quickly or more easily. There are some aspects that can be overcome and others that cannot, like cultural ones.

Do you think there is enough information about career options during the university years?

As a university professor, I come into contact with students, and in some cases I see many professors who have an outdated view of education. There are some structures that could be renovated or modified in terms of university teaching, which would make students more motivated and not so downhearted.

As a researcher, have you always been able to work on your own ideas?

In my case, yes, but it was not always like that since it depends on the context. I have found research groups that have allowed me to do what I wanted. I haven't encountered difficulty in developing my own ideas.

But we can't forget that in science there is a logic that establishes very hierarchical structures, with a head of group who makes all of the decisions, followed by the people who work in the group. In my opinion, this hierarchy should be eliminated. There are very talented people who do not necessarily have to be the ones who lead a group; however, the head of group should be the person who is the best manager. Sometimes in research, tasks of group management are superimposed on tasks of generating ideas, which seems to me to be a conceptual mistake. The person who is going to have the best ideas is not necessarily the best team leader. Now, here we're talking about a deeper transformation of the structure of how science works in the world.

There is an idea that if you are not the head of your own group by a certain age, your scientific career is stagnant.

That's true. In any company, the director is not the person who knows the technical details of how things work. There could be a manager who manages very well, but within the group there must be other people who have the scientific ideas and carry them out without managing aspects of organisation, administration, finance, etc. In any case, the head of group has to do many of these tasks without necessarily knowing how to do them or perform them in the most efficient way.

Nowadays, there is a constant fight for resources because the person who has to get the funding is the person who has to have the ideas. It is possible to have a strategy that gets funding based on the ideas of another person and a division of tasks would make this process more efficient. ■

Esteban Hoijman presented the seminar "Epithelial surveillance of stem cells: imaging embryonic dynamics across scales," at the invitation of Dr. Miguel Torres.



BYRD ALZHEIMER'S CENTER
UNIVERSITY OF SOUTH FLORIDA
United States

Bradlee Heckmann

“THE PANDEMIC HAS OPENED
THE MEDICAL COMMUNITY’S EYES
TO AN IGNORED DISEASE:
**CHRONIC FATIGUE
SYNDROME”**

Bradlee L. Heckmann is an American biologist and neuroimmunologist who works at the Byrd Alzheimer’s Center and the University of South Florida’s Health Neuroscience Institute (USF), he is also Assistant Professor of molecular medicine at Morsani College of Medicine (USF). Dr. Bradlee Heckmann’s current research focuses on modulating neuroinflammation as therapeutic targeting to treat neurodegenerative diseases, including Alzheimer’s and the role of the machinery of autophagy in this context. In addition to his academic positions, Heckmann is co-founder and CSO of Asha Therapeutics, a biotech pharmaceutical company, based in Tampa (Florida) that explores novel therapies for neurodegeneration and neuro-oncology for a variety of diseases including Parkinson’s, Alzheimer’s and myalgic encephalomyelitis/chronic fatigue syndrome/long COVID.



What is the current state of neuroimmunology?

What my laboratory is interested in, and we are fascinated by, is the functioning of the neuroimmune system. In reality, in terms of human diseases, we know that inflammation may be beneficial: it protects our body against the invasion of pathogens, infections. It is even possible that the central nervous system (CNS) defends us from things like amyloid protein plaques in Alzheimer's disease, against ischaemia and a stroke.

But my laboratory is really interested in broadening knowledge about how this process is mechanistically controlled. The last ten years have seen the interest in neuroimmunology begin to bear fruits in science and medicine, and it has brought us round us to thinking that immunity in the brain and functioning of the immune system are regulated by a cell called microglia.

But now, with the work of a series of researchers, we are learning that the brain's immune system is not what we used to think, and it is not so separate from the rest of the body as we believed. We have seen that there is a great deal of interaction between the peripheral immune system and our central nervous system, which implies a real change in our understanding of how we see regulation of immune responses in the brain.

Our laboratory, and of course many others worldwide, are really interested in understanding the details of how immunity is regulated in different scenarios, different stages of disease and in normal physiology, in the hope of being able to design future therapeutic approaches for diseases ranging from neurodegeneration to others like a stroke.

And also, Alzheimer's?

Our laboratory has the resources necessary to study a variety of pathologies or disease models and to be at the pinnacle where basic science and research meet, thanks to being part of the USF Neuroscience Institute.

Alzheimer's disease has been our daily bread. Collaborating with other groups, we have identified and characterised an LC3-associated endocytosis pathway.

As well as Alzheimer's, more recently we have been working in other areas, like the functional context of strokes, and on the resolution of bacterial and viral infections.

And, forced to some extent by the pandemic, we have begun to research the mechanisms connected with COVID, particularly long COVID or persistent COVID, and how they affect the brain.

Over 70% of patients infected by SARS-CoV-2 who lived through the disease experience prolonged symptoms or have had a sporadic reappearance of symptoms over the last months or years. In many cases, this has become what is known as long COVID, whose symptoms range from continuous muscle pain, brain fog, difficulties in logical function and, of course, fatigue. We want to know why this is happening, and what mechanisms are involved if, in the majority of cases, no infection exists.

Talking of Alzheimer's, do you think it will be possible to have preventive vaccines to avoid the progression of the disease, particularly for the people most at risk?

I think there are two answers to that question. The first is with regard to genetic risk. We know that APO E4 is the most predominant risk factor for what we typically refer to as sporadic Alzheimer, which arises in later stages of life. Over 80% of patients with Alzheimer's disease suffer sporadic Alzheimer's.

"We are learning that the brain's immune system is not what we once thought it was, it is not so separated from the rest of the body as we thought. We have seen that there is a great deal of interaction between the peripheral immune system and our central nervous system, which implies a real change in our understanding of how we see the regulation of immune responses in the brain"

In this sense, the advent of gene-editing technologies like CRISPR CAS 9 and other similar technologies, as they develop and begin to tackle the ethical questions related to gene modulation, make it quite likely that in the next 10 to 20 years there could be a viable approach to repairing genetic deficiencies or single nucleotide polymorphisms, mutations that increase the risk factors, not only in APO E4 but also in genes that are related to this disease.

Holistically, I consider that in the next 10 to 20 years we will find an approach to tackle the disease before it appears.

Another aspect of this question is the fact that there are so many variables, especially in the neuropathology of Alzheimer's disease and its pathogenesis, it is difficult to know if we need to selectively target these mutations; for instance, will it really diminish the risk? Because 50% of the people with amyloid plaques never develop the disease. But many other factors are involved in Alzheimer's, as well as amyloid beta deposition or other aspects like

phosphorylation or neurofibrillary tangles. The truth is that there has been a long debate within the Alzheimer community about the amyloid hypothesis as the cause of the disease. For instance, the tau protein hypothesis states that amyloids are irrelevant and that they only trigger the process, whereas tau is what really generates the disease.

In my opinion, the solution would be to combine the two hypotheses and probably add new ones, because there are many aspects involved.

One of the reasons why so much attention has finally been paid to this subject in recent years is the approval of drugs produced by large pharmaceutical companies like Biogen; however, their effectiveness and success have been very limited. In principle, it was a great idea, but what we can see now is that even if you administer these drugs to a patient, they have limited effectiveness.

Because we are a neuroimmunology laboratory, we focus on inflammation. We have shown, in very early pre-clinical models, that if we target specific inflammatory mediators and if we block the complex that produces certain cytokines that are responsible for inflammation, such as interleukin 1 beta, we can significantly limit the pathogenesis of the disease in mouse models.

This suggests, and is what we believe, that there is a bridge between amyloid pathology, tau pathology and neurodegeneration, and that inflammation is a central element in this mechanical process.

So, we believe that, if we are capable of treating something like neuroinflammation, this could translate into to a very effective approach to treating diseases, not just Alzheimer's, but others where the same cytokines are active, like Parkinson's and ALS, or even strokes and other diseases.

Our idea is that there could almost be a unified treatment plan that would, in essence, strike against each of these diseases using neuroinflammation, which would give effectiveness.

Do you think we might see a future revolution in neuroimmunology like the one we have seen in cancer with immunotherapy?

That is exactly the idea. I think that the advent of blocking checkpoints for the treatment of cancer has meant a particularly beneficial development for people who would have died of the disease and are now surviving; that is absolutely incredible.

The idea would be for us to see the same revolution in the field of neurology over the next 20 years, not only for Alzheimer's disease but, we hope, for many other things.

You mentioned that you are interested in how SARS-CoV-2 affects the brain...

SARS-CoV-2 is without a doubt, one of the great areas of research we have come across, particularly for us as neuroimmunologists. At the start of the pandemic, we researched what was happening in post-mortem samples of brain tissue from patients who had died of COVID. And one of the most singular things we started to see at the onset of the pandemic was that not all people had a

measurable amount of the virus in their brain, whereas in other cases they did.

We had many questions: Is this only because we are analysing these levels in people who have, unfortunately, died of the disease? What amount of virus really reaches the brain? What mechanisms govern this process?

One of the aspects that really interests us about SARS-CoV-2 and why it is so special, is that there is a condition called myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) that has basically been ignored by the medical and scientific community for years due to the fact that from a clinical perspective it was practically impossible to diagnose.

All of the patients who complain of chronic fatigue, headache, brain fog, etc, these are symptoms that are very similar to long COVID.

They said: "I was sick, I got better, a few months later I started to feel awful again and again," and the process perpetuated.

Many of them have lived through medical torment: blood tests, CT scans of the brain, MRIs etc., and the results show nothing bad in their brains, but the patients continue to be sick, and the doctors end up diagnosing a mental health problem. For most physicians, these patients are, to all intents and purposes, crazy.

The curious thing is that while the pandemic has been devastating for many people, for them it has meant that the medical community has opened its eyes to a disease that they have been struggling with for the last eight years: chronic fatigue syndrome.

The similarities between ME/CFS and long COVID are so surprising that we are learning a lot, and we, like many other groups, are discovering that there are similarities between certain virus that are believed to cause these diseases, like the human herpes virus 6, in particular, and SARS-CoV-2.

We think that it is plausible that, studying chronic fatigue syndrome and the virus that are associated with the typical pathogenesis of CFS, we might find out a lot about coronavirus and vice versa.

How many people are there in the world with this syndrome?

Calculations for the UK alone are approximately 3 million people with this syndrome and another 3 or 4 million in the USA. These are very conservative figures, so it affects many more people, although they don't even realise it.

It seems that the pandemic has been good for some people, has it for science?

During the first days of the pandemic, we didn't really know what we were up against. I think it is the first time in our history that we have had an outbreak of a disease at that level.

There have been other outbreaks, like MERS or the original SARS outbreak, but they were limited to geographical regions, and there have even been outbreaks of Ebola in Africa, limited to geographical regions, whereas the USA and most of Europe were not affected by them.

But with COVID we are speaking of millions of people all over the world who were affected.

I think this has stimulated interest in science and demonstrated that if we face a scenario in which we have to do something immediately, academic science, business -obviously- or the pharmaceutical and biotech industries are capable of responding.

You only have to remember, for instance, that the flu vaccine took decades before it had advanced enough for use in clinical practice.

With COVID, everything went a lot faster, although it could be argued that in some cases, it went too fast.

Because, faced with a new virus that nobody knew anything about, many laboratories got to work on it, trying to find a vaccine or a therapy or simply trying to understand the basic biology of the virus. Obviously, there are going to be data that are not exact. And it should also be known that fake data has been a great problem recently in the scientific community.

"If we are capable of treating something like neuroinflammation, this could translate into to a very effective approach to treating diseases, not just Alzheimer's, but others where the same cytokines are active, like Parkinson's and ALS, or even strokes and other diseases"

At the same time, the pandemic has been detrimental for other areas of research, and much of this is due to the urgency of finding a solution to the world pandemic.

Maybe one of the most important aspects has been the fact of sharing scientific information in almost real time...

Yes, and I think that this is one of the most important things to have come out of the pandemic. The process of peer review that we normally undergo, which is very strict in most cases, implies a delay in the publication of articles, but with the hurry to publish data about the pandemic we had almost instant access to what were mostly very good articles, but also to others that were more than questionable in terms of scientific validity. But, in the end, the fact of publishing information quickly is something that is good for the scientific community. ■

Bradlee Heckmann presented the seminar "The good, the bad, the ugly: the diverse roles of Rubicon in the CNS," at the invitation of M. Ángeles Moro.

EUROPEAN HEART JOURNAL SELECTS PESA CNIC-SANTANDER AS ONE OF THE 10 BEST STUDIES OF 2022

RESEARCH SUGGESTS THAT BONE MARROW ACTIVATES IN RESPONSE TO CARDIOVASCULAR RISK FACTORS. THE ACTIVATION PRODUCES AN INCREASE IN INFLAMMATORY CELLS IN BLOOD, WHICH TRIGGER A PROCESS THAT WOULD INITIATE AND LATER CAUSE THE PROGRESSION OF ATHEROSCLEROSIS

According to the *European Heart Journal*, one of the 10 most important studies published in 2022 shows that the activation of bone marrow could play an essential role in the origin and development of atherosclerosis, the process underlying many cardiovascular diseases like infarction or ictus.

Lead by **Dr. Valentín Fuster** and **Dr. Borja Ibáñez**, the research suggests that bone marrow activates in response to cardiovascular risk factors. The activation produces an increase in inflammatory cells in the blood, which triggers a process that initiates and later causes the progression of atherosclerosis.

Atherosclerosis is the most frequent cause of death worldwide, and the disease has a long course before making itself known. Identifying the disease in its initial phases (before it causes symptoms) is one of the main objectives of PESA CNIC-Santander (Progression of Early Subclinical Atherosclerosis), which began in 2010 as a collaboration between CNIC and the Santander Bank, directed by **Dr. Valentín Fuster**, General Director of the CNIC, and cardiologist and Medical Director at New York's Mount Sinai Hospital.

This study lays the foundations for fighting this disease, attacking the roots of its development. As **Dr. Borja Ibáñez**, CNIC's Director of Clinical Research, cardiologist at the Hospital Universitario Fundación Jiménez Díaz and Head of the CIBERCV group, explains, "Early identification of atherosclerosis allows us to advance in knowledge of the mechanisms that produce it, which opens the door to finding new treatments that can prevent the progression of this lethal disease."

Work has been conducted within the PESA CNIC-Santander study, a joint project between CNIC and the Santander Bank, which began over 10 years ago. The study includes

DR. VALENTÍN FUSTER:

"PESA is the CNIC's flagship project because many of the centre's cutting-edge research groups are connected to it, each of them with expertise in a specific area of cardiovascular disease. Combining the participation of basic and clinical researchers around a large cohort like PESA is unique in the world"

4,200 apparently healthy, middle-aged (40-55 years when they were recruited to the study) Santander Bank workers, who undergo a periodic follow-up that includes the latest imaging technology as well as advanced blood tests and analysis.

The study has recently been extended to continue until at least 2029, which will give a patient follow-up of almost 20 years, which is practically unique in the world.

PESA CNIC-Santander is considered one of the most important studies in the world in the field of cardiovascular disease prevention. As **Dr. Valentín Fuster** explains, "PESA is the CNIC's flagship project because many of the centre's cutting-edge research groups are connected to it, each of them with expertise in a specific area of cardiovascular disease. Combining the participation of basic and clinical researchers around a large cohort like PESA is unique in the world." ■

Hesham Sadek

“THE TRASLATIONAL SIDE
OF MEDICINE CANNOT
EXIST IN A VACUUM,
THERE MUST BE
A SOLID FOUNDATION
IN BASIC SCIENCE”

Hesham A Sadek is Professor in the in the Department of Internal Medicine at UT Southwestern Medical Center and Associate Director of the Center for Regenerative Science and Medicine. Sadek earned his medical degree at Ain Shams University School of Medicine in Cairo, Egypt, and his doctoral degree in physiology and biophysics at Case Western Reserve University. Dr. Sadek’s research focuses on cardiac regeneration. Specifically, he and his team are interested in identifying methods to activate endogenous mechanisms of cardiac regeneration in humans. Among many other awards, in 2015 he received the American Heart Association’s Established Investigator Award. Sadek has participated in the Visiting Researchers’ programme of the Catalana Occidente Group’s Fundació Jesús Serra.



“Clinical trials will be conducted at different stages of cardiac regeneration. Maybe the first 20 or 30 will not be successful, but in the end, it will happen. The technology is there, and science is constantly advancing”

Do you think you will see regeneration of the heart within your lifetime?

I have been working on it since I began in my independent laboratory 16 years ago. First, we have to bear in mind what the problem is with regeneration: if the skin has a lesion and the wound is not too deep, it will cure completely without leaving a scar. But mammals do not have that capacity in most of their tissues, except, for instance, the liver. In general, when they are cut most tissues and muscles don't grow back, whereas in other organisms like the zebra fish or other vertebrates, a limb can be cut off and grow back.

One of the first discoveries we made 12 years or so ago was that newborn mammals can regenerate their hearts completely without leaving scars, but only during the first days of life. We now know that under certain circumstances, regeneration is possible because there is a programme for it but, and we don't know why, it stops. That is to say, we know there is a door that exists, but now it is closed. That's why I say that it is easier now, because instead of asking: how I can regenerate something that has never regenerated? Now the question is: why does it activate but later stop?

At the moment, we are attempting to find the answer to that question. We have found certain aspects that are key in the loss of this capacity. When we modulate it, we can prolong this window of regeneration, we can reactivate it in an adult; we have discovered two drugs that are directed at the nodal points that detain the process.

Which is why I personally believe that I will see heart regeneration at some point in my life, since once we have identified the mechanism, we can try to attack it with

gene therapy, with repurposed drugs, new drugs... There are many ways of doing it. I think that clinical trials will be conducted at different stages of cardiac regeneration. Maybe the first 20 or 30 will not be successful, but in the end, it will happen. The technology is there, and science is constantly advancing.

Is this the only way to renew the heart?

Most of the papers presented during the CNIC Conference focused on the cell cycle of cardiomyocytes.

Cardiomyocytes are the muscle cells that contract the heart and do not divide when we are adults. Our work, and that of many other laboratories, it to make these cells divide. We are basically working on two routes to regenerate cardiac muscle: one of these is the division of cardiac muscle cells and the other is the extrinsic administration of cardiomyocytes.

We know that there are cells that can make heart cells beat: induced pluripotent stem cells (iPS). **Shinya Yamanaka**, the Japanese scientist who won the 2012 Nobel Prize for Medicine, discovered the potential of these cells. For instance, embryonic cells can be obtained from reprogrammed skin cells.

Once it is discovered that it is possible to convert these embryonic cells into any type of cell, we have the possibility of making cardiomyocytes in the laboratory for their transfusion to the patient.

Following the same lines, the cells can be expanded, we can obtain cardiac cells that beat, and they can be returned to a patient who does not have any cardiac cells because they have died in a heart attack or a viral infection. In my opinion, these are the two main ways for

cardiac regeneration: either real cardiac cells, cardiomyocytes, are obtained, probably from iPS cells or reprogrammed cells, or the endogenous cells of the heart are divided to repair the defect.

How is it that some animals maintain this capacity to regenerate throughout their lives?

When we published the first paper on the heart of a newborn mouse, we modelled it based on the zebra fish. The original zebra fish model was published in 2022, and it demonstrated that if a piece of the animal's heart is cut off, the organ spontaneously regenerates. This is the basis of the regeneration model.

Do we know why this capacity does not deactivate in the same way as it does in mammals?

There are many theories. One of them is oxidation, and that is one of the things that we are working on with CNIC. The level of oxygen saturation of an unborn mammal in the uterus is half of what we are breathing now: the blood of the foetus has approximately 50% saturation compared to the 100% we are breathing now. But as soon as it is born, with the first breath, pulmonary breathing activates. This entails an oxygen shock to the system. We think that this oxygen shock is one of the reasons why mammals lose their capacity to regenerate tissues. For instance, if we look at the zebra fish, it only has one ventricle, which means it is always mixing its oxygen and the saturation is very low.

Another thing is the amount of mechanical load that has to be borne. We, and other groups, have shown that the higher the mechanical load, the more work you need to do. It's a perfect storm, you have oxygen and then you have loads, so you need to use the oxygen to produce energy because you need to pump with strength. The zebra fish does not have much demand, it does not have much oxygen, which could be a reason why it can retain this capacity to regenerate.

Where does your scientific vocation come from?

I studied medicine in Egypt and spent some summer internships in Europe when I was a medical student. In the end, I went to the United States to research, and I was fascinated by the possibility of being able to discover something that affected the lives of patients. As a physician, it is very important to treat patients and attempt to solve their complaints. But I discovered that there was a previous stage, there were people researching so that the physicians had information about how to treat a disease or how to design a drug. I decided to form part of that stage, where something is discovered that can help patients and to develop therapies.

Do you think it is a key point for researchers to understand that what they are studying will benefit the population in general?

I think that a medical training is essential to have that mentality. Now, many of the drugs and the concepts that the therapy is based on were discovered in scientific studies that have nothing to do with humans. For instance, many of the genes we know about were discovered in

the fruit fly, and those studies are pure basic science. The translational side of medicine is where someone like me comes in and attempts to discover a way of manipulating a gene to treat a disease,

It cannot exist in a vacuum, there has to be a solid basis in very pure basic science that really has nothing to do with clinical medicine and translation.

The translational scientist is not going to find the gene that they have to manipulate to solve a disease unless another person has discovered it. So, the discovery of genes, the understanding of the communication mechanisms between cells and of cell division is pure biology. I mean that, without the first half of the story, someone like me would have nothing to study.

Basic science and applied science are essential. Institutes like the CNIC, for instance, with basic biology, cell biology, small animals, large animals and clinical medicine, are the most suitable centres because that is where the researchers that discover the bases coexist with others like me, who translate the bases to a drug, and the clinicians who apply the knowledge to a patient. It is difficult to find this continuum in a single place, obviously, but that would be the final objective.

The hope is to have this connection, like the one that exists in CNIC and other centres, but unfortunately, around the world everything is fragmented. I mean that each scientist studies what interests them. Fortunately, thanks to the exchange of ideas at conferences and congresses, and so on, we understand what other researchers are doing and we understand what can help us in our research. I can't tell you how many times I have been to conferences whose title I didn't understand but which, in the long term, have been of great use to me. I think that it is where science becomes very interesting, because you don't know how the connection will be established or how it will be relevant for you.

What do you think about the Fundación Jesús Serra fellowship?

It allowed me to establish new relations in the field of research that I wouldn't otherwise have been able to. I collaborate with two CNIC programmes: the regeneration programme and the heart failure programme. With the former, at CNIC we are developing a design line of drugs to identify new medicines that induce cardiac regeneration. And we already have a couple of candidates for testing in clinical trials.

As for the heart failure programme, we are studying the genetic mutations present in some children and families that weaken the heart or, for instance, what happens to athletes who die on the football pitch or basketball court. Usually, they have a genetic mutation in their heart that causes arrhythmias. The mutations are rare and, in general, there is no treatment for them.

We are trying to determine the magnitude of these mutations in Spain and Europe. We hope to develop a larger database. The idea is to develop a specific treatment for each mutation by repurposing already available drugs that are inexpensive. Sometimes the side effect of a drug is due to it attacking a target that it should not. The advantage of this is that the drugs are already available. ■

EXCELLENCE IN COMMUNICATION SCIENCE

LEADING JOURNALS PUBLISH CNIC SCIENCE

ELIFE

CNIC scientists uncover opposing roles of p38 proteins in cardiac hypertrophy

A study carried out by scientists at the CNIC and led by **Dr. Guadalupe Sabio** has identified a key role for the MKK3/6–p38 γ/δ signaling pathway in the development of cardiac hypertrophy. The results, published in the journal *eLife*, suggest that inhibition of p38 γ/δ could be a useful therapeutic strategy for diseases such as hypertrophic cardiomyopathy; however, this avenue remains unexplored because of the lack of specific inhibitors for these kinase enzymes. The study also shows the opposite effect upon inhibition of another member of this protein family, p38 α , indicating that long-term clinical use of p38 α inhibitors to treat chronic disease risks damage to the heart.

The heart has to satisfy this demand for blood not only under normal conditions, but also under conditions of stress. To achieve this, the heart has the capacity to increase in size, a process called hypertrophy. Cardiac hypertrophy is how the heart grows after birth and is also a normal response to physical exercise, explained first author **Rafael Romero**. But cardiac hypertrophy can also be triggered by high blood pressure and some genetic diseases.

The contractile cells of the heart, called cardiomyocytes, contain numerous molecular pathways whose activation promotes cardiac hypertrophy. "One of these is the p38 pathway, which is activated in response to stress stimuli," explained **Romero**. The p38 proteins control a broad spectrum of processes, and their dysregulation has been linked to numerous diseases, making them promising pharmacological targets for clinical use. Nevertheless, specific inhibitors have been identified for only one of the p38 isoforms, p38 α . As **Dr. Sabio** recognized, "the results of clinical trials to date have been disappointing, but other proteins of the pathway, such as p38 γ , p38 δ , or the upstream activator MKK6, are interesting possible alternative pharmacological targets."



With this in mind, the team investigated the safety and potential long-term negative effects of inhibiting MKK6. Using mice genetically engineered to lack MKK6, the scientists showed that the absence of this protein reduced life expectancy. These mice developed cardiac hypertrophy when young and developed cardiac dysfunction as they got older. Using other mouse models, the researchers found that when MKK6 is absent the activation of p38 α is significantly reduced. Nevertheless, inactivation of p38 α promoted an unexpected activation of the other branch of the pathway, consisting of the proteins MKK3, p38 γ , and p38 δ . This activation induced another of the key pathways in the development of cardiac hypertrophy, the mTOR pathway.

The study received support from the following bodies: MINECO-FEDER, American Heart Association; EFSD/Lilly European Diabetes Research; Fundación AECC y Comunidad de Madrid IMMUNOTHERCAN-CM; Instituto Nacional

de Corazón, Pulmón y Sangre; Fundación "la Caixa"; Fundación La Marató de TV3: Programa FP7 Marie Curie; EFSD Rising Star y JDC-2018-Incorporación (MIN/JDC1802).

Romero-Becerra R.; Mora A.; Manieri E.; Nikolic I.; Santamans, A.M.; Montalvo-Romeral, V.; Cruz, F.M.; Rodríguez E.; León, M.; Leiva-Vega, L.; Sanz, L.; Bondía V.; Filgueiras-Rama, D.; Jiménez-Borreguero, L.J.; Jalife J.; González-Terán, B.; Sabio, G. *MKK6 deficiency promotes cardiac dysfunction through MKK3-p38 γ / δ -mTOR hyperactivation.* **eLife**. 2022 Aug 16;11:e75250. doi: 10.7554/eLife.75250



THE NEW ENGLAND JOURNAL OF MEDICINE The polypill reduces cardiovascular mortality by 33% in patients treated after myocardial infarction

The polypill developed by the CNIC and Ferrer, which includes three drugs (aspirin, an angiotensin-converting enzyme (ACE) inhibitor, and a statin), is effective at preventing secondary adverse cardiovascular events in people who have previously had a heart attack. The polypill reduces mortality from cardiovascular causes in this population by 33%. This is the finding of the SECURE study, coordinated by CNIC. The study results were published in **The New England Journal of Medicine (NEJM)**.

SECURE included 2499 patients from 7 European countries (Spain, Italy, Germany, the Czech Republic, France, Poland, and Hungary) recovering after a myocardial infarction. The study participants were randomly assigned to receive standard therapy or the CNIC polypill.

The SECURE trial analyzed the incidence of four major cardiovascular events: death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, and emergency coronary revascularization (the restoration of blood flow through a blocked coronary artery). The study followed patients for an average of 3 years and produced conclusive results: patients taking the polypill had a 24% lower risk of these four events than patients taking the three drugs separately.

The standout finding of the study is the effect of the polypill on the key outcome of cardiovascular related

death, which showed a relative reduction of 33%, from 71 patients in the group receiving standard treatment to just 48 in the polypill group.

The study also found that patients in the polypill group had a higher level of treatment adherence than those in the control group, thus confirming the findings of the earlier FOCUS2 study, also funded by the European Union.

The SECURE trial was funded by the European Union Horizon 2020 research and innovation program (trial identifier NCT02596126).

Castellano, J.M.; Pocock, S.J.; Fuster, V. ... et al. for the SECURE Investigators. *Polypill Strategy in Secondary Cardiovascular Prevention.* **NEJM**, 2022. doi:10.1056/NEJMoa2208275

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY Scientists at the CNIC and Hospital Puerta de Hierro develop a tool to determine if dilated cardiomyopathy has a genetic origin

Scientists at the CNIC and Hospital Universitario Puerta de Hierro Majadahonda have developed a software application that predicts the likelihood that a case of dilated cardiomyopathy is caused by a genetic mutation. The research was carried out in collaboration with hospitals in Spain, Italy, and the Netherlands. The findings, published in the **Journal of the American College of Cardiology (JACC)**, will allow physicians to adjust the treatment of dilated cardiomyopathy patients appropriately and to identify family members who have also inherited the disease. The software application is available online at www.madriddcmscore.com.

Dilated cardiomyopathy is the most frequent cause of heart failure in young people and the main indication for heart transplantation in the world. Nevertheless, in many places in the world dilated cardiomyopathy patients do not undergo routine genetic screening due to the considerable cost of this procedure, which gives a positive result in only 1 in every 3 patients

The new study was led by cardiologist **Dr. Pablo García-Pavía** of Hospital Puerta de Hierro, and who is also a research scientist at the CNIC and in the Spanish Cardiovascular Research Network (CIBERCV). The study analyzed the clinical characteristics, electrocardiograms, and echocardiography data of a group of 1015 dilated cardiomyopathy patients who underwent genetic screening at 20 Spanish hospitals. The results identified 5 parameters that were more frequent in patients in whom the disease was caused by a genetic mutation.

The combined scoring of these 5 parameters in a software application, called the Madrid Genotype Score, allows the classification of patients according to the likelihood that



their disease has an origin in a heritable genetic mutation. The researcher team verified the predictive ability of the tool in an independent group of 1097 dilated cardiomyopathy patients from Italy and the Netherlands.

The software application has been made freely available to medical professionals via the website www.madrid-dcmscore.com.

Escobar-López, L.; Ochoa, J.P.; Royuela, A. ... García-Pavía, P. et al. *Clinical Risk Score to Predict Pathogenic Genotypes in Patients with Dilated Cardiomyopathy. J Am Coll Cardiol.* 2022, 80:1115-1126. <https://doi.org/10.1016/j.jacc.2022.06.040>

CELLULAR AND MOLECULAR SCIENCES

Describing a new mechanism that links inflammation and pathological cardiovascular remodelling

Immune-inflammatory response contributes to the pathological remodelling of the arteries in different cardiovascular diseases. Research published by **CMLS** has shed new light on one of the mechanisms that links immune-inflammatory response to vascular disease, by describing the key role played by the early activation marker of lymphocytes CD69. The study, a collaboration of two CIBERCV groups at the Universidad Autónoma de Madrid (UAM) and IIBB-CSIC/IIB-Sant Pau, opens the way for new therapeutic strategies.

Antigen CD69, the early activation marker of lymphocytes, is a receptor that is induced after the leukocyte stimulation. Previous research by these teams identified the role of CD69 as an oxidised low density lipoprotein



(oxLDL) receptor, a union giving an anti-inflammatory response that protects against atherosclerosis. Based on that previous work, this new study focuses on finding its possible role in the mechanisms that control inflammatory-immune response and the link with tissue remodelling in cardiovascular diseases.

By means of large-scale RNA sequencing (RNAseq) it was observed that the union of CD69 with oxLDL induces expression of PD-1 (a protein found in T lymphocytes that contributes to the control of immune response) and that this mechanism participates in regulation of immune response.

"This mechanism of PD-1 induction mediated by CD69 contributes to modulating inflammation and the cardiovascular remodelling that is produced as a consequence," explain **Francisco Sánchez Madrid** and **José Martínez González**, heads of the CIBERCV group at the UAM and IIBB-CSIC respectively, and coordinators of this new research.

Jiménez-Fernández, M.; Rodríguez-Sinovas, C.; Cañes, L.; Ballester-Servera, C.; Vara, A.; Requena, S.; De la Fuente, H.; Martínez-González, J.; Sánchez-Madrid, F. *CD69-oxLDL ligand engagement induces Programmed Cell Death 1 (PD-1) expression in human CD4+ T lymphocytes. Cell Mol Life Sci.* 2022 Aug 5;79(8):468. doi: 10.1007/s00018-022-04481-1

BRITISH JOURNAL OF PHARMACOLOGY

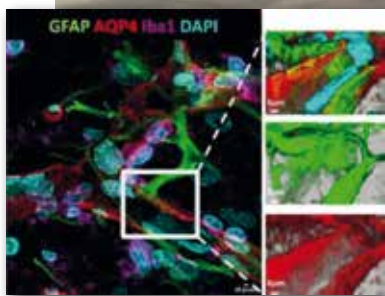
CNIC scientists identify a neuroprotective action of metoprolol after a stroke

A drug costing just €2 a shot can protect the brain during a stroke and greatly reduce long-term incapacity. Metoprolol, a beta-blocker in routine use in cardiology for more than 40 years, has now been shown to have a specific neuroprotective effect.

This is the finding of a study by scientists at the CNIC, Hospital Universitario Fundación Jiménez Díaz, and CIBERCV. The study was led by **Dr. Borja Ibáñez** and is published in the *British Journal of Pharmacology*.

The group led by **Dr. Ibáñez**—Clinical Research Director at the CNIC, cardiologist at Hospital Universitario Fundación Jiménez Díaz, and CIBERCV group leader—has demonstrated in a rat model that treatment with metoprolol protects the brain during a stroke and greatly reduces the severity of its long-term consequences. Rats that received intravenous metoprolol during the course of a stroke had less cerebral inflammation and neuronal death and better long-term improvement in neuromotor capacities.

The study received funding from the Carlos III Institute of Health; the European Regional Development Fund "A



way to build Europe” program; the Comunidad de Madrid, with cofunding from the European structural and investment funds and the Spanish State

Research Agency (Agencia Estatal de Investigación); and the European Research Council through the Horizon 2020 Research and Innovation Programme.

Clemente-Moragón, A.; Oliver, E.; Calle, D.; Cussó, L.; Gómez, M.; Pradillo, J.M.; Castejón, R.; Rallón, N.; Benito, J.M. ... *Neutrophil β 1 adrenoceptor blockade blunts stroke-associated neuroinflammation*, *BJP*. <https://doi.org/10.1111/bph.15963>

NATURE METABOLISM

European scientists discover how the body optimizes its respiratory capacity during exercise

A new study was carried out by an international team of researchers led by **Prof. Johan Auwerx** at the École polytechnique fédérale de Lausanne (EPFL) in Switzerland, working in partnership with scientists at the Spanish Centro Nacional de Investigaciones Cardiovasculares (CNIC) and the Centro de Biología Molecular Severo Ochoa (CBMSO) in Madrid. The study confirms in humans the molecular mechanism through which mitochondria adapt their main energy-generating component—the electron transport chain (mtETC)—to optimize metabolism, cardiorespiratory function, and the capacity for exercise.

Dr. José Antonio Enríquez, an author on the study and head of the CNIC Functional Genetics of the Oxidative Phosphorylation System (GENOPHOS) group, explained that the mtETC is formed by four large multiprotein complexes, CI, CII, CIII, and CIV, which can combine in various structures called supercomplexes to perform different functions and adapt to local conditions.

The protein SCAF1 (also known as COX7A2L) is a key factor in the organization of the mETC. The study shows

that SCAF1 expression is regulated in humans by population genetic variants. Study author **Dr. Sara Cogliati** explained that “the data demonstrate that there is a genetic variant of SCAF1 in humans that determines a higher expression in skeletal muscle and the heart.”

The study also shows that the frequency of the human SCAF1 variant differs between different geographical populations, “suggesting that mETC organization might contribute to the adaptation to different environmental conditions,” said **Dr. Enríquez**. The results of the study define for the first time in humans the fundamental role of the mETC in the adaptation of metabolism to varying energy demands.

The study received grant funding from the École polytechnique fédérale de Lausanne; the European Research Council (ERC); the Swiss National Science Foundation (SNSF); the Marcel Levaillant Foundation; the Fondation suisse de recherche sur les maladies musculaires (FSRMM); the National Research Foundation of Korea through a Global Research Laboratory award; the HUNT Research Centre; the Ministerio de Ciencia, Innovación y Universidades; Agencia Estatal de Investigación; the European Regional Development Fund; the Spanish Biomedical Research Networking Center on Frailty Healthy Aging (CIBERFES-ISCiii); and the Human Frontier Science Program.



Benegiamo, G.; Bou Sleiman, M.; Wohlwend, M. et al. *COX7A2L genetic variants determine cardiorespiratory fitness in mice and human*. *Nat Metab* (2022). <https://doi.org/10.1038/s42255-022-00655-0>

NATURE CARDIOVASCULAR RESEARCH

CNIC scientists identify the cause of arrhythmias and sudden death in Andersen-Tawil syndrome type 1

Two research groups at the CNIC have discovered the cause of arrhythmias and sudden death in the rare disease Andersen-Tawil syndrome type 1 (ATS1), which is caused by mutations affecting potassium channels that regulate electrical activity and the intracellular calcium cycle in cardiac and skeletal muscle.



The teams led by **Drs. José Jalife and Juan Antonio Bernal** have discovered a previously unknown function of Kir2.1 channels, which control the essential electrical properties of excitable cells such as cardiac muscle, skeletal muscle, and neurons.

The ***Nature Cardiovascular Research*** study demonstrates that these distinct Kir2.1 microdomains are found in different species and different muscle cell types, indicating that they are involved in important and conserved cell functions.

In addition, said **Dr. Bernal**, the study reports “the generation and detailed characterization of a new mouse model of ATS1.”

The project was supported by the “La Caixa” Foundation, the Instituto de Salud Carlos III with cofunding from the European Regional Development Fund and European Social Fund, Fundació La Marató de TV3, and the European Union Horizon 2020 programme.

Macías, Á.; González-Guerra, A.; Moreno-Manuel, A.I. et al. *Kir2.1 dysfunction at the sarcolemma and the sarcoplasmic reticulum causes arrhythmias in a mouse model of Andersen–Tawil syndrome type 1. **Nat Cardiovasc Res** 1, 900–917 (2022).*
<https://doi.org/10.1038/s44161-022-00145-2>

JOURNAL OF CLINICAL INVESTIGATION

CNIC scientists identify a factor that protects the heart against damage after a heart attack

A study carried out at the CNIC has identified a key factor that protects the heart after a heart attack. The study, led by **Dr. Pilar Martín**, who heads the Regulatory Molecules of Inflammatory Processes group at the CNIC, was published in the ***Journal of Clinical Investigation***. The study shows that the expression of the receptor CD69 on regulatory T lymphocytes confers protection after a myocardial infarction by acting as a checkpoint for the exacerbated inflammation that causes medium-term cardiac injury.

The study involved the participation of researchers in the Spanish Biomedical Research Networking Center on Cardiovascular Diseases (CIBERCV), the group led by **Dr. Francisco Sánchez-Madrid** at the CNIC and Hospital Universitario de La Princesa, and the group led by **Dr. José Martínez-González** at the Instituto de Investigaciones Biomédicas de Barcelona (IIBB-CSIC) and the IIB-Sant Pau. The results show that the level of CD69 expression in peripheral blood can predict the development and progression of heart failure, which has severe consequences for heart function.

The authors discovered that the expression of CD69 on regulatory T lymphocytes increases in the first hours after the ischemic event. Through experiments with mouse models, the research team showed that the absence of CD69 leads to increases in inflammation, cardiac dysfunction, and the death rate after infarction.

In one of the key experiments of the study, the scientists injected CD69-expressing regulatory T cells into CD69-deficient mice after an infarction, finding that this treatment was able to make up for the deficiency of this molecule and thus decrease cardiac inflammation and improve survival.

The study also produced promising clinical findings through a follow-up analysis of myocardial infarction patients from two independent cohorts. This analysis revealed that the level of CD69 expression on peripheral blood cells predicts the development and progression of heart failure towards severe consequences for heart function.

The study received funding from the Ministerio de Ciencia e Innovación (MCIN) through the Instituto de Salud Carlos III (ISCIII) Fondo de Investigación Sanitaria, the Comunidad de Madrid, Fundació La Marató de TV3, the Spanish Biomedical Research Networking Center on Frailty and Healthy Aging (CIBERFES), the Human Frontier Science Program, Leducq Transatlantic Networks, Marie Skłodowska-grant, and University



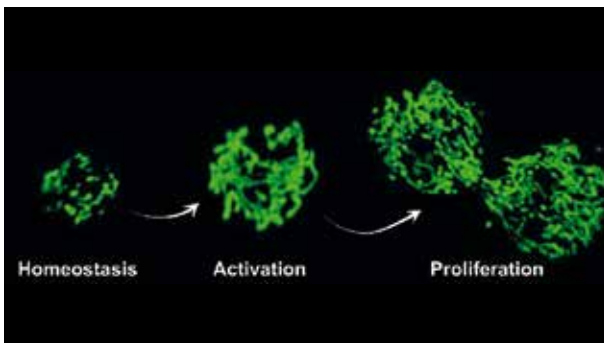
Teaching Staff Training Program of the Ministerio de Educación, Cultura y Deportes.

Blanco-Domínguez, R. ... Martínez-González, J.; Martín, P. *CD69 expression on regulatory T cells protects from immune damage after myocardial infarction.* **J Clin Invest.** 2022.
<https://doi.org/10.1172/JCI152418>

CELL STEM CELL

Researchers at CNIC, UPF, ICREA, CIBERNED and CIBERFES identify a mechanism that maintains mitochondria function in muscle stem cells and that can be stimulated in old age

Researchers at the Centro Nacional de Investigaciones Cardiovasculares (CNIC), Universidad Pompeu Fabra, ICREA, Centro de Investigación Biomédica de Enfermedades Neurodegenerativas (CIBERNED) and Centro de Investigación Biomédica en Red Fragilidad y Envejecimiento Saludable (CIBERFES) have identified a physiological mechanism that sustains the regenerative capacity of muscle stem cells, and that fails at old age. This failure can be overcome genetically and pharmacologically, hence restoring old stem cell regenerative functions.



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 fibres and expand in new stem cells.

The regenerative functions of these stem cells are known to decline with ageing. **Dr. Pura Muñoz-Cánoves**, senior investigator at the CNIC in Madrid, and ICREA professor at the MELIS Department at Pompeu Fabra University (UPF) in Barcelona, and Ciberned, and **Dr. José Antonio Enríquez**, senior investigator at CNIC and CIBERFES, and their colleagues, have found in experiments with mice that mitochondrial dynamics are required for tissue regeneration.

Mitochondrial fission facilitates muscle stem cell function via OXPHOS and mitochondrial autophagy (mitophagy) regulation. The researchers has shown that genetic loss of the mitochondria fission regulator DRP1 in mus-

cle stem cells (or during aging) blunts their proliferation and regenerative capacity, whereas its reestablishment rescues these defects. According to the results presented in **Cell Stem Cell**, normalizing mitochondrial dynamics (or increasing OXPHOS and mitophagy) in aged muscle stem cells restores tissue regeneration.

This scientific study has also involved the collaboration of researchers at the University of Cordoba and the University of Padua (Italy). The study was funded in part by grants from the European Research Council (ERC), the Spanish Ministry of Science and Innovation, "La Caixa"-Health, Human Frontier Science Program and Leduq Foundation (LeduqRedox).

Hong, X.; Isern, J.; Campanario, S.; Perdiguero, E.; Ramírez-Pardo, I.; Segalés, J.; Hernansanz-Agustín, P.; Curtabbi, A.; Deryagin, O.; Pollán, Á.; González-Reyes, J.A.; Villalba, J.M.; Sandri, M.; Serrano, A.L.; Enríquez, J.A.; Muñoz-Cánoves, P. *Mitochondrial dynamics maintain muscle stem cell regenerative competence throughout adult life by regulating metabolism and mitophagy.* **Cell Stem Cell.** 2022 Sep 1;29(9):1298-1314.e10.
 doi: 10.1016/j.stem.2022.07.009

CIRCULATION

Specific modifier genes determine the effect of mutations that cause non-compaction cardiomyopathy

Non-compaction cardiomyopathy is a heart condition caused by defects that arise during fetal development and can have diverse health impacts in affected individuals, including sudden cardiac death. The Intercellular Signaling in Cardiovascular Development and Disease group at the CNIC previously reported that this disease can be caused by two distinct mutations in the Mindbomb1 gene (Mib1).

The same group, working with groups of CIBER de Enfermedades Cardiovasculares (CIBERCV) and CIBER de Bioingeniería, has now shown that the presence of one of these Mib1 mutations does not always lead to non-compaction cardiomyopathy. Instead, the outcome depends on the genetic context provided by mu-



tations in other genes that “modify” the effect of the Mib1 mutations.

In a new article published in *Circulation*, the scientists describe how the context of mutations accompanying one supposedly “causal” mutation for non-compaction cardiomyopathy can condition both the severity and the appearance of different anomalies, so that the precise outcome depends on the patient’s specific combination of mutations.

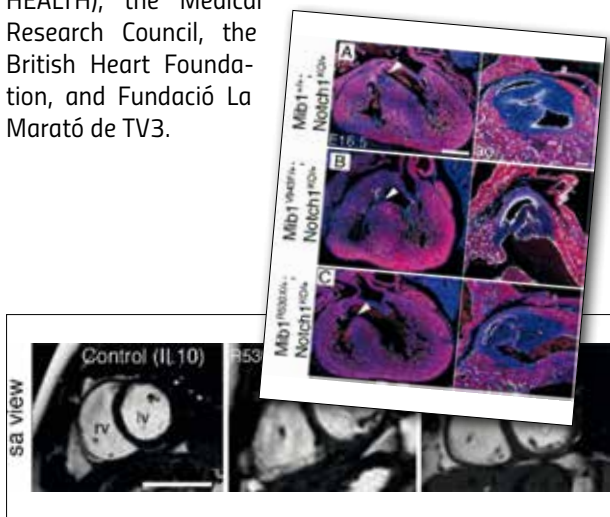
The team led by **Dr. José Luis de la Pompa** used CRISPR-Cas9 molecular-scissor technology to insert the LVNC-causing mutations into the mouse genome.

These differences suggest that LVNC patients with an Mib1 mutation may additionally harbor “mutations in other genes that contribute to the severity and diversity of the observed defects.”

To uncover what was going on, the research team sought the help of the LVNC patients and their families, as well as partners from diverse centers, especially **Dr. Juan Ramón Gimeno** of Hospital Universitario Virgen de la Arrixaca. With these stakeholders on board, the scientists were able to sequence DNA from LVNC patients carrying Mib1 mutations and from their healthy family members.

These discoveries advance specific knowledge about LVNC and more generally reinforce the idea that congenital heart disease is not always monogenic, instead involving the intervention of several mutations through oligogenic inheritance.

The study received funding from the MCIN/AEI, CIBERCV, Fundación BBVA, the European Commission (H2020-HEALTH), the Medical Research Council, the British Heart Foundation, and Fundació La Marató de TV3.



Siguero-Álvarez, M. ... De la Pompa, J.L. *A human hereditary cardiomyopathy shares a genetic substrate with bicuspid aortic valve.* **Circulation**. Nov 2022 doi: 10.1161/CIRCULATIONAHA.121.058767

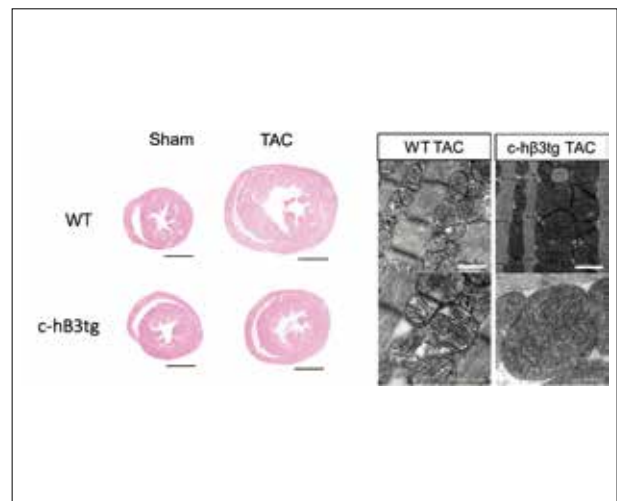
BASIC RESEARCH IN CARDIOLOGY

A new therapeutic target for the prevention of heart failure due to aortic stenosis

A study led by **Dr. Borja Ibáñez**, Clinical Research Director at the CNIC, shows that overexpression in cardiac muscle cells of beta-3 adrenergic receptor, a member of the beta adrenergic system, can prevent or even reverse heart failure in a mouse model of aortic stenosis, a condition that currently has few therapeutic options.

In the study, published in *Basic Research in Cardiology*, the CNIC team adopted an innovative gene-therapy approach to boost the expression of this receptor in the heart and thus reinforce its beneficial action.

Aortic stenosis is a progressive narrowing of the aortic valve, a ‘floodgate’ through which blood flows from the heart to the rest of the body. The condition is currently treated by replacing the damaged valve with a prosthesis.



While valve replacement technology has become much less invasive and successfully recovers valve function, the cardiac muscle, after years of being subject to stress, does not recover. Unfortunately, there is a lack of treatments able to improve cardiac muscle function and thereby alleviate heart failure resulting from a long history of aortic stenosis.

The study exploited the beneficial properties of stimulating the beta-3 adrenergic receptor, which is abundant in adipose tissue and the bladder but weakly expressed in the heart.

Through a collaboration with the CNIC Intercellular Signaling in Cardiovascular Development and Disease group, led by **Dr. José Luis de la Pompa**, transgenic mice were generated that overexpress the beta-3 adrenergic receptor in cardiomyocytes. When these mice were subjected to supravalvular aortic stenosis, they developed less cardiac hypertrophy and fibrosis than mice with normal levels of expression. The transgenic mice were also free of heart failure, and their hearts were metabolically more efficient and consumed less glucose.

Since the transgenic technology used to develop these mice is not applicable in patients, the investigators developed a gene therapy approach, whereby an innocuous virus was injected into mice to deliver the beta-3 adrenergic receptor gene specifically to cardiomyocytes, resulting in safe and efficient production of the receptor.

Working in partnership with the CNIC Viral Vectors Unit, the team designed an innocuous virus able to enter cardiomyocytes and drive elevated expression of beta-3 adrenergic receptor in the hearts of non-transgenic adult mice. When these mice were subjected to aortic stenosis, they were as equally protected against heart failure as transgenic mice overexpressing the receptor from before birth.

In a final test, the team injected the virus into non-transgenic mice with long-lasting aortic stenosis and established heart failure. In these mice, gene-therapy-induced overexpression of beta-3 adrenergic receptor recovered heart function, reduced cardiomyocyte hypertrophy, restored normal mitochondrial size and normal expression of mitochondrial fusion proteins in the heart, and increased animal survival.

The study has received funding from the Ministry of Science and Innovation of Spain (MICINN); European Commission; ERACVD Joint Translational Call 2016; European Regional Development Fund (ERDF); BBVA Foundation; CIBERCV, and TERCEL.

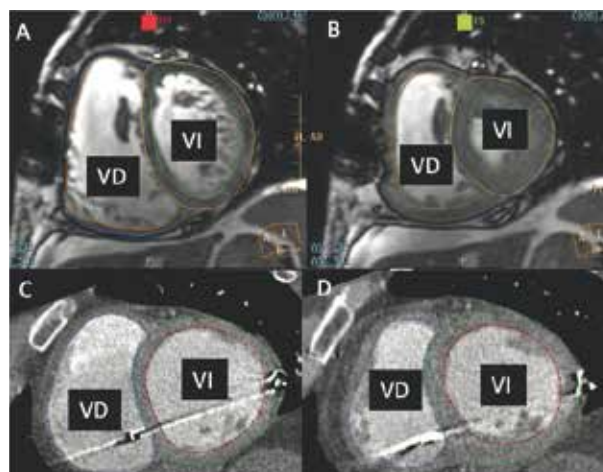
Pun-García, A.; Clemente Moragón, A.; Villena Gutiérrez, R.; Gómez, M.; Sanz Rosa, D.; Díaz Guerra, A.; Prados, B.; Medina, J.P.; Montó, F.; Ivorra, M.D.; Márquez López, C.; Cannavo, A.; Bernal, J.A.; Koch, W.J.; Fuster, V.; De la Pompa, J.L.; Oliver, E.; Ibáñez, B. *Beta-3 adrenergic receptor overexpression reverses aortic stenosis-induced heart failure and restores balanced mitochondrial dynamics*. *Basic Research in Cardiology* (2022) Nov; 117:62.
doi: 10.1007/s00395-022-00966-z

EUROPEAN JOURNAL OF HEART FAILURE

A promising drug treatment for patients with pulmonary hypertension associated with heart disease

There is currently no specific treatment for pulmonary hypertension associated with heart disease, a highly prevalent condition with a poor prognosis. Now, a study from the Centro Nacional de Investigaciones Cardiovasculares (CNIC) and Hospital Clínic de Barcelona/IDIBAPS has shown that mirabegron, a drug that acts on the beta-3 adrenergic receptor, may have a beneficial effect on right ventricular function.

The SPHERE-HF study evaluated the beneficial potential of mirabegron in patients with pulmonary hypertension associated with heart disease. The results, published in



the *European Journal of Heart Failure* do not show any improvement in pulmonary vascular resistance, the main study objective; however, they do show a beneficial effect on right ventricular function.

SPHERE-HF included 80 patients with heart disease and associated pulmonary hypertension. The patients were recruited at four tertiary hospitals—Hospital Sant Pau de Barcelona, Hospital Puerta de Hierro de Madrid, Hospital 12 de Octubre de Madrid, and Hospital Clínic de Barcelona—and were randomized to receive treatment with mirabegron or placebo over a 16-week period

All the patients were assessed by right heart catheterization to measure pulmonary pressures and by magnetic resonance imaging or cardiac computed tomography to evaluate right ventricular function. All cardiac images were evaluated by blinded experts at the CNIC.

These results suggest that beta-3 adrenergic receptor agonists have potential to improve right ventricular dysfunction, for which there is currently no treatment available suitable for chronic therapy.

The clinical trial was made possible through competitive funding from Fundació La Marató de TV3 and a collaborative partnership of five Spanish centers. The study also received funding from the European Commission (ERC-Consolidator Grant Agreement No. 819775), the Spanish Ministerio de Ciencia e Innovación, and the Comunidad de Madrid.

García-Álvarez, A.; Blanco, I.; García-Lunar, I.; Jordà, P.; Rodríguez-Arias, J.J.; Fernández-Friera, L.; Zegri, I.; Nuche, J.; Gómez-Bueno, M.; Prat, S.; Pujadas, S.; Sole-González, E.; García-Cossío, M.D.; Rivas, M.; Torrecilla, E.; Pereda, D.; Sánchez, J.; García-Pavía, P.; Segovia-Cubero, J.; Delgado, J.F.; Mirabet, S.; Fuster, V.; Barberá, J.A.; Ibáñez, B.; SPHERE-HF Investigators. *β 3 adrenergic agonist treatment in chronic pulmonary hypertension associated with heart failure (SPHERE-HF): a double blind, placebo-controlled, randomized clinical trial*. *Eur J Heart Fail* (2022) Nov 20.
doi: 10.1002/ejhf.2745



ELIFE
CNIC scientists identify the essential role of cell-surface “nanofolds” and “glue” in the mechanical response of cells

A study at the CNIC has revealed that subcellular structures called caveolae play an essential role in cell mechanics. The results suggest that impaired caveolar function could be involved in a variety of processes, including platelet aggregation, cardiovascular disease, fibrosis, and tumor formation. The study is published in *eLife* and was led by CNIC researchers **Fidel-Nicolás Lolo** and **Miguel Ángel del Pozo**. The results show that caveolae, by limiting abrupt changes in membrane tension, couple mechanical stress to the activity of integrins, thereby modifying the cellular mechanical responses.

The authors show that cells lacking this caveolar damping system have a dysfunctional mechanical response due to an anomalous increase in the expression of integrins at the cell membrane. Integrins are the main receptors for the extracellular matrix, the structure that “glues” cells to their local microenvironment.

Cells detect their microenvironment through tiny pulls and pushes that are transmitted through proteins called integrins, which are extracellular matrix receptors located on the cell surface. **Dr. Lolo** added that “integrins can switch between an inactive and an active state, with the active form being responsible for scanning the microenvironment.”

Dr. Lolo explained that the relative amount of integrins at the cell surface is controlled by two main mechanisms, the regulation of plasma membrane tension and the dynamics of integrin recycling. Caveolae are small invaginations in the cell membrane, shaped like cups or folds. These organelles are found in many cell types and can regulate cell membrane tension by changing their shape.

An appropriate cellular mechanical response is critical for tissue homeostasis—the ability to respond to envi-

ronmental challenges and maintain parameters within a physiological range. An inability to detect these environmental changes is a feature of disease processes including fibrosis, tumorigenesis, and cardiovascular disease and may play an important role in processes like platelet aggregation.

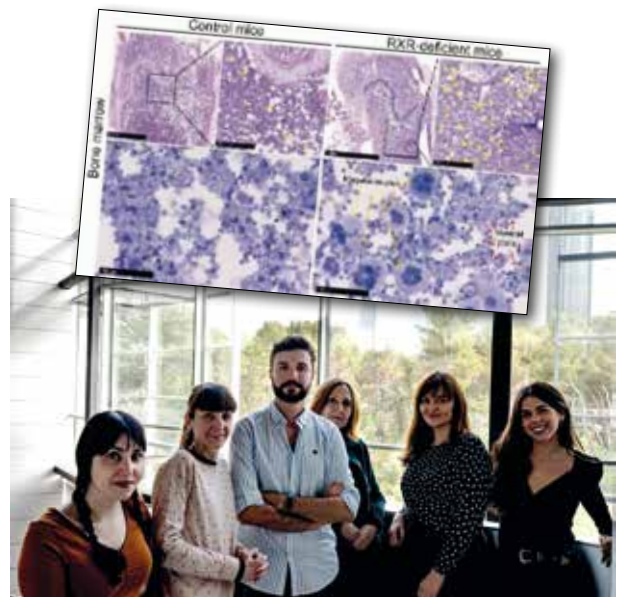
The study was supported by the European Union Horizon 2020 programme through a ITN Marie Skłodowska-Curie, the Spanish Ministerio de Ciencia e Innovación (including the Severo Ochoa Program), Fundación “la Caixa”, Asociación Española Contra el Cáncer, Fundació La Marató de TV3, and the Comunidad de Madrid.

Lolo, F.-N.; Pavón, D.M.; Grande, A.; Elósegui Artola, A.; Segatori, V.; Sánchez, A.; Trepát, X.; Roca-Cusachs, P.; Del Pozo, M.A. *Caveolae couple mechanical stress to integrin recycling and activation*. *eLife* (2022) Oct. doi.org/10.7554/eLife.82348

BLOOD
RXR, the cell protein that keeps blood stem cells young and fit

The cell protein retinoid X receptor (RXR) is a key factor in the maintenance of hematopoietic stem cells, the immature stem cells that give rise to all the blood cell lineages. RXR ensures that these cells remain youthful and fit, thereby reducing the risk of developing myeloproliferative syndromes as the body ages. The study, carried out by a team at the CNIC, demonstrates that the regulatory action of RXR on hematopoietic stem cells is essential for the maintenance of a balanced production of the spectrum of blood cell types throughout life.

The study findings, published in the journal *Blood*, could have therapeutic implications for conditions that feature excessive proliferation of myeloid blood cells, as is



the case in some diseases of the blood and cardiovascular systems.

In the article, **Dr. Mercedes Ricote's** group (CNIC) and the team led by **Dr. José Cancelas** (Cincinnati Children's Hospital) demonstrate that the elimination of RXR from hematopoietic stem cells in mice triggers chronic expansion of a subgroup of cells skewed towards megakaryocytes (the progenitors of blood platelets) and the myeloid lineage, resulting in a deficit of the lymphoid lineage and the development of myeloproliferative syndrome as these mice age. The research shows that the excessive production of inflammatory myeloid cells in the RXR-deficient mice results in the invasion by these cells of multiple tissues, especially the lung, where they cause severe damage, leading to the premature death of these mice.

Collaboration with **Dr. Sánchez-Cabo** of the CNIC Bioinformatics Unit and **Dr. Salomonis** (Cincinnati Children's Hospital) allowed the use of latest generation massive sequencing techniques and exhaustive analysis of DNA structure and gene expression in hematopoietic stem cells. The researchers emphasize the possibility of modulating RXR activity in hematopoietic stem cells through the use of drugs, some of them already used to treat cutaneous lymphomas.

The study was funded by grants from the Spanish Ministerio de Ciencia e Innovación (MICIN); Fundación La Marató de TV3; the Comunidad de Madrid, and the US National Institutes of Health.

Menéndez-Gutiérrez, M.P.; Porcuna, J ... Cancelas, J.; Ricote, M. *Retinoid X receptor promotes hematopoietic stem cell fitness and quiescence and preserves hematopoietic homeostasis*. **Blood**, November 2022
doi.org/10.1182/blood.2022016832

NATURE

Researchers characterize rare, damaged cells that block the functions of their neighbour healthy cells and identify ways to neutralize them and improve tissue regeneration

Researchers at the Universitat Pompeu Fabra (UPF), ICREA, CIBERNED, CNIC and Altos Labs, among other national and international collaborators, have characterized how damaged cells (senescent cells) that inevitably arise after injury negatively impact tissue regeneration, and how this mechanism operates actively in old age, but surprisingly also in young age. This negative action can be overcome genetically and pharmacologically, hence restoring stem cell regenerative functions.

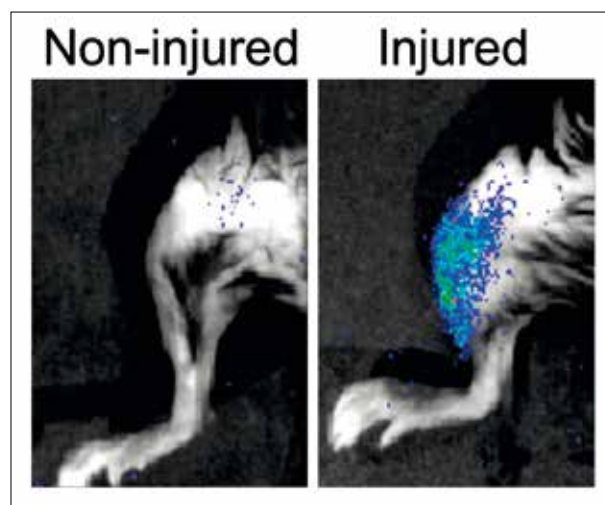
Tissue regeneration depends on a population of stem cells and its neighbouring cells, a process whose efficacy declines with aging. The reasons of this decline remain largely unknown. Scientists have found in experiments with mice that senescent cells are new reg-

ulatory components of the muscle tissue regenerating niche that blunt muscle regeneration at all stages of life. Cellular senescence is a state of irreversible cell cycle arrest that often emerges after tissue damage and in age-related diseases.

In a study published in **Nature**, the team of researchers generated the first transcriptomic atlas of senescent cells of damaged skeletal muscle of mice of distinct ages (transcriptomic refers to everything related to RNA or the structures that transcribe the information encoded originally inside a nucleus cell). Researchers found that senescent cells are widely heterogeneous, yet they display common traits, including the secretion of proinflammatory and profibrotic (that promotes an excess of fibrous connective tissue) factors. This secretion in turn, impacts the nearby stem cells and hampers their regenerative capacity, thus impairing muscle regeneration. So, it appears that what once was as a good protection tool now turns into a bad one.

Results showed that reducing the load of senescent cells (either through genetic or pharmacological treatments that induce death of these cells) improved the regeneration of aged muscles and, unexpectedly also, of young muscle. In addition to the biomedical benefits of targeting senescent cells, the new molecular information provided by the muscle senescent cell atlas could be likely transferred to understanding the function of senescence in other tissues whose senescent cells have either not been profiled at all or lack enough senescent cell numbers. The study has had the participation of the CNIC's Genomic group led by **Dr. Ana Dopazo**.

The study was funded in part by grants from the European Research Council (ERC), the Spanish Ministry of Science and Innovation, "La Caixa" Foundation, AFM, MDA, MWRF, and DPP-Spain.



Victoria Moiseeva et al. *Senescence atlas reveals an aged-like inflamed niche that blunts muscle regeneration*. **Nature**, 2022
doi: 10.1038/s41586-022-05535-x

NATURE CELL BIOLOGY

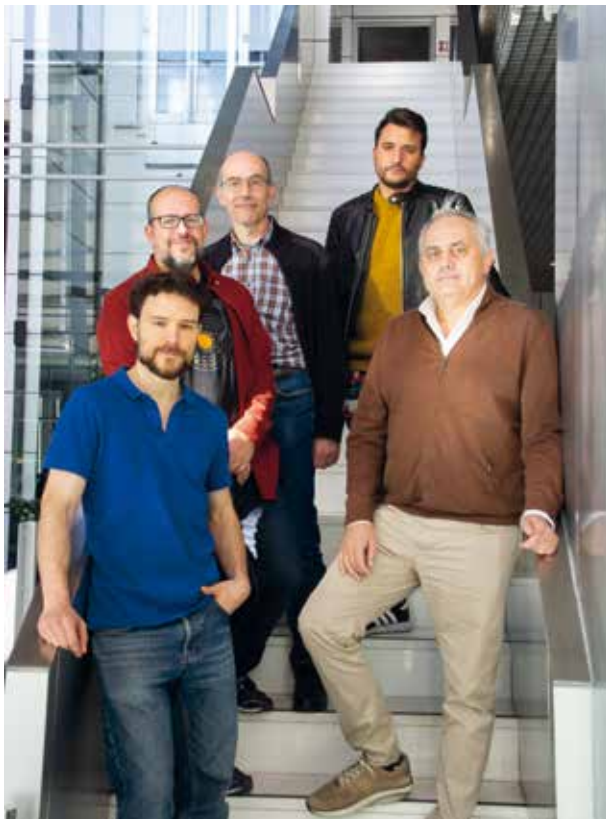
A study shows that cells possess two mechanisms to allow them to respond to different force ranges

A study carried out at the CNIC heralds a paradigm change in the field of mechanobiology. The study reveals that cells respond to forces of differing strength using two distinct mechanisms, one mediated by minute, cup-like invaginations on the cell surface called caveolae and the other by newly discovered large membrane depressions the study authors call dolines.

Study coordinator **Miguel Ángel del Pozo**, who heads the Mechanoadaptation and Caveolae Biology group at the CNIC, explained that the *Nature Cell Biology* study resolves controversies in this field. "Our results demonstrate that caveolae play an essential role in tissues that are subject to large mechanical forces (like skeletal muscle, heart muscle, blood vessels, and adipose tissue), whereas the newly identified dolines are important for the response to weak or medium-strength forces."

Cells are constantly subjected to mechanical forces of different types and intensities originating in the local microenvironment, such as blood flow, the contraction and stretching of muscle, etc. To allow cells to respond and adapt their function to these stimuli, evolution has provided them with mechanisms for detecting different types of forces.

The most well-known structures with this capacity are caveolae ('small caves' in Latin). "These tiny invaginations in the plasma membrane [the outer envelope of



the cell] are present on many types of cells and detect mechanical stimuli through changes in their physical shape. Caveolae flatten when cells swell or are stretched, rather like creases in a dress. But they reform and congregate when the cell membrane is relaxed," said **Miguel Ángel del Pozo**.

These changes modulate biochemical signaling networks in the cell, making caveolae not only mechanical adaptors, but also transducers of mechanical information. However, before this study, it was unclear if this key function required the invagination of fully formed caveolae or if the individual components caveolin-1 and cavin-1 were sufficient by themselves."

To investigate this question, the CNIC scientists set up a collaboration with biophysicist Universidad de Barcelona-IBEC, **Pere Roca-Cusachs**, to use magnetic tweezers to "elucidate which element is the mechanical sensor and which is the signal transducer," explained **Miguel Ángel del Pozo**.

In addition to these experiments, the study collected many other biophysical parameters through partnerships with Spanish and international laboratories. The collected data demonstrated that cells expressing caveolin-1 but not cavin-1 sustained a mechanical response similar to that of cells expressing both proteins (and thus able to form caveolae).

Next, the researchers tried to determine the functional difference between caveolae and the isolated role of caveolin-1, "which was not an easy task," comments **Dr. Fidel Lolo**. The caveolar response is on-off (switch-like), which only activates beyond a high force threshold and requires minutes. However, the new structures respond gradually, continuously, and immediately (within seconds) to lower and increasing force ranges.

Dr. Lolo suggested that "dolines may be especially important in cells like lymphocytes or neurons that don't form caveolae but do express caveolin-1. These cells would thus be adapted to respond to more subtle micro-environmental forces in the tissues where they reside."

The study was supported by the European Union Horizon 2020 Programme through a Marie Skłodowska-Curie ITN, the Spanish Ministry of Science and Innovation (including support through the Severo Ochoa Program), Fundación "la Caixa" (AtheroConvergence project), Asociación Española Contra el Cáncer, Fundació La Marató de TV3, and the Community of Madrid regional government ('Tec4Bio' project). ■

Lolo, F.N.; Walani, N.; Seemann, E. et al. ... Del Pozo, M.A. *Caveolin-1 dolines form a distinct and rapid caveolae-independent mechanoadaptation system*. **Nat Cell Biol** (2022).

<https://doi.org/10.1038/s41556-022-01034-3>

cnic AWARDS AND SCHOLARSHIPS

VISIT FROM THE MINISTER OF SCIENCE AND INNOVATION, DIANA MORANT

The Minister of Science and Innovation, **Diana Morant**, visited CNIC, where she met with **Dr. Valentín Fuster**, General Director of CNIC; **Cristóbal Belda**, Director of the Instituto de Salud Carlos III; **Alberto Sanz**, Managing Director of CNIC; **Luis de Carlos**, Director of the **Fundación Pro CNIC**; **Dr. Borja Ibáñez**, Scientific Director of CNIC; **Dr. Vicente Andrés**, Director of basic research of CNIC and **Icíar Areilza**, Director of the **Fundación Pro CNIC**.

On a tour of the facilities, she visited the laboratories and met with researchers **Dr. Almudena Ramiro** and **Dr. Inés García Lunar**. The Minister praised CNIC as an internationally prestigious centre and highlighted how its work allows advances in the early diagnosis, prevention and treatment of cardiovascular diseases that continue to be the main cause of death in our country.



CNIC AT THE 22nd EDITION OF MADRID'S WEEK OF SCIENCE AND INNOVATION

CNIC again participated in Madrid's Science and Innovation Week, in this its 22nd edition, with three activities open to the public: the conference "Avoiding toxicity in cancer treatments," a visit to a CNIC laboratory, and the workshop "Deconstructing the muscle."

CNIC, AT THE 13th EUROPEAN RESEARCHERS' NIGHT

CNIC participated in the 13th edition of European Researchers' Night, with two activities open to the public that were visited by over 100 people.



15th COURSE IN CARDIOVASCULAR PATHOPHYSIOLOGY "FROM SYMPTOMS TO GENES"

Organised by CNIC and the Spanish Society of Cardiology (SEC), the 15th Course of Cardiovascular Physiological Disorders "From symptoms to genes" was led by R3, R4 and R5 residents of cardiology and other fields related with cardiovascular disease, in addition to translational researchers in the area of cardiology.



CNIC PHDAY

PhDay is an open forum for undergraduate and post-graduate students, lab technicians and post-doctoral researchers that aims to help them develop their careers as scientists, exchange new ideas and make contacts.

AWARDS



DR. VALENTÍN FUSTER RECEIVES A PRESTIGIOUS AWARD FROM THE CARDIOVASCULAR RESEARCH FOUNDATION (USA)

The Cardiovascular Research Foundation (CRF) honoured **Dr. Valentín Fuster** with the Transcatheter Cardiovascular Therapeutics (TCT) 2022 Career Achievement Award.

The award recognises the extraordinary contributions that **Dr. Fuster** has made to the field of interventional cardiology in the transformation of patient care through his career endeavours, research pursuits, and mentorship of many healthcare professionals and researchers.

"MARGARITA SALAS" RESEARCH AWARDS 2022 AND FUNDACIÓN FRANCISCO COBOS FOR JOSÉ ANTONIO ENRÍQUEZ

The Autonomous Community of Madrid awarded the Margarita Salas Research Prize 2022 to the career of **Dr. José Antonio Enríquez** for his significant contributions to the understanding of mitochondrial biogenesis and bioenergetics. This award for a scientific career has a prize of €42,000 and is given in recognition of the national and international repercussions of his career. The Fundación Francisco Cobos also awarded its 16th Award for Scientific Career to **Dr. Enríquez Domínguez**. This €50,000 prize recognises his contributions to the study of mitochondrial biogenesis in the functioning of the mitochondrial respiratory chain and understanding of mitochondrial pathophysiology and ageing.



THE POLYPILL RECEIVES ABC SALUD 2022 PRIZE FOR THE BEST MEDICATION

The polypill received the ABC Salud prize for best medication of the year.



ANDRÉS HIDALGO AWARDED THE 18th CAJA RURAL DE GRANADA'S HEALTH SCIENCES PRIZE

The paper "Mapping the immune behaviour of inflammation" by the CNIC research group led by **Andrés Hidalgo** was awarded the Caja Rural de Granada's Health Sciences Prize in its 18th edition. The research, published in the prestigious review *Nature*, described "a new way of discovering immune cells during the inflammatory process in live organisms." In addition, **Andrés Hidalgo** was named member of EMBO, the European Organisation of Molecular Biology. **Dr. Hidalgo** is the sixth member of CNIC to enter EMBO, and he joins **Dr. José Antonio Enríquez**, **Dr. Miguel Ángel del Pozo**, **Dr. Miguel Torres**, **Dr. Pura Muñoz** and **Dr. Francisco Sánchez Madrid**.

DR. PABLO GARCÍA PAVÍA RECEIVES THE COMCÓRDOBA-CAIXABANK RESEARCH PRIZE

The Official College of Physicians of Cordoba, thanks to the collaboration of CaixaBank, awarded the 20th edition of the COMCórdoba-CaixaBank Research Prize to **Dr. Pablo García Pavía** for the study "Association of gene variants with prognosis in dilated non-ischaemic cardiomyopathy patients."



DAVID FILGUEIRAS RECEIVES THE YOUNG RESEARCHERS AWARD OF THE ASTRAZENECA FOUNDATION

The project "Use of remote-monitoring technology and heart electrical signals in stratification of patient-specific risk in the deterioration of heart failure and potentially lethal ventricular arrhythmias," coordinated by **Dr. David Filgueiras**, group leader of CNIC's Advanced Development in Arrhythmia Mechanisms and Therapy, and area specialist at San Carlos University Hospital, was awarded AstraZeneca Foundation's Young Researcher Award in the Cardiovascular, Renal and Metabolism category.



GUADALUPE SABIO BUZO, INCLUDED IN THE LIST OF 500 MOST INFLUENTIAL SPANISH WOMEN

Guadalupe Sabio Buzo has been included in *Yo Dona* magazine's list of 500 Most Influential Spanish Women. ■

TRAIN2GAIN
WHAT'S ON
INSIDE SCIENCE
CNIC & SOCIETY

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#15

