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CNIC NEWS AND VIEWS

1. GRANTS

REANIMA

TOWARD A NEW PARADIGM IN CARDIAC REGENERATION

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

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

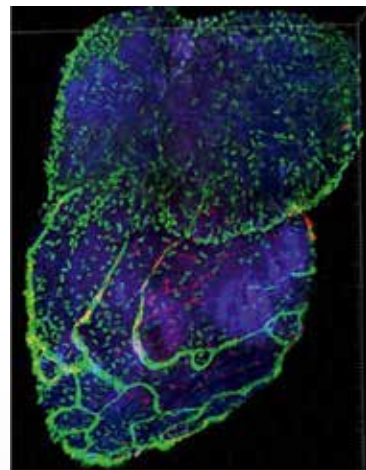
REANIMA is the first Europe-wide project to integrate basic research findings in an effort to transform them into medical applications in the field of cardiac regeneration. REANIMA is funded by the European Union's Horizon 2020 research and innovation programme under grant agreement n° 874764. Project activities range from identifying

new targets in animal models to the design of clinical trials. The project is linked to the similarly named 'REANIMA-CM' project funded by the Comunidad de Madrid, which is also coordinated by Dr Torres.

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

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

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



NEUTROCURE

EXPLOITING THE DUAL NATURE OF NEUTROPHILS TO CURE INFLAMMATORY DISEASES

Curing disease with neutrophils; this is the goal of the NeutroCure project. How will that work? "Neutrophils have a yin yang character," explains Andrés Hidalgo, whose team at CNIC is one of six member groups participating in this project coordinated by Andriy Mokhir Friedrich at Alexander University, Germany.

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

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

The goal of NeutroCure is to ensure that these substances act selectively and are controlled. To achieve this, the consortium members focus on the protein elastase, which is specific to neutrophils. The team has designed a

'chemical cage' that opens to 'release' ROS only when elastase is in highly defined anatomical locations and contexts.

The project will assess this approach in models of inflammatory disease, including arthritis, multiple sclerosis, autoimmune neuritis, lupus, and psoriasis.

The project has received European funding of €3 million for 5 years in the category H2020-FETOPEN-2018-2020- FET Open – Novel ideas for radically new technologies. The CNIC team led by Andrés Hidalgo will receive €400,000 as one of the six academic groups in the NeutroCure consortium.

The NeutroCure consortium also includes a private company, which will steer the commercialization of new medication developed in the project. The consortium members anticipate that NeutroCure will have a major societal impact by providing new treatments for severe disorders caused by the dysregulated production of ROS.



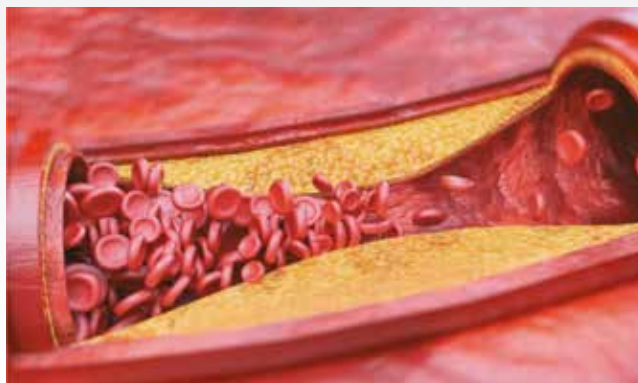
NEUTROCURE

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

Professor Jacob Fog Bentzon of Aarhus University and the CNIC has received €2 million from the European Research Council for a ground-breaking research project on atherosclerosis, one of the most frequent causes of death in the world.

Although atherosclerosis is a very common disease, much work remains to be done to define exactly what happens when fat and cholesterol are deposited in the walls of arteries, which leads to arteriosclerosis and the risk of blood clots in the heart and the brain.

Scientists only recently discovered that many of the cells found in atherosclerotic plaques are in fact vascular smooth muscle cells that have altered their appearance and function. The research group led by Professor Fog Bentzon will use the new funding to uncover the significance of these mysterious cells.



“When you look at atherosclerosis under the microscope, you see a complex mix of many types of cells. But we now know that although the cells may look different, most of them originate from the arteries’ own vascular smooth muscle cells,” says Bentzon.

“Our ultimate goal is to find new ways to treat advanced atherosclerosis in humans. And the route to this goal passes through a wide range of studies in genetically modified mice and pigs,” he adds.

THE FUNDACIÓN BANCARIA LA CAIXA SELECTS 2 CNIC PROJECTS IN ITS “PROYECTOS DE INVESTIGACIÓN EN SALUD 2018” PROGRAM

Two CNIC projects were selected by the Fundación Bancaria La Caixa for its Proyectos de Investigación en Salud program for 2018.

The projects are ‘Dysfunction of Ion Channel Complexes in Inheritable Cardiac Diseases’, led by Dr José Jalife, and ‘Nitric Oxide signaling and proteoglycans in Marfan syndrome aortopathy: mechanisms and new therapeutic targets’, led by Dr Juan Miguel Redondo.

Dr Jalife’s project adopts pioneering approaches to define the causes of sudden cardiac death in inherited cardiac diseases and identify new and more effective prevention strategies. The new techniques employed in the study include the injection of adeno-associated virus to target mutated genes to the heart cells of mice,



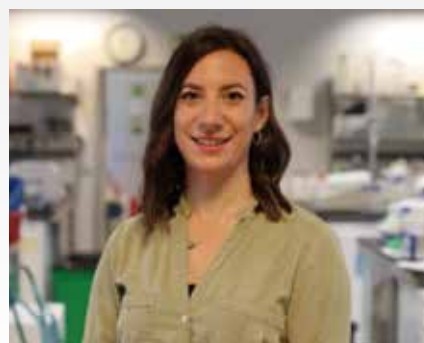
the derivation of cardiomyocytes from human induced pluripotent stem cells, and advanced proteomics and bioinformatics approaches. The project was awarded €499,895.

Dr Redondo’s project investigates the pathophysiological mechanisms underlying Marfan syndrome and the formation of aortic aneurysms and dissections. The goal is to identify new molecular targets and biomarkers that can be used to develop effective treatments. The project was awarded €500,000.

CNIC RESEARCHER SECURES FUNDING FOR 2 PROJECTS FROM THE EUROPEAN FEDERATION FOR THE STUDY OF DIABETES

CNIC postdoctoral researcher Ivana Nikolić has been awarded funding for 2 projects by the European Foundation for the Study of Diabetes (EFSD) to study the role of T cells in the development of diseases associated with obesity. The 2 awards are the EFSD–Lilly Young Investigator Award, providing €50,000 and the EFSD Rising Star Fellowship, bringing another €30,000. Dr Niković previously obtained the 2017 EFSD–Lilly Research Fellowship Award, receiving a grant of €50,000.

Dr Nikolić obtained her PhD in Immunology at the University of Belgrade in 2014. In 2015 she joined Dr Guadalupe Sabio’s lab at the CNIC with an FP7–People Marie Skłodowska - Curie Actions, MSCA - COFUND talent recruitment fellowship. These fellowships were intended to attract outstanding foreign scientists to the CNIC at an intermediate stage in their career so that they could develop their research in Spain.



Dr Nikolić exemplifies the success of this talent recruitment program. The 3 EFSD awards she has obtained support her research into the molecular mechanisms of obesity.

2. AWARDS & HONORS

VALENTÍN FUSTER AWARDED THE 2019 NATIONAL RESEARCH PRIZE

The Ministry of Science, Innovation and Universities awarded the 2019 Gregorio Marañón National Research Prize to Valentín Fuster. The jury panel awarded the prize to Dr Fuster in recognition of his unparalleled research record and his enormous contributions to the prevention, diagnosis, and treatment of cardiovascular disease. The National Research Prize, first awarded in 1982, is the highest Spanish accolade for scientific research. The aim of the award is to reward the achievements of Spanish scientists who are international leaders in their research fields and who make exceptional contributions to the advance of scientific knowledge, technology transfer, and human progress.



PURA MUÑOZ-CÁNOVES AWARDED THE JAUME I PRIZE FOR MEDICAL RESEARCH

CNIC group leader Dr Pura Muñoz-Cánoves was awarded the XXXI Rei Jaime I prize in the Medical Research category. The Rei Jaime I are awarded to people who have made outstanding contributions in their fields through work carried out mostly in Spain. The prizes are awarded annually, and each prize winner receives a gold medal, a diploma, and €100,000, on the condition that part of this money be used to fund research and enterprise in Spain.

The prize was awarded to Dr Muñoz for her work on the molecular mechanisms of aging, especially the progressive changes that take place in the stem cells of animals as they age and the possibility of manipulating these changes for regenerative medicine.



Dr Muñoz was also awarded the Lilly Foundation Preclinical Biomedical Research Prize for 2019 in recognition of her pioneering work on tissue regeneration.

RODRIGO FERNÁNDEZ RECEIVES THE MARIE SKŁODOWSKA-CURIE ACTIONS AWARD



CNIC researcher Dr Rodrigo Fernández Jiménez received the 2019 Marie Skłodowska-Curie Actions Award in the ‘Scientific Careers for Policymaking’ category for his Comprehensive Lifestyle Intervention Project (CLIP).

CLIP investigates new approaches to health promotion and disease prevention. The goal is to help policy makers devise effective strategies to promote a healthy life style among children.

The aim of the project is to convince governments that low-cost and side-effect-free health-promotion programs aimed at young people provide a potentially effective way to reduce the cardiovascular disease epidemic if integrated into national school curriculums.



SARA COGLIATI SELECTED FOR A XIV L'ORÉAL-UNESCO RESEARCH PRIZE FOR WOMEN IN SCIENCE

CNIC researcher Dr Sara Cogliati was awarded one of 5 prizes in the XIV edition of L'Oréal-Unesco For Women in Science Program for her project investigating sex-specific characteristics in cardiovascular disease. This research is crucial to finding effective treatments for heart failure in women because historically most treatments have been based on research in men, despite important differences between the sexes in the way the disease manifests. Dr Cogliati's research signals an important advance toward gender equality in the treatment of disease.

MIGUEL TORRES ELECTED A MEMBER OF THE EUROPEAN MOLECULAR BIOLOGY ORGANIZATION

CNIC group leader Dr Miguel Torres has been elected a member of the European Molecular Biology Organization (EMBO). In the words of EMBO Director Maria Leptin, “EMBO members are expert scientists who carry out pioneering research across all disciplines in the life sciences, from computer models or analysis of individual molecules and cell mechanisms to the study of higher-level systems in development, cognitive neuroscience, and evolution.”

Dr Miguel Torres’s research focuses on the regulation of embryonic development and the formation and regeneration of organs. He has made major contributions to the understanding of how gene activities regulate regionalization processes in the developing embryo and the discovery of mechanisms involved in quality control and organ regeneration.

Among his various projects, Dr Torres directs the first Spanish-coordinated international project funded by the prestigious Leducq Foundation. The project—Redox Regulation of Cardiomyocyte Renewal—aims to identify how and why adult mammals lose the capacity to regenerate the heart after injury, whereas this ability is retained in newborn infants and in adults of other animal species, including fish and amphibians.



FRANCISCO SÁNCHEZ-MADRID AWARDED AN HONORARY DOCTORATE (DOCTOR HONORIS CAUSA) BY THE UNIVERSITY OF CÓRDOBA

Professor Francisco Sánchez Madrid was awarded an honorary doctoral degree by the University of Córdoba. Dr Sánchez Madrid heads the Intercellular Communication in the Inflammatory Response laboratory at the CNIC and is full professor in Immunology at Madrid Autonomous University and Scientific Director of the Research Institute and Hospital de La Princesa, Madrid.



3. SCIENTIFIC EVENTS

CNIC CONFERENCE NEW CONCEPTS IN AGE-RELATED CARDIOVASCULAR DISEASE

The CNIC held its annual scientific meeting, the CNIC Conference, on October 24 to 26. The 2019 conference, ‘New concepts in age-related cardiovascular disease’, was organized by three CNIC researchers, Vicente Andrés, José J Fuster, and Andrés Hidalgo, and Columbia University professor Allan Tall. The meeting hosted world experts in the field of aging related to cardiovascular disease (CVD).

Population aging is one of the most important demographic phenomena of our time, and its global impact is medical, social, and economic. Age is also the most important risk factor for CVD,



yet the underlying mechanisms linking aging and CVD are still not fully understood. In recent years, studies have been published on a series of mechanisms specifically linked to aging that are completely independent from traditional risk factors. These new mechanisms, which are relevant to both cardiovascular and cerebrovascular disease, open the door to new therapies and prevention strategies. Renowned participants included CNIC Director Dr Valentín Fuster, Dr. Filip Swirski from Harvard University, Costantino Iadecola from

the Cornell School of Medicine in New York, and Paul Frenette from the Albert Einstein College of Medicine, who delivered the Company of Biologists keynote presentation. Leading Spanish experts in aging and cerebrovascular diseases attending the meeting included Dr M Ángeles Moro from Madrid Complutense University and Dr Manuel Serrano from the Biomedical Research Institute in Barcelona, who presented the EMBO keynote presentation.

THE CNIC AND CNIO JOINT WORKSHOP TO SHARE KNOWLEDGE AND BOOST SYNERGIES

Cancer and cardiovascular disease share many of the same molecular mechanisms, and it is common for studies to involve participation from experts in both fields. This is never more true than in the case of the *Centro Nacional de Investigaciones Oncológicas* (CNIO) and the *Centro Nacional de Investigaciones Cardiovasculares* (CNIC), which boast similar and complementary technological platforms. These neighboring centers of excellence, both under the umbrella of the *Instituto de Salud Carlos III* (ISCIII),

organized the CNIO–CNIC Joint Meeting to share knowledge, boost synergies, and promote joint projects.

The meeting was overseen by ISCIII Director Raquel Yotti, CNIO Director Maria Blasco, and CNIC Director Valentín Fuster. Participants reviewed the most advanced research lines at each center and emphasized the vital importance of collaborative research.

CNIC PHDAY 2019



Since its launch in 2014, the annual PhDay event has provided a platform for proposing and debating diverse science-related topics of interest to early-stage researchers. The main goals of the event are to help participants develop their careers as scientists, exchange new ideas, and establish career networks. This year's event had more than 200 participants, and the chosen theme, 'What else?', centered on career options. Entrepreneurs and scientists from academia and industry joined to discuss life after a PhD and the different paths available.

INVITED CNIC SEMINARS

During 2019, the CNIC hosted 23 invited speakers, who delivered presentations at the Center.



4. OUTREACH ACTIVITIES

SCIENCE WEEK AT THE CNIC

For *Semana de la Ciencia 2019*, the CNIC introduced 2 new activities. The 'Family Day at the CNIC' event was designed especially for younger children and their families, while the #ConCienciaCNIC one-day events consisted of scientific workshops for children with special needs.

These activities catered for children between the ages of 4 and 14, accompanied by adults, and aimed to introduce tomorrow's scientists to the world of research. Through theater, play activities, and scientific workshops, the children had fun, but also learned from the experiments carried out by CNIC volunteers.



5. NEW PARTNERSHIPS

THE CNIC AND THE SEC LAUNCH A STUDY AIMED AT CHANGING CLINICAL PRACTICE AFTER AN INFARCTION

The CNIC and the Spanish Society of Cardiology (SEC) joined forces to launch a pioneering clinical trial in Spain: REBOOT. In the words of principal investigator Dr Borja Ibáñez, “the ambitious aim of this trial is to change clinical practice guidelines for the treatment of acute myocardial infarction.” The trial will test the effect of maintaining beta-blocker therapy after hospital discharge in a cohort of 8500 patients.

Beta-blockers are drugs that reduce heart rate, blood pressure, and cardiac contractility (strength of contraction). This promotes cardiac diastole (filling), which improves heart function and blood flow in the coronary arteries. Most of the evidence supporting the use of beta-blockers in heart attack patients comes from before the current era of widespread use of reperfusion therapy. Despite this, the recommendations in European and American guidelines for beta-blocker therapy in these patients have remained unchanged for decades.

REBOOT will be the first trial in the reperfusion era to study if the administration of beta-blockers after an acute myocardial infarction influences the incidence of death, reinfarction, and hospital readmission for heart failure.

The trial will randomize 8500 patients to receive beta-blocker therapy or no beta-blocker therapy. Participants will be followed up for a minimum of 2 years and a maximum of 3 years. Outcome measures will include the incidence of clinical events and adherence to the randomized therapy, recorded at 13, 15, and 36 months. A subsample of 1000 patients will be assessed for quality of life during follow-up.

This research topic is of such high relevance that another 3 European trials similar to REBOOT are planned, in Sweden, Norway, and Denmark. In total, more than 20,000 patients with similar characteristics will be randomized to beta-blocker therapy or no beta-blocker therapy after a myocardial infarction with ventricular dysfunction.



6. SOCIAL & CNIC

THE PRO-CNIC FOUNDATION RENEWS ITS COMMITMENT TO THE CNIC UNTIL 2028

Pro-CNIC Foundation President Luis de Carlos and General Secretary of Scientific Coordination Rafael Rodrigo formalized an agreement to renew the commitment of this body of 12 private companies to support the CNIC until 2028. The Pro-CNIC Foundation is an innovative example of public-private collaboration that has allowed the CNIC to establish itself as a world leader in biomedical research, contributing to the CNIC gaining Severo Ochoa accreditation in recognition of its international research excellence. Through the Pro-CNIC Foundation, 12 leading Spanish companies channel their business knowhow and financial support to the CNIC, representing a benchmark in successful scientific patronage. The companies participating in the Pro-CNIC Foundation are Acciona, Santander Bank, BBVA Bank, Endesa, the Mapfre Foundation, the Mutua Madrileña Foundation, the Ramón Areces Foundation, the Repsol Foundation, Inditex, “la Caixa”, Prisa, and Telefonica.

The Pro-CNIC Foundation enables the CNIC’s research to have a direct impact on patient care and health improvements in the general population. The Pro-CNIC Foundation also helps in the conversion

of innovations into patents that generate an economic return and support research and development in Spain.



A HEART ATTACK SURVIVOR DONATES BOOK SALE PROCEEDS TO THE CNIC

A heart attack survivor is donating the proceeds from her book to the CNIC after 'coming back to life'. On July 14, 2014, Paula Elena Ramos came back from the doors of death. Without warning, and with no family history or prior symptoms, Paula Elena had a third-degree atrioventricular block. She tells her story in her book a "Historia del corazón que sembró una galaxia en un cuerpo eléctrico," and all income from the sale of the book are being donated to arrhythmia research at the CNIC, specifically in the Advanced Development in Arrhythmia Mechanisms and Therapy laboratory led by Dr. David Filgueiras.



PARTICIPANTS IN THE V CONGRESS OF SCIENTIST-ENTREPRENEURS VISIT THE CNIC



As part of the activities program linked to the V Congress of Scientist-Entrepreneurs in May, a group of participants spent a day at the CNIC learning about the center's activities

and installations. The visited facilities included the Advanced Infrastructure for Translational Imaging (TRIMA), part of the ICTS Distributed Biomedical Imaging Network (ReDIB).