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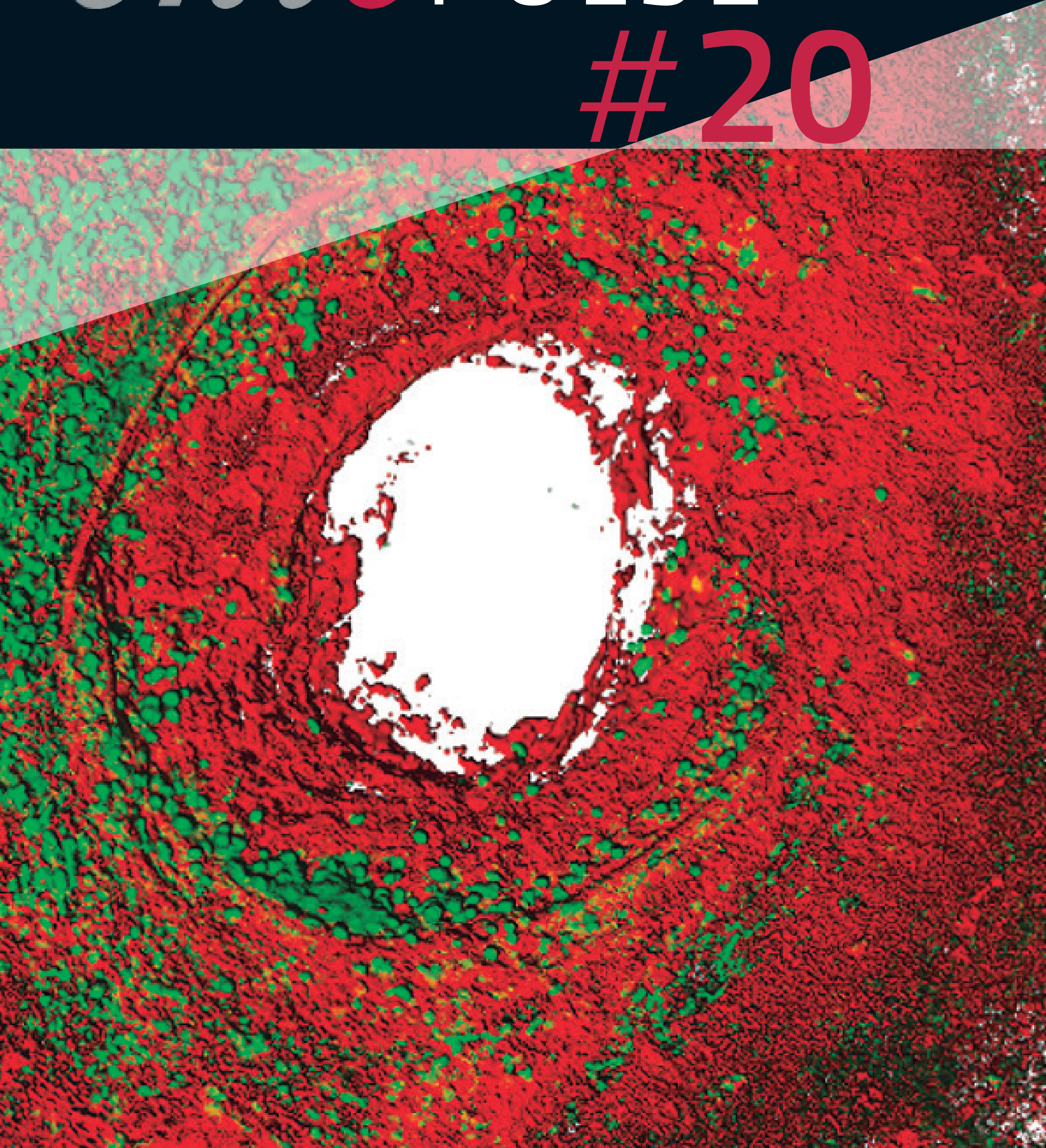

contenidos #20

EDITORIAL: TRAIN2GAIN

4 CNIC Conference "9th Annual Cardiovascular Bioengineering Symposium".

8 RES@CNIC-SEC, a consolidated initiative in cardiology training

WHAT'S ON

13 Jonathan Kipnis: "Science is not just a luxury. It is infrastructure for the future"

18 Giuseppe Danilo Norata: "Without cholesterol, there is no party"

20 Benjamin L. Prosser: "Delving into neuroscience has definitely meant delving into a new world"

23 Daniel Ketelhuth: "We sometimes joke that 'research' just means looking again and again"

27 Yasuki Fukita: "What I really wanted to do was merge physics and biology"

30 Claudia Monaco: "We think we know a lot about cardiovascular disease, but in reality, we don't"

35 Gabriel Núñez: "There is no single, perfect microbiota"

39 Ajay Shah: "It's not that cancer researchers are smarter, but they have had certain advantages"

41 Isabel Gonçalves: "Many of my research questions come from my patients"

44 Erik Biessen: "I would like to explore how the brain regulates inflammation"

46 Luis A. Moreno Aznar: "Obesity is complex, but it can be prevented and improved if we act on all fronts"

49 Juan Domingo Pascual Sánchez: "As a clinician, it frustrates me that we don't see clear benefits for the patient".

INSIDE SCIENCE

52 Three CNIC projects will receive more than €5 million in the ERC Advanced Grant call for proposals

54 CNIC participates in GRACE, a European project that seeks to transform cardiovascular care through innovation and collaboration

55 CNIC receives two prestigious Marie Skłodowska-Curie grants for research projects in immunology and cardiovascular health

55 CNIC researchers receive funding from the AECC to promote their projects

56 CNIC at the presentation of the program "Generation D: Building the AI Generation"

57 Excellence in scientific dissemination

CNIC & SOCIETY

Awards

Activities

EXCELENCIA SEVERO OCHOA

Fundaciónprocnic

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RES@CNIC-SEC, MUCH MORE THAN A TRAINING PROGRAMME.

At CNIC we're particularly proud of having consolidated the RES@CNIC-SEC programme, an initiative designed to bring resident physicians in the first stages of their MIR training in cardiology or related specialist fields closer to cutting-edge biomedical research.

We have offered this programme, run in conjunction with the Spanish Society of Cardiology, since 2012 and during that time over 230 young physicians from all over Spain have had the opportunity to take up 4-9 week training internships in our laboratories. The experience enables them to gain practical knowledge of advanced research techniques as they work in a scientific environment of excellence, in direct contact with leading researchers in the cardiovascular field.

From the outset, our aim has been to foster a vocation for research, showing that clinical practice and research are not parallel routes but disciplines that complement and empower each other, and to build bridges for future collaboration between Spanish National Health System hospitals and the CNIC.

The experiences of the people who have participated confirm this objective is being achieved. Many participants highlight how their time on the programme opened up new professional horizons, strengthened their scientific curiosity and, in some cases, became the start of a stable career in research.

For us, this represents a dual achievement: on the one hand we contribute to training young physicians, giving them a broader, more critical perspective on medicine; on the other, we nourish our own research groups with the clinical experience and motivation of professionals who are the future of cardiology.

So, RES@CNIC-SEC is much more than a training programme. It is a decisive commitment to young talent, to the integration of basic science and clinical practice, and to the discipline of cardiology whose cornerstone is knowledge and innovation. ■

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

CNIC CONFERENCE: 9th ANNUAL CARDIOVASCULAR BIOENGINEERING SYMPOSIUM

The Spanish National Centre for Cardiovascular Research (CNIC) brought together international leaders in the field of cardiovascular bioengineering to discuss heart failure, tissue regeneration and cell therapy in Madrid.

Recent years have seen significant progress in the field of cardiovascular bioengineering, showing its potential in the development of ground-breaking custom therapies aimed at patients with heart failure. It is increasingly clear that heart failure is a complex, multifactorial disease. That's why a deeper understanding of its pathophysiology is key to driving the development of effective new therapeutic strategies. In parallel, the translational sphere has seen significant progress, with pioneering clinical research focusing on the remuscularization of damaged myocardia.

The 9th Annual Cardiovascular Bioengineering Symposium, co-funded by the National Institute of Health (USA), highlighted cutting-edge research in areas such as stem cell biology, cardiac regeneration, vascular biology, the metabolism, and cardiology.

The event was organised by Florian Anton Weinberger (CNIC), Hesham Sadek (CNIC / University of Arizona), Jianyi (Jay) Zhang (University of Alabama at Birmingham), Miguel Torres (CNIC) and Thanh Nguyen (University of Alabama at Birmingham) with guest speakers of international prestige such as Glynnis Garry and Joseph Hill (UT Southwestern Medical Center), Maria Kontaridis (Gordon K. Moe Professor and Chair of Biomedical Research and Translational Medicine) and Eduardo Marbán (Executive Director, Smidt Heart Institute, Cedars-Sinai Medical Center).

Dr Zhang is a leading figure in myocardial bioenergetics and stem cell therapy for cardiac repair. He was chosen to head up the UAB (University of Alabama at Birmingham) Biomedical Engineering Department in 2015 and his impressive career spans research, publications, and mentoring. His work focuses on heart failure, an irreversible, multifactorial condition that seriously affects public health worldwide.

Zhang explained that progress in the development of treatments for this condition is slow because it requires decades of meticulous research. Although cell therapies are not yet standard, he noted, "recent trials show both their safety and promising results."

His team has achieved major advances in areas such as the injection of cardiomyocytes derived from stem cells, which has been shown to improve heart function in pig models and stimulate cell regeneration. He also works on modified mRNA technology (SMRT), temporarily inducing cardiomyocyte division without causing arrhythmias, which has also been effective in animal models.

"These approaches balance regeneration and safety, although there are still challenges such as improving directed intravenous delivery." He added, "New lines of research include umbilical cord stem cells, cell-less products such as extracellular vesicles and cardiomyocyte patches."

Zhang firmly believes that cell therapy has a promising future in cardiovascular medicine and underscores the importance of events like the CNIC Conference, which promote global progress in the fight against heart failure.

The work of Dr Maria Kontaridis, Director of Research at the Masonic Medical Research Institute combines research in molecular biology with strategic leadership in cardiovascular, genetic, and neurodevelopmental diseases. She specialises in cell signalling, a field that allows her to study diverse diseases -from congenital heart diseases to autism and cancer- since cell mechanisms are similar in different tissues. Her laboratory uses advanced tools such as CRISPR, induced pluripotent stem cells (iPSC), transcriptomics and phosphoproteomics to discover how specific genetic mutations cause diseases and how they could be corrected at origin.

Her approach is based on a change of paradigm: starting with the clinical disease in order to research its molecular causes. This has led her work in the direction of personalised medicine and contributed to the development of new gene therapies, some of which have already been approved by the US Food and Drug Administration (FDA). In particular, she studies the genetic and molecular connection between heart diseases in children and neurodevelopmental disorders.

Dr Kontaridis researches the link between congenital heart diseases and neurodevelopmental disorders like autism. She has observed that both can share early genetic mutations affecting multiple systems, which suggests common molecular pathways in the development of the heart and brain. "This opens up the possibility of early intervention, or even the use of gene editing with CRISPR," she commented.

Regarding CRISPR, she acknowledged that, although the discovery generated great enthusiasm, it has taken years to perfect and make safe and precise. Nowadays, she says, "gene editing has significantly matured and is becoming another key tool in modern medicine, combined with advanced therapies like nanoparticles and immunotherapy, which marks a milestone in the transformation of medical science."

Commenting on the future of cardiovascular regenerative medicine, Dr Eduardo Marbán indicated that the traditional strategy of using pluripotent stem cells to generate cardiac tissue has been a complex process. Despite more than two decades of research, he says, "these cells have still not shown clear therapeutic effectiveness in large scale clinical trials. Examples such as those presented by Dr Keiichi Fukuda (Keio University, Japan) at the CNIC Conference show developments in individual cases but are still preliminary outcomes."

Dr Marbán is a renowned cardiologist and researcher whose career has focused on innovation in the treatment of heart diseases, from the creation of the first biological pacemaker to pioneering developments in cell therapy. Since 2004, his laboratory has researched cardiac progenitor cells, particularly their origin and therapeutic potential. One of his greatest achievements has been the development of Deramiocel, a cell therapy currently undergoing clinical trials, for the treatment of cardiomyopathy associated with Duchenne muscular dystrophy, a fatal, rare disease affecting cardiac and skeletal muscle.

Faced with such limitations, Marbán's laboratory decided to take a different route: he work has focused on a type of endogenous cardiac stem cell without resorting to pluripotent stem cells or genetic engineering. This line of research has given rise to nine clinical trials, at least two of which have had promising results, with a third trial ongoing. "If the FDA gives its approval, Deramiocel will become the first cell therapy authorised for a heart disease (to date, the ones approved are for cancer or orthopaedics)."

One of the major advantages of this therapy is that it does not require genetic or chemical engineering. "These are primary cells, with no abnormalities, which significantly reduces the risks associated with other, more complex treatments," he said.

A fundamental discovery of his research was that the therapeutic effect of cells was due not so much to their direct integration in cardiac tissue but rather to the release of exosomes, small extracellular vesicles loaded with non-coding RNA. This has led to the development of new drugs based on these specific RNAs, eliminating the need to administer live cells. These molecules are more stable, reproducible, and easier to manage than cells, which is a step along the road to more practical, scalable therapies.

Faced with this new challenge, the range of treatments is still limited. Hill commented that the drugs currently available to combat obesity have demonstrated effectiveness but also risks and limitations: they must be continuously administered, can have significant side effects, and do not guarantee sustained improvement. "The question is: if you lose 20 kilos, does your diabetes disappear? Sometimes. Does your cardiac health improve? We still don't know for certain. We have seen improvements in quality of life but not in mortality," he added

The American cardiologist, Joseph Hill, one of the world's leading experts in cardiovascular research, highlighted the importance of fostering spaces where clinical physicians and basic scientists can come together. "For a long time we have lived in parallel worlds. Physicians speaking one language and scientists another. But when we come together at events like this conference, new ideas arise, barriers break down and progress is made to the benefit of patients," Hill noted.

For this specialist, such interdisciplinary interaction is particularly important in times like ours, when rapid advances are being made in biomedical knowledge. Many of the conference sessions had a strong translational component, with research already pointing to clinical applications. However, he warned, "Some of these ideas will become useful therapies and others will not; however, constant dialogue between science and medicine is essential."

ill's talk focused on one of the most concerning conditions of our times: heart failure with preserved ejection fraction (HFpEF). "This condition is different to hypertrophic cardiomyopathy and is experiencing an alarming increase worldwide," he explained. Its spread is closely linked to the global increase in obesity, a phenomenon that affects developed countries and regions with fewer resources alike.

Although this syndrome is still not fully understood, the scientific community is starting to identify some of its fundamental causes. One of the major factors is meta-inflammation, a type of chronic inflammation induced by metabolic dysfunction. "Our laboratory has shown that meta-inflammation plays a key role in the development of HFpEF. And, as obesity increases worldwide, this type of inflammation is becoming a serious driver of cardiovascular diseases."

Faced with this new challenge, the range of treatments is still limited. Hill commented that the drugs currently available to combat obesity have demonstrated effectiveness but also risks and limitations: they must be continuously administered, can have significant side effects, and do not guarantee sustained improvement. "The question is: if you lose 20 kilos, does your diabetes disappear? Sometimes. Does your cardiac health improve? We still don't know for certain. We have seen improvements in quality of life but not in mortality," he added.

That's why he believes the solution will come with a combined approach: classic prevention (diet, exercise), new pharmacological therapies and future research. "For half a century we have known that taking care of ourselves works. New drugs are promising, and I'm optimistic, but I maintain we still have a long road ahead."

With a career in cardiology spanning three decades, Hill has witnessed radical transformations in the management of cardiovascular diseases. "Today, we have technologies such as TAVR or stents, which have saved thousands of lives. Before, 30% of patients died after a heart attack. Now, that figure is only 3%," he highlighted. Nevertheless, such success has brought a new challenge: a growth in the number of heart failure cases due to the persistent damage in hearts that survive a heart attack but in a weaker state.

In this context, he distinguishes two broad types of heart failure: HFpEF, for which there are still no effective treatments, and HFrEF (heart failure with reduced ejection fraction), which is better understood and treatable with the many effective drugs available on the market.

Nevertheless, access and treatment adherence are still a problem. "Asking a patient to take six or eight different drugs a day is complicated, particularly in countries like the United States where cost is an obstacle," Hill noted.

He showed his support for the idea of the polypill, a strategy that combines various drugs in a single daily dose tablet. "For many people, particularly patients with limited financial resources or who are averse to taking multiple drugs, it can be a valuable tool. Its main limitation is that there can be no personalised adjustments, but it is worth considering for certain cases," he concluded.

With over three decades of experience as a cardiologist specialised in heart failure and transplants, Dr Mariell Jessup, Chief Science and Medical Officer of the American Heart Association (AHA) has witnessed enormous progress in the treatment of these diseases. "Renin–angiotensin–aldosterone system inhibitors have radically transformed the treatment of heart failure. They have significantly improved patient survival and quality of life," she noted, talking about ACE inhibitors, ARBs and the more recent neprilysin inhibitors (ARNIs).

Despite this progress, Dr Jessup warns that inequality of access to and application of tried and tested treatments continues to be a great challenge, particularly for the most vulnerable populations. "Limited access to qualified physicians, high costs and the complexity of treatments make it difficult to achieve healthcare equality. It is absolutely vital to tackle these systemic problems in order to guarantee nobody gets left behind," she insisted.

From her position at the AHA, Jessup has worked extensively to lessen the distance between science and clinical practice in unattended communities. "We have spent over twenty years translating scientific advances into real clinical solutions. Our aim is that life-saving interventions should reach all demographic and regional groups with an emphasis on equity and access."

Dr Jessup's views on low and middle income countries are quite clear: the key is in primary prevention. "Eliminating tobacco consumption and controlling blood pressure are cost-effective interventions with a great impact. They can drastically reduce the burden of cardiovascular morbidity worldwide," she stated.

HAn aspect that Dr Jessup considers fundamental is the effective integration of the patient's voice in research, health policies and healthcare models. "We cannot design solutions without listening to the people who need them. Clinical guidelines should be culturally sensitive, patient-focused, and applicable to diverse populations," she stressed.

Jessup also brought up a major pending issue: the cardiovascular health of women. Although heart diseases are the main cause of death among women worldwide, this sector of the population still does not receive the necessary care. "It is essential to increase women's own awareness of their cardiovascular risk. What's more, we need a higher amount of specific research, and the adequate participation of women in clinical trials," she affirmed.

The gap is directly related with the social determinants of health like poverty, education, or gender inequality. "Limited access to healthcare has a disproportionate impact on women. Health systems should prioritise the elimination of structural and economic obstacles," she insisted.

As a global leader in cardiovascular health, Dr Jessup is clear about her commitment to women's health: "We should never stop talking about it. To close the gap between cardiovascular outcomes between men and women, we need constant advocacy, more investment in specific research and more representation of women in all spheres." ■

RES@CNIC-SEC, A CONSOLIDATED INITIATIVE IN CARDIOLOGY TRAINING

The RES@CNIC-SEC Programme promoted by SEC, the Spanish Society of Cardiology, and CNIC, the Spanish National Centre for Cardiovascular Research, is a consolidated training initiative aimed at resident physicians in the first stages of the MIR programme in cardiology or other specialities related with cardiovascular diseases.

This programme, accredited by the SEC Accreditation Committee, offers a maximum of 25 medical professionals each year the opportunity to take up a training internship lasting between 4 and 9 consecutive weeks in CNIC laboratories.

Since 2012, a total 236 first or second year cardiology residents who are SEC members have participated in the programme. The 133 men and 103 women have come from 85 different hospitals in different regions of Spain, with San Carlos University Hospital (Madrid) contributing the highest number of interns (18%), followed by Ramón y Cajal University Hospital (Madrid) and a high number from Virgen del Rocío University Hospital (Seville) (6%) and Navarra University Hospital (Pamplona).

The main aim of the RES@CNIC-SEC Programme is to foster a vocation for research among young physicians, facilitating direct contact with state-of-the-art techniques in biomedical research. During the internship, they work in an environment of scientific excellence supervised by CNIC researchers and add to their training with theoretical modules given by experts in cardiovascular research.

This initiative also seeks to lay the foundations for future scientific collaboration between residents of the Spanish National Health System, with institutional support from the SEC and CNIC.

Carlos Nicolás Pérez García is a veteran of the RES@CNIC programme, who participated in 2016. Currently active in CNIC, he is part of the Translational Laboratory for Cardiovascular Imaging and Therapy led by Dr Borja Ibáñez, actively participates in observational cohort studies like PESA, and the recently started REACT, as well as in clinical trials coordinated from CNIC's Clinical Trials Technical Unit. "This career path would probably not have been possible without the opportunity RES@CNIC offered me," he acknowledges.

Carlos Nicolás remembers his participation in the RES@CNIC programme as one of the most outstanding training internships of his residency period. "I participated in 2016, during my first year as a cardiology resident, and it was my first real exposure to cardiovascular research from a non-clinical perspective."

Carlos Nicolás joined the experimental pathology of atherosclerosis line of Dr Jacob Bentzon's group and, although at the time his previous experience with science had been limited to the clinical sphere, working in a basic research environment helped him understand an absolutely fundamental dimension of cardiovascular medicine, which takes place in the laboratory, far from patients but with a direct impact on their future.

During his time with Dr Bentzon's group, he observed how the molecular and cell mechanisms explaining atherosclerotic disease are dissected, which gave him much more comprehensive perspective on the scientific process. "It was essential to understand cardiovascular research in a context other than the clinical but equally important; without this type of research the real translation of knowledge to medical practice would not be possible."

Thanks to his participation in the programme, Carlos Nicolás was able to acquire a solid grounding in experiment design and, in particular, in the use of rigorous laboratory technique, which had not formed part of his previous training. "I was able to familiarise myself with microscopy and the histological staining protocols applied to animal models of atherosclerosis, learning to interpret images and data from a perspective of cell and structure."

He underscores that thanks to this experience he "had to develop a more fine-tuned critical thinking and understand the scientific logic underpinning many of the developments that we later translate to clinical practice."

Miguel Ángel Martín Arena, a cardiology resident at La Paz University Hospital in Madrid, describes his personal experience in the RES@CNIC program as enriching, "both from a scientific and human point of view."

During his stay, he says, "I had the great opportunity to get involved in real basic research at the highest level and to be in contact with true leaders in cardiovascular research worldwide. For me, it was an unforgettable experience and a unique opportunity to see how research is conducted from the micro to the macroscopic level. And from a human perspective, I met unique colleagues and wonderful people who taught me and accompanied me throughout the process."

Miguel Ángel believes that this program has allowed him to develop and enhance his curiosity, to ask himself why things happen and to try to find answers to his questions. "It has also allowed me to get closer to biochemistry and basic biology, which I had forgotten so much from my degree, and to realize that they are the basis of what we later apply in clinical practice. Finally, I have learned to develop resilience, as research requires a great deal of effort and sacrifice, often without full reward, hence the importance of not giving up, as perseverance is the key to achieving long-term goals."

Unlike most of the participants, Miguel Ángel joined Dr. Jose Antonio Enríquez's group, whose laboratory conducts basic research. He acknowledges that the experience was very positive. "It has allowed me to understand and learn how mitochondria work and how their integrity is key to the proper functioning of the cardiovascular system. I believe that the fact that basic and clinical researchers work together in the same laboratory is essential, because each of them brings a different perspective to the same problem, and that is very enriching. It has also allowed me to understand complex laboratory techniques, to appreciate the time and effort involved in each of them in order to advance research, and that having a leader and guide is key to the team functioning well, as they are the driving force that pulls the rest along in difficult times."

In his opinion, his experience has made him realize that without biomedical research, it is impossible to understand what doctors do on a daily basis. "They are complementary disciplines that feed off each other and enable us to advance knowledge, understand pathophysiological processes, research new molecules and treatments, and ultimately treat patients better. As for my future career, it helped me to confirm that I want to be able to devote part of my time to research, to try to contribute something to the scientific community with my efforts. In Spain, this is not always easy to achieve, and seeing doctors at the CNIC who are able to do so gave me the strength to fight for it."

Laura Fuertes Kenneally also joined Dr. Jose Antonio Enríquez's group. "Joining Dr. Enríquez's group allowed me to acquire key skills in molecular and cellular biology and to step outside my clinical comfort zone to develop a more critical eye, capable of questioning many assumptions. Beyond technical skills, what struck me most was sharing my daily work with a teaching team passionate about discovering the mechanisms of disease, in an environment of collaboration and constant intellectual stimulation."

Her experience in this basic research group developed key skills such as critical thinking, rigorous interpretation of scientific literature, experimental design, and the formulation of well-structured research questions. "It also allowed me to hone my ability to communicate results clearly and effectively, as well as to integrate error as a fundamental part of the scientific process."

As a cardiologist, her experience in Dr. Enríquez's group, which focused on mitochondrial metabolism and its involvement in cardiovascular pathophysiology, was very enriching. "For a doctor in training, getting involved in basic research is a unique opportunity to delve deeper into the underlying mechanisms of diseases, something that clinical routine rarely allows. It is true that, in the hustle and bustle of daily practice, we sometimes fail to see the immediate importance of this training. It feels distant from our routine, its results can be slow, and the practical application is not always obvious. However, it is crucial to understand that basic research is the foundation on which all future medicine is built," she emphasizes.

"Doctors also have a lot to contribute to basic research. Our clinical perspective can help design experiments that reflect the complexity of human physiology, ensuring that conditions are as close as possible to the reality of the patient. In addition, we can facilitate the 'bureaucratic leap' necessary to transfer discoveries from animal models to human application."

He acknowledges that one of the most valuable lessons he learned on a personal level was multidisciplinary teamwork: collaborating with exceptional professionals in their respective fields—biologists, bioinformaticians, biotechnologists—who share the same scientific curiosity. "This constant exchange of ideas, approaches, and solutions around a common goal not only enriched my research vision, but also helped me grow as a person. Finally, something that is often underestimated is that research is, above all, an exercise in creativity. It goes far beyond applying pre-established clinical protocols: it involves connecting unexpected ideas and approaching problems from alternative perspectives."

Raquel Frías García-Lago heard about the programme from older residents who encouraged her to take advantage of the experience and discover the project's activities. From the start, she says, "I felt included." At the Translational Laboratory for Cardiovascular Imaging and Therapy, "they included us in the SPHERE clinical trial, and that is how I began to analyse cardiovascular MRIs."

Thanks to that, "I had the opportunity to participate in animal experimentation projects related with pulmonary hypertension, gain a deep understanding of the readings obtained during catheterisation and even get started on some interventional techniques. For me, the experience awoke a great interest in research because both with animal models and MRI analysis we considered situations typical of daily clinical practice, which allowed us to broaden our knowledge and formulate questions that I might not have considered in the routine of daily healthcare."

Raquel, who is currently working as a visiting scientist at Dr Garcia Lunar's laboratory believes that "having participated in this programme from the start of my residency has encouraged me to think in a different way and stimulated my scientific curiosity, particularly about diseases that are less known by residents in their first years, like pulmonary hypertension, amyloidosis or cardiotoxicity."

One of the aspects that most impressed her during her time with the RES@CNIC programme was the professionalism and rigorous approach of the centre's professionals. "Their excellence alongside their open attitude and willingness to teach play a key role in residents getting an in-depth understanding of how a quality research project is conducted."

She also highlights CNIC's state-of-the-art installations and access to high-quality imaging tests, animal facilities and advanced laboratories. In addition, "the training sessions throughout the programme are a basic added value, as they are led by experts in different diseases, many of whom are national or international leaders in their field."

Carlos Nicolás also emphasises the human and scientific quality of the environment, access to cutting-edge technology, and the possibility of full participation in real research projects. He also notes, "the programme includes structured theoretical training, which facilitates a comprehensive understanding of cardiovascular research."

During her internship, Raquel was able to understand the level of organisation and planning a complex research project requires, and to consider the bioethical implications that need to be taken into account at each stage. "The experience enabled me to develop a more structured and critical perspective on research."

Although it is difficult to know how this experience will influence her future career in medicine, what she is clear about is that she liked having an insider's view of how a research project progresses and understanding the implications involved in participating in these projects. "The programme is of great value in bringing research to the young in an accessible way, facilitating understanding of basic principles and enabling each resident to study as far as their interest takes them. In my case, it was a motivational experience that has driven me to continue collaborating with the working group led by Carlos Nicolás and Inés García Lunar, both of whom I can continue to learn a lot from, and with whom I would like to continue to progress along this route of training and research."

Laura emphasizes that her participation in the @ResCNIC program consolidated her vocation for research and shaped the professional path she is currently following. "I am now enjoying a Río Hortega grant from the ISCIII at the General Hospital of Alicante, which allows me to combine clinical care with research focused on cardiac rehabilitation and heart failure. Thanks to this experience, I also understood the importance of integrating research into clinical practice. I recognize that research during residency is often perceived as an extracurricular activity that consumes what little free time we have. However, it is essential to encourage research to be an inherent and continuous part of medical training."

Luis Díaz spent just two months in the program at Dr. Ana García Álvarez's laboratory (Translational Research in Heart Failure and Pulmonary Hypertension), but it was enough to understand the fundamentals of research. "In the field of image analysis, which is what I have been able to develop the most, I have been taught to be methodical and rigorous. I have learned that reproducibility is essential. From a clinical point of view, the evaluation of so many imaging tests has given me agility and critical thinking skills, and I am now able to judge what is pathological and what is not.".

From the very beginning, Luis felt part of the team and integrated into day-to-day activities. "When my colleagues at the hospital ask me how it went, I always tell them that I couldn't say whether the CNIC selects researchers with a keen interest in teaching and collaboration or whether it is the center itself that instills this character in its members, but it is certainly a trait common to all the people I have met there."

For Luis, this program has shed a lot of light on an obscure area that is little explored by young doctors, namely basic research. "It has made me see the huge amount of work that goes into achievements and advances, especially the most important ones. It has been a reality check on how overwhelming research can be without a solid team, but even so, the program has only increased my interest in a career that combines it with clinical work."

For Carlos Nicolás, the RES@CNIC programme marked a turning point in his view of medicine. "It enabled me to discover that research and clinical practice are not separate roads, but are, of necessity, interconnected. Thanks to the experience, I became aware of the opportunities exiting for young cardiologists with a scientific vocation."

"In fact, thanks to the programme I found out about the existence of initiatives like the CARDIOJOVEN SEC/CNIC competitive grant I later obtained in 2022. This enabled me to complete the online Clinical Trial Masters at the London School of Hygiene and Tropical Medicine (University of London, UK) at the same time I was doing my doctorate."

For Raquel, her positive experience means that she recommends the programme to any resident physician because "it brings anyone starting out their residency closer to research in an enjoyable way, at a good time to do so, as it can change your outlook on the coming years and encourage you to participate in a project, or simply enjoy the very good experience, and learn from different animal models or theories as you understand what goes in to the publication of a scientific paper."

Laura agrees: "I would definitely recommend it. RES@CNIC is an opportunity to step away from the frenetic pace of healthcare and reflect on the 'why' behind what we do every day. It allows you to acquire a solid foundation in research and changes the way you think, giving you an analytical perspective. In addition, direct contact with top-level scientists opens doors to future collaborations. On top of all that, you get to meet and connect with other residents from all over Spain. This creates a network of contacts and a shared learning environment that lasts way beyond your time at CNIC."

Carlos Nicolás shares their opinion. "I would recommend the RES@CNIC programme to any cardiology resident who is curious about research or who wants to broaden their scientific training. It's a unique experience, which not only enables you to acquire knowledge and technical skills in surroundings of the highest level but also opens doors to new opportunities for professional development. It is a long-term investment that can transform both your outlook and opportunities in the field of cardiovascular medicine."

Miguel Ángel agrees with them: "It's a unique opportunity to get involved in high-level basic and translational research. Whether you like research or not, I think it's a necessary step during your residency to understand how a research laboratory works. It also helps you appreciate the effort involved in dedicating yourself to it and understand that, without it, medicine would not advance."

Miguel Ángel emphasizes the fact that "from the very beginning, you are working with your hands in a laboratory, you are an active part of it, and you are fully integrated into the line of research they are conducting. I would also highlight the opportunity to be in contact with leading figures in the cardiovascular field and listen to them talk about their project and the advice they give to younger people. Finally, I would highlight the human aspect. I was very fortunate to be able to do the program in Dr. Enríquez's laboratory, a sensational team that integrated and supported me from the very beginning and with whom I am still in contact today. I am very grateful to them."

Luis recommends the program to all residents in cardiology or cardiovascular surgery who are interested in research. "I think it's an incredible experience to get started in this field, being guided by people with a lot of experience. It also represents a unique opportunity to establish links between the hospitals of origin and the CNIC."

The beneficiaries of this program are not only the participants. The CNIC groups that host them, especially those dedicated to basic research, also benefit significantly. The incorporation of cardiology professionals brings new approaches and perspectives to their research work, which is especially valuable in groups made up mainly of biologists or biochemists.

And last, but not least, Carlos highlights the strategic value of the programme as an entry point to future collaborations with the CNIC and its role as a catalyst for physicians who want to include research as an essential part of their medical careers.

The programme is open to people who meet the following requirements

- In the first or second year of the MIR programme in cardiology or a related speciality.
- SEC member.
- Certification in English of B2 or equivalent level.
- Applications should be submitted exclusively online via the CNIC website:

https://www.cnic.es/es/convocatoria/rescnic-sec-cnic

The selection process includes financial help for travel and accommodation expenses for participants coming from hospitals outside the Community of Madrid.

The RES@CNIC-SEC programme is another example of SEC and CNIC's commitment to training in translational research in the cardiovascular field and to the development of young talent, which is a key element to progress in knowledge about and the treatment of cardiovascular diseases, the first cause of death in the world. ■

Principal Investigator and the Alan A. and Edith L. Wolff Distinguished Professor of Pathology and Immunology at Washington University

Dr. Jonathan Kipnis: "SCIENCE ISN'T JUST A LUXURY. IT'S INFRASTRUCTURE FOR THE FUTURE"

Dr. Jonathan Kipnis is a Principal Investigator and the Alan A. and Edith L. Wolff Distinguished Professor of Pathology and Immunology at Washington University, where he also serves as a Professor of Neurology, Neuroscience, and Neurosurgery, and Director of the Brain Immunology and Glia (BIG) Center. His research focuses on the interactions between the immune system and the central nervous system, aiming to understand the cellular and molecular mechanisms underlying neurodegenerative, neuropsychiatric, and mental disorders, as well as healthy aging. He has received NIH Director's Pioneer Award in 2018 and is an elected member of the National Academy of Medicine (2022). Known for his groundbreaking contributions to immunology and neuroscience, his work has been recognized both nationally and internationally.

What Is Brainwashing?

Every organ in the body produces metabolic waste. Think of it like your household plumbing: clean water comes in through pipes, and dirty water is flushed out through sewage systems. In our tissues, blood vessels deliver nutrients and oxygen, while lymphatic vessels remove waste.

The brain, being one of the most metabolically active organs, has an abundance of blood vessels to supply everything it needs. But how does it remove waste, especially given that there are no lymphatic vessels within the brain tissue itself?

To solve this, the brain has evolved a unique waste-clearance system. Our brains are surrounded by a fluid called cerebrospinal fluid (CSF). This fluid enters the brain alongside arteries, washes through the brain tissue, and exits along with veins, eventually draining into the dura mater—the protective outer layer of the brain. Recently, lymphatic vessels were discovered within the dura mater, and this is where the brain's waste is ultimately drained. Though complex, this system appears to work effectively.

The concept of the brain needing to be "cleaned" isn't entirely new—we've long suspected that waste removal in the brain is crucial. What's new is the growing evidence showing how and when this "brainwashing" happens, and how essential it may be to prevent neurological diseases.

For example, recent research, including work from my lab and others, has shown that part of this cleansing activity takes place during deep sleep. During sleep, neurons fire in synchronized patterns, creating slow waves that seem to drive the flow of CSF through the brain. These waves help carry waste through and out of brain tissue—essentially washing the brain while we sleep.

Disrupting this system can have serious consequences. In studies with Alzheimer's models, for example, when the function of the brain's lymphatic vessels is impaired, waste products like beta-amyloid accumulate more quickly. This supports the idea that poor waste clearance may play a direct role in the development of diseases like Alzheimer's, Parkinson's, frontotemporal dementia (FTD), and other age-related neurological disorders—all of which are marked by inflammation, waste buildup, or both.

In short, ensuring your brain gets a proper "wash" each night—especially through quality deep sleep—may be more important than we ever imagined.

How has the discovery of lymphatic vessels in the brain changed your understanding of neurological diseases?

Most of what we currently know comes from experimental studies, in my lab and many others. We've used various mouse models of neurological disorders like Alzheimer's and Parkinson's to explore this. In these models, we can interfere with the brain's lymphatic vessels through genetic manipulation, surgery, or pharmacological methods.

When we impair the lymphatic function in these mice, their disease symptoms get significantly worse. That tells us that the proper functioning of these vessels is crucial for managing brain waste—and likely plays a role in the progression of neurodegenerative diseases.

Now, that's in mice. The key question is: does this apply to humans? We do know now that humans also have lymphatic vessels in the brain, which was an important discovery in itself. The next step is to gather concrete evidence linking lymphatic dysfunction to human disease, particularly neurodegenerative conditions. That part is still emerging.

There's some buzz around recent work in China. I'm absolutely not involved, but I came across it online. Apparently, some centers there are performing a procedure called lymphatic venous anastomosis (LVA) in Alzheimer's patients. This involves surgically connecting lymphatic vessels to veins in the neck to improve waste clearance from the brain (or to unclog the clogged lymphatics).

They claim to have seen notable improvements in these patients. While there's only a small publication on this so far, several clinicians and researchers on social media have reported witnessing the surgeries firsthand. If these results hold up in peer-reviewed research, it would be truly phenomenal.

But isn't that a pretty aggressive procedure?

Surprisingly, no. From what I understand, it's a relatively simple surgery performed in the neck area. Clinicians have described it as straightforward—but I admit, when I first heard about it, I thought it sounded a bit wild. Still, if it works, it could open up entirely new treatment avenues.

Do you think this could be a future cure for Alzheimer's?

It's hard to say just yet. It might be too soon to talk about a "cure," but the possibility is intriguing. It actually reminds me of something that happened years ago, shortly after we discovered the brain's lymphatic vessels. I was at the University of Virginia, and I showed our findings to John Jane Sr., a legendary neurosurgeon and department chair. He was already ill at the time, but still incredibly sharp. After seeing the data, he told me, "This could play a major role in Alzheimer's. Maybe one day we'll treat it with neurosurgery."

And I thought it was a crazy idea at the time — this was about 10 years ago. But he was clearly far more visionary than I was.

Imagine if Alzheimer's disease could be cured with a simple procedure—do you think that's possible?

I don't know if it can be cured, but I do believe that enhancing and maintaining the function of the brain's lymphatic vessels could potentially delay the onset of Alzheimer's. Curing an ongoing neurodegenerative disease is extremely difficult but delaying its onset—that's a more achievable goal, in my opinion.

Maybe surgical approaches like lymphatic venous anastomosis (LVA) could help in the later stages of Alzheimer's, but I don't believe surgery will be the universal solution. Personally, I think boosting lymphatic function with drugs or other non-invasive methods is more promising. In fact, I've co-founded a company (Rho Bio) focused on developing such treatments. I'm optimistic and hope to live long and dementia free

Are there any other ways to help clean or maintain these brain vessels?

Yes, and the best one we know of right now is sleep—especially deep sleep. During deep sleep, our brain seems to have the highest clearance activity. But remember, waste removal in the brain is a two-step process.

First, the cerebrospinal fluid (CSF) has to move through the brain tissue to collect waste. Then, it has to be flushed out properly. Think of the brain like a house, you can bring clean water in, but if you don't flush the dirty water out, you're left with a swamp. It is important to produce new, clean CSF; removing the old, dirty CSF; ensuring good flow through the brain tissue, and of course, functional lymphatic drainage is critical.

This is why I don't think one single drug will ever solve it all—it will require a multifaceted approach.

You mentioned sleep. But as people age, they often sleep less and worse. And we're living through a global insomnia crisis. Could that lead to a dementia epidemic in the near future??

That's a fair concern, but I'm actually more optimistic than that. Here's why: If the brain's clearance system really works best at night—and that's still up for debate—then we need to ask: Can we find a way to make this clearance process more efficient?

Think about it. Most biological systems aren't perfect. Our immune system, for instance, needs vaccines to fight pathogens and therapies to help fight cancer. So, what if we could do the same for brain waste clearance? Imagine if we could develop a method to supercharge brain cleaning, so instead of needing 7–8 hours of sleep, you could get the same benefit in just 2 or 3 hours. Or even more radically—what if we could clean the brain during the day, eliminating the need for sleep altogether? That's my dream. It sounds far-fetched now, but I love this idea.

All this still sounds a bit like science fiction to me.

Curing cancer sounded like science fiction just 20 years ago, too. Science moves fast, and what sounds far-fetched today could be tomorrow's reality.

Can the immune system help clear waste from the brain or support brain function??

Absolutely. The immune system is like the maintenance crew in a Formula One team. Even with the best driver (your brain), if the maintenance team isn't functioning well, you'll never win the race. Immune cells support blood vessel function, cerebrospinal fluid (CSF) production, waste removal and even lymphatic vessel performance-

So, if the immune system is dysfunctional, the brain suffers too. On the other hand, a well-regulated immune system can detect problems and even help fix them. It's crucial.?

Yes, 100%. I totally agree. For a long time, neuroimmunology lived in the "dark ages" where the brain and immune system were seen as enemies. The old thinking was: "Keep them separate. Immune activity in the brain is always bad." But that's no longer the case. Now we know that they constantly communicate, and when balanced properly, the immune system can help the brain heal and function better.

But of course, if it's overactive or dysfunctional—like in autoimmune diseases—then yes, it can cause damage. That's why understanding how to modulate immune activity in the brain is key.

But animal models aren't always accurate, right?

Exactly. That's a major limitation. Animal models often represent just one aspect of a

complex human disease. You can manipulate the immune system in animals and get certain results, but it doesn't always translate to people.

Still, experiments in more straightforward systems—like spinal cord injury models—show that removing specific immune cells can actually worsen outcomes. That tells us: these cells are necessary. The immune system is part of the brain's support network.

Inflammation is often seen as harmful to neurological diseases.

Yes, and that's another outdated idea. Inflammation isn't always bad. Take cancer, for example, it's also associated with inflammation. But in that case, some types of inflammation help fight the disease. It's all about context.

Sometimes inflammation is part of the body trying to fight or prevent disease, and other times it may contribute to it. We need to understand what role it's playing in each specific case rather than labeling it as good or bad.

How can knowledge from immunotherapy in cancer be used to treat neurodegenerative diseases like Alzheimer's?

That's a great question. We're still in early days, but some cancer immunotherapy concepts are being evaluated in neurology too. For example, PD-L1 inhibitors, commonly used in cancer, are now being evaluated in clinical trials for Alzheimer's—there's one happening in Israel right now.

It's a different disease, so the approach and dosage are different, but the core idea is the same: boost or release the immune system's ability to help. In 10 or 20 years, we may have enough long-term data to see if people who received cancer immunotherapies are less likely to develop neurological diseases like Alzheimer's.

There's already some interesting evidence from vaccines as well—certain vaccines have been linked to lower rates of Alzheimer's, though we don't fully understand why yet.

You sound very optimistic. So, let's dream big — if you had unlimited money and technology, what kind of experiment or project would you pursue?

That's a fun thought. If I had unlimited money and all the tools I could imagine, I think I'd still stay in my current area—because I truly believe we're on to something important. The direction is solid. But of course, with unlimited resources, we could move faster and get bigger. We've already learned a lot from mouse models about brain clearance and how to manipulate it. The next step would be moving into larger animals, like pigs, sheep or even monkeys, before making the leap to clinical trials in humans. That's where the cost explodes—and that's where unlimited money would really help. It could fast-track this translational research.

I'd also want to do multi-modal approaches—targeting 2 or 3 key pathways at once: improving CSF flow, supporting lymphatic function, and boosting the immune component. Then I'd evaluate the impact across diseases like Alzheimer's, Parkinson's, and others.

Also, we're very interested in cellular therapies for neurological diseases, inspired by what's been done in cancer immunotherapy. With more funding, we could really push forward designing smart, targeted cellular strategies and again evaluating them in larger animal models before clinical translation.

But I'll say this—unlimited money can dull your creativity. It's healthy to have limits. I believe funding should be sufficient, but not infinite. That challenge forces innovation.

And speaking of funding—how's the situation right now in the U.S.?

It's still not as bad as it may seem from the outside. The NIH budget as a whole hasn't changed yet, which is a good thing, and I think it continues. However, people working on developing vaccines for future pandemics — an extremely important area of research — are unfortunately being targeted. This is both terrible and devastating.

But in my own field, neuroimmunology, we haven't seen cuts so far. Thank God. And frankly, with how rapidly our politicians are aging, they probably realize they'll need these brain-focused therapies sooner rather than later!

All jokes aside, American science is going strong. Yes, we're going through a politically volatile time. It feels like a volcano right now, but I hope it'll settle. And the US will continue to lead the world's science.

As scientists, we should focus on our science and let the work speak for itself.

Science must stay apolitical. These days, everyone wants to be a politician, even scientists. They're doing interviews, talking policy—but I'm not sure that helps. I believe we contribute best by doing the work, showing the world that what we produce is vital, meaningful, and has immediate health benefits.

So, do you believe that science is essential to keeping America strong?

Absolutely. You can't make or keep America great without great science. That's what built this country's leadership in the modern world—innovation, research, and technology.

I half-joke sometimes: we should have a slogan like "Make American Science Great Again"—because without it, the rest eventually crumbles. Unfortunately, many politicians don't seem to get that. Science isn't just a luxury. It's infrastructure for the future.

And I'll say this, as scientists, they have some responsibility too. Somewhere along the way, we lost a bit of the public's trust. Not because science isn't working—but because a few bad players made headlines. And the media magnifies every scandal.

Look, in farming, there are cheaters. In law, in business—everywhere. But that doesn't mean the entire profession is corrupt. Most scientists are just decent, hardworking people. We're motivated by curiosity. But that curiosity leads to real solutions—new medicines, diagnostics, therapies. And unfortunately, I think we've done a poor job communicating that value to the public.

The pandemic should have shown the world how vital science is, isn't it?

You'd think so, right? COVID-19 should've been the moment where people said: "Thank God for science." Scientists came together from all over the world, many working non-stop to create a vaccine in under a year. That's unprecedented. It's incredible.

But oddly, it became divisive. Especially with vaccines, which should be seen as one of the greatest human achievements.

My daughter—she's in college—just made a TikTok video explaining that vaccines are life-saving and don't cause autism. She broke it down so simply, with facts, and I thought: this is what we need. Clear, relatable, accessible science communication.

Still, the problem isn't just misinformation, it's also the perception of greed. Pharmaceutical companies made huge profits, and for some people, it seemed like money mattered more than lives. That damages public perception.

But again—this is why we need science. Not panic. Not politics. Just real, honest research to explore the long-term effects. We don't need fear—we need data. We need to regain public's trust to have their support as we are pushing the frontiers of what's possible. ■

Full Professor of Pharmacology at the Department of Excellence of Pharmacological and Biomolecular Sciences, University of Milan

Dr. Giuseppe Danilo Norata: "NO CHOLESTEROL, NO PARTY"

Dr. Giuseppe Danilo Norata is a Full Professor of Pharmacology at the Department of Excellence of Pharmacological and Biomolecular Sciences, University of Milan, Italy. He graduated in Pharmacy in 1996 and obtained his PhD in Experimental Medicine from the University of Siena in 2002. From 2002 to 2004, he completed a postdoctoral fellowship at the Karolinska Institute in Stockholm (Sweden). His research focuses on the molecular mechanisms involved in vascular and cardiometabolic diseases and their connection with immunometabolism from a translational perspective. He has published over 190 papers in the field of cardiovascular and immunometabolic diseases and has participated as a speaker and chairman at various international conferences. Additionally, he is the co-chair of the European Atherosclerosis Society (EAS) Congress Committee and a member of the Faculty of the International Atherosclerosis Research School and the European Working Group on Immunometabolism.

What is your main area of research?

My main area is immunometabolism, an emerging research field that explores how cell metabolism influences immune cells. This area is exciting because it connects two branches of science: cellular metabolism, which biochemists studied extensively decades ago, and immune cell plasticity. My research focuses on cholesterol metabolism and sterol disorders, highlighting how they impact immune function.

What are the key findings in this area?

There are three main topics that connect cholesterol metabolism with immune cell activation. The starting point is the understanding that atherosclerosis, a key research area at CNIC, is not just a consequence of increased plasma cholesterol. We now recognize that hypercholesterolemia actively drives inflammation and immune responses in the vessel wall.

Is this a new concept, or are we just beginning to understand it better?

We've long known that atherosclerosis is an inflammatory disorder and that cholesterol is a key driver. Traditionally, cholesterol was understood to induce an inflammatory response in the bone marrow. However, we focus on the molecular mechanisms by which immune cells sense changes in cholesterol metabolism, altering their activation status. This knowledge extends beyond atherosclerosis, offering new therapeutic targets for cardiovascular and immune-related diseases. As a pharmacologist, I am particularly interested in molecular mechanisms that could lead to innovative treatments.

Does this research open new opportunities for drug development?

Yes, and it extends beyond traditional cholesterol-lowering drugs. We already have highly effective medications that lower plasma cholesterol and reduce cardiovascular risk. However, I'm exploring additional pathways linked to cholesterol metabolism that could provide novel pharmacological targets, beyond just lowering cholesterol levels.

Can we use vaccines or immune system manipulation to make immune cells resistant to cholesterol or lipoproteins?

That's a tricky question. The phrase "No Cholesterol, No Party" suggests that elevated plasma cholesterol is the starting point for atherosclerosis. Prevention plays a crucial role, but cholesterol-related diseases are tricky because hypercholesterolemia is often silent until a major event, such as a heart attack, occurs. Unlike hypertension or diabetes, which have noticeable symptoms, high cholesterol is harder to detect without biochemical tests.
This is why early screening is essential, particularly for individuals with genetic predisposition. A key emerging concept is "primordial prevention," which emphasizes lifelong healthy habits from childhood, such as physical activity and a balanced diet. While these measures may seem basic, they are proving to be highly effective even in resource-limited settings.

Additionally, we now have effective drugs for primary prevention, such as statins, which are inexpensive and widely available. New pharmacological approaches, including PCSK9 inhibitors and bempedoic acid, offer further options, particularly for high-risk patients with familial hypercholesterolemia (FH). In severe cases, such as homozygous FH, patients can experience heart attacks as early as age 10 if left untreated, highlighting the need for early intervention.

With poor dietary habits becoming more common, could we face a cholesterol epidemic in the coming decades?

This issue should be examined from two perspectives. Cholesterol itself is not always linked to poor diet; rather, an overall deteriorated lipid profile, including high triglycerides, is often associated with unhealthy eating habits.
Dietary patterns have changed dramatically in recent decades. A striking example is seen in FH patients. Previously, these individuals had high LDL cholesterol but normal triglyceride levels. Now, their children not only inherit FH but also exhibit hyperlipidemia and obesity due to poor diet. This shift is transforming cardiovascular diseases into broader cardiometabolic disorders, making prevention even more urgent.

Cardiovascular disease is a global pandemic. Do we have enough drugs to treat everyone, and can national healthcare systems sustain the costs?

This is a critical challenge. Data from the Global Burden of Disease project show that cardiovascular disease remains the leading global cause of death, accounting for 18 million deaths annually, with 9 million due to ischemic heart disease. Hypercholesterolemia is a key contributor, alongside diabetes and other risk factors.
The challenge is that as life expectancy increases, patients accumulate multiple risk factors, requiring simultaneous treatment for different conditions. In the past, an elderly patient might have taken one or two medications. Now, many require multiple drugs for cholesterol, hypertension, and diabetes, increasing healthcare costs.
To manage this, we must adopt personalized medicine, targeting expensive new therapies for those who will benefit most. Advances in imaging and early detection of atherosclerosis will help guide treatment decisions, potentially reducing hospitalizations and overall costs. In Italy, for example, hospital expenses consume 85-88% of healthcare budgets, while only about 6% is spent on drugs. A small increase in drug spending could significantly reduce hospitalization costs, maintaining overall financial balance.

What are the biggest challenges in cardiovascular research for the coming years?

Despite advances in managing cholesterol, diabetes, and triglycerides, patients still have residual cardiovascular risk. New factors, such as elevated lipoprotein(a) [Lp(a)], are emerging as significant risk contributors. Several drugs targeting Lp(a) are in advanced clinical trials.
Inflammation is another key issue. While anti-inflammatory drugs have shown benefits in reducing cardiovascular events, they can also increase infection risks. This creates a delicate balance, as inflammation plays a crucial role in immune defense. Future research must refine personalized approaches to minimize risks while maximizing benefits, especially for high-risk patients.

What advice do you give to your students?

Primarily, resilience is key. A career in science is challenging, but passion and perseverance are essential. Funding opportunities vary by country, but good ideas, strong collaborations, and international networks can lead to success. I encourage my students to embrace discovery and innovation.

Do you have any thoughts on the global political landscape and its impact on research?

I don't have direct insights, but I believe Europe must focus on strengthening its research ecosystem. While U.S. scientists express concerns about funding, they continue to progress. In Europe, we should use this moment as an opportunity to enhance collaboration and investment in research. We need to come together and further enhance the quality of European research. This is already evident in several opportunities available at the European level, not only through specific funding calls. For instance, we have the ERA for Health grants, which are awarded to different European cities. Additionally, the European Union has recently agreed on a cardiovascular research agenda. Similar to what was done for oncology years ago, cardiovascular disorders will now be a key priority for European research in the coming years. This presents a unique opportunity to further elevate the quality of European research, from basic science to translational studies and clinical applications.

Is this your first visit to this center?

Yes, this is my first time here. However, I was already familiar with many researchers by name, having met them at various conferences. This center has a long and distinguished history as a milestone in cardiovascular research in Spain, so it's a pleasure to be here. I had the opportunity to engage in discussions with three researchers: Sancho (David), Vicente Andrés, and Carlos Perez Medina. They are working in three distinct fields, yet our conversations quickly led to interesting experimental discussions. It was insightful to exchange ideas, and I also had the chance to offer some suggestions. This kind of academic interaction is a valuable exercise in advancing research together. ■

Associate Professor in the Department of Physiology at the Perelman School of Medicine at the University of Pennsylvania

Benjamin L. Prosser: "STEPPING INTO NEUROSCIENCE HAS DEFINITELY MEANT STEPPING INTO A NEW WORLD"

Dr. Benjamin L. Prosser is an Associate Professor in the Department of Physiology at the Perelman School of Medicine at the University of Pennsylvania. In addition, he serves as Deputy Director of the Pennsylvania Muscle Institute (PMI) and Director del Center for Epilepsy and NeuroDevelopmental Disorders (ENDD). He is also a member of the graduate groups in Cell and Molecular Biology and in Biochemistry and Molecular Biophysics. Dr. Prosser's research focuses on physiology, muscle biology, neurodevelopmental disorders, antisense oligonucleotides, heart failure, cytoskeleton, microtubules and RNA biology. His laboratory seeks to understand the cellular and molecular mechanisms underlying muscle and neurological diseases, with the goal of developing new therapies for these disorders.

What is your main area of research?

The main focus of my research has been on cardiac mechanics and mechanobiology, really since I started my lab at Penn Medicine about ten years ago. We've been particularly interested in the cardiac cytoskeleton, the internal scaffolding that organizes heart muscle cells—and how this structure regulates the mechanical properties of those cells.

One of the early questions we explored was how microtubules, which are long, rigid elements of the cytoskeleton, behave in a beating heart cell. Imagine these structures having to endure constant contraction and relaxation—every second, every day. We began by visualizing these microtubules in action and found they behave almost like springs inside the heart cell. This fascinating observation sparked our broader interest in how the microtubule cytoskeleton responds to mechanical stress and contributes to the heart's overall mechanics.

That line of research has evolved into identifying changes in the microtubule cytoskeleton that we believe impair cardiac mechanics in heart disease. We've since moved toward developing therapeutic strategies targeting those changes, with the goal of improving cardiac function in heart failure. This work has become increasingly translational, and we're now collaborating with several biotech partners to advance this therapeutic pipeline.

My team also focused on a different story. While microtubules regulate the mechanical properties of cells, they also serve as tracks for transporting cargo inside the cell. We became very interested in how this transport, particularly of RNA and ribosomes, contributes to remodeling heart muscle cells during stress.

When the heart experiences stress, whether it's physiological (like during exercise or pregnancy) or pathological (like high blood pressure), it grows—a process known as hypertrophy. But the direction of growth matters: does the cell get longer or thicker? That dimensional change impacts function, and the big question has been: what molecular and subcellular processes decide this?

We believe we've identified a new model in which intracellular cargo transport plays a central role in dictating heart cell geometry—whether it elongates or thickens—and this has important functional implications.

How do you study this process? Do you use imaging techniques?

Yes, our lab relies heavily on advanced high-resolution microscopy—both live-cell and fixed-cell imaging. Since we're particularly interested in how RNA and ribosomes are transported within the cell, we use live-cell imaging to track their movement along microtubule tracks in real time.

We then apply different types of stress to these heart muscle cells—mimicking physiological or pathological conditions—and monitor how cargo transport changes. For example, we look at shifts in the direction, speed, or quantity of cargo being transported, and how those changes influence where and how the cell builds new proteins. Ultimately, this helps us understand how the cell grows and remodels in response to its environment.

How could your work on microtubules and cargo transport lead to new treatments for heart disease?

In many forms of heart disease, particularly cardiomyopathies, the heart undergoes pathological remodeling or hypertrophy. Since the heart is made up of billions of individual muscle cells, the way each of those cells grows has a major impact on the function of the entire organ. If all the heart muscle cells get thicker, the heart wall thickens, which can restrict its ability to fill properly. Conversely, if the cells elongate excessively, the heart dilates—resulting in dilated cardiomyopathy and impaired contraction.

What we're aiming to understand is the cellular decision-making process: what determines whether a heart muscle cell grows in length or in width? If we can identify the molecular pathways that control this remodeling, we could potentially redirect growth in disease settings. For instance, in conditions that typically cause pathological lengthening, we might be able to either reduce that lengthening or promote thickening to preserve function. The ultimate therapeutic goal is to precisely control the geometry of heart cell growth in order to maintain or restore healthy cardiac function.

What kinds of therapeutic approaches could this lead to in the future?

A key focus of our work is identifying the molecular machinery that regulates intracellular cargo transport—particularly motor proteins that travel along microtubules. These motor proteins move in different directions: some move cargo toward the cell center, others toward the periphery. We're currently screening small molecules that can modulate the activity or directionality of these motors, with the idea that we could control how cargo is distributed within the cell—and, as a result, influence the cell's growth pattern.

In terms of therapeutic strategy, this could involve genetic manipulation of motor proteins or microtubule regulators, but more feasibly, we're focusing on small molecules that can selectively alter microtubule function. In fact, in today's presentation, I'll be showing data on a few such compounds that appear to influence whether a heart muscle cell becomes longer or thicker. In a clinical context, you could envision applying these compounds to guide heart remodeling in a beneficial direction, potentially offering a novel approach to treat or prevent heart failure.

I read that part of your research now focuses on brain disorders, particularly following your daughter's diagnosis. Was neuroscience something you were interested in before?

No, not really. I'm happy to talk about it's actually become a whole other half of my lab. I won't be presenting that work today, as I'm here mainly to speak about our cardiac research, but yes, this area has become deeply personal.

My daughter was born in 2018, and just a few days later, she began experiencing seizures. A couple of months after that, she was diagnosed with a rare genetic neurodevelopmental disorder. She's six years old now. She's severely disabled—nonverbal, just learning to stand and take a few steps—but she's a happy child. And that's the most important thing.

Was it difficult transitioning from cardiac to brain research? How did that begin?

At first, I assumed many people were already studying this disorder, and honestly, I wasn't sure what I could contribute coming from a cardiac background. But I quickly realized it was a relatively newly identified condition—

only described in 2009—and there were only a few research groups worldwide focused on it.

So, I started reaching out. I found neuroscientists and clinicians on campus who knew about brain development and genetic disorders, and we formed a team. That effort grew into a large, interdisciplinary center focused on neurodevelopmental disorders and epilepsy, with both clinical and translational arms.

What kind of work is the center doing now?

On the clinical side, our goal is to better understand these rare disorders—how they present, how they evolve. Just in the last year, we've seen over 100 children with this specific condition in our clinic. Given that only about 1,000 children are known to have it globally, that means we've seen nearly 10% of the worldwide population. That's helped us learn a great deal.

On the translational side, we're working on gene-targeted therapies to address the root genetic causes. Because we know exactly what mutation causes this disorder, we have a clear target for therapy. We've developed a few therapeutic candidates and hope to move into first-in-human trials in the next few years. It's an exciting and hopeful time.

And I imagine your work on this rare disorder could help advance research on other brain conditions too?

That's certainly the hope. Right now, we're focused on two specific genetic causes of brain disorders, but the infrastructure we're building—both in terms of clinical evaluation and therapeutic development—is designed to scale.

We're particularly focused on disorders of the synapse—the site of communication between neurons. The two genes we're studying both encode proteins that function at the synapse, and there are many other rare diseases caused by mutations in synaptic proteins. By developing expertise in this area, we aim to extend our work to a broader group of synaptic disorders, often referred to as "synaptopathies." The knowledge and tools we're building can—and should—benefit many more children and families.

How do you see your research impacting families affected by rare neurological disorders?

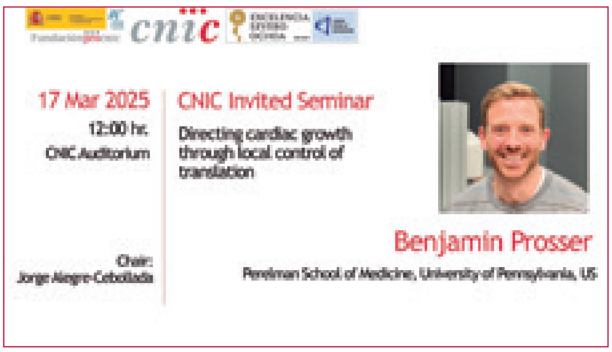
Very directly. We've become very connected with the patient community, and honestly, that's where I feel I can make the most meaningful impact. Being a scientist and a parent gives me a unique perspective—it keeps science rigorous but always grounded in what matters most: the lives and hopes of families.

We're now developing gene therapies that, if successful, would be the first of their kind to enter a child's brain. There's real risk in that, and an immense responsibility. It's not just about advancing science, it's about building trust with families, especially when you're asking them to consider enrolling their child in a first-in-human trial.

I feel very fortunate to be in a position where I can do this work, and I never forget that it's a privilege.

You're now deeply involved in clinical trial planning and drug development—did you study medicine or come from a clinical background?

No, I didn't go to medical school, I'm a PhD. So much of what I'm doing now, especially on the translational and clinical side, is new to me. Planning clinical trials, navigating regulatory pathways, none of that was in my original training. But you learn as you go. You learn what you need when you need it. ■



University of Southern Denmark

Daniel Ketelhuth: "WE JOKE SOMETIMES THAT "RESEARCH" JUST MEANS YOU NEED TO SEARCH AGAIN—AND AGAIN, AND AGAIN"

Prof. Daniel Ketelhuth is a leading researcher in cardiovascular disease (CVD). A pioneer in the field of immunometabolism, his research has shown that the dysregulation of tryptophan metabolism via the kynurenine pathway and other metabolic alterations in immune cells play a significant role in modulating vascular inflammation. Prof. Ketelhuth currently leads a research team at the University of Southern Denmark, dedicated to advancing our understanding of how various metabolic targets can influence CVDs, particularly atherosclerosis and abdominal aortic aneurysms (AAA). Over the past two decades, he has published nearly 90 articles and mentored more than 30 students and fellows.

Your studies suggest the immune system plays a role in heart disease. Can you explain how?

My research focuses on CVDs—primarily atherosclerotic cardiovascular disease, but we're also studying abdominal aneurysms, which can be related to atherosclerosis. Broadly speaking, we're interested in vascular inflammation, or inflammation in the vessel wall, and how we can modulate this process.

CVDs are characterized by extensive vascular inflammation, a pivotal driver in their pathogenesis. In these conditions, the immune system plays a critical role, with immune cells infiltrating the vessel, releasing inflammatory cytokines, and contributing to tissue remodeling and damage. Interestingly, these immune responses are intricately linked to intracellular metabolic changes within the immune and vascular cells themselves.

For example, when immune cells become activated, they undergo metabolic reprogramming, switching from a resting state that relies primarily on mitochondrial metabolism to a more glycolytically active state that supports rapid proliferation and effector functions. If not properly controlled, this shift fuels the local inflammatory response and exacerbates the disease process.

Another interesting aspect of the metabolic skewing during inflammation is that various intermediate metabolites, on different pathways, are not just substrates for energy or biosynthesis but also can interact with proteins and also act as signaling molecules. Some of these metabolites can also interact directly with DNA or with specific receptors, providing an additional layer of regulation over cell function in the context of inflammation.

How could your research on metabolism lead to new treatments for cardiovascular disease?

Alongside many others, including David Sancho at CNIC, we're studying what's known as immunometabolism, the metabolism of immune cells—and how this metabolism can actually dictate whether a cell becomes inflammatory or not. Therefore, if we take a deeper look, we're particularly interested in pinpointing the main intracellular metabolic pathways involved in deleterious and protective processes in the artery wall.

For example, we can inhibit enzymes or knock out their encoding genes in specific cells or whole animals and then evaluate how these modifications impact cellular functions and disease processes. What's particularly interesting about immunometabolism is that the metabolic reprogramming we see in immune cells is, in many ways, similar to what happens in cancer cells. This opens up a really exciting possibility: drugs originally developed to target cancer cell metabolism might also be repurposed to treat cardiovascular diseases.

In our lab, we've been exploring this idea in some projects. We've recently assessed a compound that was originally developed for a rare genetic disease characterized by an enzymatic imbalance leading to severe lactate acidosis. This enzymatic imbalance is also found in various cancers, driving the drug to also be considered for trials for both solid tumors and blood malignancies. Our results, which were recently published, showed that the drug could actually protect mice from developing atherosclerosis. And in a separate model of abdominal aneurysm, it also provided protection. So, this opens a new path where we might use metabolic therapies—not just in cancer—but also in cardiovascular and inflammatory diseases.

By modulating metabolism in immune and also vascular cells, we can influence how these cells behave in the vascular wall, which could help reduce inflammation and prevent or treat atherosclerosis and aneurysms.

Are there some lifestyle or dietary changes that could support better heart health based on your findings?

Yes, that's a really important point—what we're seeing now is an epidemic of metabolic dysregulation worldwide. Conditions like obesity and diabetes are massively increasing, and they're not just metabolic issues, they directly affect the immune system. That's why immunometabolism is so relevant. It helps explain how these metabolic diseases are tied to cardiovascular conditions like atherosclerosis and aneurysms.

Of course, there's strong evidence that improving lifestyle—like diet, exercise, sleep—has a positive effect on the immune system and reduces disease risk. Unfortunately, we know it's hard to get people to change their behavior long-term. So, part of our research is about finding drugs that can replicate some of those benefits, even if lifestyle changes aren't fully happening.

But that raises another challenge: if we have a drug for everything, will people stop caring about their health altogether? It's a bit of a philosophical and societal dilemma.

And then you have these new drugs like Ozempic or other GLP-1 receptor agonists. Obesity and type 2 diabetes are already huge risk factors for cardiovascular disease, and these drugs seem to hit several birds with one stone. There's a recent meta-analysis showing that these drugs can reduce blood pressure, which, of course, relates to weight loss induced by these drugs. Interesting, though, is the possibility that the benefits of weight loss might also impact immunometabolism, potentially playing a significant role in protecting against atherosclerosis.

But the question is, do people have to stay on these drugs for life? We still don't fully know the long-term side effects. I hope they won't turn out to be harmful, because so far, the clinical benefits are very strong—not just in terms of weight loss but also in reducing cardiovascular risk, which could have a massive public health impact. Daniel Ketelhuth

Going back to what I just said, mechanistically, we still don't completely understand how these new drugs work. It's probably not just through glucose regulation. That's something the field needs to keep investigating. For us, right now, we're not directly researching Ozempic or GLP-1s, but we're definitely watching the space closely.

How has technology changed the way you do research—from when you started until now?

It has changed tremendously. When I first moved to Stockholm, it was the era of GWAS—genome-wide association studies. Everything was about identifying SNPs and mutations and understanding how they might relate to disease.

But today, the field has taken a huge leap forward. We now have single-cell sequencing, which allows us to analyze gene expression at the level of individual cells. We're also starting to see epigenetic profiling at the single-cell level, and there are even discussions about doing single-cell metabolomics—which would have been unthinkable not that long ago.

Another game-changer is spatial transcriptomics. This technology brings in a whole new dimension by mapping gene expression directly in tissue sections, allowing you to see not just what genes are expressed, but where in the tissue this is happening. That spatial context is crucial, especially in complex tissues like the vascular wall.

What excites you most about the future of heart disease research?

I'm excited about the intersection of big data, single-cell analysis, and spatial transcriptomics. These tools reveal previously hidden layers of disease mechanisms. Also, understanding how metabolic dysfunction contributes to inflammation in the context of both cardiovascular disease and also aging, which could unlock preventive strategies that change the course of disease decades in advance.

What breakthroughs do you foresee in cardiovascular research in the coming years?

A deeper understanding of how lifestyle and metabolic imprinting affect long-term inflammation and disease risk. There's growing evidence that early-life exposures — even in utero — can program immune cells toward disease-prone states. Identifying and potentially reversing these imprints will be revolutionary.

Will the immune system be the central key?

Absolutely. The immune system is the common thread across many cardiovascular diseases, autoimmune, cancer, and infections. A dysfunctional immune system underlies much of the pathology in the natural process of aging. If we can understand and modulate immune system aging, the benefits could be enormous.

How do you find mentoring students?

My group is relatively small. I currently supervise four PhD students and one postdoc. We also work closely with four associated technicians. In addition, I always have master's students and short-term trainees who stay with us from a few months to one year. So, in total, the group tends to be around 10 to 12 people.

Mentorship is definitely one of the most important—and challenging—parts of being a PI. It's really an art in itself. In fact, at Karolinska, and I believe also in Denmark, we're required to complete training in pedagogy to

become "official" supervisors. In Sweden, it should be at least five weeks of formal training. I've completed that, and it definitely helps, but of course most of what you learn is on the job, and case by case.

I've been mentoring students for just over 10 years now, and I'd say I'm much better at it today than I was when I started. Nevertheless, a lot of how I run my group is influenced by what I learned from my own mentors, both the things I admired and the things I felt should be done differently. One of my main mentors was actually involved in the advisory board for CNIC early on, and I learned a great deal from working with him.

For me, one of the most important aspects of mentoring is just being available. We meet religiously once a week—Tuesdays at 8:30—for a one-hour group meeting where everyone brings raw data, shares challenges, and discusses experiments. It's also a space to plan large experiments that need team coordination. Those meetings are key for building team spirit and momentum.

Motivation is another huge part of my role. Research is tough—maybe 10% success, 90% failure.

Someone once told me, "failure is just a way to improve your research."

We joke sometimes that "research" just means you need to search again—and again, and again. It's about persistence and learning from what doesn't work. I also try to help my students gain confidence in what they present and ensure their conclusions are solid.

Do you give your students career advice or broader guidance?

Yes, we talk about that a lot. I try to share not just scientific knowledge, but also what I've learned about navigating a career in science. I make it very clear what a privilege it is to work in academia. It's a life of constant learning. Every day brings something new, and we're often standing right on the edge of the next major shift.

Right now, I think we're living through one of those shifts. The pace of technological advancement—especially with omics—is producing an explosion of data, but we're still learning how to navigate and make sense of it. It's overwhelming at times but incredibly exciting to be part of shaping what comes next.

In terms of clinical impact, the future lies in precision medicine. We already have effective general treatments—statins, antihypertensives, aspirin—but they've likely reached their limit in terms of population benefit. Now we need to understand why some people don't respond, and tailor treatments accordingly.

For example, in our work, we're asking whether metabolic dysregulation at the cellular level, particularly in immune cells—might be a key to this. Does the expression of certain metabolic enzymes relate to whether cells are inflamed or not? Could this link to somatic mutations, which are studied by José Javier Fuster here at CNIC, or to accelerated immune aging? Diseases like type 2 diabetes and cardiovascular disease are strongly tied to aging, and we suspect that these metabolic changes may be pushing parts of the immune system into an "aged" inflammatory state earlier than normal.

That's the kind of deeper understanding we need to really shift how we treat disease—and being part of that journey is what makes research so rewarding.

Although you have been living in Scandinavia for the past 20 years, you originally come from Brazil. Have you ever thought about returning?

Of course, it's always in the back of my mind. I've been away for some time and feel very settled in Europe. But I love collaborating with Brazilian researchers and never say never. The scientific environment in Brazil is more challenging, but that also breeds creativity and resilience. I owe a lot to my education in Brazil, particularly at the University of São Paulo, which provided a solid foundation in scientific exploration and opened the doors to international research opportunities that have shaped my career. ■

Kyoto University Graduate School of Medicine, Department of Molecular Oncology

Yasuki Fukita: "WHAT I REALLY WANTED TO DO IS THE FUSION OF PHYSICS AND BIOLOGY"

Prof. Yasuyuki Fujita, PhD, from Kyoto University's Graduate School of Medicine, specializes in how normal epithelial cells eliminate cancer cells through competition. He first conceived this model as a student and later became the first to demonstrate it for normal vs. cancerous epithelial cells in Nature Cell Biology (Hogan et al., 2009). Born in Osaka, he studied medicine at Kyoto University and completed most of his Ph.D. at Osaka University, researching intracellular signaling under Prof. Yoshimi Takai. He then spent five years in Berlin at the Max-Delbrück-Center for Molecular Medicine, where he discovered Hakai, a protein involved in disrupting cell-cell adhesion (Neuron, 1998; Nature Cell Biology, 2002). From 2002 to 2011, he led a group at University College London's MRC Laboratory for Cell and Molecular Biology, focusing on epithelial cell competition. Since then, he has continued this research at Hokkaido University and, since 2020, at Kyoto University.

What exactly is cell competition?

Cell competition is a process in which cells with different properties compete for survival or space. Often, abnormal, or aberrant cells are identified and eliminated by other cells, maintaining tissue health. This process also plays a role in the early stages of cancer. When oncogenic mutations occur in a single cell, neighboring cells can recognize and eliminate them, acting as a natural cancer-prevention mechanism.

Miguel Torres was the first to demonstrate that cell competition occurs during mouse embryonic development, showing that abnormal cells are eliminated to ensure proper body formation. His 2013 study published in Nature had a significant impact on the field. I started working on cell competition in 2009, and after being impressed by his findings, I invited him to Japan for a talk. Since then, we have maintained a strong connection, discussing cell competition mechanisms despite our different research focuses.

Spain is a strong hub for cell competition research—Ginés Morata, based at a cancer center, first discovered cell competition in Drosophila, making him the "father" of the field. Japan is also advancing rapidly in this area, and today, both countries are at the forefront of cell competition research. We frequently invite Ginés and Miguel to our conferences in Japan, including a major international meeting last summer.

How does cell competition help prevent cancer in our bodies?

Although not yet fully demonstrated, our research using mouse models suggests that when cancerous cells emerge, they can be eliminated through cell competition. This phenomenon is observed across multiple species, including Drosophila and zebrafish, indicating it is a conserved biological mechanism.

We also found that various environmental factors, such as chronic inflammation and high-fat diets, can weaken cell competition. For example, in obese mice, cell competition decreases. This suggests that lifestyle choices may influence our body's ability to eliminate early-stage cancer cells.

Does this mean our diet and lifestyle can influence how well our healthy cells fight against cancer?

While we do not yet fully understand how cells recognize abnormal ones, this is a major question in the field. Miguel and I are actively investigating potential triggers that enhance or suppress cell competition. We are particularly interested in how environmental conditions influence this process.

Why do some cancer cells evade the immune system while others do not?

The immune system typically responds at later stages of cancer development. In the very early stages, normal cells may act as the first line of defense, eliminating abnormal cells before the immune system is involved. This highlights the potential importance of cell competition as a protective mechanism in early cancer prevention.

How close are we to using your findings to develop cancer treatments?

If we can fully understand the mechanisms behind cell competition, it could be applied to cancer prevention. Our research indicates that a low-glucose diet—achieved through intermittent fasting or a ketogenic diet—can enhance cell competition in mice and promote the elimination of cancer cells. However, we still need more detailed studies to determine how this can be translated into practical applications.

Additionally, we have identified a drug that promotes cell competition, which could be another potential avenue for treatment. While cell competition may not be applicable to advanced malignancies, it could be valuable for early-stage cancer prevention.

Could we one day train healthy cells, like the immune system, to better fight cancer?

That is one of our key goals. Since we know that low glucose promotes cell competition, modifying environmental conditions or cell behavior could enhance our body's natural defenses against cancer. However, we must first clarify the underlying mechanisms before developing a viable treatment.

Could future treatments involve creating "super healthy cells" through diet, drugs, and lifestyle adjustments?

Advances in genetic sequencing allow us to identify individuals at higher risk for certain cancers, such as pancreatic or colon cancer. In the future, we might tailor interventions to strengthen specific organs' defenses against cancer. We know that certain individuals may have a higher predisposition to diseases like pancreatic or colon cancer. With the increasing accumulation of sequencing data, it's possible that in the future, by analyzing DNA, we could gain a deeper understanding of these tendencies. This could guide us in identifying individuals at higher risk for certain cancers, such as pancreatic cancer. In turn, we could explore ways to boost the pancreas' defense mechanisms to reduce the risk. This kind of tailored approach might become possible as sequencing data continues to advance. However, we are still in the early stages of understanding how to fully utilize this information. One thing we've found is that cell competition, which can influence cancer development, behaves differently across tissues. For example, when we compare the lung, intestine, and pancreas, we observe that cell competition is very active in the intestine. But in the lung, cell competition may be less pronounced, and sometimes cells can escape from this competition, potentially leading to tumorigenesis. However, we still don't fully understand why cell competition occurs differently in various tissues. Understanding why competition differs between tissues is an important area of research.

Immunotherapy is becoming a standard treatment for many cancers. Could it be combined with cell competition research to find a cure?

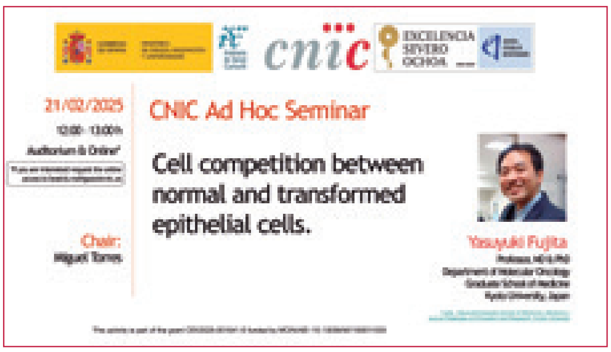
I'm not entirely sure whether cell competition can be applied to highly malignant cells. What we have shown so far is that cell competition seems to occur at earlier stages of cancer. So, while I'm uncertain if cell competition research could directly lead to cancer treatments, it may offer insights into prevention strategies.

Currently, there are no drugs proven to truly prevent cancer. The closest example is anti-inflammatory drugs, like aspirin, which have been shown to reduce the risk of colon cancer, but that's about it. So, cancer prevention could be a major focus in the future. Cell competition, in particular, could play a role in such preventive approaches, and that is my ultimate goal.

The biggest challenge is proving that a drug can effectively prevent cancer. Typically, this requires studying large populations—millions of people with and without the drug—to observe long-term outcomes. However, many researchers worldwide are working on developing diagnostics for precancerous conditions. Once these diagnostic tools are available, the effects of cancer-preventive drugs can be scientifically assessed. By monitoring the progression of pre-cancerous cells—whether they evolve into malignant ones or disappear—prevention strategies can be better understood. If such diagnostic methods are developed, we could see significant progress in preventive medicine.

If you had unlimited time and resources, what would you study?

What I really wanted to do, but haven't yet achieved, is the fusion of physics and biology. My background is in medicine, but I became interested in science when I was around 18 or 19. At that time, I wanted to pursue something revolutionary, something that no one had tried before. I realized that there are three major fields in science: physics, chemistry, and biology. The fusion of chemistry and biology has already been explored, as has the fusion of physics and chemistry. But there hasn't been as much focus on the fusion of physics and biology. ■



Institute of Rheumatology, Imperial College London

Dra. Claudia Monaco: "IN CARDIOVASCULAR DISEASE, WE THINK WE KNOW A LOT. BUT IN REALITY, WE DON'T"

Claudia Monaco trained as a cardiologist and PhD with Professor Attilio Maseri at the Catholic University of Rome, Italy, before moving to the Kennedy Institute of Rheumatology, Imperial College London to work with Professor Marc Feldmann. She moved to the University of Oxford in 2011, where she became Professor of Cardiovascular Inflammation. Her group was the first to establish innovative experimental methodology for the isolation, culture and targeting of live cells from human atheroma lesions. Her work allowed the elegant characterization of the inflammatory and synthetic properties of human atherosclerosis, establishing toll-like receptors as important activators of innate immunity in atherosclerosis. The Cardiovascular Inflammation Team is now focused on interpreting the functional diversity of immune cells in atherosclerosis with single cell biology techniques and devise strategies for their selective targeting.

What is the role of macrophages in the development of atherosclerosis, and how has our understanding of their function evolved?

We are focused, in particular, on macrophages and what their function is in atherosclerosis. I think it's quite interesting, because different types of macrophages have different functions in the development of atherosclerosis. Before, we thought that all macrophages were bad—that all macrophages and the whole immune system were actually promoting atherosclerosis. But now we know the picture is much more complex than that.

It's very related to what macrophages are, where they're seeded, and how they establish themselves in specific niches. There are some macrophages, like the lipid-associated macrophages, that definitely promote disease. But there are others—vascular macrophages that are already present within the vessel wall—that actually act like guardians of the artery and are protective.

I think it's very important—this direction we're going in, toward more targeted therapies. The idea is not to block all macrophages, because some are actually your friends. You need to look after them, especially the ones in the artery, while others are really pushing things toward a dangerous, disease-promoting path. This duality is really important, especially from a therapeutic perspective. That's why we're so fixated on understanding this better.

And how can you tell the difference between the "good" macrophages and the ones you want to block? What kind of techniques do you use?

We use single-cell biology a lot. We're not yet in the clinical space, but we've identified good markers. If those markers prove reliable, it would be easy to translate this into new tools to look at different macrophages in vivo. There's also the potential to tailor imaging—not just therapeutics, but also how we visualize these macrophages.

The key idea we want to get across is that there isn't just "one" macrophage type. We always said that macrophages are very pleiotropic—that they can take on different phenotypes—but that didn't always seem to matter because we thought they all eventually just changed into each other. But actually, that's not quite true.

There is some dynamic flexibility, yes, but it's quite reproducible which path they take. They really adapt specifically to their environment. For example, in the adventitia, they adopt a very specific phenotype, and in the intima, a different one. And these phenotypes remain pretty stable during atherosclerosis, and also in health and disease. They're not just switching randomly between states, they're adapting in a niche-specific way, just like cells in any other organ. That's important because it means we can start visualizing and treating patients differently more precisely.

You mentioned you're still in the experimental phase and not yet in clinical trials. How far is immunotherapy for cardiovascular disease?

I think there have been some early trials, and there are more and more now that are targeting inflammation in atherosclerosis. It's really a booming field. We waited a long time to get here. The field was slow to move in this direction because so much focus was on lowering cholesterol, which is of course important—but inflammation wasn't really explored until recently.

Studies like the CANTOS trial and others have started targeting cytokines, and I think we are going in the right direction. But progress is still very slow. One big reason is the lack of imaging tools. Imaging is only now reaching the level where we can maybe use it instead of relying on hard cardiovascular outcomes in trials.

If you look at cancer, for example, you can track things much faster, look at the size of the tumor, and see how the patient is responding. Same for diseases like rheumatoid arthritis, where you can scan the joints or use PET imaging. Those imaging methods have been around for decades, and they've made it possible to run smaller trials that are either based on imaging or give you very clear, early outcomes.

But with cardiovascular disease, we still have to look at how patients are doing over 5, 10 years. That's a big challenge. These trials are very expensive, especially because biologic drugs cost so much. So pharmaceutical companies need to make a huge financial commitment. The more we can improve imaging, the more we'll be able to run meaningful trials that evaluate new biologics or targeted agents, like nanotechnology-based ones.

I think evolution isn't just about immunology, it's also about how we study this in the real world. Other fields can run smaller trials to understand how things work and then move on to larger outcome trials. But here, with trials like the CANTOS trial—which involved over 10,000 patients and a very expensive biologic—that kind of scale is almost unheard of in other diseases like rheumatoid arthritis.

So yes, the challenges are really at the clinical stage—how we bring all this incredible knowledge about the immune system into cardiovascular medicine. The real barrier is economic.

You're a cardiologist—you worked in Rome for many years, and then you moved to Oxford. You trained as a cardiologist, and then you also shifted into doing experiments and research. How do you combine these two areas?

Well, combining clinical duties and research is one of the biggest challenges you can attempt to do. I think if you're doing clinical research—like outcomes-based research or imaging studies—then it's easier to combine with clinical work. But if you're developing science at the molecular level, it's much harder to do both. At least I couldn't manage it as well as I would have liked.

There's a big divide between what we think we know and what we actually know. We have this concept of how atherosclerosis develops, how the immune system contributes—but in reality, we don't really understand the specific mechanisms at play. I felt that, to bridge this gap, I had to go back to the basics. That meant not only using experimental models but also working with human samples. I saw a huge opportunity in single-cell biology has been a big opportunity—for all of us—to understand human immunology at a very detailed level. Because if we only look at mice, then the gap between mouse and human, and then from preclinical to clinical stages, is massive.

For example, we really need access to human vascular tissue. But as cardiologists, we've moved so much toward percutaneous approaches to the coronary arteries, so we don't actually remove them anymore. That's why I work a lot with vascular surgeons. They still operate in a way that allows us to obtain human tissue—but that might not last. Even vascular surgery is moving more and more toward stenting, which means we'll eventually lose the ability to get that tissue. We have this narrow window of opportunity where we can still work with tissue from patients, and I felt I had to take it. I'm very vocal about this having a short window before vascular surgery becomes entirely percutaneous, which of course is an advancement, but it also cuts us off from the chance to study real human tissues.

It seems like improvements in clinical treatment are making things harder for basic science in a way.

Exactly. It's advancing, but at the same time, it means that now we have this critical window. I always say vascular surgeons do research, collect tissue, because we need to analyze what the cells are really doing. Just relying on blood studies, on systemic inflammation, doesn't tell us much about what's happening in the atherosclerotic artery. The immune cells inside the artery are very different in their programming compared to circulating cells in the blood.

Most cells come from the blood—but there are also some embryonic macrophages that form inside the artery and never circulate. And even the ones that come from the blood and stay in the artery for 10 years, they acquire very specialized instructions. You can take monocytes from blood and run as many blood tests as you want—but that doesn't tell you what's actually happening inside the artery.

They behave differently, they look different, they've changed their shape and function completely. This creates a gap in what we can understand—it seems like we're missing something in these studies. We can't see all the different effects a drug might have if we only look at peripheral blood. I think the real answers are also in the vascular tissue, in the atherosclerotic plaque itself. We need to go as close to the source as possible—to find real targets, and to see the real effects of drugs on atherosclerotic tissue.

Because a lot of clinical trials have targeted systemic inflammation. But that's not the same as inflammation within the plaque. The drivers of plaque inflammation may be different.

We know systemic inflammation is a risk factor, yes, but what you see in the blood isn't necessarily what's happening in the plaque. We often assume it is—because it's convenient. But in cardiovascular disease, especially cardiology, we never actually look at the plaque. We look at the lumen. Intravascular ultrasound (IVUS) is the only way to get a glimpse of the arterial wall. Experimentally, we might look at blood from the heart in very complex ways—but we're still mainly looking at circulating markers. We're not really studying the tissue itself.

As a cardiologist with experience of treating patients, do you think your clinical background influences the kinds of research questions you ask?

Yes. And there are two things that help me a lot, I think. And that's why I never stop clinics, even though they told me several times to stop clinics. I think I... I don't like to stop the clinics because I enjoy that interaction.

I think, being a scientist, your rewards are very long-term. If you're a doctor, the rewards are quite immediate, because the patient is happier, yes—you can give the treatment. So, I think it gives me a lot of motivation to serve the patient. But at the same time, I think research is also a good way to serve patients.

Because as a clinician I've learned a lot from basic scientists. They're much better at developing techniques at the bench, and so I have great respect for my scientific colleagues. But sometimes, as a clinician, you can see what really matters. And it makes you particularly attached to a specific disease, you know? Basic scientists are sometimes across fields.

This study gives me the determination and the drive to really try and solve atherosclerosis.

As a child, did you always envision yourself pursuing a career in science or medicine, and eventually going into research??

I always wanted to be a doctor. I was a bit of a sickly child, so probably I was exposed to the medical environment quite a lot. So, it ended up that I always said I wanted to be a doctor. But then I disappointed my dad in the long run, because he thought I would become a doctor—like, I don't know, a general doctor—and then he could have me very close to where we are. But instead, you know, my career went abroad. I don't think he's been very happy that I left.

Particularly, I didn't want to be a scientist when I was young. I was very fascinated with doctors. Probably I had this sense of helping people, serving people. For me that's quite important. I learned everything about cardiology in Italy, with Professor Attilio Maseri, who was a great precursor in this field—immune cell activation, particularly in acute coronary syndrome. I learned a lot from him and still carry that imprint into my work.

I also worked with other good mentors in the UK— Professor Mark Feldman—and I learned a lot about the immune system from him and how to stop inflammation. I try the best I can to stand on the shoulders of these two giants to create an understanding of the fine-tuning of the immune system in arteries—in health and disease.

I'm in a rheuma-immunology environment that also does cardiovascular research. I can stay between fields, which benefits me greatly—to always be at the interface between immunologists and cardiovascular people. And I find that this is quite unique. It's quite difficult to replicate everywhere.

Now, cardiovascular immunology is becoming more established, and there will be more and more of these interfaces. Like you have here, also at CNIC—you have more of this interface. So, this is all forming. This is the future.

When I started, you couldn't do this combination anywhere. So, then my options were traditionally quite limited. Now, maybe I could consider moving somewhere in Europe, US—going back to Italy—if there is a funding structure that allows the same level. But of course,

you know, there are problems with funding in every country at the moment. So, it's a bit optimistic. I wouldn't go to Italy just for the sake of going to Italy. Work is very important to me, and I need to have the right combination to move anywhere.

Maybe—maybe you will first come here to do your research at CNIC.

Yes, exactly. Why not? Why not?

You mentioned you had very good mentors in your career—and I suppose you still do. But now, you're also a mentor, you have students in your lab. So, what difference do you find between when you were young and these young students today?

This is a difficult question, because this is a question where you can go down two completely different routes. One would be: we used to work so much harder—and I hate this. I hate the people that go down that path. I hate to say that. I go down after all—we used to be in the lab until late...

I think the new students have a much better ability. The new generations are more well-rounded in the sense that they don't want to completely lose themselves in work or research—and I think this is a positive thing for their lives, absolutely. I see that shift as quite important. Maybe because in Oxford, there is a tradition where you have to have a social life with your college. They organize things. They try to create an environment where students—even postgraduates—can be social if they want to. I like that culture. And this is typical of Oxford, and I love it.

Because they can do so much stuff that I didn't. You know, at our time, there was this idea that you had to negate yourself, to pursue your discipline with no limits—and I think this is not good in the long run.

But I would say: new generations tend to know their topic very well but perhaps do not broaden their horizons as much as they should, be curious of other disciplines. And I battle so much against that. You know, they really get into this thing, they get the PhD, and you do the viva, and they know only this. And maybe they know it very well—but it's very related to that topic. Now there's a lot to catch up on.

So probably, as a reflection, they lost a lot of things. But I always try to tell them that it's important to see how other fields are evolving. Maybe there's an idea you need. Maybe there's a pathway you didn't think about—but it's important in cancer, and maybe it's important also in cardiovascular disease.

I always think that if you're at the interface between two fields, you move faster. Because you can learn, other colleagues can inspire you. So don't look only at your own.

And the other thing I always tell them is that I think, in cardiovascular disease, we think we know a lot. But in reality, we don't. And we always have to revisit the evidence.

Maybe they have a new—a different way—to see their lives and their careers. It's something that really changed.

Yes, but also—even in the field of knowledge of atherosclerosis—we always teach the students: this is how atherosclerosis evolves. In reality, the evidence for our modelling is always very scattered. Because it might be in mice, or in another system. But how it is in humans—we don't really know. So always be prepared to question your assumptions. Don't always follow what other people tell you. You have to have your own ideas. And you always have to challenge the paradigm. ■

Department of Pathology at the University of Michigan in Ann Arbor

Dr. Gabriel Núñez Ollero: "THERE IS NO UNIQUE, PERFECT MICROBIOTA"

Dr Gabriel Núñez Ollero holds a degree in medicine and surgery from the University of Seville, Spain. Between 1979 and 1984 he undertook post-doctoral training as a researcher at the University of Texas Medical Center, Dallas. Later, between 1985 and 1990, he completed his clinical residency with the Department of Anatomic and Molecular Pathology at Washington University in Saint Louis, Missouri. In 1991, he accepted a position as assistant professor in the Department of Pathology at the University of Michigan in Ann Arbor, where he was promoted to Full Professor in 2001. He currently holds the Paul de Kruif Endowed Professorship in Academic Pathology. His laboratory identified genes NOD1 and NOD2, the first members of the Nod-like receptor family, a class of pattern-recognition receptors that mediate cytosolic sensing of micro-organisms. Dr Núñez and his colleagues showed that genetic variation in an NLR family member, NOD2, is strongly associated with susceptibility to Crohn's disease.

You research the connection between the microbiota and inflammatory and autoimmune diseases. Could you explain how the microbiota influences these diseases?

The microbiota is a complex system. Looking at it in figures, the number of bacteria that make up our microbiota is larger than that of our own somatic cells. In fact, in terms of amount, we could say that we are more bacteria than human. The same thing happens at gene level since the number of genes in the microbiota is higher than those of our own genome. It's clear that some diseases are directly caused by microbiota. Some people die from infections caused by micro-organisms that were already in their bodies. A clear example of this is sepsis: when a bacterium reaches the bloodstream causing septic shock. The origin is often a bacterium already existing in the patient's organism rather than one acquired in the hospital. There are other diseases, like ulcerative colitis and Crohn's disease, with a major genetic component, but in which certain intestinal micro-organisms also play a role. In these cases, we know that the microbiota is a necessary factor in the disease's progression.

Then there are many other diseases which the microbiota is considered to influence, although it is not clear to what extent. For instance, in atherosclerosis it has been found that certain metabolites produced by bacteria can foster development of the disease. However, we don't know whether atherosclerosis would occur in the same way without the presence of these bacteria or if their influence merely accelerates the process.

The list of diseases in which the microbiota is believed to play a role is getting longer. Studies have researched its association with autism, liver diseases and many other conditions. However, most studies used animal models, so it isn't yet clear whether the effects are the same in humans. What we do know for sure is that, in conditions like sepsis or septic shock, the bacteria that cause the condition come from the patients themselves and, in some cases, can be fatal.

How can we help or contribute to improving our microbiota?

Each of us has a unique, different microbiota. Colonisation of the microbiota begins immediately after birth, influenced by the mother, physical contact with her, the hospital environment, doctors, and nursing staff. From that moment the gastrointestinal tract and the skin start to become populated with micro-organisms. However, most microbiota are found in the gut since this is where most nutrients are available. There are fewer bacteria on the skin because there are fewer sources of nourishment.

Nutrition plays a fundamental role in the microbiota. Diet can also drastically change its composition in under 48 hours. For instance, a diet rich in meat or one that is vegan generates significant changes in gut microbiota. Many bacteria depend on vegetable fibre to survive. Although our organism cannot digest fibre, it reaches the colon, where certain bacteria ferment it, producing compounds that are beneficial for our health.

The relationship between the human body and the microbiota is known as mutualism: we provide nourishment and a stable environment for these micro-organisms and they, in return, offer metabolic benefits, protection against infectious diseases and other essential functions. It is a balance that benefits both sides.

And then there's diet.

The microbiota can be modified in various ways, but some are more efficient than others. Diet is a key factor that can significantly change it. Nevertheless, another element with a profound effect on its composition is the use of antibiotics. When we take antibiotics, we eliminate certain bacteria that are sensitive to them, which temporarily changes the microbiota. Although many of these bacteria can colonise the intestine again when treatment is suspended, there is always a reservoir of resistant micro-organisms that survive and contribute to its recovery.

The use of antibiotics during infancy is a particularly important issue. There is evidence that frequent use during the first years of life may be related with a higher risk of developing allergies and other diseases in adulthood. That's why guidelines recommend using antibiotics only when strictly necessary, not just to avoid antimicrobial resistance but also to minimise possible long-term effects on the microbiota and health in general.

Probiotics, prebiotics...

Probiotics contain live micro-organisms, like those found in yoghurt. But it isn't clear whether taking them has a significant impact on gut microbiota. When we ingest these micro-organisms, they do not remain in the digestive system for long because they are naturally eliminated. That's why I always say, "Eat yoghurt if you like it, because it is a healthy food, but don't expect great probiotic benefits." To date, no studies have conclusively shown that eating yoghurt or other probiotics significantly changes the microbiota, partly because it's very difficult to design studies that verify this with any certainty.

However, treatments based on microbiota have proved effective for some conditions. A specific case of this is pseudomembranous colitis, a serious infection caused by Clostridioides difficile, a bacterium that releases toxins causing severe intestinal inflammation. This disease usually appears when the prolonged use of antibiotics reduces the diversity of gut microbiota, allowing uncontrolled pathogenic overgrowth of the bacterium.

In such cases, faecal microbiota transplantations have proved to be a highly effective, inexpensive treatment. This consists of transferring the full range of gut microbiota from a healthy donor to the patient to restore bacterial balance in their intestine. In the USA, the donation usually comes from family members, whereas in Europe donors are medically evaluated and selected to guarantee they carry no pathogens.

Previously, this procedure was performed in a rudimentary way, with the microbiota administered via a tube. Nowadays, we have white capsules specially designed to contain the necessary bacteria, which makes treatment more accessible.

You mentioned the acquisition of bacteria when we are born. Many studies show that babies delivered by caesarean section have a microbiome different to children born by natural childbirth.

It isn't clear if it's better or worse. What has been confirmed is that their microbiotas are different during the first months of life. Some studies suggest that around the sixth month of life these differences can balance out due to maternal and environmental contact. To date, there is no clear evidence of a significant, long-term effect. It is true that babies born by caesarean section initially have a different microbiota, but this usually balances out in a few months. So, it doesn't seem to be a deciding factor for health in general.

What does seem to have been shown is that populations living in more isolated environments, such as indigenous communities in the rainforest, have a microbiota that is

much more diverse than the populations of industrialised areas.

Yes, precisely. They have greater microbial diversity and species of bacteria that we no longer have. It is thought that some of these bacteria formed part of the human microbiome in the past but have become lost due to changes in nutrition and our modern lifestyle. Diet plays a fundamental role in this difference.

Are there microbiota banks to preserve these bacteria before they eventually disappear?

Yes, there are initiatives to preserve the microbiota of indigenous communities, like those of Colombia, Peru, or Brazil, because these populations have a microbiota very different from ours. This is due, in large part, to their diet, which is very different from the western diet.

And if someone lived with them for a long period, could they acquire part of their microbiota?

I don't know if there are specific studies about this, but it seems likely. There is evidence that bacteria can pass between people who live together, for instance, between siblings. Although each person has their own microbiota, those of siblings, although not identical, are usually more similar to each other than to those of unrelated individuals.

Of course, because although they have grown up in the same environment, they were born at different times, possibly in different hospitals, and that also influences the microbiota they acquire from birth.

Exactly. The moment and the circumstances of birth influence our initial microbiota, but then factors like diet, environment and contact with other people also play an important role in its development.

Is there an "ideal" microbiota that would protect us from all diseases?

There is no unique, perfect microbiota, but we do know that certain groups of bacteria can protect us against some diseases. For instance, there are populations of bacteria that help prevent oral route infections. However, we still do not fully understand how they work, or which species exactly are responsible for this protection.

Could we use this knowledge to develop protective strategies?

That isn't clear yet. The human microbiome is incredibly diverse; estimates are that each person is host to between 500 and 1000 different bacterial species. This variability makes it difficult to identify an "ideal" microbiota applicable to everyone.

You studied at the University of Seville and then went to the USA to do a post-doctorate.

Yes, I studied medicine in Seville. I went to the USA when I was 24. My case was a little different to most researchers who leave Spain. I went on my own. I studied medicine, I did the MIR residency exams and obtained seventh place in Spain. I was planning to accept a position in Madrid's Puerta del Hierro hospital because they had a good immunology department. But in 1978, while I was at a conference in Rome, I met a professor who offered me a place in his laboratory in Texas. I knew of him, but we had never met in person. If I had not gone to that conference, my life would have taken a completely different route. My intention had been to go abroad later, after I had completed my training in Spain. I had no idea I would go so early.

First, I went to Texas, then San Luis, and finally I arrived in Michigan, where I have been for 30 years. I'll probably retire there. But since 2019, I have spent the winters in Europe because that season in Michigan is very harsh. First, I went to Lisbon, then Madrid, Germany -in Freiburg- and now I've returned to Seville. I'm also professor at the University of Osaka, Japan, where I spend one month a year. So you could say that I live on three continents.

Have you ever considered returning to Spain?

No. The thing is, we all have a crisis, an existential crisis. Most people who emigrate do it for financial reasons. Many think that when they arrive in another country, they'll get rich, but the reality is different. Return? No. Really, it's a myth, because it almost never happens. Very few people return with a large fortune, like the returnee emigrants, the indianos, who bought fine houses in Asturias: these were the few, the majority remained abroad.

In my case, when I left, it was not for financial reasons, but because I wanted to train as a researcher. It was a personal choice. The existential crisis can arise after five or ten years, when you realise that you are settled, and you probably won't return. That's when you ask yourself: do I really want to live here or not?

I didn't have a strong connection with Spain at that time. Yes, I had family in Seville, but it wasn't a question of that. It was about deciding where I wanted to live: in this country, in the United States or somewhere else. And the time comes when you have to make a decision, above all when you finish your training, and you need to find a stable job with prospects. Sometimes you spend a year thinking about it, exploring alternatives, wondering what the right path is. But there comes a time when things are clear, and you just carry on.

But now you're choosing the best each place has to offer, so to speak?

When the time came to retire, I decided not to do it abruptly. The American system is quite flexible in that way. In academia, you don't have to follow a strict route up and down. I thought about retiring in 10 years and decided to start to spend the winters away from Michigan and transition gradually.

I had lots of projects and grants, but I opted to reduce the size of my laboratory and not renew. Fortunately, my university allowed me to do this with no problem. There, you have the possibility of maintaining your own laboratories and managing work at your own speed in a progressive way.

Did you always want to study bacteria?

No, not at all. My initial focus was immunology, cancer and then innate immunity and microbiology. Since the pathology of inflammatory diseases is closely related with innate immunity and infections, getting into the study of microbiota came naturally. I started working on microbiota around 2008-2009.

From your experience in different countries, do you see much difference in how research and teaching are set up?

Yes, there are many, particularly in Japan, where the system is very different. Now I am older, I spend a lot of time mentoring, helping young researchers. In Osaka, for instance, I am mentor to two young professors. And in Seville, at IBIS (the Institute of Biomedicine of Seville), I organise activities and support for predoctoral and post-doctoral researchers.

What does mentoring consist of?

This year, for instance, I organised a congress between three research centres in Seville. It was the first time something like that had happened. And it was the students themselves who prepared the event and presented the speakers. It was a way of teaching them to organise this type of meeting.

Do you think Europe should learn from the American research model?

In the United States, organisation of research and finance work very differently. Centres are independent and their funding doesn't rely on a central organisation, only on the resources a centre can find. They do get support from projects, local government, or state grants, but each department and hospital manages its own finances. There is no unified national system; each institution has the freedom to contract whoever they choose. They are financially autonomous: if they have a lot of money in the bank, they can contract more staff and operate with more flexibility. Conversely, if they have limited financial resources, they need to make adjustments. Here, hospitals depend on the Social Security, and everything is a lot more bureaucratic. This has advantages and disadvantages.

These are uncertain times for scientific research in the USA. How is the situation affecting your work?

For the academic community and for the researchers who form a part of it, the recent changes have been quite radical. We still don't know with any certainty what the outcomes will be. There are rumours about possible cuts in the science budget and certain subjects being eliminated, but there is still no definitive information. Many projects are on hold, and the future of funding is still uncertain, which has generated great concern amongst academics. For instance, one of the approved cuts affects overheads (indirect spending). Before, if research was given $100,000 funding, an additional percentage was added to cover these costs, which might vary between 30% and 70% depending on the institution (e.g., as much as 70% for Harvard). Now, the percentage has been reduced to 15% across the board. This cut represents a significant loss of available funding. Although the measure has been approved, a judge has blocked its application for the time being. Nobody knows what will happen in the future.

You participated in Fundación Occident's Visiting Researchers Programme at CNIC, but you had to leave due to the COVID pandemic. Would you like to return to CNIC?

I loved being at CNIC, and I wouldn't mind returning. I had 15 days remaining when I had to leave suddenly and return to the USA in March 2020 due to COVID. ■

Executive Dean of the Faculty of Life Sciences & Medicine at King's College London and the British Heart Foundation (BHF) Professor of Cardiology

Ajay Shah: "IT'S NOT THAT CANCER RESEARCHERS ARE SMARTER, IT'S JUST THAT THEY'VE HAD SOME IMPORTANT ADVANTAGES"

Professor Ajay Shah is the Executive Dean of the Faculty of Life Sciences & Medicine at King's College London and the British Heart Foundation (BHF) Professor of Cardiology. He also holds the title of James Black Professor of Medicine, is Director of the King's BHF Centre of Research Excellence, and an Honorary Consultant Cardiologist at King's College Hospital. His main research focuses on the pathophysiology of heart failure in both experimental models and patients. He is renowned for pioneering work on NADPH oxidase (NOX) proteins and redox signaling in the cardiovascular system. He has a long-standing interest in nitric oxide (NO) signaling in the heart, including recent studies on neuronal NO synthase (nNOS) in humans.

What are the current challenges in treating heart failure?

There are two major challenges. The first is that we don't currently have any treatments that can cure heart failure. Existing therapies can slow the progression of the disease or help control symptoms, but they don't cure it. One reason might be that most treatments don't primarily target the heart itself. They work on the circulation of other parts of the body and only indirectly affect the heart. We still lack therapies that act primarily within the heart.

The second challenge is that our approach to treating heart failure is not very personalized. In English, we say it's a "one-size-fits-all" model—we follow a set protocol and apply it to everyone. But if you look at cancer treatment, for example, it's much more individualized. Doctors carefully study the characteristics of the tumor and the patient to choose a more specific, tailored therapy.

So, personalized medicine is still quite limited in heart failure?

Exactly. Personalized medicine in heart failure is still very primitive. That's one of the biggest gaps—we need better ways to tailor therapy to individual patients.

Which do you think is easier to achieve: a cure or personalized treatment?

In science and medicine, you always have to try all approaches. Neither is easy. We definitely need continued research to discover new treatments, especially ones that directly target the heart. That kind of research takes time.

Personalization, on the other hand, might progress more quickly. Advances in AI, machine learning, and data analysis are making it easier to understand individual patient differences. With technologies like big data analytics, we can more efficiently identify patient subtypes and potentially match them with the right treatments.

But it's important to note even with personalization, we're still using existing therapies—and I doubt those will be enough, even if we apply them perfectly. So, we need both new treatments and more personalized application.

Are there any promising therapies on the horizon that might directly target the heart?

There are several promising directions, but it depends on the cause of heart failure. Heart failure isn't a single disease, it's a syndrome that can result from many different underlying problems.

For example, if someone develops heart failure due to a heart attack, the issue is the loss of heart muscle. One exciting area of research is cardiac regeneration—trying to regrow or repair heart muscle. Here at our own institution, our teams are working on advanced therapies, including genetic approaches to stimulate the heart to regenerate muscle. This could become a viable treatment in the future for those patients.

Then there's another large group, people with what's called heart failure with preserved ejection fraction (HFpEF). These patients have heart failure even though their heart's pumping strength is relatively normal. It's becoming increasingly common, especially as the population ages. For HFpEF, we currently have very few effective treatments.

In my lab, for instance, we're researching how the heart uses energy -its metabolism- and how we might intervene there. That might be a promising area for new therapies.

What causes this second type of heart failure to be increasing so much?

Several factors are contributing, especially aging. The global population is getting older, and aging is one of the biggest risk factors for HFpEF. It's not just the chronological age either, it's about the biological age, which can vary a lot between people.

Other major contributors include obesity, high blood pressure, and diabetes. These conditions are all on the rise, especially in developed countries. Obesity, for example, is almost a pandemic in itself. And while we now have some effective obesity treatments, it's only one piece of the puzzle, many people with HFpEF are not obese.

So, this type of heart failure really needs more research. It's where we have the most to gain.

We're likely heading toward a kind of heart failure "pandemic"?

In some ways, we're already there. These risk factors -aging, obesity, hypertension, diabetes- are widespread. But it's important to remember they increase risk; they don't guarantee someone will develop heart failure.

What we need to understand better is why some people with these risk factors go on to develop heart failure while others don't. What mechanisms are there at play? And how can we prevent or treat it effectively? That's where a lot of research needs to focus.

It feels like cancer research is advancing faster than cardiovascular research, especially in terms of personalized medicine, gene therapy, and immunotherapy. Is that because more research effort is going into cancer?

It's a really interesting observation, and I think you're partly right. One key difference is that cancer is more accessible from a diagnostic perspective. When someone is diagnosed with cancer, the first step is often a biopsy; you can analyze the tumor tissue in great detail. In blood cancers, it's even easier.

With heart failure, it's much more difficult to get tissue from the heart. We do sometimes take biopsies, but it's invasive and not feasible for most patients. That makes detailed characterization of the disease much harder.

But now, with advances in imaging like MRI and PET, and with modern blood-based diagnostics, we can start to gather more information without needing heart tissue. Genetic data, too, is becoming easier and cheaper to collect and analyze. So, I think we're at a turning point where cardiovascular research could begin catching up.

So, do you think the gap between cancer and cardiovascular research can be closed?

I do. It's not that cancer researchers are smarter, it's just that they've had some important advantages: easier access to tissue, a clearer staging system, maybe more funding. But as we gain more tools and computational power, I believe we can make huge strides in cardiovascular research too.

And what about research centers like CNIC or the British Heart Foundation? What role do they play?

They're absolutely critical. These kinds of centers bring together experts from multiple disciplines -genetics, proteomics, imaging, clinical medicine, data science, AI-. That kind of interdisciplinary environment is essential if we want to tackle big questions like curing heart failure or truly personalizing care.

It's almost impossible for small, isolated teams to do this kind of work now. Even large centers need to collaborate with other institutions globally to make real progress. But places like this provide the foundation—the critical mass of people and skills—to push things forward in a meaningful way. ■

Professor and senior consultant at the University of Lun (Sweden)

Isabel Gonçalves: “SEEING PATIENTS INSPIRES MY RESEARCH”

Isabel Gonçalves is a professor and senior consultant at the University of Lun (Sweden). Her research focuses on cardiovascular disease and diabetes. She is the principal investigator in EXODIAB (Excellence in Diabetes Research in Sweden), leads a team at Cardiovascular Research - Translational Studies, and is a researcher in EpiHealth, a project focused on epidemiology for health.

A Portuguese research in Sweden.

I went to Karolinska Institute in the late ‘90s as a medical student, just to try doing research in a different place because I had already done some research in Lisbon. I really liked the atmosphere—it was very international and high-tech.

I had the opportunity to conduct research while continuing my clinical education. I’m a doctor from Lisbon, and when I first went to Stockholm, I was already in the final years of medical school. I returned to Portugal because I wanted to be a clinician, but in Sweden, they told me, “Here, you can combine clinical work with research.” The opportunity to integrate both fields really captivated me. Sweden had excellent infrastructure, funding, and a very diverse international environment. That’s why I stayed. I went back and forth for many years, and then finally, I settled there. In the meantime, my husband also received a job offer in Sweden. We moved together, thinking, “We’ll just do our PhDs and then go back home.” But after the PhD, we thought, “We’ll just complete our residencies and then return.” Then it became, “Let’s do a short postdoc, and then we’ll go back.” And then, “I’ll just finish this grant…” And suddenly, 23 years later, I’m still here. It felt like a never-ending postdoc, but now I’m a full professor leading a very international research team of 17 people from about 10 different nationalities.

ou mentioned that your lab consists of 176 people from 10 different nationalities. Do you think this diversity benefits research?

Oh, absolutely. Diversity is essential. Different cultures bring different approaches to problem-solving, different inspirations. It’s incredibly enriching. We need both men and women, all working toward the same goal. More perspectives mean more brainpower. If everyone thought the same way, it would be very boring—and possibly ineffective. I love the diversity. It is one of the things that motivates me to get up in the morning.

Since your studies and your move to Sweden, have you always focused on cardiovascular disease and atherosclerotic plaques, or have you changed direction over the years?

No, I was always focused on the cardiovascular system. I started collecting my first samples in Portugal as a medical student because I noticed that surgeons were discarding them. Initially, I wanted to be a surgeon, so I assisted in surgeries in my free time. I saw them throwing away this incredibly important material—the very substance that causes fatal diseases—and thought, “We should study this.” That is how it all started.

I had a strong curiosity about these deadly plaques that we were removing from patients to help them become better. I felt an urgent need to understand them: What are they? Why are they formed? That curiosity drove me. I had already done some basic research in Portugal, but in Sweden, I saw the potential of even more advanced technology that could help me study these plaques in greater depth. At the time, those high-tech machines were not often available in Portugal. So I decided to take my samples there to learn also from the brilliant minds in Sweden.

Portugal also needed more clinicians, so I felt I could return home to treat patients. But research became my passion.

Throughout my career, I balanced my time—50% research, 50% clinical practice. It was like a hobby that became an integral part of my life. Of course, sometimes it felt like I was working 100% in both fields! But I loved it. Eventually, the professor who welcomed me in Stockholm moved to Lund University, so when I returned from Portugal, I went to Lund instead. I also had clinical experiences in Germany, which was another enriching cultural and professional experience. Learning Swedish was tough—I had to take evening classes—but it was worth it.

Now that you are a full professor, do you still have time to see patients and conduct research?

Yes. Since becoming a full professor—well, I was 39 at the time —I reduced my clinical time. Before that, I divided my time equally: 50% with patients, 50% with my research group. Now, I spend about 30% in the clinic and 70% in research. So I still balance my "hobby" with patient care.

How important is it to do both? Some people focus solely on research or clinical practice, but you have maintained both.

For me, it is essential. Seeing patients inspires my research. When I treat someone, I see a problem that needs solving. Clinical work provides immediate fulfillment—you help rapidly one patient at a time. But research has the potential to help many people, though it takes years to see the results. This combination is a luxury! I love having both immediate and long-term impacts.

Some of the research questions I investigate actually come from my patients. They ask questions I don't always have the answers to, so I take those questions back to the lab. Years later, after countless experiments, I can get closer to giving them answers. That is an incredible feeling. It makes my research meaningful because I remember the faces of the people who inspired it.

Atherosclerotic plaques are a leading cause of death worldwide. Can early detection make a significant difference?

Absolutely. These plaques cause heart attacks and strokes. If we detect them early, we can treat them before they become dangerous. In my research, we use two main strategies. One approach is to study plaque mechanisms—how they form and rupture—so we can develop targeted treatments to prevent them. The other approach involves blood markers or imaging techniques to detect plaques before they cause harm.

Biomarkers seem like an easier solution for clinical practice compared to imaging, which requires specialized equipment. How early can biomarkers detect plaques?

Biomarkers are easier to implement because they only require a blood test for instance. But the challenge is identifying the right molecules—there are many substances in the blood, so we need to find the most relevant markers. Imaging is also crucial, especially non-invasive techniques like ultrasound, which doesn't use radiation and can be done with portable devices. This makes it accessible even in low-resource settings. Both approaches are promising for the future.

Can we detect the plaques early, or even before they appear??

That's a $1 million question, right? But of course, there are many ways to approach it. My research group is working on two main strategies. One involves studying plaques to understand the mechanisms behind their formation or rupture, which can lead to strokes. By understanding these mechanisms, we can potentially find new ways to "calm" the plaques down or prevent them from forming altogether. So, this is one branch of my research.

The second branch focuses on understanding what happens inside the plaque—how some molecules leak out and enter the bloodstream. These molecules could eventually serve as biomarkers, which could be detected through a blood test. It is a simpler way to get valuable information compared to imaging.

Now, about imaging techniques: we are exploring ways to take images of the blood vessels to identify when plaques are forming or whether an existing plaque is dangerous. These two approaches—biomarkers in the blood and imaging—are the main focus of my lab in Sweden at the moment.

You mentioned biomarkers earlier, and this might sound like a silly question, but would the first approach (biomarkers) be easier to implement in clinical practice than the imaging one? Imaging requires specific machines, and it is more expensive, right? How early can we detect these markers in the blood?

Yes, biomarkers are easier to transfer into clinical practice. With blood tests, you only need a small drop of blood, and from that, you can get a lot of information. The challenge is that there are so many substances circulating in the blood, so identifying the right molecules can be tricky. You would likely need a combination of several key molecules to get accurate results. That is one challenge with biomarkers. On the other hand, I really enjoy the non-invasive imaging techniques, like ultrasound and computed tomography. Ultrasound, in particular, doesn't require radiation, and it is an exciting tool because it's easy to use, portable, and relatively inexpensive. You could even use it in low-resource settings, where there is no access to advanced equipment. Imagine using a handheld ultrasound device to screen large populations or help differentiate high-risk from low risk subjects, which is something I think might have a lot of potential for the future. The goal is to create simple, portable, and affordable methods that can help people, especially in places where more expensive and high-tech equipment is not available. I really believe in bringing simple solutions to the people who need them most.

Do you think these simple methods could change the cardiovascular landscape in the next few years?

Absolutely. It is happening gradually. For example, cholesterol levels are already a well-known biomarker, and in recent years, markers like CRP (C-reactive protein, indicating inflammation) have gained traction. As we continue to discover more specific biomarkers, the outlook is promising. When it comes to imaging, we're already using ultrasound widely, especially for pregnant women, but also in cardiovascular disease. The work we're doing—developing new algorithms and techniques to enhance imaging—isn't too far from being implemented. We're already using the machines, so it is just a matter of refining them to help identify plaques more clearly. Of course, there are challenges, and things always take longer than we'd like. Researchers tend to be optimistic! One of the hurdles in technology development is the new regulations in Europe (MDR), which are more demanding. The regulatory aspect requires a lot of work, but we're already making progress there. So, I don't think it will take too long before we get to where we want to be.

At CNIC, we have a large study with Nordic countries called REACT. Does this align with your work?

That sounds exciting! It is similar to studies we're conducting in Sweden. Collaboration is essential, and proving results across multiple cohorts strengthens our findings. I'd love to work together.

What advice would you give future cardiologists and researchers?

I think the most important thing for future cardiologists is that despite all the technology that's emerging, they should always remember the human aspect of their work. I came across a quote by Sir Osler that I really like: "They may sometimes cure, often treat, but always comfort." I find this really meaningful, and I think it's an essential aspect of being a cardiologist.

For me, mentoring is one of my life's missions. Helping the new generation is one of the keys to making a positive impact. I feel a responsibility to pass on what I have learned, no matter how little that may seem. It's something I take deeply to heart. In a way, it's similar to how I approach working with patients: you help them improve their health, and with research, you help them make better progress in science. For the researchers, I always encourage them to learn from their mistakes. My son, who is a teenager, often talks about the concept of "journey before destination," which he reads about in his fantasy books. It's not just about the outcome, but about the process. Mistakes are fantastic learning opportunities, so I tell them to be positive, embrace their errors, and pursue their passion.

What I try to do is help them find their goals. And when the time comes for me to leave this world, I hope people will say that I was a little crazy, but that I contributed to helping patients and supporting my younger colleagues. They may be students today, but they will be my colleagues tomorrow. I feel a responsibility to help them become not just excellent professionals, but also amazing human beings.

That reminds me of something we did recently. We created an article about former students who were here 15 or 20 years ago. Now, they're leading departments and making an impact in their respective countries. We interviewed four or five of them to hear their reflections on their time here and the journey they've taken to reach leadership roles.

I think this ties into what Osler said—"comforting people." Research is a long-term way of helping people, advancing knowledge that ultimately improves their lives. Another principle I always tell them—and one I try to live by myself—is: treat others the way you would like to be treated. These are my guiding values: passion, kindness, and empathy. If you can't cure someone or provide the perfect treatment, at least you can offer them comfort because at the end of the day, we are all human. That's my approach.

Do you remember when you were a teenager? Did you always know you wanted to be a doctor?

Yes, since I was three years old. I was frequently sick as a child and spent a lot of time in hospitals. Back then, parents weren't allowed to stay overnight with their children, so I would be alone in the hospital. I cried a lot, of course, but I also developed this sense that hospitals were places where healing happens, where you can help people. That sense of wanting to help stuck with me. I always knew I wanted to be a doctor. Over time, I considered different specialties, but I always knew I wanted to help others through medicine. It's funny—and again my son recently taught me the concept of "journey before destination," which is something I now truly appreciate. It feels like I've always been on that journey. ■

Head of the Experimental Vascular Pathology group of CARIM (MUMC)

Erik Biessen: "I WOULD LOVE TO EXPLORE HOW THE BRAIN REGULATES INFLAMMATION"

Prof. Erik Biessen graduated in Biophysical Chemistry at Groningen University, Netherlands (1985). He joined the Division of Biopharmaceutics of Leiden University as a post-doctoral fellow and was selected for the prestigious Netherlands Heart Foundation (NHF) funded Molecular Cardiology Program to become Established Investigator in 2001. Since 2007 he is heading the Experimental Vascular Pathology group of CARIM (MUMC), with a part-time affiliation at the Institute for Molecular Cardiovascular Research of RWTH Aachen. Dr. Biessen aims for curiosity-driven cross-disciplinary research with an open eye for valorization of findings. Through the years his focus has shifted from biophysical chemistry, via medicinal chemistry and drug targeting to cardiovascular pathophysiology research, deploying a systems medicine approach.

What does your main research focus nowadays?

My primary focus is on cardiovascular immunology, specifically the inflammatory processes underlying cardiovascular diseases. I take a global approach, connecting patterns not just in the vascular system but also in the heart and related comorbidities such as diabetes, obesity, and liver disease. My aim is to untangle common pathways shared among these conditions and understand how they interconnect.

How do you approach this research? Do you use any special tools?

My background is in physical chemistry, so my path into medical research was somewhat unexpected. During my first postdoc, I designed glycolipids with potent cholesterol-lowering activity, which led me into cardiovascular research. My supervisor at the time also had an interest in this field, and through a career project funded by the Netherlands Heart Foundation, I became deeply involved in studying cardiovascular diseases.

In the early 2000s, research focused on lipids and cholesterol as primary disease drivers. However, I suspected there were additional factors at play, particularly inflammation. Initially, when I was in Leiden, our findings were based on mouse models, but I soon realized human disease differs significantly from mouse models due to variations in anatomy, diet, and immune systems. This realization led me to Maastricht and the University Hospital, where I had access to human biobanks. Seeing a human plaque for the first time was eye-opening—it looked completely different from mouse models. That experience prompted me to integrate data science and omics analysis into my research, using human tissue data to generate hypotheses, which we then validate in mouse models.

What kind of omics techniques do you use?

We primarily use bulk RNA sequencing, complemented by metabolomics, lipidomics, and proteomics. Our current cohort is much larger than our previous one—24 times bigger—which gives us more statistical power. In the past four years, we have also incorporated spatial techniques, such as single-cell analysis, to determine how cells interact within tissue environments.

We analyze spatial patterns in tissue samples, identifying areas where certain metabolites or inflammatory cells cluster. For example, by looking at metabolic layers alongside phenotypic data, we can understand how inflammation manifests in different tissue regions. This allows us to explore interactions that might be key in disease progression and could potentially be targeted therapeutically.

Given the influence of comorbidities in cardiology, how difficult is it to achieve personalized medicine for cardiovascular disease?

It is indeed challenging because cardiovascular disease is not a singular entity—it is interconnected with many other conditions, such as diabetes and liver disease. I approach this from a globalist perspective, looking for shared pathways across different diseases.

Recent advances in single-cell analysis and precision medicine have led to a fragmentation of disease understanding. This makes it more difficult for pharmaceutical companies to develop broad treatments. Instead of aiming for highly individualized treatments, I support a precision medicine approach where we use a larger battery of treatments and companion diagnostics to identify which patients will benefit most from specific drugs.

This approach is also used in cancer research.

Yes, oncology is ahead in this regard, likely because cancer has long been studied at a molecular level. However, there are promising developments in cardiovascular disease as well. For instance, new diabetes and obesity drugs have been shown to reduce cardiovascular risk. While we are still at the beginning of understanding these effects, I believe such drugs will play a significant role in future treatments.

How do you manage mentoring students while maintaining your research activities?

Our group consists of about 25-30 people, and I am fortunate to have a formidable team of experienced researchers. I directly supervise three to four PhD students, while senior staff members supervise others. Additionally, I have a co-chair who has developed her own research line and now leads PhD students as well.

I enjoy mentoring, but I have noticed a shift in student expectations over the years. They now prefer closer, more frequent supervision. When I was a PhD student, I met with my supervisor only a few times per year, which fostered independence but was inefficient. Today, I meet with my students weekly or biweekly and have informal discussions almost daily. I try to balance close guidance with encouraging independence, helping them grow as researchers without micromanaging them.

If you had unlimited funding and technology, what major challenge would you focus on?

Scientifically, I would love to explore how the brain regulates inflammation, particularly in relation to diabetes. Brain-immune interactions are a fascinating and emerging field.

From a healthcare perspective, the biggest challenge will be ensuring an excellent quality of life after major cardiovascular events, such as heart attacks or heart failure. As the population ages, we need better strategies for recovery and long-term management.

Do you have any collaborations with CNIC's researchers?

Yes, I do. I know Carlos Pérez Medina, and we have two ongoing mutual projects. We were connected through a collaborator in Bordeaux, who is an expert in antibody development. He brought us together, and our collaboration started about 3-4 years ago, just before the COVID-19 pandemic.

Interestingly, before that, without me knowing, I was already connected through another collaborator, Jacob Bentzon. I had collaborated with him in the early 2000s, and he was also involved in transgenic pig research. My collaboration with him was another key link to CNC.

What are your impressions of our institute?

I am impressed. The infrastructure is well-organized, with centralized platforms and expert staff available on-site. This setup fosters collaboration and efficiency. It is something I hope to advocate for in Maastricht, as having a centralized, well-equipped research institute benefits both researchers and the advancement of science.

IIS Aragon (the Aragon Health Research Institute)

Luis A. Moreno Aznar: "OBESITY IS A COMPLEX ISSUE, BUT IT CAN BE PREVENTED AND IMPROVED IF WE ACT ON ALL FRONTS"

Luis A. Moreno Aznar, Doctor in Medicine and Surgery with a diploma in Human Nutrition and Public and Community Health and has been a researcher for 43 years. For 6 years, he worked in the Paediatrics Department at Lille University Hospital (France) and in the Laboratory of Inherited Metabolic Disorders at the Pasteur Institute, Lille, where he developed his interest in epidemiological clinical research in the field of paediatric nutrition. His group, "Growth, Exercise, Nutrition and Development (GENUD)" (GIIS066) was already established and became a consolidated group with the Government of Aragón's first call for accreditation of research groups, later joining IIS Aragón (the Aragón Health Research Institute). This facilitated the group's inclusion in Carlos III Health Institute's CIBERObn (Centre for Biomedical Network Research on the Pathophysiology of Obesity and Nutrition).

The title of your talk is "Improving lifestyle to prevent obesity". Why that approach?

Obesity is a global pandemic that particularly affects the paediatric population. Its causes are multiple: genetics, biology, socio-economic status, social factors and, above all, lifestyles. In the realm of healthcare, the factor where we have the greatest opportunity for intervention is precisely lifestyle.

But in order to modify it, we need to understand how lifestyle influences the development of obesity, and this must be analysed from the perspective of a lifecycle, which begins as early as conception. The foetal period, the first two years of life, infancy, and adolescence are key stages because that is when many habits are formed.

Let's talk about this pandemic. What is the current situation in Spain?

We have monitoring systems that give us quite precise data on childhood obesity. According to WHO criteria, around 40% of children in Spain between the ages of 6 and 9 are overweight or with obesity. Although this figure may be a slight overestimation, in any case, it affects at least a third of our children.

The prevalence amongst adults is a little lower and more frequent among women than men, although I don't have the exact figures to hand.

It is important to speak of "children with obesity" and not "obese children" It's about acknowledging we're speaking about people, not labels. People with obesity participated in the recent European Congress on Obesity, and they highlighted something fundamental: obesity is a disease, not a personal decision.

At what age can obesity begin to develop? And when did the rise in the number of cases start?

Some children present obesity for very clear genetic causes, although this is a very small fraction, around 5%. Most of them have a genetic predisposition, but what makes the difference is environment: the more adverse the environment, the earlier obesity appears, even within the first months or years of life.

Regarding the increase, the national study we conducted in 1984 found between 3% and 5% of children with obesity. We could not have imagined what the future would hold. The big change happened at the end of the 1980s and in the 90s and was common to all developed countries.

What was the change due to? What were the determining factors?

There was not a single cause. Eating habits changed: we went from a traditional diet to one with more processed foods. Physical activity also declined: before, children played in the street a lot, nowadays that's less common and has been replaced with sedentary activities, first television and now screens.

It's the result of various elements: worse diet, less physical activity, less sleep and a more sedentary lifestyle. Each taken on its own might not be enough to cause obesity, but together they create a very favourable environment.

And how can this situation be reversed?

There are two levels: research and intervention.

In research, the key is to design rigorous studies to identify the most effective strategies. It isn't about saying "eat more fruit and vegetables", it's about planning well, having the right resources and, above all, correctly implementing programmes: knowing who the participants are, how to communicate the information, whether it manages to promote real change, etc.

We are also working on listening more to children and their families. Healthcare professionals often start off from a position of dominance. We know what science says and we try to impose it, but we forget to ask them how they experience that reality.

A surprising example that came from a qualitative study we did with adolescents was the issue of being home alone. Many children are alone after school, which gives them freedom but also

generates stress and insecurity. They eat whatever they want and go to bed whenever they want, which influences their health habits.

On political, social and industrial levels, what can be done?

From a political stance, we need more investment in prevention. There are good professionals and programmes, but they lack resources. Moreover, in Spain, healthcare is devolved from central government. Each regional autonomous community has its own programmes, which do not always have sufficient resources.

In terms of the food industry, without demonising, they do have a certain responsibility. The industry has improved the composition of certain products, particularly for brands aimed at more demanding consumers. But progress needs to be made in consumer information.

I think, for instance, the Nutri-Score system is useful but not perfect. The European Union should make efforts to agree a common system that is clear and easy to understand.

And individual responsibility? What is the patient's role in all of this?

It's undeniable that we all have a certain responsibility for our health. But it's also true that genetics explains up to 60% of the individual factors that influence obesity. For someone with a strong predisposition it is a difficult, constant struggle.

People who live with severe obesity have often tried to change many times, going on a diet, doing exercise, and they are exhausted. That's why many of them resort to resources such as bariatric surgery or new drugs such as GLP-1 antagonists.

Such treatments can be useful, but they are not a magic wand. They work better if they go hand in hand with good habits. What's more, they don't work the same for everyone. And yes, they also have benefits that go beyond weight loss, particularly in improving metabolic factors.

What do you think the short term perspectives for obesity are in Spain?

I'm moderately optimistic. Before the pandemic, we already saw signs of stabilisation and even a reduction in child obesity. COVID-19 was a hiatus, but I think that we can resume that trend.

However, we have to seriously tackle social inequalities, because people with less resources are more likely to suffer obesity: they eat lower quality foods, do less exercise, sleep less...

Here is a positive case: in a project with the Red Cross, we worked with vulnerable families who could not cover the costs of food. Some of them were only given financial help and basic guidance; others followed an educational programme on healthy lifestyles. And we saw that even in very difficult contexts, with the right support, families can improve.

Do you have any practical advice for parents and educators?

Perseverance is key. Vegetables are a clear example. Many children don't like them at first, but studies show that if they are offered them 10 or 12 times, eventually they accept them. The most common mistake is to stop trying at the second or third attempt.

We must encourage a food repertoire that is more varied and natural. And teach them to appreciate the real flavour of foods beyond salty and sweet.

It's also essential to share family time: meals, games, outdoor activities. And to do so without reproach or assigning guilt, but with commitment. Because, yes, obesity is a complex issue, but it can be prevented and improved if we act on all fronts.

Do you have any joint projects with the CNIC?

In collaboration with Dr Rodrigo Fernández's group, I'm currently developing a project funded by the Carlos III Health Institute that aims to identify food consumption biomarkers and the dietary, physical activity, sedentary, and sleep patterns among different population groups. To do so, metabolomic analyses are being conducted in three different studies: Meli-Pop, I.Family y PESA. ■

Scientific Director of the CIEN Foundation (Centre for Research on Neurological Diseases)

Pascual Sánchez-Juan: "AS A CLINICIAN, IT FRUSTRATES ME THAT WE DON'T SEE CLEAR BENEFITS FOR THE PATIENT"

Dr Pascual Sánchez-Juan is Scientific Director of the CIEN Foundation (Centre for Research on Neurological Diseases) dependent on the Carlos III Health Institute (ISCIII) Dr Sánchez-Juan is an expert in dementia research and has headed the Cognitive Deterioration Unit of Santander's Marqués de Valdecilla University Hospital, the institution where he is also scientific director of the Valdecilla Biobank.

What are the CIEN foundation's lines of research?

At the CIEN Foundation we're researching biomarkers in neurodegenerative diseases, a field that is currently abuzz with activity, particularly regarding markers in blood. Until now, good markers for Alzheimer's came from analysing cerebrospinal fluid or PET scans, which are both costly and invasive. The latest major development is that we can use a blood test to detect the disease with similar levels of sensitivity and specificity to those of traditional methods, which is a complete game changer for diagnostic scalability.

Does that mean more accessible early diagnosis?

Exactly. What's more, for the first time in over two decades, treatments that modify disease progression rather than just relieving symptoms are on the horizon. For more than two decades there was no new treatment for Alzheimer's disease. What we had were symptomatic drugs, which relieved the effects but did not modify the course of the disease. Now, for the first time, treatments are starting to arrive that promise to act on the biology of Alzheimer's. Specifically, on one of the proteins that accumulate in the brain: amyloid protein. These new drugs can reduce their accumulation, which in turn delays the progression of symptoms. However, in order to administer these treatments effectively, a precise diagnosis is essential. That's why we need reliable biomarkers and the possibility of studying a broader population. In addition, all indications are that the sooner treatment begins, the better the prognosis. So we are at a key moment in our discipline: new, modifying treatments are starting to arrive at the same time as we have increasingly effective diagnostic tools. Even so, there are still many unknowns. There are gaps in knowledge that we need to overcome if we want to optimise the use of these treatments, not only current ones but also those in development which act on other targets that may be more efficient. What we are seeing now is only the tip of the iceberg.

What is the focus of current research?

One of our main lines is identifying individuals at a pre-clinical stage; that means they have the condition but aren't showing any symptoms yet. With studies like the Vallecas cohort, which began in 2011, we've been following cognitively healthy people over the age of 70 for years. Even back then we observed that some people presented the condition in blood, and now we are following their 5 and 10-year progressions in terms of cognitive symptoms, cerebral atrophy, and other markers. That gives us very valuable information.

What new technologies are being applied?

We are using artificial intelligence, genetics, and digital markers such as spontaneous language analysis to detect risk even before the onset of symptoms. For instance, we train algorithms with people who we know to have markers, and that way we can fine tune predictive capacity. We want to reach determinism: to be able to say who will, in all likelihood, develop the disease and to be able to treat it in time.

What is the role of markers in blood in risk stratification?

We use a blood marker called phosphorylated tau 217, which is a type of circulating tau protein. It comes from the brain and is very specific to that organ, although it can be detected in blood. Phosphorylated tau 217 levels have an almost linear association with neurodegeneration, which is why it's considered a very useful marker.

We have data from the Vallecas Project, where we observe that this marker has a very good association with cognitive deterioration. That is to say, we see progressive atrophy in the brains of people who have higher levels of phosphorylated tau 217 in particular in the hippocampus, which is the area associated with memory. We also observe how other markers of neurodegeneration or inflammation, measured sequentially, increase over time.

Are you also studying inflammatory biomarkers?

We are specifically interested in a marker that comes from astrocytes, the cells that support the brain. This marker appears expressed in astrocytes when they are activated or "angry" so to speak, for instance, in response to some type of brain damage.

When this happens, astrocytes activate, get bigger and begin to express a protein called GFAP (glial fibrillary acidic protein). At that moment, the function changes: it can absorb cells or act more aggressively towards the damage it has detected.

The interesting thing is that in Alzheimer's disease this protein -expressed by the reactive astrocyte cell- appears at high levels in plasma although, curiously, the change is not so evident in cerebrospinal fluid. This finding has led us to interpret GFAP in plasma as a possible marker of astrocyte reactivity, which is associated with a worse prognosis.

We have observed that people with high levels of this marker tend to have greater cognitive decline and more cerebral atrophy over time. Indeed, GFAP has been included in new proposals for Alzheimer's disease diagnostic criteria, although it is not yet clear what role it plays or how we should use it in clinical practice. In our case, what we have done

with this marker is analyse it in a project called VARS (Vallecas Alzheimer Center Reina Sofia). This has enabled us to show for the first time in humans, based on postmortem measurements taken from patients brains, that high levels of GFAP in blood are related with astrocyte activation.

What is the value of having a brain bank like the one in your centre?

mmense. It means we can compare clinical samples taken in life with the postmortem neuropathology within an unbeatable time period (around 140 days). This offers us a unique window to validate biomarkers and better understand the mechanisms of the disease.

Another of your research areas is co-pathologies in Alzheimer's disease...

We are also studying how co-pathologies affect different biomarkers, how we can detect some of these pathologies using new biomarkers and how we can detect some of these diseases using new biomarkers. For instance, we are attempting to detect the protein TDP-43. When it is analysed in blood, it is not a good marker. But we are looking for it in extracellular vesicles, which seems to be a more promising approach

This isn't a new strategy; it has already been used in other contexts. What is interesting is that we have seen how, in diseases like ALS or frontotemporal dementia, the TDP-43 encapsulated in vesicles is more sensitive as a marker than its free form in plasma.

We are applying the same approach for Alzheimer's patients, and we have already seen some quite promising preliminary results.

In short, our approach is to study biomarkers in the context of the co-pathologies presenting in the brains of our patients to better understand the complexity of the disease and move towards a more precise and personalised characterisation.

So should we stop talking about "Alzheimer's disease" as a single entity?

Completely. We should think of it more as Alzheimer's syndrome, where multiple vectors come together: amyloid, tau, vascular, synuclein, TDP-43, and so on. Today we don't have accessible biomarkers for many of these proteins, but when we do have them, we will be able to be much more precise in both diagnosis and treatment.

There are over 138 potential drugs for Alzheimer's in 182 clinical trials.

Alzheimer's is also a complex, multifactorial disease. Let's say there are two routes. One is to act as early as possible, during the initial stages, on the first thing that appears, which is amyloid protein. We already have drugs for that, which show good clinical results, at least in part. But it is clear that when symptoms already exist, we are probably going to need other targets, like inflammation or the tau protein, which are also involved in Alzheimer's. And, in addition, we have to consider co-pathologies: many patients present more than one neurological disorder, and that might require specific treatments, which are also in development, when they become available.

This is much more complex than the idea of a "magic bullet" to cure Alzheimer's. Like what happened with cancer, we are faced with an enormous biomedical challenge. And the brain is much more complex than any other peripheral organ.

Even so, I am optimistic. Major steps have been made. Genetics is helping give us a better understanding of the causes. Every day we are making more precise diagnoses earlier, and the first treatments are arriving.

As a clinician, it frustrates me that we don't see clear benefits for the patient, but it's only a matter of time. The first antiamyloid drugs have already been approved by the European Medical Agency and will soon be available.

It's a social demand...

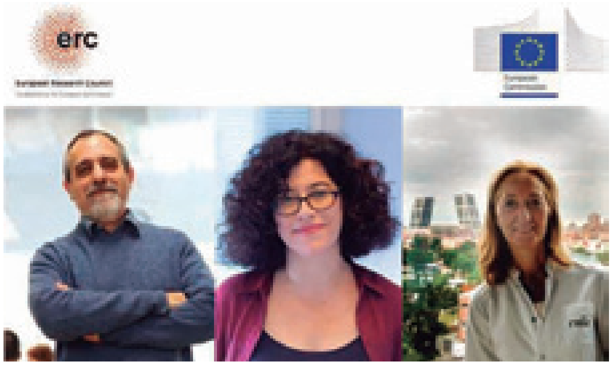
Exactly, there is a social need: this is like when the first stroke units were created. In the early days, treatments were limited and not risk-free, so it was done in a controlled way. But just having the patient in a specialist unit improved prognosis because everything was done better. And then came more effective treatments, like embolectomy. ■

THREE CNIC PROJECTS RECEIVE MORE THAN €5 MILLION IN ERC ADVANCED GRANT FUNDING

Three projects from the CNIC have received European Research Council (ERC) Advanced Grant funding from the European Commission. ANTI-ATHERO: Age-Associated Antigens in Atherosclerosis Immunity and Immunotherapy, led by Dr. Almudena Ramiro, and MINTRAF: Cell-Cell Communication by Mitochondrial Intercellular Traffic, led by Dr. José Antonio Enríquez, will each receive €2.5 million over the next 5 years.

The project Nab-Heart: Nanobody-Targeted Camk2d Inhibition for Cardiac Arrhythmia, led by Dr. Silvia Priori, professor of cardiology at the University of Pavia (Italy) and head of the Molecular Cardiology group at the CNIC, has been awarded an ERC Advanced Grant in the area of "Prevention, Diagnosis, and Treatment of Human Diseases." The grant guarantees total funding of €2.5 million, of which €250,000 will go to her Molecular Cardiology laboratory at the CNIC.

The goal of the ERC program is to fund 'frontier' ideas with potential to revolutionize health and society. Its main criterion is to support excellence in research. ■



ANTI-ATHERO: Age-Associated Antigens in Immunity and Atherosclerosis Immunotherapy

- Principal investigator: Dra. Almudena Ramiro, head of the B Lymphocyte Biology group.
- Budget: €2,5€ millions.
- Project Duration: 5 years.

ANTI-ATHERO, led by Dr. Almudena Ramiro, will investigate how the immune system—specifically the antibody response—is altered in atherosclerosis. The team will employ a novel approach that enables them to precisely distinguish between the early and late stages of the disease.

The aim of the project is to characterize the immune response involved in atherosclerosis in unprecedented detail, with the goal of identifying antibodies or antigens that could serve as therapeutic targets. "What is truly innovative about this proposal," says Dr. Ramiro, "is applying an immunotherapeutic approach to a cardiovascular condition—something long considered unfeasible."

While immunotherapy has transformed cancer treatment, its application in cardiovascular disease has only begun to gain traction over the past 25 years. With this project, the research team will generate a detailed map of the immune response, "helping us pinpoint targets that could allow us to modulate the immune system for therapeutic benefit."

ANTI-ATHERO explores how this immune response evolves in the context of aging—a critical factor in the development of atherosclerosis. "We know that the immune system also ages, and that the function of certain immune components changes significantly over time," explains Ramiro. "In our studies, we have observed that B lymphocytes show signs of premature aging during atherosclerosis, resembling the effects of natural aging. This suggests that the disease may accelerate aging within the immune system itself."

Dr. Ramiro's team is particularly interested in identifying which age-related immune mechanisms are triggered during the early stages of atherosclerosis—including in experimental models using young animals. This approach is rooted in the idea that atherosclerosis should be studied not only as a cardiovascular disease, but also as a condition with strong immunological and degenerative components.

The project will combine several complementary approaches. On one front, the researchers will use animal models to track the progression of atherosclerosis and study the accompanying immune response. In parallel, they will translate these findings to the clinical setting by focusing on a pathology closely linked to atherosclerosis: abdominal aortic aneurysm.

The project will also explore subclinical atherosclerosis to assess whether any of the identified immune targets could serve as prognostic markers. To support this aim, the researchers will use data from the PESA study (Progression of Early Subclinical Atherosclerosis), led by CNIC General

Director Dr. Valentín Fuster. This long-running study tracks apparently healthy individuals—those with no history of cardiovascular events—who nonetheless begin to show early signs of disease. "This cohort is ideal for identifying prognostic markers over time, thanks to the availability of repeated samples from the same individuals," explains Ramiro. Dr. Ramiro believes that ANTI-ATHERO will yield transformative insights into the interplay between aging, the immune system, and atherosclerosis. "Our findings could significantly advance not only cardiovascular research, but also our understanding of other age-related and autoimmune diseases." ■

MINTRAF: Cell-Cell Communication by Mitochondrial Intercellular Traffics

- Principal Investigator: Dr. José Antonio Enríquez, head of the Functional Genetics of the Oxidative Phosphorylation System group (GENOXPHOS).
- Budget: €2,5€ millions.
- Project Duration: 5 years.

The MINTRAF project aims to solve one of the great puzzles of modern cell biology: how mitochondria—our cells' energy-producing organelles—are transferred between cells. These organelles carry their own DNA and, as CNIC researchers discovered in 2020, can move from one cell type to another—for example, from heart cells to immune cells such as macrophages.

MINTRAF will investigate how this transfer occurs, whether the migrating mitochondria become integrated into the recipient cells, and what effects this process might have on health. In particular, the researchers will explore its potential impact in contexts such as cancer and organ transplantation.

While there is growing evidence of mitochondrial transfer between cells, scientists still do not fully understand how the process occurs, what triggers it, or what role it plays in the body. MINTRAF will investigate this phenomenon in depth, aiming to resolve these questions and explore potential applications in future therapies.

Dr. José Antonio Enríquez, the project leader and an expert in mitochondrial genetics, explains that understanding this process may be particularly important in the context of organ transplantation. "If mitochondria from the donor are transferred to recipient cells, they could trigger immunological or metabolic complications. In addition, recent studies suggest that mitochondrial exchange may act as a cellular rescue mechanism after injury—for example, in the aftermath of a heart attack."

To investigate these questions, MINTRAF will bring together a multidisciplinary team of scientists working with unique cellular and animal models. These models will allow researchers to observe mitochondrial movement in living organisms—including cases where the nuclear DNA is identical but the mitochondrial DNA differs.

A key innovation of the project is that, for the first time, the transfer of mitochondrial DNA between cells will be studied in humans—observing how this exchange occurs within the same individual.

The goal is to understand how and why mitochondrial transfer occurs, both under normal physiological conditions and in disease. In particular, the project will investigate whether this exchange plays a role in cancer progression, the immune response, and the outcome of medical treatments such as bone marrow transplantation or mitochondrial therapies.

The team has already developed genetically modified mice that enable real-time tracking of mitochondrial transfer between cells. This will allow researchers, for the first time, to create a comprehensive map of the process—identifying which cell types donate or receive mitochondria, when the transfer occurs, and what effects it produces.

Dr. Enríquez explains: "Understanding how and why mitochondria are transferred between cells is important not only for basic science, but also for transforming how we treat serious diseases—such as cancer or mitochondrial disorders—and for designing more effective cellular therapies." ■

Nab-Heart: Nanobody-Targeted Camk2d Inhibition for Cardiac Arrhythmias

- Principal Investigator: Dr. Silvia Priori, Scientific Director of the ICS Maugeri network-University of Pavia (Italy) and Head of the Molecular Cardiology group at the CNIC.
- Budget: €2.5 million, with €250,000 allocated to the CNIC.
- Project Duration: 5 years

The Nab-Heart project—coordinated by Dr. Priori of the University of Pavia (Italy) in collaboration with her laboratory at the CNIC—will develop a new treatment to prevent dangerous heart arrhythmias. The research teams will work on developing a new, highly selective, cardio-specific biological inhibitor targeting the CaMKII delta enzyme, a crucial mediator of arrhythmogenesis in various heart diseases.

This approach would overcome the limitations of currently available antiarrhythmic drugs, ensuring effective treatment free of adverse effects. The safety, selectivity, and efficacy of the drug will be evaluated in cell models and multiple animal models to facilitate its development as an innovative treatment for patients. ■

CNIC joins GRACE, a European project aimed at transforming cardiovascular care through innovation and collaboration

The CNIC has been allocated €405,625 for its involvement in GRACE (Growing, Reaching, Advocating for Change and Empowerment), a European project aimed at transforming cardiovascular care through innovation and collaboration. Co-funded by the Innovative Health Initiative (IHI), GRACE will run for 54 months and has a total budget of €19.6 million.

The CNIC's participation will be led by Dr. Borja Ibáñez, CNIC Scientific Director, cardiologist at Fundación Jiménez Díaz, and a group leader in the Spanish cardiovascular research network CIBERCV. "The CNIC will bring its experience in leading clinical trials in the areas of coronary artery disease and the cardiac microcirculation, as well as its extensive knowledge on the use of cardiac magnetic resonance as a key diagnostic tool for cardiovascular diseases."

This group of diseases, which includes coronary artery disease, heart failure, and atrial fibrillation, significantly impairs patient quality of life and places a large economic burden on healthcare systems.

The CNIC's contribution will center on coronary microvascular disease, an underdiagnosed condition also known as microvascular angina. Dr. Ibáñez explains that, "many patients experience symptoms of chronic angina, yet catheterization studies reveal no evidence of coronary artery obstruction, a condition known as ischemia with no obstructive coronary arteries (INOCA). We know that the problem often lies in the microvessels supplying the heart muscle; however, diagnosing microvascular disease is complex and can only be accomplished in centers equipped with the technological capacity for advanced invasive studies."

CNIC scientists have developed an innovative magnetic resonance methodology that can detect these alterations non-invasively. Within GRACE, the diagnostic efficacy of this method will be tested in angina patients through a CNIC-led international clinical trial including centers in Spain, the Netherlands and Germany.

Under the coordination of Dr. Borja Ibañez, the CNIC will contribute to GRACE's key focus areas of angina, atrial fibrillation, heart failure, aortic stenosis, and diagnostic tools such as cardiac magnetic resonance

Dr Ibañez underlined that, "Placing magnetic resonance imaging at the center of coronary artery disease diagnosis will simplify the complex care pathway, which currently involves numerous diagnostic procedures and interventions that often yield inconsistent results."

The goal of GRACE is to develop innovative, scalable, and sustainable solutions to drive innovation in cardiovascular disease management. To achieve this, the project will not only leverage magnetic resonance imaging but also utilize advanced technologies to enhance early detection and diagnosis through portable devices, empower patients with personalized digital interventions, optimize healthcare resources, support medical professionals with decision-making systems, and accelerate the adoption of scalable and interoperable technological innovations.

In addition to the CNIC-led study, the CNIC will participate in four other European pilot studies in GRACE focused on improving the management of atrial fibrillation, heart failure, aortic stenosis, and cardiac surgical processes. These studies will explore ways to leverage advanced technologies, remote monitoring, optimized protocols, and personalized approaches to enhance diagnosis, treatment, and recovery. Each study will evaluate the clinical, economic, and social impacts of the interventions tested, ensuring that GRACE delivers tangible benefits for both patients and healthcare professionals.

The project brings together 25 strategic partners spanning academia, healthcare, industry, and patient advocacy. Participating organizations include leading hospitals, universities, research institutes, and medical technology companies. With participants in Spain, France, Italy, the Netherlands, Germany, the United Kingdom, Israel, and South Korea, GRACE will validate its findings across diverse healthcare systems to ensure broad impact and scalability.

As part of the Project GRACE consortium, the CNIC will play a key role in the research and development of innovative methodologies to improve the diagnosis, treatment, and prevention of cardiovascular diseases, strengthening Spain's leadership in this field.

Summing up, Dr. Ibañez says, "Technology has revolutionized biology and medicine. Now is the time to focus on the unmet needs of global public health. GRACE will concentrate on adopting innovative technologies to enhance the management of cardiovascular diseases, bridging the gap between innovation and its integration into healthcare services, and ensuring safer, more efficient, and sustainable solutions."

This project is co-funded by an IHI joint undertaking through grant agreement 101194778, financed by the Horizon Europe programme of the European Union and the industrial associations COCIR, EFPIA, EuropaBio, MedTech Europe and Vaccines Europe. ■

CNIC researchers receive AECC funding for their projects

Three CNIC (Spanish National Centre for Cardiovascular Research) researchers have been awarded funding by the AECC (the Spanish Association Against Cancer) in its 2024 call for projects aimed to boost immunotherapy research and the training of young scientists.

David Sancho received an AECC 2024 General Projects award of 295,500 euros. His project focuses on the development of a new strategy to strengthen antitumour immune response based on stimulation of the interaction between cells of the immune system.

Fidel-Nicolás Lolo Romero is the recipient of AECC 2024 funding for research to the amount of 200,000 euros for his study on tumour immune infiltration, which is key to improve the effectiveness of immunotherapy treatments against cancer.

Thirdly, Adrián Belinchón was awarded 1,143.82 euros from the AECC 2024 Programme for Summer Laboratory Internship, an initiative aimed at training young scientists.

This support strengthens CNIC and the AECC's commitment to research, promoting scientific progress that can improve treatments and open the door to novel therapeutic approaches to cancer. ■

The CNIC receives two prestigious Marie Skłodowska-Curie grants for immunology and cardiovascular health research projects

The CNIC (Spanish National Centre for Cardiovascular Research) has been awarded two Marie Skłodowska-Curie Post-doctoral Fellowships within the Horizon Europe Programme. The funding will enable the development of ground-breaking research in immunology and cardiovascular health, with a significant impact on our understanding of immune and neurodegenerative diseases.

Dr Pablo Rodríguez Silvestre, postdoctoral researcher in the immunobiology group headed by Dr David Sancho, will receive a grant to undertake the project, FADIR (Dissecting the role of fatty acid oxidation in dendritic cell function and regulation of immune responses). His research will focus on the role of fatty acid oxidation in conventional dendritic cells and their influence on the regulation of immune response.

The study will use innovative murine models and an interdisciplinary approach to uncover the interconnections between the metabolism ad immunological function in different tissues, both in basal state and in diseases. The funding awarded is 194,074.56 euros and the duration of the grant is 24 months.

Dr Jennifer Monereo Sánchez, post-doctoral researcher with the Cardiovascular Imaging and Population Studies group led by Dr Valentín Fuster, will receive a grant to conduct the project BrainAtCardio (Brain health in Atherosclerosis and Cardiovascular risk in mid-life, a PESA-Brain project).

Her research will look into the relationship between cardiovascular health and Alzheimer's disease at early stages, with a special emphasis on subclinical atherosclerosis and cardiovascular risk factors among middle aged people. Through the PESA-Brain study, this project will use advanced neuroimaging technologies, blood biomarkers and cognitive assessment to analyse the influence of cardiovascular health on cerebrovascular integrity and the first signs of Alzheimer's. The funding awarded amounts to 194,074.56 euros over 24 months.

These Marie Skłodowska-Curie grants underscore CNIC's commitment to excellence in biomedical research and consolidate its position as an international reference in the study of cardiovascular and immunological diseases. The funded projects not only contribute to advancing scientific knowledge but could also open up new routes for the prevention and treatment of diseases with a high impact on public health.

The European Commission will award a total 417 million Euros to 1696 post-doctoral researchers for their work at top-tier universities, research centres, public and private organisations in addition to small and medium enterprises.

Of the award winners, 43.8% are women, and the selected applicants represent almost 95 different nationalities who will work in 47 countries both in Europe and worldwide. ■

CNIC at the presentation of the programme 'Generación D: Construyendo la Generación IA'

Spain's Ministry for Digital Transformation and of the Civil Service and the Spanish Ministry of Science, Innovation and Universities presented the programme *'Generación D: Construyendo la Generación IA'* (Generation D: Building the AI Generation) with a 120 million euro investment from Red.es. The profile of the programme's beneficiaries is post-doctoral (43%), predoctoral (17%) and technical (41%). The presentation was attended by the representative of the Ministry for Digital Transformation and of the Civil Service, Óscar López, and the Secretary of State for Science, Innovation and Universities, Juan Cruz Cigudosa.

Under the auspices of "cardiotrAIning" (the Plan for Training in AI and Big Data for Cardiovascular Health) coordinated by Dr Borja Ibáñez and Dr Fátima Sánchez Cabo, the CNIC is training 15 professionals in artificial intelligence and its application to cardiovascular health thanks to the ambitious training programme that forms part of the Spanish government's Plan for Recovery, Transformation and Resilience with funding amounting to almost 4 million euros over four years.

In addition to CNIC, the other three organisations selected to execute the programme, which depends on the Spanish Ministry of Science, Innovation and Universities, are the Spanish National Research Council (CSIC), the Barcelona Supercomputing Center (BSC) and the Spanish National Centre for Cancer Research (CNIO).

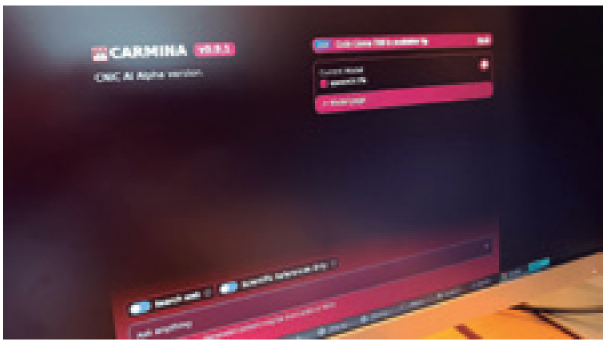
Red.es is an agency under SEDIA (the Secretariat of State for Digitization and Artificial Intelligence) attached to the Ministry for Digital Transformation and of the Civil Service; the Secretariat's mission is to promote this initiative, which also includes a training plan equivalent to 240 ECTS credits.

The programme is financed by the Plan for Recovery, Transformation and Resilience, through EU Next Generation funding within investment 4 of component 19. ■

CARMINA: The AI model for cardiovascular research developed by the CNIC

Researchers from the Computational Systems Biomedicine group at the Spanish National Cardiovascular Research Centre (CNIC) are developing **CARMINA**, an artificial intelligence (AI) assistant designed to support cardiovascular research.

It is a system based on language models and information retrieval that **provides specialised answers to biomedical questions**, ensuring data privacy by operating exclusively within the CNIC. This ensures that users' conversations and data will not be used for commercial purposes or exploited externally, unlike commercial models such as ChatGPT, DeepSeek and Gemini.



To evaluate CARMINA's performance, **RAGQA**, a complementary internal initiative that measures the accuracy, completeness and clarity of AI-generated responses, has been launched. Specifically, this project compares CARMINA's answers with those provided by professionals, including cardiologists and researchers, with the aim of improving its capabilities and optimising its application in biomedical research.

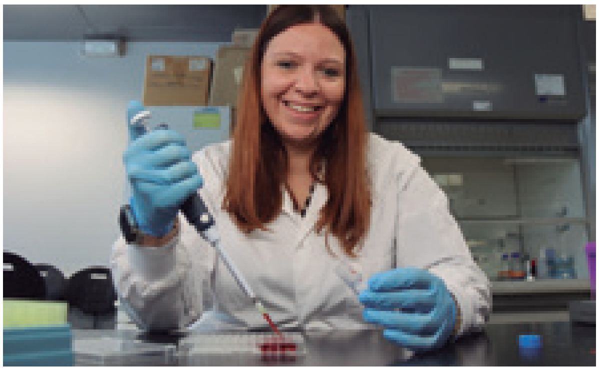
'CARMINA and RAGQA are part of the CNIC's commitment to the integration of artificial intelligence in biomedical research, ensuring that these technologies are developed and evaluated with the utmost scientific rigour,' says Fátima Sánchez Cabo, Principal Investigator of the CNIC's Computational Systems Biomedicine group. ■

Fundación La Caixa awards 5 grants to young CNIC researchers

Fundación La Caixa has awarded 5 of its 100 new doctoral and post-doctoral grants to young researchers of the CNIC (Spanish National Centre for Cardiovascular Research) for them to conduct their projects at the research centre. With its INPhINIT doctoral and Junior Leader post-doctoral grants, Fundación La Caixa has the double objective of retaining and attracting talent to drive excellence in research in these countries. The people at CNIC awarded these grants in 2024 are Christina Reyburn Valés and Belén Campos Olmo, with predoctoral INPhINIT Incoming grants; Yago Rodríguez Carreras and Marcos Luis Femenía Muiña with predoctoral INPhINIT Retaining grants; and William Joyce, recipient of a post-doctoral INCOMING grant. ■

Scientific Higlights

Nature Communications: CNIC research identifies a key protein for 'burning' fat



A new study conducted at the CNIC and CNIO, led by Guadalupe Sabio and Cintia Folgueira, has uncovered a mechanism through which the body burns brown fat and converts it into heat. This process plays a protective role against obesity and related metabolic diseases.

The mechanism now identified is controlled by the protein called MCJ, present in mitochondria (the organelles of the cell where energy is produced). Sabio and Folgueira have discovered that, when the MCJ protein is removed from obese mice, these animals produce more heat and lose weight. The researchers have also managed to reduce the weight of obese mice just by having them transplanted with fat without that protein.

Obesity is the result of either excessive food intake or inadequate total energy expenditure. We now know that adipose tissue –body fat–, in addition to storing energy, plays a crucial role in the management of that energy by the body.

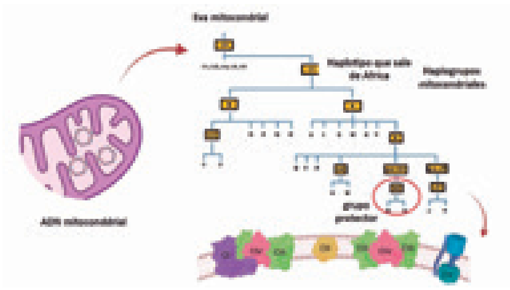
There are two types of fatty or adipose tissue: white and brown. White adipose tissue mostly stores energy, while brown fat (its cells have more mitochondria and that gives them a brown hue) is responsible for heat generation or thermogenesis, the process that maintains body temperature and which is triggered by cold or other stimuli.

The researchers also observed that "animals without MCJ in brown fat are protected against health problems caused by obesity, such as diabetes or increased blood lipids," explain the two scientists. Therefore, they believe that the MCJ protein could be a new therapeutic target to correct diseases associated with obesity.

The research is now seeking to develop a therapy to block this protein in obese patients, but to do so they must first investigate whether the MCJ protein has vital functions in other tissues. At the same time, Guadalupe Sabio says, "we are trying to see if these changes in fat affect tumour growth or cachexia – loss of muscle and fat – which is also sometimes linked to cancer."

Cicuéndez B, Mora A, López JA, Curtabbi A, Pérez-García J, Porteiro B, Jimenez-Blasco D, Latorre-Muro P, Vo P, Jerome M, Gómez-Santos B, Romero-Becerra R, Leiva M, Rodríguez E, León M, Leiva-Vega L, Gómez-Lado N, Torres JL, Hernández-Cosido L, Aguiar P, Marcos M, Jastroch M, Daiber A, Aspichueta P, Bolaños JP, Spinelli JB, Puigserver P, Enriquez JA, Vázquez J, Folgueira C, Sabio G. Absence of MCJ/DnaJC15 promotes brown adipose tissue thermogenesis. Nat Commun. 2025 Jan 13;16(1):229. doi: 10.1038/s41467-024-54353-4. PMID: 39805849.

Communications Biology: The European mitochondrial lineage may protect against severe forms of COVID-19



A study published in the journal Communications Biology shows that specific genetic variants in the mitochondrial DNA of Europeans may protect them against the more severe forms of COVID-19. The results of the study provide new clues to the origin of individual differences in the response to infection. The research was led by Dr. José Antonio Enríquez, head of the GENOXPHOS group at the CNIC and a member of the Spanish research network on frailty and healthy aging (CIBERFES).

The study identified patterns suggesting a possible relationship between certain mitochondrial haplogroups (genetic variants shared by individuals with a common ancestor) and susceptibility to more severe forms of COVID-19. "The study demonstrates the importance of the mitochondrial HV lineage as a protective factor against the severe consequences of infection with SARS-COV2, supporting the idea that mitochondria play a key role in the response to infectious disease," explained José Antonio Enríquez.

These results advance our understanding of the variability in the response to SARS-CoV-2 and may help to improve the personalized care of patients with COVID-19.

The study analyzed data from more than 14300 patients in the SCOURGE registry (Spanish Coalition to Unlock Research on Host Genetics on COVID-19) and confirmed that individuals with genetic variants found in the HV lineage—the most common mitochondrial lineage among Europeans, accounting for 37%–58% of the European population–had a lower risk of developing severe forms of COVID-19. Mitochondrial DNA is the only part of the human genome that is inherited exclusively through the maternal line and plays a key role in the cellular generation of energy and the inflammatory response

In addition to the CNIC and CIBERFES, acclaimed Spanish and international institutions participating in the study included the University of Santiago de Compostela (USC), Marqués de Valdecilla University Hospital–IDIVAL, Nuestra Señora de Candelaria University Hospital, La Paz University Hospital, and the Autonomous University of Nuevo León (México).

The study used advanced genetic analysis models to identify data patterns, revealing how previous pandemics may have influenced the current distribution of these genetic variants in Europe through the process of natural selection.

Cabrera-Alarcon JL, Cruz R, Rosa-Moreno M, Latorre-Pellicer A, de Almeida SD; Scourge Cohort Group; Riancho JA, Rojas-Martinez A, Flores C, Lapunzina P, Sánchez-Cabo F, Carracedo Á, Enriquez JA. Shaping current European mitochondrial haplogroup frequency in response to infection: the case of SARS-CoV-2 severity. Commun Biol. 2025 Jan 9;8(1):33. doi: 10.1038/s42003-024-07314-y. PMID: 39789223; PMCID: PMC11718132

Immunity: CNIC scientists discover how the gut modulates the development of inflammatory conditions

A study led by David Sancho at CNIC in Madrid reveals how an increase in intestinal permeability allows the natural gut bacteria to cross the intestinal barrier and reach the bone marrow, where they induce epigenetic changes—modifications that alter gene activity without affecting DNA sequence—in the stem cells that give rise to immune cells. The epigenetic changes induced by the translocated gut bacteria generate "trained" immune cells primed to respond more efficiently to future infections. However, this same ability to amplify the immune response can also aggravate the inflammatory conditions such as cardiovascular and neurodegenerative diseases. The new study highlights the key role in this process of a protein called Mincle, expressed in cells of the innate immune system.

The study is published in the journal Immunity and was conducted in collaboration with research teams led by José Luis Subiza (Inmunotek S.L., Alcalá de Henares), Carlos del Fresno (IdiPaz, Madrid), Salvador Iborra (Universidad Complutense de Madrid) and Juan Duarte (Universidad de Granada).

Trained immunity explained David Sancho, who leads the Immunobiology lab at the CNIC, allows macrophages and other cells of the innate immune system to respond more efficiently to future encounters with bacteria, fungi, or viruses. "The protection this mechanism provides against viral and fungal infection has been demonstrated in animals with heightened intestinal permeability, which resulted in a stronger inflammatory response and greater resistance to infection."

Until very recently, scientists believed that specific—or adaptive—immunity was the only type with memory, able to generate cells that 'remember' previous encounters with pathogens and unleash a specific immune response. In contrast, the innate immune response, which is not specific to a particular pathogen, was believed to lack memory. "We now know that innate immunity can be 'trained' to produce a stronger response to later, unrelated infections. What is more, the effects of this training are long-lasting," explained Dr. Sancho.

The findings of the study open new routes to understanding the relationship between gut health and systemic diseases, underlining the importance of a healthy diet and a balanced microbiota as key elements in disease prevention.

The study was funded by the Spanish Ministerio de Ciencia, Innovación y Universidades-Agencia Estatal de Investigación (AEI); the European Union NextGenerationEU/PRTR; the Comunidad de Madrid; Fundación Científica de la Asociación Española Contra el Cáncer; Worldwide Cancer Research; European Research Council; Inmunotek S.L., y Fundación "la Caixa".

Robles-Vera I, Jarit-Cabanillas A, Brandi P, Martínez-López M, Martínez-Cano S, Rodrigo-Tapias M, Femenía-Muiña M, Redondo-Urzainqui A, Núñez V, González-Correa C, Moleón J, Duarte J, Conejero L, Mata-Martínez P, Díez-Rivero CM, Bergón-Gutiérrez M, Fernández-López I, Gómez MJ, Quintas A, Dopazo A, Sánchez-Cabo F, Pariente E, Del Fresno C, Subiza JL, Iborra S, Sancho D. Microbiota translocation following intestinal barrier disruption promotes Mincle-mediated training of myeloid progenitors in the bone marrow. Immunity. 2025 Feb 11; 58 (1-16). doi: 10.1016/j.immuni.2024.12.012j.immuni.2024.12.012

JACC CardioOncology: CNIC scientists design an effective treatment strategy to prevent heart injury caused by a class of anticancer drugs

A team of scientists at CNIC, working in collaboration with international partners, has designed a strategy for preventing the cardiotoxic effects of anthracyclines, a widely used class of anticancer drugs. Cardiotoxicity is a frequent adverse secondary effect of cancer therapy with these drugs. The study, published in JACC: CardioOncology, demonstrates that treatment with the SGLT2 inhibitor empagliflozin can mitigate the cardiac injury associated with anthracycline therapy.

Using an advanced experimental model, the CNIC team showed that administration of a 20 mg daily dose of empagliflozin preserved the contractile function of the hearts of pigs treated with anthracyclines and protected the metabolism of the heart muscle. The protective effect of empagliflozin identified in the study involves an increase in the myocardial consumption of ketone bodies. This preserves the production of ATP (adenosine triphosphate, the main source of transferable energy in living cells) and mitochondrial function. "Treatment with empagliflozin protects the heart by directly addressing the metabolic processes affected by the cancer therapy," said Dr. Ibáñez.

Our study demonstrates that empagliflozin prevents structural alterations in cardiomyocytes such as cellular atrophy and DNA damage. These results underline the potential of SGLT2 inhibitors not only in the treatment of heart failure, but also as a preventive therapy in cancer patients receiving treatments associated with severe cardiovascular side effects. The study, funded by the European Commission (ERC-CoG 819775), the Spanish Ministry of Science, Innovation and Universities, and the Community of Madrid regional government, opens the way to new clinical trials in patients at high risk.

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Nature: CNIC scientists discover a type of immune cell that produces defensive "shields" in the skin.

A team at the CNIC led by Dr. Andrés Hidalgo has discovered a specialized population of neutrophils in the skin that produce extracellular matrix, helping to maintain the skin's resistance and integrity. The study, published in Nature, demonstrates that the immune system not only targets pathogens, but also physically strengthens the skin to prevent them entering the body.

Neutrophils are an important type of circulating immune cell. The specialized neutrophils described in the new study populate the skin, where they produce collagen and other matrix proteins that strengthen the skin barrier. The discovery broadens understanding of the immune system and may lead to new strategies for treating skin diseases, inflammation, diabetes, and age-related conditions.

Although neutrophils are best known for their microbicidal properties, the new study reveals an unexpected role for these cells in the generation and remodeling of the subepidermal extracellular matrix. The extracellular matrix is critical for maintaining the structure and function of the skin and other tissues, acting as a barrier to the entry of microorganisms and toxins.

The study, demonstrates that these neutrophils help to maintain skin integrity under normal conditions and are activated in response to injury to generate protective structures around wounds that prevent the entry of bacteria and toxins.

The study further shows that this structural function of skin neutrophils is regulated by the TGF-β signaling pathway. By genetically deleting this pathway in mice, the authors showed that the deposition of extracellular matrix was diminished, resulting in skin that was more fragile and permeable. Hidalgo notes that.

This suggests that the interaction between the immune system and the body's structural components is much more direct than previously believed.

Another fascinating result emerging from the study is that the activity of these skin neutrophils follows a day-night pattern, adjusting the production of extracellular matrix according to the body's circadian cycle. As a result, the skin of mice is more resistant at night than during the day, thanks to the nocturnal peak in neutrophil activity.

Hidalgo underlines that, “This finding opens new avenues for investigating how internal body rhythms influence tissue defence, regeneration and repair.”

For Hidalgo, now at Yale University School of Medicine, the discovery of matrix-producing neutrophils not only broadens knowledge about innate immunity, but also suggests new treatment strategies for skin diseases and immunological disorders. He explains, “These findings will help develop treatments to strengthen the skin barrier in patients with inflammatory diseases or immunological alterations, including patients with diabetes and older adults.”

The study was supported by funding from Fundación “la Caixa”, the Boehringer Ingelheim Foundation, the National Institutes of Health, and the Swiss National Science Foundation

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NEJM: A drug used to treat diabetes improves the prognosis of patients undergoing cardiac valve intervention

A drug used to treat diabetes improves the prognosis of patients with aortic stenosis treated by transcatheter aortic valve implantation (TAVI). The results of a new clinical trial including 1,250 patients shows that medication with dapagliflozin after this treatment reduces the rates of death and hospital admission attributed to heart failure over a one-year follow-up. The trial was coordinated by the CNIC and Hospital Álvaro Cunqueiro de Vigo, and the study results are published in The New England Journal of Medicine.

Aortic stenosis is a degenerative disease that typically progresses slowly, narrowing the aortic valve opening through which blood is pumped from the heart to the rest of the body. As a result, the heart muscle has to work harder, and this can lead to heart failure, angina, or even sudden cardiac death due to malignant arrhythmias. Traditionally, this condition has been treated by heart valve replacement surgery. But the surgical risk for elderly patients is very high, and this limits their access to this intervention.

Before the new study, there were no treatments available to improve the prognosis of patients recovering after TAVI.

Both dapagliflozin and the related medication empagliflozin work by inhibiting sodium-glucose cotransporter 2 (SGLT2) and were originally developed as treatments for diabetes. However, they are also effective treatments for heart failure and have become key elements of the treatment of this condition. Despite the efficacy of these drugs, the mechanism through which SGLT2 inhibitors improve the prognosis of heart failure patients has remained a mystery. Dr. Borja Ibáñez—CNIC Scientific Director, cardiologist at Fundación Jiménez Díaz, group leader in the Spanish cardiovascular research network (CIBERCV), and the scientific coordinator of the trial—explains that, “Given the medical importance of this question, we have worked on it extensively, and we recently demonstrated that these drugs increase the energetic capacity of the heart by altering how the myocardium [heart muscle] utilizes nutrients to generate energy.” That study was published recently in JACC: CardioOncology.

Although patients with aortic stenosis frequently progress to heart failure, they have generally been excluded from clinical trials investigating the benefits of SGLT2 inhibitors. Dr. Raposeiras adds that, “Those trials also included minimal representation of elderly patients.”

This is precisely what inspired Dr. Ibañez’s team at the CNIC to conduct a clinical trial in the specific population of elderly patients treated with TAVI.

DapaTAVI is an independent trial conducted in Spain with no funding from the pharmaceuticals industry at 39 Spanish hospitals. The trial included 1,250 patients with severe aortic stenosis who were recovering after TAVI and at high risk of heart failure. Half of the study participants were treated with dapagliflozin after the TAVI procedure, while the remaining half received standard care. Analysis at the end of one year of follow-up showed that the rates of death and hospital admission due to heart failure were significantly lower in the dapagliflozin-treated group.

Summarizing the findings, second principal investigator Dr. Ignacio Amat-Santos—an interventional cardiologist at Hospital Universitario de Valladolid and a CNIC research scientist—says that, “This study demonstrates that we can further improve the prognosis of patients treated with TAVI, an especially vulnerable patient group.” CNIC General Director Dr. Valentín Fuster, a coinvestigator on the trial, underlines that, “The results of DapaTAVI will have an enormous impact on a growing number of patients and will help to extend their life expectancy with improved quality of life.” “DapaTAVI,” notes Dr. Ibáñez, “is an integral part of the CNIC’s strategy begun seven years ago to lead pragmatic clinical trials with no pharmaceutical industry involvement and with the goal of transforming global clinical practice.” Dr. Xavier Rosselló, of hospital son Espases de Palma de Mallorca and a CNIC scientist, adds that “These clinical trials, managed from the CNIC Clinical Trials Coordination Unit, are a demonstration of Spanish scientific leadership, as well as the commitment of the Spanish medical community.”

The investigators conclude that DapaTAVI marks a breakthrough in cardiovascular research and could transform the treatment of these patients throughout the world.

The study received funding from the Carlos III Health Institute, the Spanish Society of Cardiology, the Galician Society of Cardiology, and the Castilla y León Regional Health Authority.

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Circulation: The heart remembers: scientists describe how early-life cardiac injury in parents influences the development and function of the heart in the next generation

Scientists at the CNIC and the University of Bern have found that heart surgery in male mice early in life creates a "memory" passed down to the next generation. Published in Circulation, the study suggests that a parental history of heart surgery should be considered when evaluating cardiovascular health in descendants.

Stress during the first years of life can have effects that last into adulthood. Less is known, however, about the possible inheritance of the consequences of early-life stress by the next generation. Now, scientists at the Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC) and the University of Bern in Switzerland have discovered that heart injury early in life in one generation of mice triggers changes in cardiac function in their offspring. The study is published in the journal Circulation.

A family history of heart attack is known to influence an individual's risk of cardiovascular disease. Moreover, the risk for offspring is greater if a parent experienced a heart attack earlier in life. Nevertheless, it has remained unclear if heart injury in a parent directly influences the cardiovascular system of the next generation. Almost 30,000 children require heart surgery every year in Europe, so exploring whether the "memory" of early-life cardiac injury can be transmitted to the next generation offers an important opportunity to increase our understanding of cardiovascular disease and to improve the collection of medical histories.

The new study, led by Nadia Mercader of the CNIC and the University of Bern, analyzed if experimentally induced cardiac injury in male mice could produce an inherited effect in the next generation. The results, explains study first author Benedetta Coppe, of the University of Bern, show that the offspring of fathers with early-life cardiac injury had altered heart function. "The offspring of injured fathers showed evidence of altered heart development, characterized by transient expansion of the left ventricle during the first weeks after birth. This surprised us, since the only difference between the newborns was that in one group the father had experienced cardiac injury early in life, while in the other group the father was uninjured." The offspring of injured fathers also showed alterations in their responses to cardiac injury. These changes included improvements in cardiac remodeling (changes in the size, shape, and function of the heart after induced injury) compared with the offspring of uninjured fathers. This superior cardiac remodeling was associated with an increased volume of blood ejected by the heart per minute.
After injury, the heart normally switches its energy source from lipids to glucose, and this results in an accumulation of lipids in the heart tissue. Dr. Mercader explains that, "Curiously, the offspring of injured fathers accumulated fewer lipids in response to induced heart injury and had higher concentrations of circulating lipids in the blood. These observations suggest that the metabolism of mice with this 'family history' recovers better when these mice are themselves subjected to cardiac injury." The changes observed in the offspring of injured fathers indicate that cardiac surgery in the first weeks after birth leaves a lasting "memory" that can eventually be transmitted to the next generation. The researchers conclude that the findings open the way to a better understanding of the impact of heart disorders and underline the potential value of including family surgical history when collecting patient medical histories. The study was supported by funding from the European Union Horizon 2020 Programme (grant 819719) and an interdisciplinary grant (UniBeAQ20 ID Grant) from the University of Bern.

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Circulation Research: Breakthrough gene therapy offers hope for rare, deadly heart disease in young men

A team at the Centro Nacional de Investigaciones Cardiovasculares (CNIC) has developed an innovative gene-therapy strategy that could transform the treatment of arrhythmogenic right ventricular cardiomyopathy type 5 (ARVC5), a rare and highly penetrant inherited cardiac disorder with an elevated risk of sudden cardiac death. This disease is particularly devastating in young men and lacks a cure, with current treatments focusing on palliative care.

The study, led by Dr. Enrique Lara-Pezzi, head of the Molecular Regulation of Heart Failure group at the CNIC and a member of the Spanish cardiovascular research network (CIBERCV), demonstrates that the introduction of a healthy version of the TMEM43 gene directly into cardiac muscle cells significantly improves heart function and prolongs survival in a mouse model of the disease.

The new method is the result of more than 10 years of collaboration between a clinical team at Hospital Puerta de Hierro Majadahonda led by Dr. Pablo García-Pavía, who also heads the Inherited Cardiomyopathies group at the CNIC, and the basic–translational group led by Dr. Lara-Pezzi. This longstanding partnership has allowed the team to advance the understanding of this disease and offer an effective alternative for its treatment. After the identification of the first patients in Spain with ARVC5 at Hospital Puerta de Hierro, the two groups worked together to create, in 2019, the first model to replicate the disease in animals. Now, the researchers have taken a step further by developing a treatment for the disease in this experimental model.

ARVC5 is caused by mutations in a gene called TMEM43 that provoke severe arrhythmias and can cause sudden death. The disease is particularly aggressive in young men, reducing their life expectancy to below 42 years. While implantable cardioverter-defibrillators (ICDs) are used to prevent sudden death, there are no available treatments to stem progression of the disease. In the study, published in Circulation Research, the CNIC team developed a gene therapy using adeno-associated viruses (AAV)—a safe delivery system for human patients—to deliver a functional copy of TMEM43 directly into the cardiac muscle cells of the experimental mice.

The results are promising: the treatment not only improved cardiac contraction and reduced fibrosis, but also significantly prolonged the life of mice with ARVC5-like disease. A single dose of the treatment was enough to prevent the electrical and structural alterations typical of the disease.

First author Dr. Laura Lalaguna explains that, "This advance takes us closer to a possible cure for this devastating disease. By increasing the amount of functional TMEM43 protein in the heart, we were able to counteract the toxic effects of the mutant version of the protein, and this resulted in improved heart function and put a brake on disease progression." Treatments for heart failure associated with hereditary cardiomyopathies are often ineffective, and Dr. Lara-Pezzi is keen to underline the potential application of the new strategy in the treatment of other diseases of this type. "AAV gene therapy has enormous potential to offer specific solutions and cures not only for ARVC5, but also for other inherited cardiac disorders." The study marks a key advance in the search for more effective treatments for rare diseases and could transform the prognosis of affected patients, alleviating the burden of hereditary cardiac diseases and reducing the need for continuous medical surveillance, to the benefit of both patients and health care systems.

The study was supported by the Pathfinder Cardiogenomics program of the European Innovation Council (project DCM-NEXT; 101115416); grants PID2021-124629OB-I00, TED2021-129774B-C22, and PLEC2022-009235 from the Ministerio de Ciencia e Innovación (MCIN/AEI/10.13039/501100011033); the NextGenerationEU recovery instrument through the PRTR (Plan de Recuperación, Transformación y Resiliencia de España); and the European Regional Development Fund.

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Nature Communications: A type of immune cell strengthens immunotherapy and prevents tumor relapse in animal models

Scientists at the CNIC, working in collaboration with the Instituto de Investigación Biomédica de Barcelona (IRB Barcelona), have discovered a new immunotherapy strategy that reduces cancer recurrence in mouse experimental models. The study, published in Nature Communications, shows that a specific subtype of immune cell—type I dendritic cells— is especially effective at activating a strong immune response and generating immune memory against cancer.

Dendritic cells act as sentinels of the immune system, presenting tumor antigens to T lymphocytes to initiate an immune response against malignant cells. However, there are multiple dendritic cell subtypes, and until now it was unclear which is the most efficient at generating a sustained, protective response to tumors.

First author Ignacio Heras-Murillo, of the CNIC, explains: "The finding is important because most current therapies focus on enhancing the immune response that is already in place. In contrast, this dendritic cell-based immunotherapy aims to induce a new, specific immune response against the tumor."

Describing the strategy, study co-supervisor Stefanie Wculek—formerly at the CNIC and now at IRB Barcelona—explains that dendritic cells are extracted from the cancer-bearing mouse, loaded in the lab with tumor-derived antigens, and then reintroduced into the animal to activate specific T lymphocytes. The results show that type I dendritic cells not only trigger an immediate response against the primary tumor but also induce long-lasting immune memory capable of preventing tumor relapse. CNIC scientist David Sancho, who led the study, adds that immunotherapy with type I dendritic cells presenting the tumor antigen triggers an immune memory response that prevents the growth of a second, similar tumor. In other words, the treatment helps prevent relapse in the mouse models. Further studies will be needed to assess the potential of this approach for preventing metastasis and its possible synergy with other antitumor therapies.

The study was supported with funding from the CNIC; the Ministerio de Ciencia, Innovación y Universidades (MICIU), the Agencia Estatal de Investigación, the European Union NextGenerationEU/PRTR; the Comunidad de Madrid; the "la Caixa" Foundation; Asociación Española Contra el Cáncer, and Worldwide Cancer Research (25-0080).

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Developmental Cell: CNIC team reveals how the heart is organized from the earliest stages of embryonic development

A study published today in the journal Developmental Cell uncovers new insights into how the heart forms during the earliest stages of embryonic development. The research, led by scientists at the Centro Nacional de Investigaciones Cardiovasculares (CNIC), shows that the heart originates from two distinct cell populations that form independently—but in a coordinated manner—from the very beginning of development: specifically, from the onset of gastrulation, the process by which the embryo begins to organize its basic cellular layers.

"This discovery is highly significant," says CNIC scientist Miguel Torres, head of the Genetic Control of Organ Development and Regeneration Group and senior author of the study together with Miquel Sendra. "It helps us understand how the heart is structured in its earliest phases, which may allow us to identify the roots of certain congenital heart defects. It also opens new doors for regenerative medicine and tissue bioengineering."

Until now, it was thought that cardiomyocytes—the muscle cells of the heart—and endocardial endothelial cells—which line the heart's inner surfaces—originated from a single precursor population.

However, the new study, based on in vitro mouse embryo culture, advanced microscopy, and cell tracing techniques, reveals that these two cell types originate from separate regions within the mesoderm, one of the three germ layers of the early embryo.

Although they develop separately, the two cell populations enter the embryo simultaneously and migrate in a coordinated fashion toward the region where the primitive heart tube begins to form. According to the researchers, this synchronized behavior points to the presence of highly precise organizational mechanisms at a stage when the embryo still lacks most visible structures.

The study also shows that, despite being fated to form the heart, these cells retain the potential to contribute to the development of other organs—highlighting their versatility and importance in early embryogenesis.

The study was funded by the "la Caixa" Foundation (ID 100010434); the Company of Biologists; the Spanish State Research Agency; the European Commission's H2020 program REANIMA, and CARDIOBOOST-CM of the Community of Madrid.

It also received support from the ERDF 'A way to build Europe' (ReDIB ICTS TRIMA@CNIC infrastructure, MCIN).

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Circulation Research: CNIC scientists uncover how the immune response drives atherosclerosis—the root cause of heart attacks and strokes

Scientists at the CNIC in collaboration with national and international research centers, have identified a key immune cell subtype involved in the development of atherosclerosis. In a study published in Circulation Research, the team tested an experimental therapy in animal models based on immunosuppressive nanoparticles and demonstrated that it can slow disease progression.

The new CNIC research, conducted by the Immunobiology Group led by David Sancho, reveals that conventional type 1 dendritic cells (cDC1s) play a key role in this inflammatory process. The team used mouse models to analyze how the presence or absence of these cells influences atherosclerosis development.

"We used genetically modified mice fed a high-cholesterol diet to replicate the conditions that promote atherosclerosis," explains lead author Miguel Galán Burgos. "When we artificially increased the number of cDC1s, arterial lesions worsened. But when the mice lacked cDC1s specifically, plaque formation was significantly reduced—even with an unhealthy diet."

A key innovation in the study was the development of an experimental therapy based on nanoparticles loaded with the immunosuppressant dexamethasone and coated with antibodies. These nanoparticles were developed in collaboration with Jesús Ruiz Cabello and Susana Carregal Romero, from the Molecular and Functional Biomarkers research group of the Center for Cooperative Research in Biomaterials (CIC biomaGUNE) in San Sebastian.

The nanoparticles were specifically designed to target cDC1s. "When we administered the nanoparticles in animal models of atherosclerosis, we observed a marked reduction in plaque size and in the associated inflammatory response. Importantly, this approach controlled arterial inflammation without impairing the body's ability to fight viral infections", explain the authors.

The results reinforce the role of cDC1s in driving atherosclerosis and introduce a promising new therapeutic approach that tackles the immune root of the disease. By precisely targeting the immune cells involved, this strategy could offer a safer, more effective alternative to current treatments, minimizing systemic side effects.

The project was supported by funding from the Spanish Ministry of Science, Innovation, and Universities (MICIU): PID2022-137712OB-I00, PID2021-123238OB-I00, PID2022-139218OB-I00, CNS2023-143944, RYC2020-030241-I, PID2022-142842OB-I00, CPP2021-008310 and CPP2022-009762, funded by the State Research Agency and the European Union NextGeneration EU/PRTR. Additional funding was provided by the Community of Madrid (P2022/BMD-7333 INMUNOVAR-CM) and Fundación "la Caixa" (LCF/PR/HR23/52430012 and LCF/PR/HR22/52420019).

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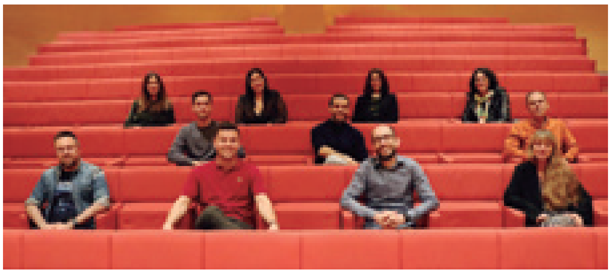
Nature Biomedical Engineering: Descubren un método para estudiar proteínas mecánicas y su relación con enfermedades musculares



A team at the CNIC, led by Dr. Jorge Alegre-Cebollada, has developed an innovative method, called TEVs-TTN, for studying the specific mechanical functions of proteins through their controlled cleavage, a process that renders the proteins unable to sense and transmit mechanical force. The study results extend knowledge about the development of muscular diseases.

The study, published in Nature Biomedical Engineering, demonstrates that interrupting mechanical transmission by the protein titin precipitates muscular diseases. This finding opens new routes to understanding muscular dystrophies and other diseases associated with the protein titin.

Titin is the largest protein in animals and plays a critical role as the structural linchpin of sarcomeres, the contractile units of muscle cells. Mutations in the titin gene (TTN) are a leading cause of congenital muscular diseases and cardiomyopathies, explains first author Dr. Roberto Silva-Rojas.

"In the absence of experimental animal models with titin-cleavage mutations, our approach allows a structured and targeted analysis of the impact of these types of alterations. This makes TEVs-TTN an ideal tool for testing therapies designed to mitigate the effects of impaired sarcomere integrity." One intriguing finding of the study is that titin cleavage caused complete disintegration of sarcomeres over the course of a few days, leaving muscle cells devoid of their basic functional unit. Nevertheless, these cells survived, suggesting that similar processes might operate in other situations, such as muscle tears, heart failure, or cardiotoxicity associated with chemotherapy.

The methodology developed at the CNIC marks a milestone in the study of how protein mechanics contribute to tissue and organ physiology. Just as titin is critical for force transmission in sarcomeres, other proteins, such as dystrophin, dystroglycan complexes, integrins, and lamins, play critical roles in extracellular matrix regulation and cell membrane integrity. The new tool will enable the research team to confirm or refute hypotheses about the functioning of these proteins. These advances, in turn, could pave the way to the development of new therapeutic strategies for many diseases beyond those affecting muscle.

The study was funded mainly by the European Resarch Council through the ProtMechanics-Life Consolidator Grant (101002927) and a postdoctoral fellowship from the European Molecular Biology Organization to Dr. Silva-Rojas (EMBO ALTF 417-2022).

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CNIC & SOCIETY

Silvia G. Priori to Receive ACC Valentin Fuster Award for Innovation in Science

Dra. Silvia G. Priori has been awarded the 2025 Valentin Fuster Award for Innovation in Science by the American College of Cardiology in honor of their remarkable contributions to the cardiovascular profession. The Valentin Fuster Award for Innovation in Science recognizes an ACC member who has made significant contributions to cardiovascular medicine as a champion of scientific research, an innovator in the delivery of science through novel mechanisms and an international voice on the importance of embracing scientific inquiry to improve the care of cardiovascular patients and promote heart health

Tribute to Dr Valentín Fuster at the Jiménez Díaz Foundation

Dr. Valentín Fuster General Director of the Spanish National Centre for Cardiovascular Research (CNIC) led the second session of the series of conferences organised by the Fundación Jiménez Díaz (FJD) University Hospital to celebrate its 90th Anniversary. In conversation with Dr Borja Ibáñez, the CNIC's Scientific Director and FJD cardiologist, Dr Fuster spoke about medical vocation, the value of mentors and the need for human-centred medicine.

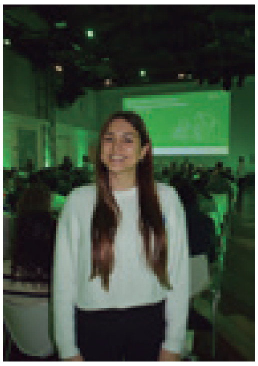
An audience of almost 300 filled the hospital's main lecture hall to hear Fuster speak about his personal trajectory, ranging from his childhood or training in Edinburgh to his leadership at Mount Sinai in New York. "Technology cannot replace a human relationship, only complement it. We need to recover the clinical gaze, physical examination and, above all, listen to the patient," he said, highlighting his advocacy of medicine based on empathy and service.

International Day of Women and Girls in Science

The CNIC celebrated International Day of Women and Girls in Science with inspiring activities to promote STEM careers, highlighting female talent and its training programs.

In addition, on the occasion of International Women's Day (March 8) and European Cardiovascular Risk Prevention Day (March 14), the CNIC organized a special event aimed at the general public that addressed cardiovascular risk prevention in women.

CNIC research into cardiotoxicity in cancer wins the AECC prize for best scientific article of 2024



The article entitled "Anthracycline Cardiotoxicity Induces Progressive Changes in Myocardial Metabolism and Mitochondrial Quality Control: Novel Therapeutic Target", whose first author is the CNIC researcher Anabel Díaz-Guerra, was awarded first prize for the best scientific article of 2024 written by recipients of the AECC Predoctoral Grants. Her research, published in the review JACC: CardioOncology. identified possible therapies for the cardiotoxicity of anthracyclines, drugs habitually used in cancer treatment, which is estimated to affect a third of people who survive cancer.

Cardiovascular disease in women: a call for action from Europe

On International Women's Day, the European Parliament hosted the event "A wake-up call: Key trends and policy issues in cardiovascular health for women and girls," which addressed gender inequalities in cardiovascular disease. Dr. María Rubini, cardiologist and researcher at the CNIC and chair of the European Society of Cardiology's Gender Working Group, actively participated with a presentation that highlighted the urgent need to raise awareness, promote gender-sensitive research, and encourage the inclusion of women in clinical trials. Rubini called on policymakers to integrate the gender perspective into the EU Cardiovascular Health Plan and the Equality Strategy, positioning the CNIC as a key voice in the fight for more equitable cardiovascular health for women. 'It is essential to raise awareness of CVD in women, as it is the leading cause of death in the EU, with more deaths than all cancers combined,' she said

CNIC, participant in the International Be Open About Animal Research Day

CNIC participated in the International Be Open About Animal Research Day organised by the European Animal Research Association (EARA), the international organisation that highlights the importance of responsible, regulated animal research limited to experiments that cannot yet be conducted without them.

CNIC at the European Meeting on Science, Technology, and Innovation

The Spanish National Centre for Cardiovascular Research (CNIC) is again an active participant in the European Meeting on Science, Technology, and Innovation (Transfiere) 2025. The event is the main meeting for R+D in the south of Europe and its aim is to share scientific and technological knowledge, promote innovation, connect science and business, and facilitate the transfer of knowledge so that scientific and technological developments reach people's daily lives

CNIC obtains the "Equality in the Workplace" (DIE) distinction from the Women's Institute

The CNIC has obtained the "Equality in the Workplace" (DIE) distinction, awarded by the Ministry of Equality through the Women's Institute, in recognition of its commitment and excellence in the application of equality policies. This distinction, which will be valid for five years, also means that the CNIC will join the DIE Network, a platform for the exchange of best practices among the 197 organizations recognized for their work in promoting equal treatment and opportunities for women and men in the workplace.

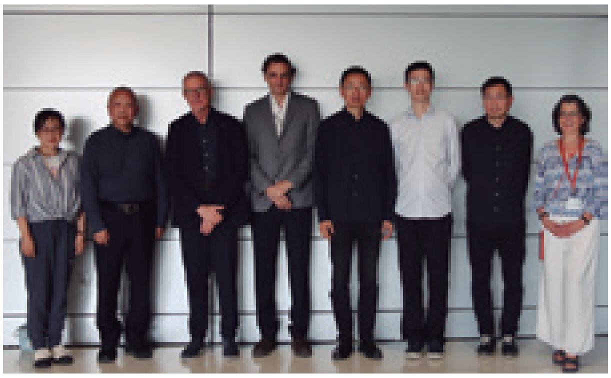
Igualdad en la Empresa 2024

4th ESO Program at CNIC

CNIC participates in the 4th ESO+Company Program of the Community of Madrid, opening its doors to offer educational stays to interested students from public or charter schools. This program at CNIC seeks to bring the educational system closer to the field of cardiovascular scientific research.

Visit by the Mapfre Foundation to the CNIC

Visit by the University of Shanghai to the CNIC



Visit by representatives of the State Attorney's Office to the CNIC

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