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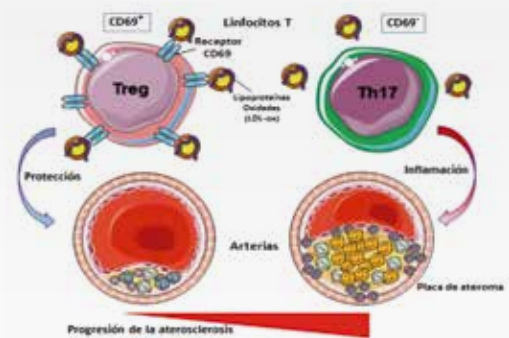
SCIENTIFIC HIGHLIGHTS BY PUBLICATION DATE

CIRCULATION

EXPRESSION OF A MOLECULE IN BLOOD CELLS PREDICTS ATHEROSCLEROSIS RISK

Earlier detection of cardiovascular disease is a step closer thanks to the findings of team of CNIC scientists led by Francisco Sánchez-Madrid and Pilar Martín. The researchers found that the expression level of the molecule CD69 in blood cells inversely predicts the appearance of subclinical atherosclerosis (developing before symptoms appear) independently of classical cardiovascular risk factors. The results, published in *Circulation*, show that the expression of CD69 in circulating lymphocytes correlates inversely with the presence and extent of subclinical atherosclerosis

The origin of atherosclerosis and its progression to acute myocardial infarction and stroke involve an essential contribution from the inflammatory immune response. However, according to Francisco Sánchez-Madrid, “The relationship between lipid metabolism and the immune



response is not well understood. The established hypothesis is that oxidized low-density lipoproteins (LDL_{ox}) induce the recruitment of inflammatory immune cells and their accumulation in the plaque; however, there is also evidence that cells and tissues can respond to LDL_{ox} by inhibiting proinflammatory signals.”

The new study identifies the molecule CD69 as a T cell receptor for oxidized lipoproteins that contributes to the control of inflammation and thus prevents the development of atherosclerosis. “Binding of LDL_{ox} to CD69 triggers the adoption of an anti-inflammatory profile by T lymphocytes that protects against the development of atherosclerosis in mice and humans,” explained Pilar Martín. The project was supported by the Spanish Cardiovascular Disease Research Network (CIBER-CV).

Tsilingiri, K., de la Fuente, H., Relano, M., Sanchez-Diaz, R., Rodriguez, C., Crespo, J., Sanchez-Cabo, F., Dopazo, A., Alonso-Lebrero, J. L., Vara, A., Vazquez, J., Casanovas, J. M., Alfonso, F., Ibanez, B., Fuster, V., Martinez-Gonzalez, J., Martin, P., & Sanchez-Madrid, F. (2019). oxLDL Receptor in Lymphocytes Prevents Atherosclerosis and Predicts Subclinical Disease. Circulation, 139(2), 243-255. doi:10.1161/circulationaha.118.034326

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

SLEEPING LESS THAN 6 HOURS A NIGHT INCREASES CARDIOVASCULAR RISK

People who sleep fewer than 6 hours a night may be at increased risk of cardiovascular disease compared with those who sleep between 7 and 8 hours, suggest the results of the PESA CNIC-Santander Study published in the *Journal of the American College of Cardiology* (JACC). The study indicates that poor-quality sleep increases the risk of atherosclerosis—the build-up of plaque in the arteries throughout the body.

The researchers explained that “this new study emphasizes that we need to include sleep as one of our weapons in the fight against heart disease—a factor that is neglected in our society every day. This is the first study to show that objectively measured sleep is independently associated with atherosclerosis throughout the body, not just in the heart.”

The goal of the study, which included almost 4000 PESA CNIC-Santander participants, was to evaluate the impact of sleep duration



and interrupted sleep on atherosclerosis. The study differs in several ways from previous studies on sleep and heart health. Crucially, it is larger than many earlier studies and was conducted in a healthy population; in contrast, many previous studies included people with sleep apnea or other health problems. Another important difference is that whereas other studies relied on questionnaires to determine how much sleep participants had, the new study used actimetry to obtain objective measures of sleep. As the researchers pointed out, “what people say and what they do are often different.”

Dominguez, F., Fuster, V., Fernandez-Alvira, J. M., Fernandez-Friera, L., Lopez-Melgar, B., Blanco-Rojo, R., Fernandez-Ortiz, A., Garcia-Pavia, P., Sanz, J., Mendiguren, J. M., Ibanez, B., Bueno, H., Lara-Pezzi, E., & Ordovas, J. M. (2019). Association of Sleep Duration and Quality With Subclinical Atherosclerosis. Journal of the American College of Cardiology, 73(2), 134-144. doi:10.1016/j.jacc.2018.10.060

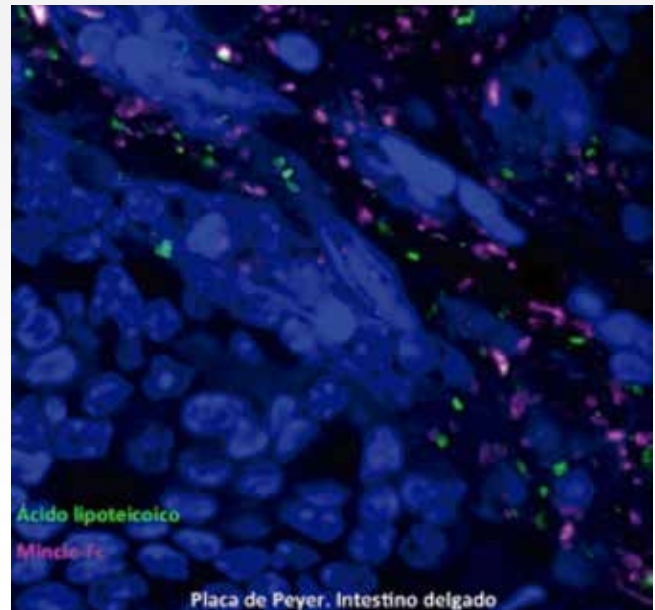
IMMUNITY

A NEW "WATCHDOG" THAT CONTROLS INTESTINAL BACTERIA

The immune response to our intestinal microbiota ensures that these microorganisms remain in their proper place. When the intestinal immune barrier is damaged, the gut bacteria can spread and cause inflammation throughout the body. Now, a study by scientists from the CNIC and the Universidad Complutense in Madrid reveals a new mechanism in the regulation of this immune barrier.

The study, published in *Immunity*, identifies a mechanism through which intestinal bacteria such as *Lactobacillus* strengthen the intestinal barrier to support a mutually beneficial relationship and prevent inflammation. The results have potential implications for the treatment of diseases featuring the spread of commensal bacteria outside the gut, as occurs in some metabolic disorders.

The research team propose that a new treatment strategy for these conditions could be the use of probiotics ('beneficial' intestinal microorganisms) or prebiotics (nutrients that promote the growth



of beneficial microorganisms); however, the mechanisms underlying this strategy are so far unknown.

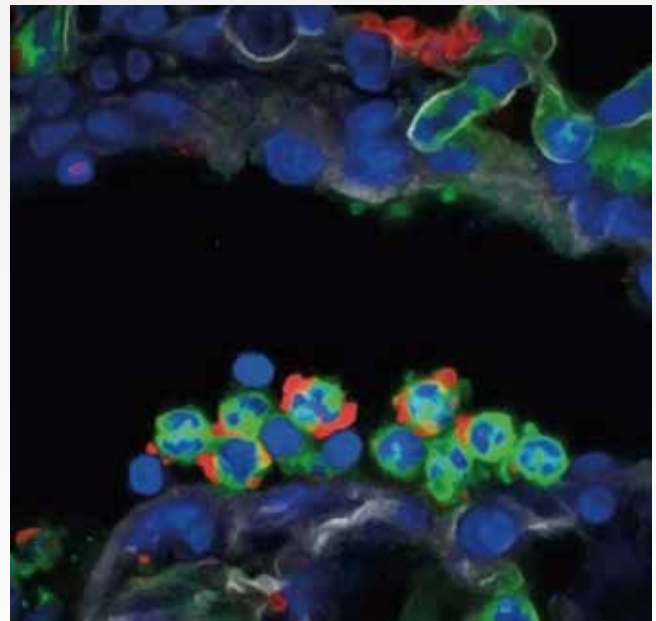
Martinez-Lopez, M., Iborra, S., Conde-Garrosa, R., Mastrangelo, A., Danne, C., Mann, E. R., Reid, D. M., Gaboriau-Routhiau, V., Chaparro, M., Lorenzo, M. P., Minnerup, L., Saz-Leal, P., Slack, E., Kemp, B., Gisbert, J. P., Dzionek, A., Robinson, M. J., Ruperez, F. J., Cerf-Bensussan, N., Brown, G. D., Bernardo, D., LeibundGut-Landmann, S., & Sancho, D. (2019). Microbiota Sensing by Mincle-Syk Axis in Dendritic Cells Regulates Interleukin-17 and -22 Production and Promotes Intestinal Barrier Integrity. *Immunity*, 50(2), 446-461. doi:10.1016/j.immuni.2018.12.020

IMMUNITY

AN IMMUNE "CLOCK" THAT CONTROLS INFECTIONS AND CARDIOVASCULAR DISEASE

CNIC scientists have demonstrated the existence of an immune "clock" that coordinates the day/night cycles through the activity of a class of leucocytes called neutrophils. Neutrophils constitute the body's main line of defense, but their action can also damage healthy cells of the cardiovascular system. This newly discovered clock determines when neutrophils are activated and when it is time to eliminate them from the circulation. First author José María Adrover explained that the researchers have identified "a series of molecules in the neutrophil nucleus and cell membrane that respond to diurnal (circadian) patterns in lightness and darkness and regulate the migration and localization of neutrophils in the body." The study was carried out by the CNIC research group led by Andrés Hidalgo and is published in *Immunity*.

Due to the worldwide high prevalence of infectious and cardiovascular diseases, the study could have wide-ranging clinical implications. The team is currently working on ways to manipulate this immune clock with drugs to induce diurnal or nocturnal immunity, depending on the needs of each patient. This therapeutic approach could be valuable for people at risk of cardiovascular events and for immune-compromised patients susceptible to infection.



Adrover, J. M., Del Fresno, C., Crainiciuc, G., Cuartero, M. I., Casanova-Acebes, M., Weiss, L. A., Huerga-Encabo, H., Silvestre-Roig, C., Rossaint, J., Cossio, I., Lechuga-Vieco, A. V., Garcia-Prieto, J., Gomez-Parrizas, M., Quintana, J. A., Ballesteros, I., Martin-Salamanca, S., Aroca-Crevillen, A., Chong, S. Z., Evrard, M., Balabanian, K., Lopez, J., Bidzhekov, K., Bachelierie, F., Abad-Santos, F., Munoz-Calleja, C., Zarbock, A., Soehnlein, O., Weber, C., Ng, L. G., Lopez-Rodriguez, C., Sancho, D., Moro, M. A., Ibanez, B., & Hidalgo, A. (2019). A Neutrophil Timer Coordinates Immune Defense and Vascular Protection. *Immunity*, 50(2), 390-402. doi:10.1016/j.immuni.2019.01.002

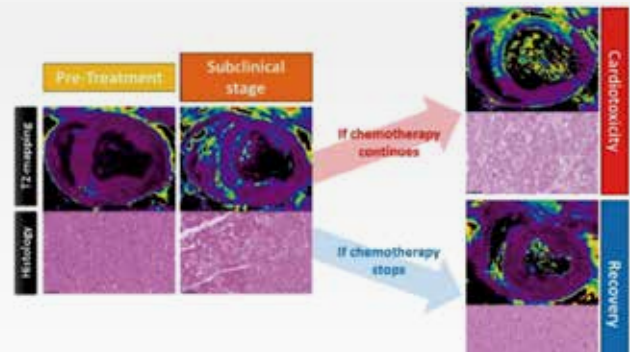
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

A VERY EARLY MARKER OF CARDIAC DAMAGE TRIGGERED BY CANCER TREATMENT

Researchers at the CNIC identified a very early marker of cardiac damage in patients undergoing therapy with anthracyclines, a family of drugs commonly used to treat cancer. This finding will enable the early diagnosis of the cardiotoxicity associated with this group of widely used chemotherapy drugs.

Dr Borja Ibáñez coordinated the study, published in the *Journal of the American College of Cardiology* (JACC). As Dr Ibáñez explained, the results have important implications for therapy because the detection this drug-induced damage at very early stages will permit “the implementation of treatments to prevent further deterioration in heart function and a clinical management more closely adapted to the needs of each patient.” The identified marker is affected much earlier than any of the markers used in current clinical practice.

This valuable discovery was possible thanks to a new pig model of anthracycline-induced cardiotoxicity developed by the CNIC team. In the study, animals received increasing doses of the



anthracycline drug doxorubicin over 10 weeks. This strategy allowed the accumulation of the drug in the heart muscle without major exposure of other organs.

The results of the JACC study may help to prevent the severe secondary effects experienced by cancer patients receiving chemotherapy. Moreover, the study may also open the way to new therapies based on mitochondrial transplantation.

Galan-Arriola, C., Lobo, M., Vilchez-Tschischke, J. P., Lopez, G. J., de Molina-Iracheta, A., Perez-Martinez, C., Aguero, J., Fernandez-Jimenez, R., Martin-García, A., Oliver, E., Villena-Gutierrez, R., Pizarro, G., Sanchez, P. L., Fuster, V., Sanchez-Gonzalez, J., & Ibanez, B. (2019). Serial Magnetic Resonance Imaging to Identify Early Stages of Anthracycline-Induced Cardiotoxicity. Journal of the American College of Cardiology, 73(7), 779-791. doi:10.1016/j.jacc.2018.11.046

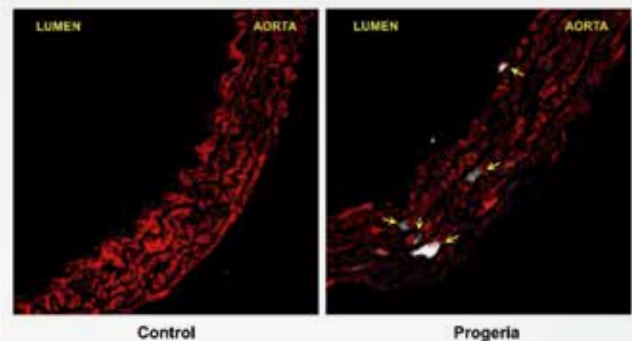
EMBO MOLECULAR MEDICINE

NEW THERAPEUTIC TARGET FOR BLOCKING EARLY ATHEROSCLEROSIS IN PROGERIA

Researchers at the CNIC and the Universidad de Oviedo have discovered a new molecular mechanism involved in the premature development of atherosclerosis in mice with Hutchinson-Gilford progeria syndrome (HGPS). The results, published in *EMBO Molecular Medicine*, identify a potential therapeutic target for this severe genetic disease.

The study, co-directed by Vicente Andrés of the CNIC and the CIBERCV and Carlos López Otín of the Universidad de Oviedo, identifies a molecular mechanism involved in the accelerated development of atherosclerosis in progeria. In addition, the results identify a pharmacological treatment that slows the progression of atherosclerosis and extends the lifespan of progeroid mice.

The study, featured in an editorial in the journal, shows for the first time that “stress in the endoplasmic reticulum (ER stress) and the associated unfolded protein response (UPR) are involved in the death of vascular smooth muscle cells in progeroid mice,” explained first author Magda Hamczyk.



The research team used the compound tauroursodeoxycholic acid (TUDCA), which reduces the negative consequences of the activation of the ER stress and UPR pathways. Treatment of progeroid mice with TUDCA inhibits the progression of vascular disease, including vascular smooth cell loss and atherosclerosis. TUDCA also prolonged the lifespan of progeroid mice, which die from the complications of atherosclerosis.

Hamczyk, M. R., Villa-Bellosta, R., Quesada, V., Gonzalo, P., Vidak, S., Nevado, R. M., Andres-Manzano, M. J., Misteli, T., Lopez-Otin, C., & Andres, V. (2019). Progerin accelerates atherosclerosis by inducing endoplasmic reticulum stress in vascular smooth muscle cells. EMBO Molecular Medicine, 11(4), e9736. doi:10.15252/emmm.201809736

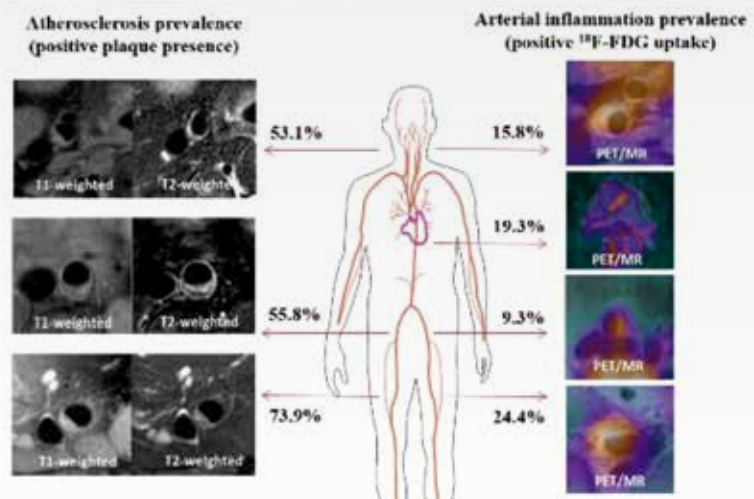
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

ADVANCED IMAGING TECHNOLOGY PREDICTS CARDIOVASCULAR RISK FROM INFLAMMATION DETECTED IN ARTERIES

Using advanced PET/MRI technology, researchers at the CNIC have detected arterial inflammation in regions that have yet to develop atherosclerotic plaques. These results from the PESA-CNIC-Santander study were published in JACC. The research team used this innovative technology to analyze the inflammatory process in the arteries of a group of people who had already developed atherosclerotic plaques.

The results show that inflammation is present at early stages of atherosclerosis, above all in regions that have not developed plaques. The

¹⁸F-FDG PET/MRI in PESA



study also shows that this arterial atherosclerosis can be an early indication of the later appearance of plaques that underlie cardiovascular disease and events such as heart attack and stroke. The researchers are currently analyzing the role of arterial inflammation in this process; this information will help to establish early diagnosis and develop new anti-inflammatory therapies for this disease.

Fernandez-Friera, L., Fuster, V., Lopez-Melgar, B., Oliva, B., Sanchez-Gonzalez, J., Macias, A., Perez-Asenjo, B., Zamudio, D., Alonso-Farto, J. C., Espana, S., Mendiguren, J., Bueno, H., Garcia-Ruiz, J. M., Ibanez, B., Fernandez-Ortiz, A., & Sanz, J. (2019). Vascular Inflammation in Subclinical Atherosclerosis Detected by Hybrid PET/MRI. Journal of the American College of Cardiology, 73(12), 1371-1382. doi:10.1016/j.jacc.2018.12.075

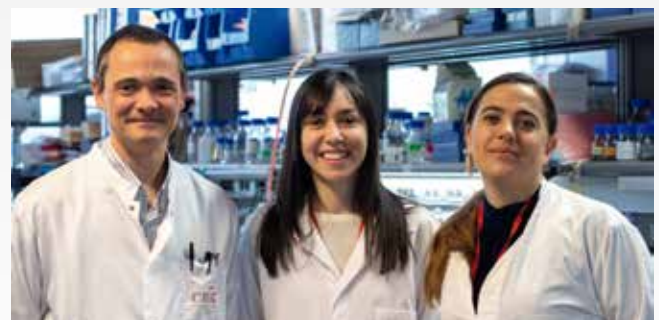


JOURNAL OF EXPERIMENTAL MEDICINE

ADIPONECTIN, THE HORMONE THAT PROTECTS WOMEN AGAINST LIVER CANCER

A team at the CNIC has found an explanation for the lower rate of liver cancer in women. The answer lies in the hormone adiponectin, which is produced in higher amounts in women than in men and protects the liver against the development of the main form of liver cancer, hepatocellular carcinoma. In their quest to understand why people with obesity have a higher risk of developing liver cancer, the CNIC research group led by Guadalupe Sabio found that adiponectin is more abundant in women and slim people. The study, published in the *Journal of Experimental Medicine*, shows that adiponectin protects the liver against the development of hepatocellular carcinoma.

The research team showed that adiponectin, a hormone produced by adipose tissue, has an anticancer effect in the liver. In a group of healthy individuals, the team found that women produce more adiponectin than men. Describing the study, Dr. Sabio commented, "the circulating levels of adiponectin decline with the development of obesity and after puberty in men, and these are precisely the populations with higher rates of liver cancer. This observation prompted us to study the phenomenon in depth."



The results "open routes to combating a cancer for which there is currently no specific treatment. One approach would be to use adiponectin itself, while another option is to use metformin, a drug used to treat diabetes that targets the same anticancer protein as adiponectin."

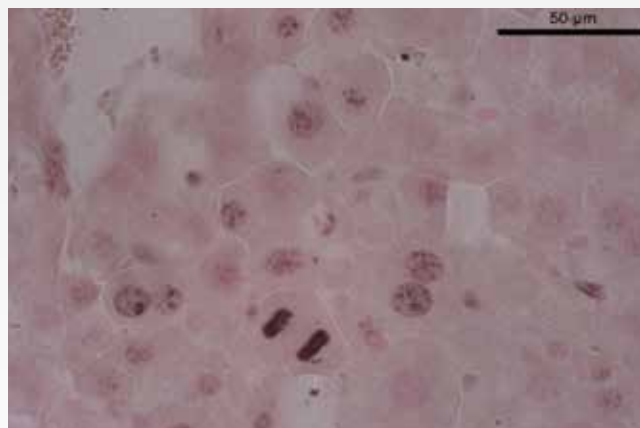
Manieri, E., Herrera-Melle, L., Mora, A., Tomas-Loba, A., Leiva-Vega, L., Fernandez, D. I., Rodriguez, E., Moran, L., Hernandez-Cosido, L., Torres, J. L., Seoane, L. M., Cubero, F. J., Marcos, M., & Sabio, G. (2019). Adiponectin accounts for gender differences in hepatocellular carcinoma incidence. Journal of Experimental Medicine, 216(5), 1108-1119. doi:10.1084/jem.20181288

NATURE

THE PROTEIN P38GAMMA IDENTIFIED AS A NEW THERAPEUTIC TARGET IN LIVER CANCER

A research team at the CNIC led by Guadalupe Sabio has discovered that the protein p38 γ , one of the four types of p38 kinase, is essential for the initiation of cell division in liver cells. This indicates that “p38 γ could be a useful therapeutic target for liver cancer,” said Sabio, adding, “we are now developing inhibitors of this protein to test in this cancer.” The study was published in *Nature*. The four members of the p38 kinase family are so similar that at first they appear to have overlapping or redundant functions. Detailed analysis of their three-dimensional structures revealed that one of the four, p38 γ , also shares close similarities with another family of proteins called CDKs. These proteins are well-known regulators of cell division and the cell cycle and play a well-established role in the development of cancer.

The results were truly promising: “in mice lacking p38 γ or treated with inhibitors to block its activity, the development of hepatocellular carcinoma was slowed,” said the researchers. These results, claimed Sabio, “could be extrapolated to human patients.” Indeed, work with colleagues at Salamanca University Hospital shows that the amount of p38 γ increases with liver fibrosis, a process that precedes cancer and is much higher in liver cancer patients. These results suggest that in the future it may be possible



to treat this type of cancer with drugs that specifically target p38 γ . The advantage of targeting p38 γ is that this enzyme appears to control the initiation of the cell cycle in response to stress, and therefore inhibiting this process would not affect tissues that are constantly proliferating, such as the intestinal lining or hair follicles.

*Tomas-Loba, A., Manieri, E., Gonzalez-Teran, B., Mora, A., Leiva-Vega, L., Santamans, A. M., Romero-Becerra, R., Rodriguez, E., Pintor-Chocano, A., Feixas, F., Lopez, J. A., Caballero, B., Trakala, M., Blanco, O., Torres, J. L., Hernandez-Cosido, L., Montalvo-Romeral, V., Matesanz, N., Roche-Molina, M., Bernal, J. A., Mischo, H., Leon, M., Caballero, A., Miranda-Saavedra, D., Ruiz-Cabello, J., Nevzorova, Y. A., Cubero, F. J., Bravo, J., Vazquez, J., Malumbres, M., Marcos, M., Osuna, S., & Sabio, G. (2019). p38gamma is essential for cell cycle progression and liver tumorigenesis. *Nature*, 568(7735), 557-560. doi:10.1038/s41586-019-1112-8*

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

EARLY INTERVENTION IN PRESCHOOL IS A UNIQUE OPPORTUNITY FOR PROMOTING A HEALTHY LIFESTYLE

Children may have a better chance of avoiding unhealthy habits linked to obesity and cardiovascular disease later in life if they are taught properly about healthy behaviors in preschool, CNIC researchers have shown in a first-of-its-kind study.

The researchers focused on children living in a socioeconomically disadvantaged community, a situation frequently linked to higher rates of obesity, heart disease, and other health issues. Valentin Fuster created and led the trial, called the FAMILIA Project at Mount Sinai Heart. The results were published in the *Journal of the American College of Cardiology*.

“Results from this new study prove that early intervention is effective in preschool-age children, but we believe this can also promote healthy behaviors among their caregivers and teachers and have a far-reaching impact”, explained Dr Fuster.

This study follows other successful interventions led by Dr Fuster in Colombia and Spain, but FAMILIA is unique in being the first time the health promotion curriculum has been implemented in a multi-ethnic, underprivileged urban population. Its precedent is the Comprehensive Health Program (SI!). This intervention program is designed to promote cardiovascular health from preschool to high school through intervention in four areas: nutrition, body and heart awareness, physical activity, and emotional management.



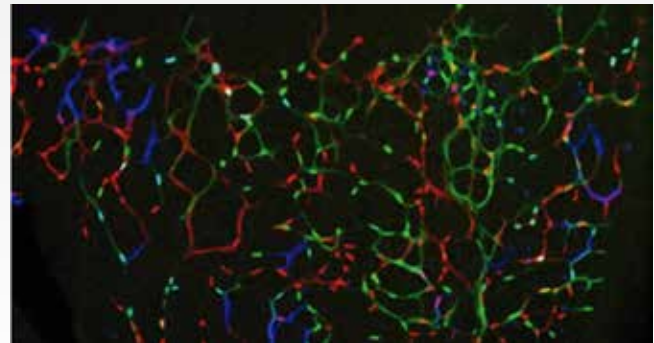
*Fernandez-Jimenez, R., Jaslow, R., Bansilal, S., Santana, M., Diaz-Munoz, R., Latina, J., Soto, A. V., Vedanthan, R., Al-Kazaz, M., Giannarelli, C., Kovacic, J. C., Bagiella, E., Kasarskis, A., Fayad, Z. A., Hajjar, R. J., & Fuster, V. (2019). Child Health Promotion in Underserved Communities: The FAMILIA Trial. *Journal of the American College of Cardiology*, 73(16), 2011-2021. doi:10.1016/j.jacc.2019.01.057*

NATURE COMMUNICATIONS

A NEWLY IDENTIFIED MECHANISM CAN BE TARGETED TO BOOST ANGIOGENESIS

Scientists of the CNIC led by Rui Benedito discovered a cellular and molecular mechanism that can be exploited to induce productive and sustained angiogenesis in tissues that have become ischemic due to reduced blood supply.

Until now, tissue regeneration treatments based on vascular growth factors have not succeeded in inducing effective angiogenesis—the process through which the body generates new blood vessels. The new results, published in *Nature Communications*, suggest that it might be possible to manipulate the newly discovered mechanism to achieve optimal therapeutic angiogenesis.



The identified mechanism could also explain the failure of several clinical trials seeking to boost angiogenesis in ischemic hearts after a myocardial infarction. Rui Benedito says that the results “significantly increase our understanding of the biology of blood vessels and will enable us to design better therapeutic strategies to induce effective angiogenesis in injured or ischemic tissues.”

Pontes-Quero, S., Fernandez-Chacon, M., Luo, W., Lunella, F. F., Casquero-Garcia, V., Garcia-Gonzalez, I., Hermoso, A., Rocha, S. F., Bansal, M., & Benedito, R. (2019). High mitogenic stimulation arrests angiogenesis. *Nature Communications*, 10(1), 2016. doi:10.1038/s41467-019-09875-7

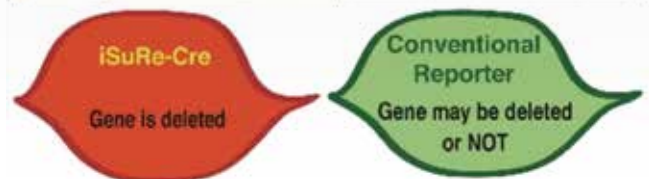
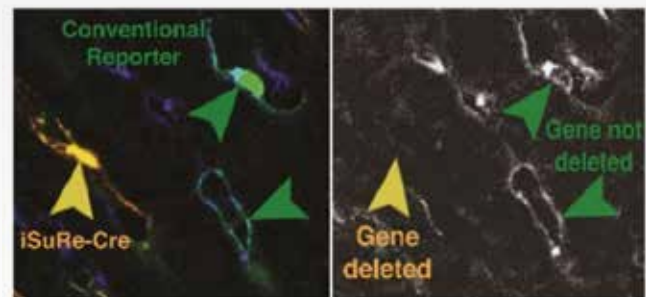


NATURE COMMUNICATIONS

A NEW GENETIC TOOL TO MODIFY AND UNDERSTAND GENE FUNCTION

Scientists of the CNIC led by Rui Benedito have developed a new genetic tool (iSuRe-Cre) that provides certainty in Cre-inducible genetic modifications, a key technique for understanding gene function.

Most analysis of gene function in biomedical research relies on the use of Cre-lox technology. Cre-Lox technology allows the regulation of gene expression at any time or in any cell type thanks to the ability of the Cre recombinase protein to recognize and recombine lox sites introduced at specific locations in the mouse genome, leading to the deletion of the genes being studied. Despite the major impact of Cre-loxP technology on biomedical research, numerous studies have demonstrated the need for caution in its use. The main problem is that the Cre activity level is often insufficient to fully recombine and eliminate expression of the target gene, generating uncertainty about whether the desired genetic modification has been achieved. To overcome this technical hurdle, the CNIC team developed an innovative method based on a new allele called iSuRe-Cre. iSuRe-Cre is compatible with all existing Cre/CreERT2/lox alleles and guarantees high Cre activity in the cells that express the fluorescent reporter. This ultimately increases the efficiency and reliability of the analysis of Cre-dependent gene function. Moreover, the use of the new iSuRe-Cre mice permits the induction of multiple genetic deletions in the same cell. This important property allows the study



of functional genetic interactions or epistasis—how the function of one or more genes depends on the function of another.

Lead investigator Rui Benedito says that the new genetic tool will be of great interest in biomedical research “because it significantly increases the ease, efficiency, and reliability of genetic modification in the mouse, the most widely used animal model in research.” The study was published in *Nature Communications*.

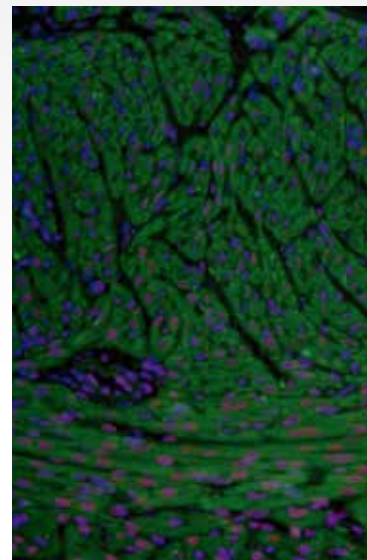
Fernandez-Chacon, M., Casquero-Garcia, V., Luo, W., Francesca Lunella, F., Ferreira Rocha, S., Del Olmo-Cabrera, S., & Benedito, R. (2019). iSuRe-Cre is a genetic tool to reliably induce and report Cre-dependent genetic modifications. *Nature Communications*, 10(1), 2262. doi:10.1038/s41467-019-10239-4

CIRCULATION RESEARCH

AN ESSENTIAL PROTEIN FOR CORRECT HEART CONTRACTION AND SURVIVAL

A team of scientists led by Dr Enrique Lara Pezzi at the CNIC identified the RNA-binding protein SRSF3 as an essential factor for proper heart contraction and survival. In a study published in *Circulation Research*, the researchers found that loss of cardiac expression of SRSF3 leads to a critical reduction in the expression of genes involved in contraction. Knowledge of the mechanism of action of SRSF3 in the heart could open the way to the design of new therapeutic approaches for the treatment of heart disease. The identification of mRNA capping as a mechanism that protects against the development of systolic heart failure could open the way to the development of urgently needed therapeutic tools to combat this disease.

Ortiz-Sanchez, P., Villalba-Orero, M., Lopez-Olaneta, M. M., Larrasa-Alonso, J., Sanchez-Cabo, F., Marti-Gomez, C., Camafeita, E., Gomez-Salineró, J. M., Ramos-Hernandez, L., Nielsen, P. J., Vazquez, J., Muller-McNicoll, M., Garcia-Pavia, P., & Lara-Pezzi, E. (2019). Loss of SRSF3 in Cardiomyocytes Leads to Decapping of Contraction Related mRNAs and Severe Systolic Dysfunction. *Circulation Research*, 125(2), 170-183. doi:10.1161/CIRCRESAHA.118.314515



JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

CNIC COORDINATES AN INTERNATIONAL CONSENSUS DOCUMENT ON THE USE OF MAGNETIC RESONANCE IMAGING AFTER A HEART ATTACK

The CNIC coordinated the first international consensus document providing guidelines on the conduct of magnetic resonance imaging studies after a myocardial infarction in clinical trials or experimental models. The document concludes that the main outcome parameter in studies assessing new treatments should be absolute infarct size—the percentage of the left ventricle that is irreversibly damaged. The recommended timing for magnetic resonance imaging is between 3 and 7 days after the infarction.

The document, coordinated by Dr Borja Ibáñez, addresses the need within the cardiovascular community for guidance on the best protocols, the best techniques, and the most appropriate situations for conducting a magnetic resonance imaging study after a heart attack. The document was published in the *Journal of the American College of Cardiology* (JACC).

The document's contents were defined during an international meeting held at the CNIC with support from Philips. The meeting



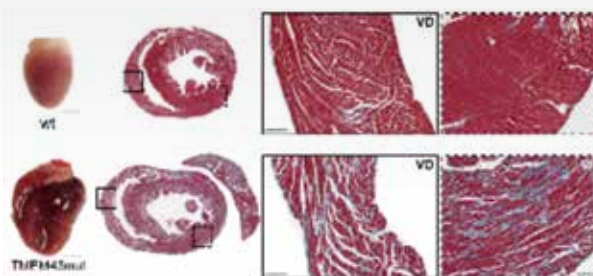
brought together a multidisciplinary group of 16 experts in the field from the USA, Canada, the UK, France, Germany, Sweden, the Netherlands, Greece, Switzerland, Singapore, and Spain, including Dr David García-Dorado of the CIBERCV.

Ibanez, B., Aletras, A. H., Arai, A. E., Arheden, H., Bax, J., Berry, C., Bucciarelli-Ducci, C., Croisille, P., Dall'Armellina, E., Dharmakumar, R., Eitel, I., Fernandez-Jimenez, R., Friedrich, M. G., Garcia-Dorado, D., Hausenloy, D. J., Kim, R. J., Kozerke, S., Kramer, C. M., Salerno, M., Sanchez-Gonzalez, J., Sanz, J., & Fuster, V. (2019). Cardiac MRI Endpoints in Myocardial Infarction Experimental and Clinical Trials: JACC Scientific Expert Panel. *Journal of the American College of Cardiology*, 74(2), 238-256. doi:10.1016/j.jacc.2019.05.024

CIRCULATION

POSSIBLE TREATMENT BREAKTHROUGH FOR THE RARE DISEASE ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY TYPE 5

Scientists at the CNIC and Puerta de Hierro Majadahonda Hospital have discovered a possible treatment for arrhythmogenic right ventricular cardiomyopathy type 5 (ARVC5), a fatal genetic disease for which there is unfortunately no cure. The research team, whose findings were published in *Circulation*, showed that strategies to inhibit the protein kinase GSK3 in transgenic mice with ARVC5 reduce fibrosis and improve heart function.



The research team tested several candidate therapeutic approaches in the mouse ARVC5 model. While treatments directly targeting fibrosis were ineffective, positive results were obtained with two

strategies for inhibiting GSK3, one based on pharmacological inhibition and the other on overexpression of the calcineurin subunit CnA β 1.

Nevertheless, the scientists warn that the transgenic mouse model does not reproduce all disease characteristics. For example, male and female mice are equally affected, whereas the human disease

is much more aggressive in men than in women. Having identified a possible route for effective treatment for the disease in mice, the research team is now working to translate the results to patients. Using the mouse model, the scientists are testing drugs used to treat human heart failure to see if they are effective against ARVC5. The team is also investigating gene therapy strategies that could improve heart function or even cure the disease.

*Padron-Barthe, L., Villalba-Obrero, M., Gomez-Saliner, J. M., Dominguez, F., Roman, M., Larrasa-Alonso, J., Ortiz-Sanchez, P., Martinez, F., Lopez-Olaneta, M., Bonzon-Kulichenko, E., Vazquez, J., Marti-Gomez, C., Santiago, D. J., Prados, B., Giovino, G., Gomez-Gavero, M. V., Priori, S., Garcia-Pavia, P., & Lara-Pezzi, E. (2019). Severe Cardiac Dysfunction and Death Caused by Arrhythmogenic Right Ventricular Cardiomyopathy Type 5 Are Improved by Inhibition of Glycogen Synthase Kinase-3beta. *Circulation*, 140(14), 1188-1204. doi:10.1161/CIRCULATIONAHA.119.040366*

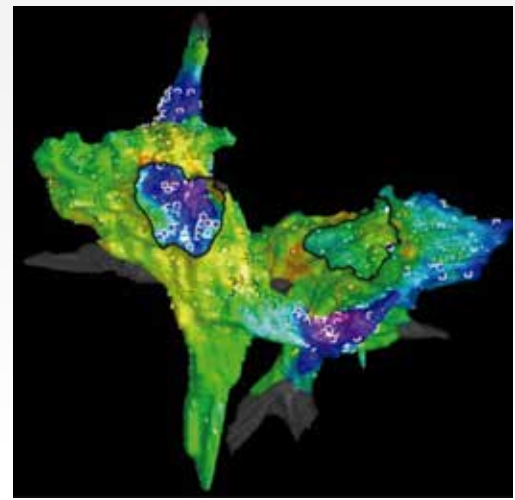
CIRCULATION RESEARCH

A NEW METHOD TO IMPROVE TREATMENT OF ATRIAL FIBRILLATION

Researchers at the CNIC, the Hospital Clínico San Carlos in Madrid, and the Spanish cardiovascular research network (CiberCV) discovered a new method to optimize ablation of atrial fibrillation (AFib), one of the most common forms of irregular heartbeat (arrhythmia). The study was featured on the cover of the journal *Circulation Research*.

The new method allows ablation procedures to be tailored to the specific needs of individual patients with persistent AFib, identifying the key regions to treat with high precision. Moreover, the method costs no more than the conventional procedure and there is thus no obstacle to its use by most centers experienced in AFib ablation.

The investigators propose that the new algorithms could be easily incorporated into conventional electroanatomical navigation systems, increasing the precision



and reducing the cost of patient-specific procedures for the ablation of persistent AFib.

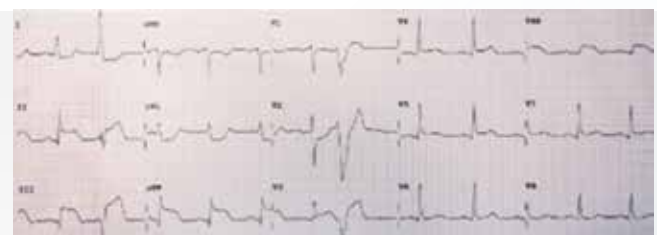
*Quintanilla, J. G., Alfonso-Almazan, J. M., Perez-Castellano, N., Pandit, S. V., Jalife, J., Perez-Villacastin, J., & Filgueiras-Rama, D. (2019). Instantaneous Amplitude and Frequency Modulations Detect The Footprint of Rotational Activity and Reveal Stable Driver Regions as Targets for Persistent Atrial Fibrillation Ablation. *Circulation Research*, 125(6), 609-627. doi:10.1161/CIRCRESAHA.119.314930*

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

THE RATE OF CORONARY INTERVENTION IN CORONARY-SYNDROME PATIENTS: AN INDEX OF HEALTH SYSTEM PERFORMANCE LINKED TO SURVIVAL

CNIC scientists have found that a higher rate of coronary revascularization during hospitalization for non-ST segment elevation acute coronary syndrome (NSTEMACS) is associated with better patient survival 2 years after hospital discharge, whether analyzed at the hospital, national, or supranational level.

The article was published in the *Journal of the American College of Cardiology*, and CNIC researchers Héctor Bueno, Xavier Rosselló, and Stuart Pocock believe that the findings will help to define and update quality-care guidelines for acute myocardial infarction, such as those recommended by the Acute Cardiovascular Care Association of the European Society of Cardiology. The revascularization rate in patients admitted for NSTEMACS



can serve as an index of health-care quality at the hospital, national, or supranational level. The CNIC researchers also affirmed that these results highlight “the importance of addressing the mismatch between clinical practice guideline recommendations and common medical practice.”

One of the study’s main conclusions is that there is a need for more dynamic referral procedures to ensure that NSTEMI patients are rapidly transferred from centers with limited facilities to centers with a catheterization laboratory.

*Bueno, H., Rossello, X., Pocock, S. J., Van de Werf, F., Chin, C. T., Danchin, N., Lee, S. W., Medina, J., & Huo, Y. (2019). In-Hospital Coronary Revascularization Rates and Post-Discharge Mortality Risk in Non-ST-Segment Elevation Acute Coronary Syndrome. *Journal of the American College of Cardiology*, 74(11), 1454-1461. doi:10.1016/j.jacc.2019.06.068*

CELL METABOLISM

A NEW MECHANISM FOR THE TRANSFER OF MATERNAL GENETIC MATERIAL

CNIC researchers have defined the dynamics of the transfer of mitochondrial DNA, a type of genetic material, from mothers to their offspring. The study was published in *Cell Metabolism*. Using experimental mouse models, the research team led by Dr José Antonio Enríquez found that when the mother's cells contain more than one mitochondrial DNA variant, this genetic transfer from mother to pup is controlled by two mechanisms: first during the development of the egg (oocyte), and later during the early stages of embryonic development. The scientists explained that "this control is aimed at preventing the co-occurrence of various types of mitochondrial DNA in the new individual," which can lead to the development of mitochondrial diseases.

The information provided in the new study is important for two reasons. Understanding the mechanisms that regulate the segregation of the mitochondrial genome is necessary for the development of strategies to prevent mother-to-child transfer of mutated mitochondrial DNA that cause mitochondrial diseases. The new findings will also help scientists to devise ways to prevent different types of mitochondrial



DNA co-occurring in the same cell as an unwanted result of medical interventions; this phenomenon, known as heteroplasmy, is a potential risk of mitochondrial replacement therapy.

The study shows that heteroplasmy can alter the metabolism of embryonic cells, inducing increased mitochondrial production of reactive oxygen species. This produces changes in the morphology of the inner mitochondrial membrane and in the molecular machinery for energy production.

*Latorre-Pellicer, A., Lechuga-Vieco, A. V., Johnston, I. G., Hamalainen, R. H., Pellico, J., Justo-Mendez, R., Fernandez-Toro, J. M., Claveria, C., Guaras, A., Sierra, R., Llop, J., Torres, M., Criado, L. M., Suomalainen, A., Jones, N. S., Ruiz-Cabello, J., & Enriquez, J. A. (2019). Regulation of Mother-to-Offspring Transmission of mtDNA Heteroplasmy. *Cell Metabolism*, 30(6), 1120-1130. doi:10.1016/j.cmet.2019.09.007*

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

AN ORAL ANTICOAGULANT DELAYS THE APPEARANCE OF ALZHEIMER DISEASE IN MICE

Scientists at the CNIC have identified a possible treatment for Alzheimer disease. Working together with a scientific team at The Rockefeller University in New York, the investigators have shown that treatment with the oral anticoagulant dabigatran delays the appearance of Alzheimer disease in mice.

The results, published in the *Journal of the American College of Cardiology*, show that after a year of treatment with dabigatran, mice had no memory loss and no reduction in cerebral circulation. This treatment also reduced typical Alzheimer symptoms, including cerebral inflammation, blood vessel injury, and amyloid protein plaques.

Dabigatran is more effective, has fewer side effects than classical anticoagulants, and is approved for the treatment of several diseases. Study coordinator Dr Marta Cortés Canteli, a CNIC researcher funded through the Miguel Servet program, highlighted the value of the study: "This discovery marks an important advance toward the translation of our results to clinical practice to achieve an effective treatment for Alzheimer disease."



Placing the study in a broader context, Dr Valentín Fuster, CNIC General Director and a lead author on the study, commented, "neurodegenerative diseases are very closely linked to disease in the cerebral blood vessels. The study of the links between the brain and heart is the major challenge for the next ten years."

Further studies are needed in patients, but the research team believe that dabigatran has the potential to normalize cerebral blood flow in Alzheimer patients. "An individualized treatment strategy such as this will first require the development of a diagnostic tool to identify those Alzheimer patients with a tendency to coagulation. This will be an important line of research in the coming years," indicated Dr Cortés Canteli.

*Cortes-Canteli, M., Krueyer, A., Fernandez-Nueda, I., Marcos-Diaz, A., Ceron, C., Richards, A. T., Jno-Charles, O. C., Rodriguez, I., Callejas, S., Norris, E. H., Sanchez-Gonzalez, J., Ruiz-Cabello, J., Ibanez, B., Strickland, S., & Fuster, V. (2019). Long-Term Dabigatran Treatment Delays Alzheimer's Disease Pathogenesis in the TgCRND8 Mouse Model. *Journal of the American College of Cardiology*, 74(15), 1910-1923. doi:10.1016/j.jacc.2019.07.081*

NATURE COMMUNICATIONS

THE 'AIRBAG' THAT PROTECTS CELLS AGAINST STRESS

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

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



Echarri, A., Pavon, D. M., Sanchez, S., Garcia-Garcia, M., Calvo, E., Huerta-Lopez, C., Velazquez-Carreras, D., Viaris de Lesegno, C., Ariotti, N., Lazaro-Carrillo, A., Strippoli, R., De Sancho, D., Alegre-Cebollada, J., Lamaze, C., Parton, R. G., & Del Pozo, M. A. (2019). An Abl-FBP17 mechanosensing system couples local plasma membrane curvature and stress fiber remodeling during mechanoadaptation. *Nature Communications*, 10(1), 5828. doi:10.1038/s41467-019-13782-2