3 Scientific Highlights

BY PUBLICATION DATE

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Immunity

CNIC SCIENTISTS DISCOVER HOW THE GUT MODULATES THE DEVELOPMENT OF INFLAMMATORY CONDITIONS

This study, led by Dr. David Sancho, reveals how increased intestinal permeability allows 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 that are primed to respond more efficiently to future infections. However, this same ability to amplify the immune response can also aggravate 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 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; the European Research Council; Inmunotek S.L.; and Fundación "la Caixa".

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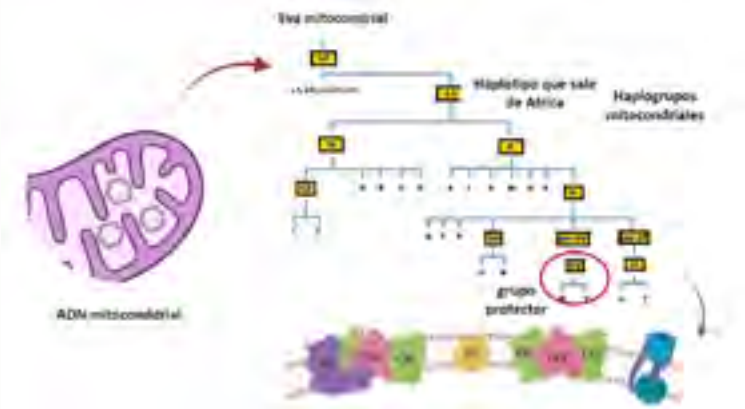
Communications Biology

THE EUROPEAN MITOCHONDRIAL LINEAGE MAY PROTECT AGAINST SEVERE FORMS OF COVID-19



This study showed 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).

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JACC CardioOncology

THE EUROPEAN MITOCHONDRIAL LINEAGE MAY PROTECT AGAINST SEVERE FORMS OF COVID-19

This study, led by Dr. Borja Ibáñez , and conducted in collaboration with international partners, presents 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. This study demonstrates that treatment with the SGLT2 inhibitor empagliflozin can mitigate the cardiac injury associated with anthracycline therapy.

Medina-Hernández D, Cádiz L, Mastrangelo A, Moreno-Arciniegas A, Fernández Tocino M, Cueto Becerra AA, Díaz-Guerra Priego A, Skoza WA, Higuero-Verdejo MI, López-Martín GJ, Pérez-Martínez C, de Molina-Iracheta A, Caballero-Valderrama M, Sánchez-González J, Sancho D, Fuster V, Galán-Arriola C, Ibáñez B. SGLT2i Therapy Prevents Anthracycline-Induced Cardiotoxicity in a Large Animal Model by Preserving Myocardial Energetics. JACC CardioOncol. 2025 Feb;7(2):171-184. doi: 10.1016/j.jaccao.2024.12.004. Epub 2025 Feb 4. PMID: 39967204; PMCID: PMC11866421.

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 for elimination, but also prevents them entering the body by physically strengthening the skin.

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

Vicanolo T, Özcan A, Li JL, Huerta-López C, Ballesteros I, Rubio-Ponce A, Dumitru AC, Nicolás-Ávila JÁ, Molina-Moreno M, Reyes-Gutierrez P, Johnston AD, Martone C, Greto E, Quílez-Alvarez A, Calvo E, Bonzon-Kulichenko E, Álvarez-Velez R, Chooi MY, Kwok I, González-Bermúdez B, Malleret B, Espinosa FM, Zhang M, Wang YL, Sun D, Zhen Chong S, El-Armouche A, Kim KK, Udalova IA, Greco V, Garcia R, Vázquez J, Dopazo A, Plaza GR, Alegre-Cebollada J, Uderhardt S, Ng LG, Hidalgo A. Matrix-producing neutrophils populate and shield the skin. Nature. 2025 May;641(8063):740-748. doi: 10.1038/s41586-025-08741-5. Epub 2025 Mar 19. Erratum in: Nature. 2025 May;641(8065):E10. doi: 10.1038/s41586-025-09082-z. PMID: 40108463; PMCID: PMC12074881.

New England Journal of Medicine

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 clinical trial including 1,250 patients showed that medication with dapagliflozin after TAVI reduces the rates of death and hospital admission attributed to heart failure over a one-year follow-up period. The trial was coordinated by the CNIC and Hospital Álvaro Cunqueiro- Vigo.

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.

Raposeiras-Roubin S, Amat-Santos IJ, Rossello X, González Ferreiro R, González Bermúdez I, Lopez Otero D, Nombela-Franco L, Gheorghe L, Diez JL, Baladrón Zorita C, Baz JA, Muñoz García AJ, Vilalta V, Ojeda-Pineda S, de la Torre Hernández JM, Cordoba Soriano JG, Regueiro A, Bordes Siscar P, Salgado Fernández J, Garcia Del Blanco B, Martín-Reyes R, Romaguera R, Moris C, García Blas S, Franco-Peláez JA, Cruz-González I, Arzamendi D, Romero Rodríguez N, Díez-Del Hoyo F, Camacho Freire S, Bosa Ojeda F, Astorga Burgo JC, Molina Navarro E, Caballero Borrego J, Ruiz Quevedo V, Sánchez-Recalde Á, Peral Disdier V, Alegría-Barrero E, Torres-Llergo J, Feltes G, Fernández Díaz JA, Cuellas C, Jiménez Britez G, Sánchez-Rubio Lezcano J, Barreiro-Pardal C, Núñez-Gil I, Abu-Assi E, Iñiguez-Romo A, Fuster V, Ibáñez B; DapaTAVI Investigators. Dapagliflozin in Patients Undergoing Transcatheter Aortic-Valve Implantation. N Engl J Med. 2025 Apr 10;392(14):1396-1405. doi: 10.1056/NEJMoa2500366. Epub 2025 Mar 29. PMID: 40162639.

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' that is passed on to the next generation. The study suggests that a parental history of heart surgery should be considered when evaluating cardiovascular health in descendants.

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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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 experimental mouse models. The study, 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.

This 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; Fundación "la Caixa"; Asociación Española Contra el Cáncer; and Worldwide Cancer Research (25-0080).

- Heras-Murillo I, Mañanes D, Munné P, Núñez V, Herrera J, Catalá-Montoro M, Alvarez M, Del Pozo MA, Melero I, Wculek SK, Sancho D. Immunotherapy with conventional type-1 dendritic cells induces immune memory and limits tumor relapse. Nat Commun. 2025 Apr 9;16(1):3369. doi: 10.1038/s41467-025-58289-1. PMID: 40204706; PMCID: PMC11982544.

Circulation Research

BREAKTHROUGH GENE THERAPY OFFERS HOPE FOR RARE, DEADLY HEART DISEASE IN YOUNG MEN

The CNIC team led by Dr. Enrique Lara-Pezzi 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 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 European Union NextGenerationEU/PRTR; and the European Regional Development Fund.

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Nature Biomedical Engineering

A NEW METHOD FOR STUDYING MECHANICAL PROTEINS AND THEIR INVOLVEMENT IN MUSCULAR DISORDERS

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 findings extend knowledge about the development of muscular diseases. This study demonstrates that interrupting mechanical transmission by the protein titin triggers the development of muscular diseases. This finding opens new routes to understanding muscular dystrophies and other diseases associated with the protein titin.

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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Circulation Research

CNIC SCIENTISTS UNCOVER HOW THE IMMUNE RESPONSE DRIVES ATHEROSCLEROSIS—THE ROOT CAUSE OF HEART ATTACKS AND STROKES

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

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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Science Translational Medicine

A HOSPITAL IMAGING TECHNIQUE USED IN CANCER CARE IMPROVES THE MONITORING AND TREATMENT OF ATHEROSCLEROSIS

Scientists at the CNIC have shown that 18FDG-PET, an imaging technique widely used to study other conditions, can also be used to monitor atherosclerosis by measuring cellular metabolism within arterial plaques. These findings could improve the clinical management of this disease and accelerate the development of new treatments.

The study received funding from the ERC under the European Union's Horizon 2020 research and innovation programme; the Spanish Ministry of Economy, Industry, and Competitiveness (MEIC), with co-funding from ERDF; the Instituto de Salud Carlos III, with ERDF/EU co-funding; the Madrid regional government; and Fundación "la Caixa" (AtheroConvergence).

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activity is associated with glycolytic enzyme expression across multiple cell types and is trackable by FDG-PET. Sci Transl Med. 2025 Aug 13;17(811):eado6467. doi: 10.1126/scitranslmed.ado6467. Epub 2025 Aug 13. PMID: 40802740.

European Heart Journal

GENES LINKED TO SUDDEN CARDIAC DEATH INCREASE THE RISK OF HEART FAILURE IN PATIENTS WITH GENETIC DILATED CARDIOMYOPATHY

A study led by Dr. Pablo García-Pavía and Dr. Fernando Domínguez—investigators at the CNIC and cardiologists at Hospital Universitario Puerta de Hierro and CIBERCV—shows that patients with genetic dilated cardiomyopathy who experience severe arrhythmias are at an elevated risk of developing advanced heart failure and requiring a heart transplant. The study was conducted through collaboration among 19 Spanish hospitals and the analysis of more than 1,200 patients.

This study received funding from the Instituto de Salud Carlos III (PI20/0320) with ERDF co-funding and the Pathfinder Cardiogenomics Programme of the European Union's European Innovation Council (project DCM-NEXT; project 101115416).

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New England Journal of Medicine & The Lancet

CNIC-LED REBOOT CLINICAL TRIAL CHALLENGES 40-YEAR-OLD STANDARD OF CARE FOR HEART ATTACK PATIENTS

The REBOOT study, coordinated by the CNIC together with the Mario Negri Institute in Milan, shows that beta-blockers do not benefit patients who survive an uncomplicated myocardial infarction while maintaining normal cardiac function. The finding challenges established medical practice in place for more than four decades.

The results, published simultaneously in *The New England Journal of Medicine* and *The Lancet*, and presented at the *European Society of Cardiology (ESC) Congress* in Madrid, mark a paradigm shift in post-heart attack treatment.

Funded by the CNIC, the study results simplify and optimize post-heart attack treatment, reducing side effects and improving patients' quality of life.

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European Heart Journal

A NEW STUDY FINDS THAT, AFTER A HEART ATTACK, WOMEN HAVE A WORSE PROGNOSIS WHEN TREATED WITH BETA-BLOCKERS

The REBOOT study, coordinated by the CNIC and presented at the 2025 ESC Congress, revealed important sex-specific differences in beta-blocker therapy after myocardial infarction in patients with preserved cardiac function. While men showed no benefit or harm, women with fully normal heart function (LVEF ≥ 50%) faced higher risks of death, reinfarction, or heart failure when treated with beta-blockers.

The REBOOT clinical trial, funded by the CNIC, was carried out through collaboration with the Spanish Society of Cardiology (SEC) and CIBERCV.

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European Heart Journal

CNIC SCIENTISTS REPORT THE FIRST USE OF CRISPR ACTIVATION TO TREAT A CARDIAC DISEASE IN A MOUSE MODEL

An international multidisciplinary team led by the CNIC, with participation from scientists at Hospital Universitario Puerta de Hierro and the University of California San Diego, has demonstrated that CRISPR-based gene activation (CRISPRa) can be used to treat genetic heart disease *in vivo*. This study, presented at the ESC Congress in Madrid, paves the way for novel targeted therapies for patients with genetic cardiac disorders. This approach could be especially useful for patients with conditions caused by mutations in genes too large to be targeted with conventional gene therapy.

The study was funded by the Spanish Ministry of Science, Innovation, and Universities, the Spanish cardiovascular research network (CIBERCV), and the European Innovation Council of the European Union.

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Developmental Cell

A CNIC TEAM REVEALS HOW THE HEART IS ORGANIZED FROM THE EARLIEST STAGES OF EMBRYONIC DEVELOPMENT

A study published in *Developmental Cell* uncovered new insights into how the heart forms during the earliest stages of embryonic development. The research, led by scientists at the CNIC, shows that the heart originates from two distinct cell populations that form independently—but in a coordinated manner—from the onset of gastrulation, the early developmental process in which the embryo begins to organize its basic cellular layers.

The study was funded by Fundación "la Caixa" (ID 100010434), the Company of Biologists, the Spanish State Research Agency, the European Commission H2020 programme REANIMA, and CARDIOBOOST-CM from the Community of Madrid. It also received support from the ERDF (ReDIB ICTS TRIMA@CNIC infrastructure, MCIN).

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New England Journal of Medicine

MAJOR INTERNATIONAL STUDY CONFIRMS THAT BETA-BLOCKERS ARE NO LONGER NEEDED IN POST-INFARCTION PATIENTS WITH NORMAL HEART FUNCTION

This landmark meta-analysis, presented at the 2025 American Heart Association Congress, concludes that beta-blockers do not reduce death, recurrent heart attack, or heart failure in patients who experience a myocardial infarction but maintain normal cardiac function (ejection fraction ≥50%). Led by the CNIC, the study pooled individual data from 17,801 patients across five major clinical trials—REBOOT, REDUCE-AMI, BETAMI, DANBLOCK, and CAPITAL-RCT—representing the most comprehensive analysis to date. The results showed no clinical benefit from beta-blocker therapy in this population, regardless of age, sex, or type of drug used.

The study was supported by funding from the CNIC, the Swedish Heart and Lung Foundation, Region Stockholm, the South-Eastern Norway Regional Health Authority; Research Council of Norway, the Danish Heart Foundation, Novo Nordisk Foundation, and the Research Institute for Production Development in Kyoto.

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Journal of Experimental Medicine

NEUTROPHILS ARE LESS AGGRESSIVE AT NIGHT, EXPLAINING WHY NIGHTTIME HEART ATTACKS CAUSE LESS DAMAGE THAN DAYTIME EVENT

A CNIC study explains why heart attacks that occur at night are less severe than those that strike during the day. The study, led by Dr. Andrés Hidalgo's group at the CNIC, shows that neutrophils—a type of white blood cell—have an internal clock that regulates their aggressiveness throughout the day and determines the extent of damage they cause to the heart after a heart attack. The researchers also developed a pharmacological strategy in experimental models to block the molecular clock in neutrophils, keeping them in a 'nighttime' state and thereby reducing their harmful potential during a heart attack.

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