INSIDE SCIENCE
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WHAT'S ON
CNIC & SOCIETY

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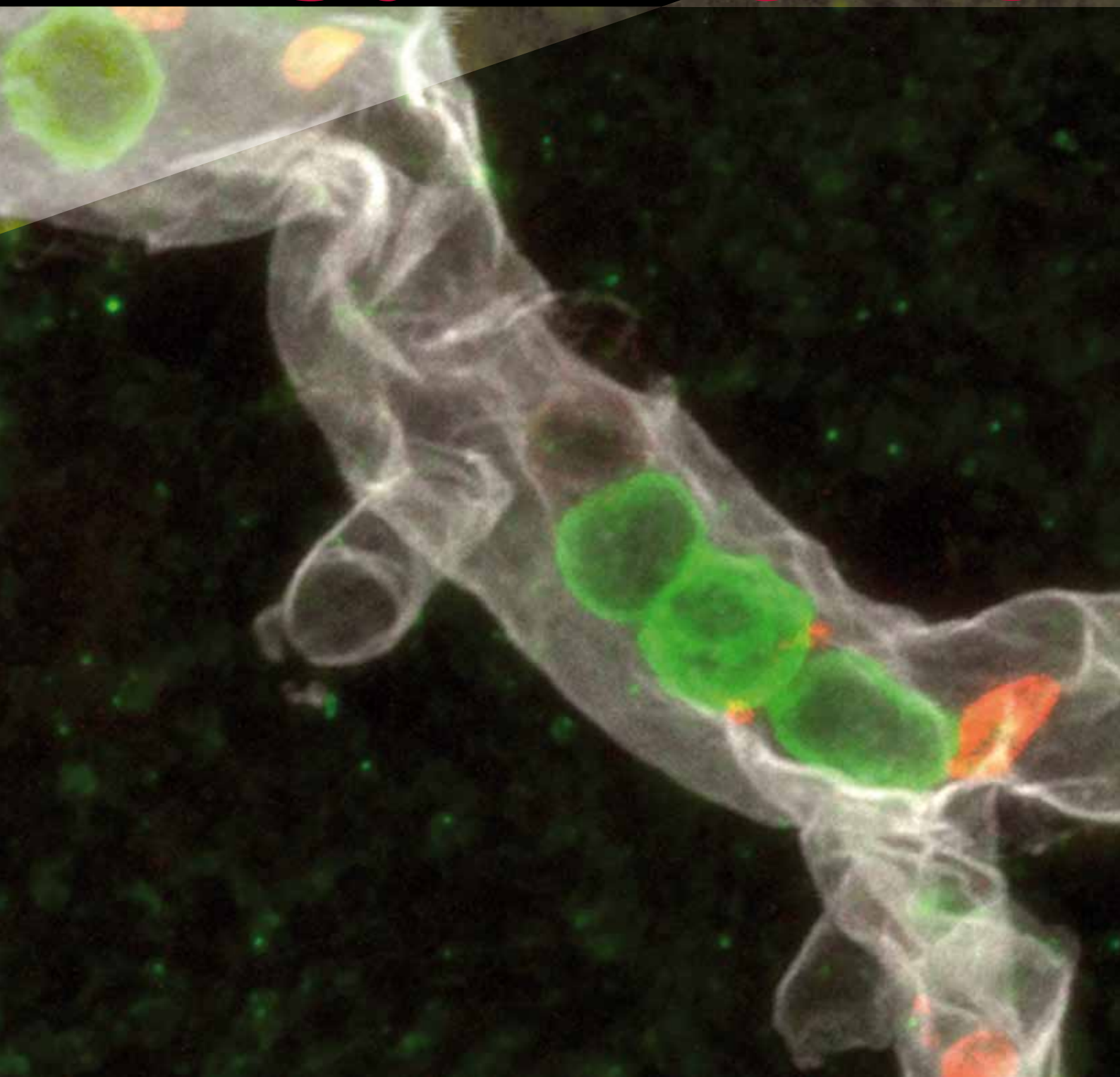
summer'15



contents summer'15

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More on the CNIC at www.cnic.es
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EXCELENCIA SEVERO OCHOA

Dr. Valentín Fuster, Director of the CNIC

TECHNOLOGY FOR HEALTH PROMOTION

I have always been interested in technology, something that is very evident from all my work on diagnostic imaging techniques. But health promotion can also be fostered through the accessible everyday technology of mobile phone and tablets. My fellow cardiologist Eric Topol, considered one of the originators of *m-Health*, predicted years ago that smart phones would come to be used to monitor our vital signs.

Research shows that interventions to promote a healthy lifestyle work best with children between the ages of 3 and 6. This has prompted us to launch the *Programa SÍ!* and other similar initiatives that have made waves even in the US. Nonetheless, we can't close our eyes to the adult population, who are currently the most affected by the risk factors that lead to cardiovascular disease. At the CNIC, as in many other research organizations, scientists are investigating how to promote life style changes in this challenging population, who have already acquired unhealthy habits.

Without going that far, I think that these devices can be an excellent tool for health promotion, and with the Pro CNIC Foundation we have put this conviction into practice with the launch of a new app, *El círculo de la salud.* The app has already been downloaded by thousands of users, a number set to rise soon with the launch of the English language version, *Circle of Health.*

The key to preventing the six modifiable risk factors for cardiovascular disease is to keep appropriate healthy habits continuously in mind. And the app achieves precisely this, by repeating, repeating, and repeating reminders of what users should do, or to be more precise, avoid doing, to maintain themselves in top form.

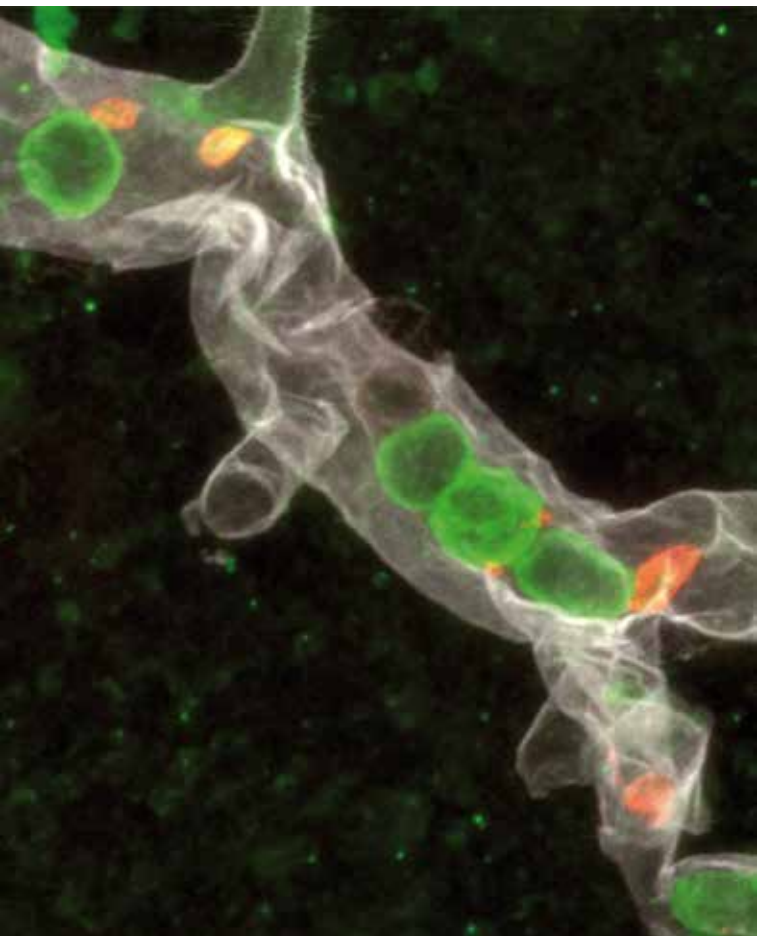
Our hope is that *Circle of Health* will be an indisputable advance in research—many others of which have been driven by technology—in the fight against cardiovascular disease that spurs us on.

SCANNING OF FLOWING BLOOD BY WHITE BLOOD CELLS CAN TRIGGER CARDIOVASCULAR INJURY

In an article published in the journal ***Science,*** CNIC researchers have reported that a subtype of the body's main defensive agents—the white blood cells, or leukocytes—actively scan flowing blood for activated platelets, a process that can lead to many types of cardiovascular accident, including common events such as stroke.

If you ask your doctor to predict your chances of having a cardiovascular accident, for example a stroke or a heart attack, he or she would likely tell you that it's not so easy to do because we still don't know exactly how these events start. Your physician would also tell you that in spite of this there are certain markers that are highly predictive. One of these markers is the blood content of a specific type of leukocyte—the neutrophil. The other is the presence in flowing blood of activated platelets, which are responsible for coagulation and are the targets of such well-known drugs as aspirin. The question, from the biological point of view, is if the involvement of these two cell types is a mere coincidence or if they cooperate to initiate vascular injury.

The research was led by **Dr. Andrés Hidalgo,** group leader in the department of Atherosclerosis, Imaging and



Epidemiology, and was achieved through partnerships with the CNIC Advanced Imaging Unit and groups at the Madrid Complutense University and others in Germany, the USA and Japan. Through this collaborative effort, the team discovered a surprising mechanism that explains how neutrophils and activated platelets cooperate to trigger cardiovascular events.

To investigate this phenomenon, the researchers used advanced microscopy techniques to look directly inside the blood vessels of living tissues. With these techniques the team was able to observe individual neutrophils and platelets during the inflammatory process. The first surprising finding was that the neutrophils that stick to the walls of the inflamed vessel extend a kind of cellular protrusion or arm into the vessel, and that this protrusion has a high concentration of a highly adhesive protein. The second unexpected observation is that some blood platelets stick to this protein on the neutrophil protrusion. Surprisingly, the only platelets that stick to this structure are those that are activated, the very kind that are a predictive marker of cardiovascular events. The final observation, and perhaps the most surprising, is that this adhesive protein is also able to send signals to the neutrophil to start an inflammatory response. It is this response that ultimately leads to vascular injury.

To investigate how this process underlies vascular accidents, the researchers induced stroke, septic shock or acute lung injury in mice in which the adhesive protein was absent or blocked. The team found that in all of cases the degree of damage in the tissues affected (brain, liver or lung) was significantly less severe than in unmodified or untreated animals.

The study explains old clinical observations, and has immediate implications for understanding the origin of many of the most prevalent types of cardiovascular events.

The study also illustrates how the latest technology helps scientists to discover the elegance of previously unknown biological processes, processes that can now be manipulated to prevent or treat diseases that have a devastating effect on human health.

HOW TO STOP 'BONE-EATING' CELLS AND REDUCE THE RISK OF OSTEOPOROSIS

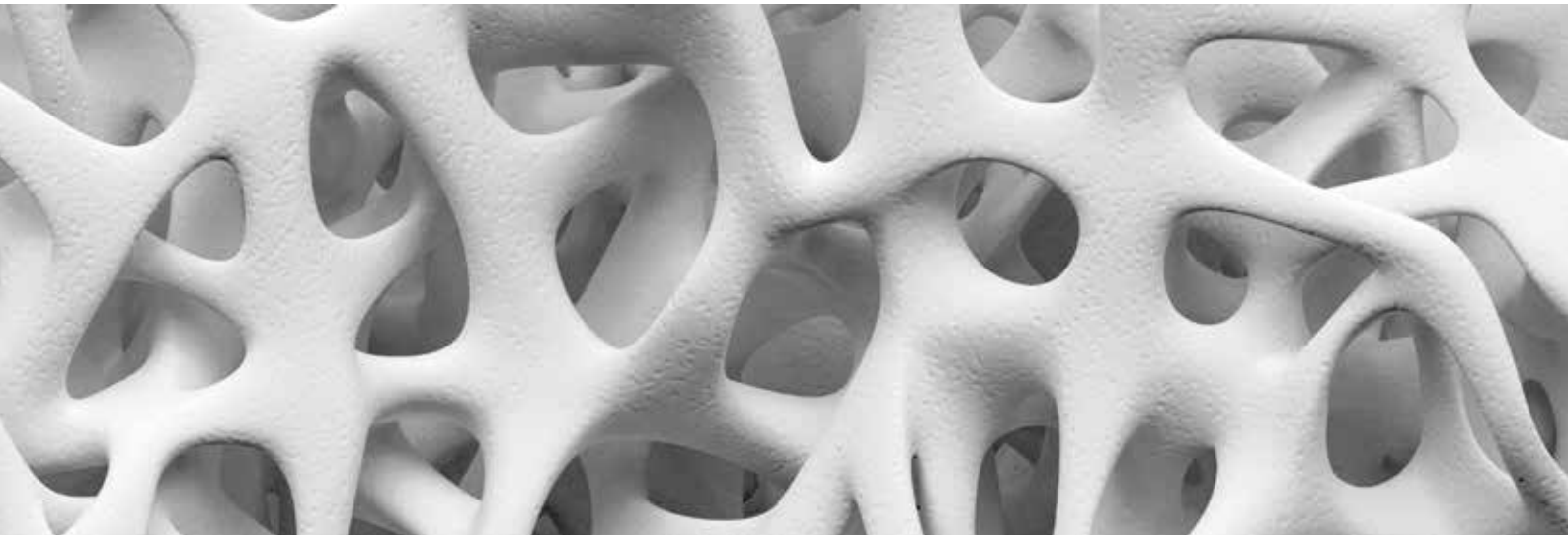
Osteoporosis is a disease that affects all bones of the skeleton and is caused by a loss of bone resistance. As a result, the bones become more prone to fracture spontaneously or in response to minimal trauma. Each year millions of people suffer bone fractures related to osteoporosis, and the number is set to increase in the future due the aging of the population. Age, together with gender, body weight and dietary habits, are risk factors that can lead to the loss of bone through osteoporosis.

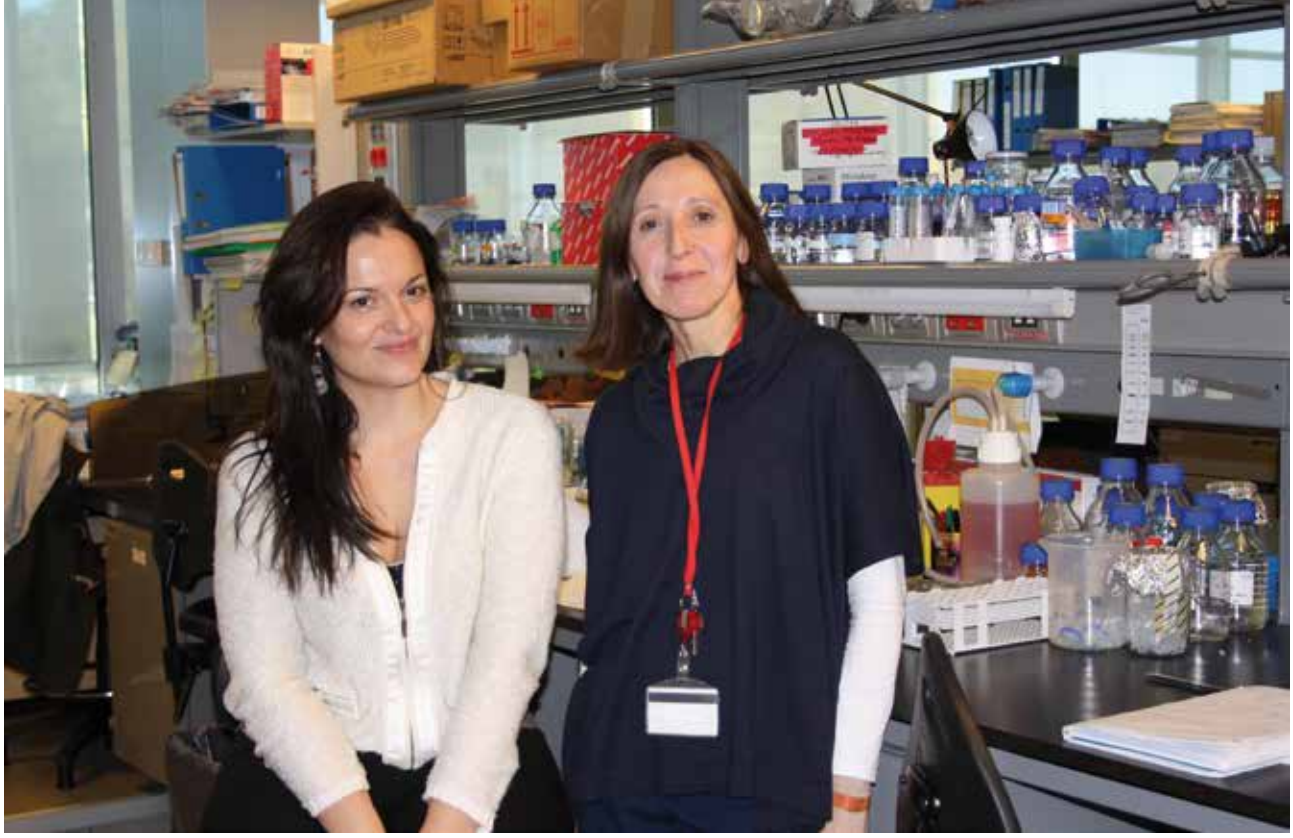
Although osteoporosis has always been thought of as a disease that affects postmenopausal women, the experts warn that it can also affect men. Osteoporosis is associated with an increase in the differentiation and activation of the cells that degrade bone—the osteoclasts—leading to a pathological increase in the rate of bone reabsorption. Therefore the development of new therapies able to reduce the activity of these cells could be of great use in the prevention and treatment of osteoporosis.

A group at the CNIC, working in collaboration with other groups at the same center and in Barcelona, Belgium and France, has discovered a novel mechanism through which it is possible to increase bone mass by controlling these 'bone-eating' cells. The findings were published in the ***Journal of Clinical Investigation.***

The group led by **Dr. Mercedes Ricote,** with **Drs. Mª Piedad Menéndez** and **Tamás Rőszer** as first authors, has demonstrated that the differentiation and activation of osteoclasts is a process controlled by retinoid X receptor (RXR).

RXR is a protein found in the interior of cells, where it detects the presence of lipids and derivatives of vitamin A. This triggers the expression of specific genes, through which RXR controls developmental processes, immunity, homeostasis and metabolism. The CNIC researchers have demonstrated that in osteoclast progenitor cells RXR

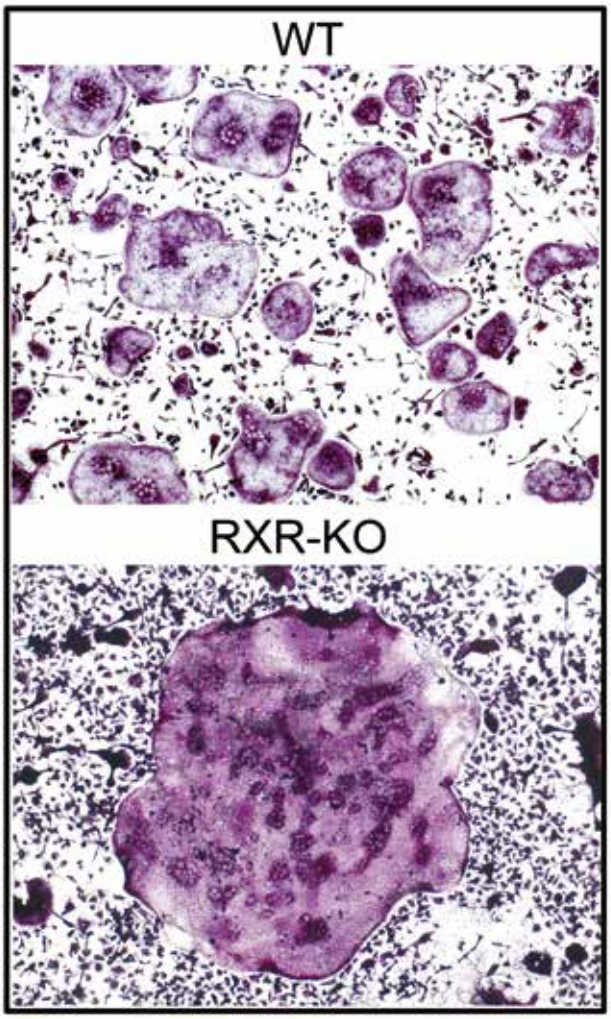




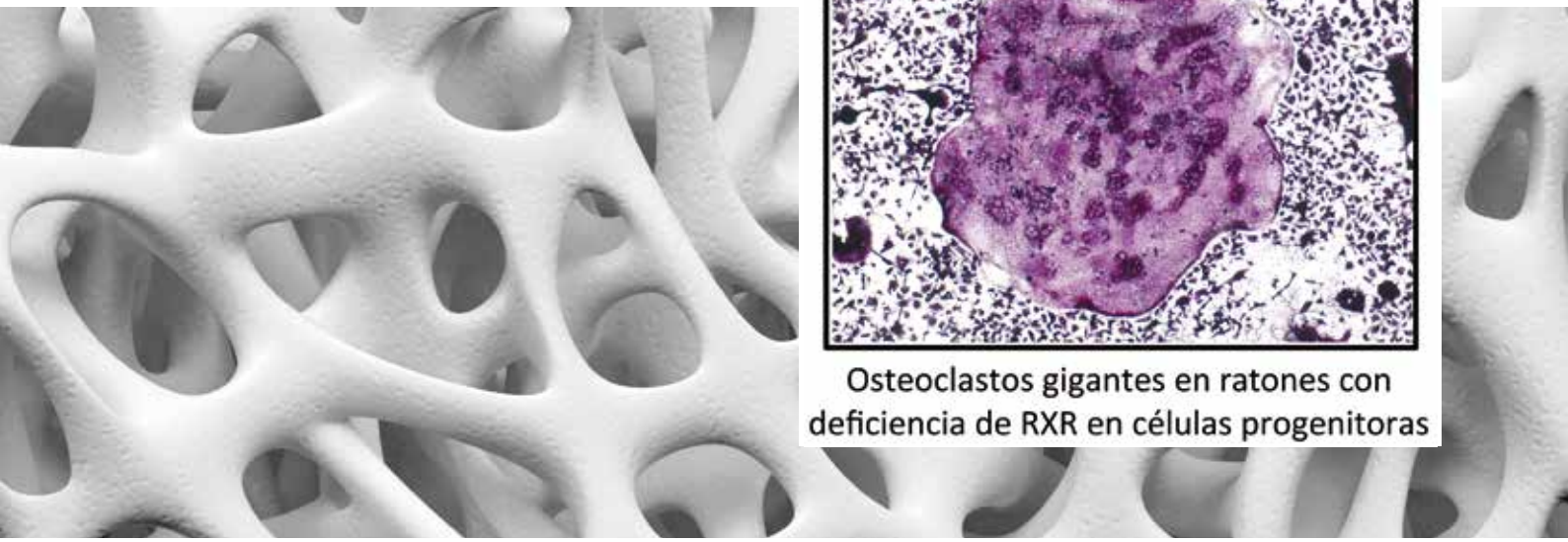
controls the expression of MAFB, a key molecule in the process of osteoclast generation.

Through the use of genetically modified mice, these scientists demonstrated that the loss of RXR function in osteoclast progenitor cells gives rise to the development of giant osteoclasts that unexpectedly lose the capacity to reabsorb bone. Consequently, male mice develop denser bones under normal physiological conditions and females are protected against the loss of bone mass associated with low estrogen levels, a frequent occurrence in postmenopausal women.

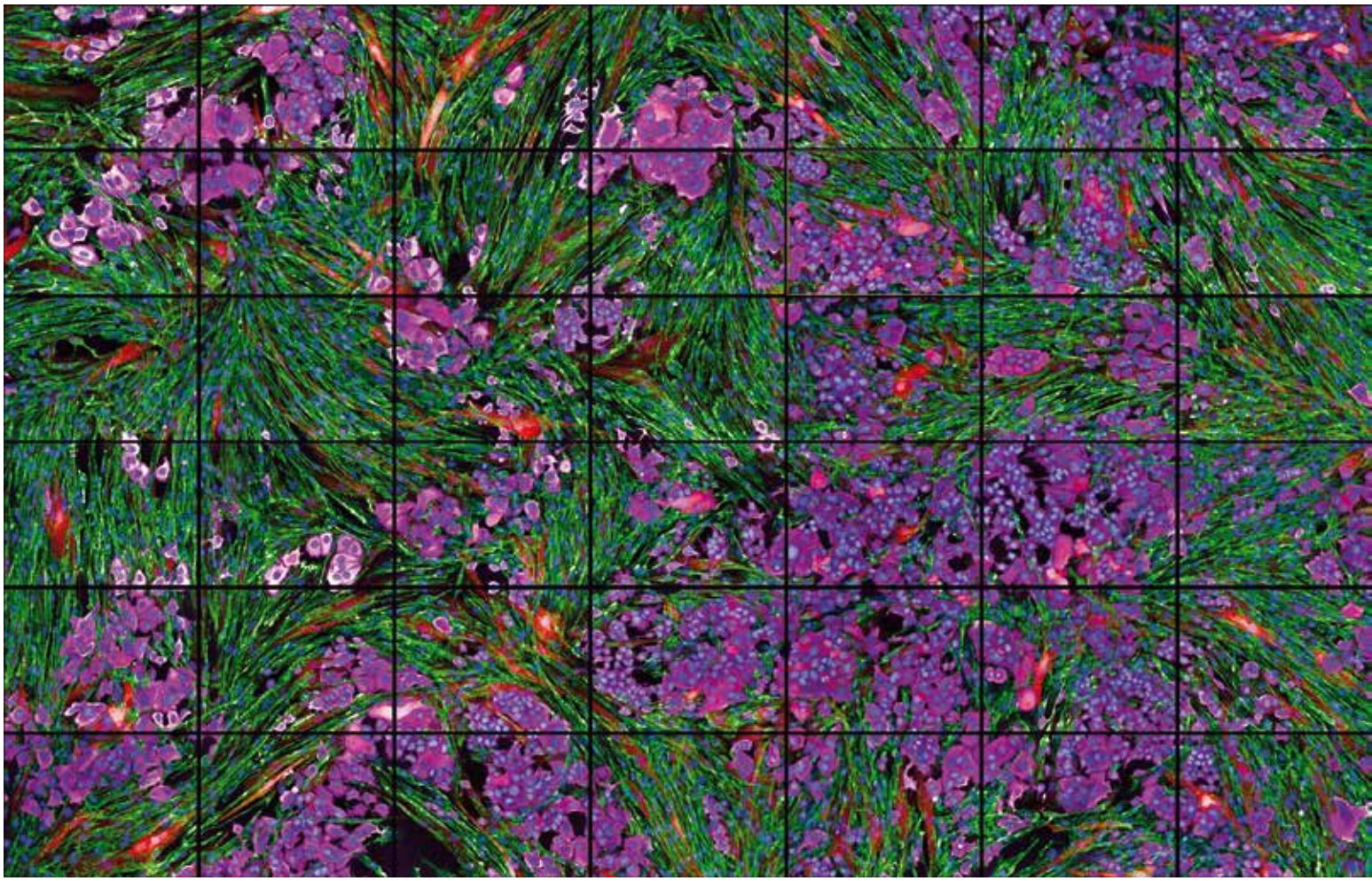
An interesting feature of this study is the demonstration that selective activation of RXR with bexarotene, a drug currently used to treat cutaneous lymphomas, completely blocks osteoclast differentiation. The possible use of drugs to modulate RXR activity, and therefore the formation of osteoclasts, could have implications for the treatment of diseases associated with the loss of bone mass.

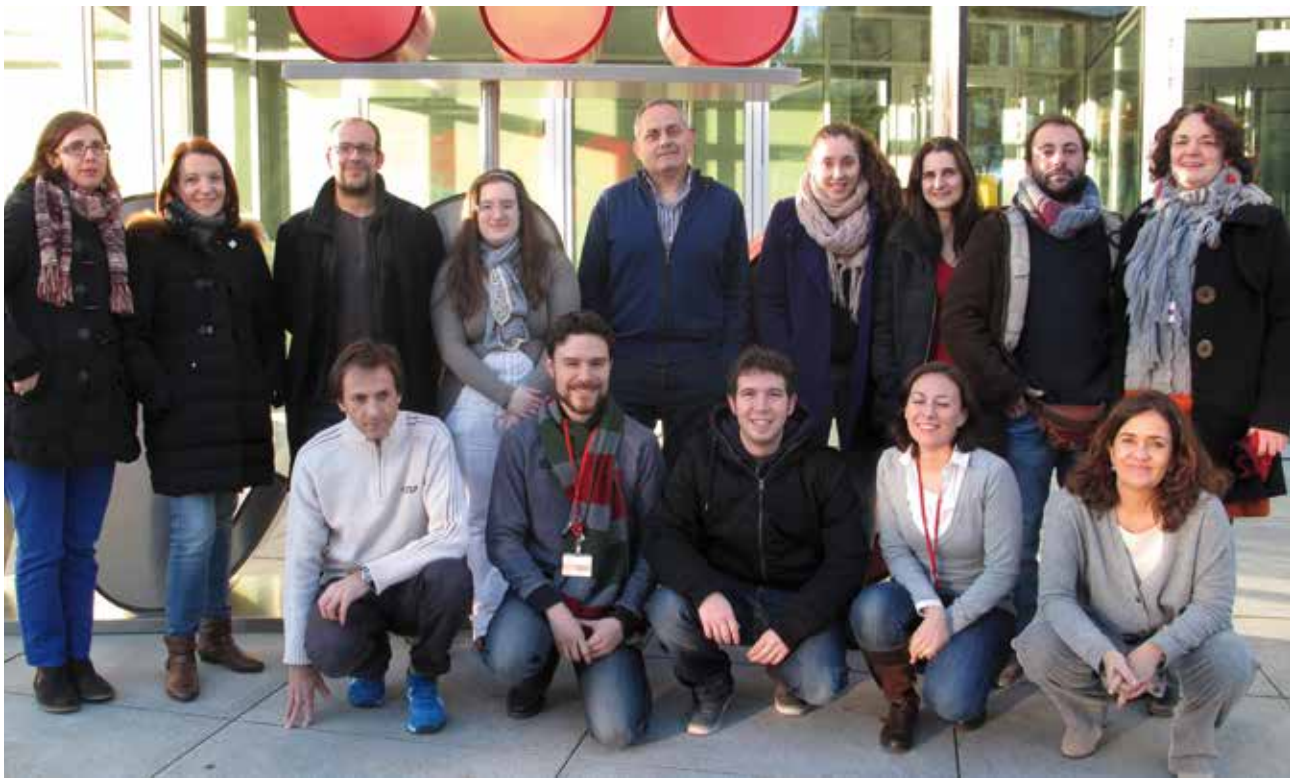


Osteoclastos gigantes en ratones con deficiencia de RXR en células progenitoras



THE MECHANISM THAT CONTROLS LOCALIZATION OF THE PROTEIN RAC1 IN THE CELL NUCLEUS, CRUCIAL FOR UNDERSTANDING THE CONTROL OF CELL SHAPE AND TUMOR INVASION





The sustained presence in the nucleus of the protein Rac1 produces changes in nuclear morphology that are important in several biological processes, including malignant cancer. This is the finding of the research group directed by **Dr. Miguel Ãngel del Pozo** at the Centro Nacional de Investigaciones Cardiovasculares (CNIC), who, in the latest edition of ***Developmental Cell,*** describe the important impact that nuclear localization of this protein has on the capacity of cells to migrate and invade tissues.

The existence of nuclear Rac1 has been known for a few years, but mystery has surrounded how this localization is regulated and what function it plays. The new study identifies the molecular mechanism that regulates transport of Rac1 between the nucleus and the cytoplasm. Once in the nucleus, Rac1 promotes structural changes that facilitate its deformation to enable the cell to migrate through confined spaces.

In the study, published in ***Developmental Cell,*** the CNIC researchers describe the importance of the correct subcellular localization of Rac1, "which is what ultimately controls its state of activation. The sustained presence of Rac1 in the nucleus translates into alterations to the organization of the nuclear membrane through changes in nuclear actin, and this causes changes in nuclear shape," explains **Dr. Del Pozo.**

The authors have identified specific genetic sequences required for exit of Rac1 from the nucleus, both in Rac1 itself and in other proteins involved in this process. These sequences provide potential targets for the development of future therapies. "Our results confirm the need for dynamic regulation of Rac1 in the nucleus, and at the same time serve as the basis for the identification of future molecular targets associated with the reduction of the levels of this protein in the nucleus," explains first author **Dr. Inmaculada Navarro.**

The authors explain that the first step toward tumor invasion require the activation of signaling mechanisms implicated in the control of the actin cytoskeleton. According to **Dr. Del Pozo,** "These processes permit changes in cell shape that favor migration to neighboring tissues. In the case of tumor cells, this migration produces metastasis."

In this process, tumor cells need to modify both the position and shape of their nuclei in order to be able to pass through the narrow pores present in the surrounding matrix. "Learning about the molecular mechanisms that control nuclear shape is therefore crucial for understanding tumor invasion," underlines **Dra. Navarro.**

Rac1-mediated nuclear deformation would thus favor the ability of cells to adapt their shape, thus enabling them to pass through these small pores, an essential mechanism not only in diseases like cancer but also in physiological processes like embryonic development and wound healing, says **Dr. Del Pozo.**

To confirm that their findings obtained at the cell and molecular level are relevant to pathological processes, the authors studied Rac1 localization in healthy tissue and samples from highly metastatic human tumors. "Nuclear Rac1 accumulation is very high in samples from highly aggressive prostate tumors, and its level correlates with the grade of malignancy," remarks **Dr. Navarro.** The study published in ***Developmental Cell*** thus points to the possible use of the level of nuclear Rac1 as a marker of tumor progression.

SHARED LEARNING BETWEEN TWO GIANTS OF CARDIOVASCULAR RESEARCH

In just 5 years the CNIC has gone from promising newcomer to establish itself as a pioneering center on the world stage, and its tutelage under its former "big brother" has transformed into a relationship between equals.

Mount Sinai Heart is one of the best cardiology centers in the world; indeed the institute's website proudly declares its position as 10th ranking cardiology center in the USA. Here in Spain we're not so keen on rankings, but without doubt the Centro Nacional de Investigaciones Cardiovasculares (CNIC) is one of the leading centers in cardiovascular research, both nationally and in Europe.

More than 5000 kilometers separate these two institutions, but they are united through a partnership program established by CNIC "General Director" **Valentín Fuster** when he took charge of the Spanish center, combining this role with his leadership of the prestigious American hospital.

Borja Ibáñez, director of the CNIC's new Clinical Research Department, has been famliar with this agreement from the start, as he was working at Mount Sinai when **Dr. Fuster** took on the Spanish challenge. "At first, the idea was to potentiate translational and clinical research," recalls **Ibáñez,** who subsequently moved to Madrid to steer the partnership project.

The interinstitutional partnership is built around diagnostic imaging in cardiology, a discipline in which **Fuster** has played a pioneering role. The first fruit of the agreement was the shared use of latest generation magnetic resonance imaging technology, and this subsequently led to the establishment of two branches within the program at Mount Sinai: one more clinical and directed by **Javier Sanz,** an spanish cardiologist working at Mount Sinai for more than 10 years, and another centered on molecular imaging and led by **Zahi Fayad,** both based in New York.

The CNIC-Mount Sinai collaboration agreement is one of those relationships that evolves over time. It would unfair to deny that at first the American hospital made the bigger contribution. Indeed, the initial idea was for CNIC researchers to train at Mount Sinai for a period and then take their accumulated experience back to Madrid. Many of today's CNIC researchers honed their expertise within the framework of this agreement, through a number of distinct programs such as CardioImagen or CardioJoven, which trained junior researchers at three locations, Johns Hopkins University, Mount Sinai, and the CNIC.

But in just 5 years the CNIC has gone from promising newcomer to establish itself as a pioneering center on the world stage, and its tutelage under its former "big brother" has transformed into a relationship between equals. **Dr. Ibáñez** is currently enthused about the latest programs within this transatlantic collaboration. The latest "jewel in the crown" is TAN-SNIP (TRANS-ATLANTIC NETWORK TO STUDY STEPWISE NONINVASIVE IMAGING AS A TOOL FOR CARDIOVASCULAR PROGNOSIS & PREVENTION), which works toward the ambitious goal of transforming the epidemiology of cardiovascular disease. The idea is to see if lasting behavioral changes can be instilled in individuals in whom diagnostic imaging has detected a high risk of developing disease, but who have yet to show any symptoms.

In this project the CNIC and Mount Sinai are partnering with some of the other prestigious players in the field, including the famous Framingham Study, which has been central to defining the classic cardiovascular risk scores.

But shared research with Mount Sinai is not limited to this study. Projects within this partnership range from the development of new technology to pioneering research into gene therapy for pulmonary hypertension. As **Dr. Ibáñez** concludes, "we began with training programs, but we are now working together as a coordinated unit, the perfect example of a joint venture."

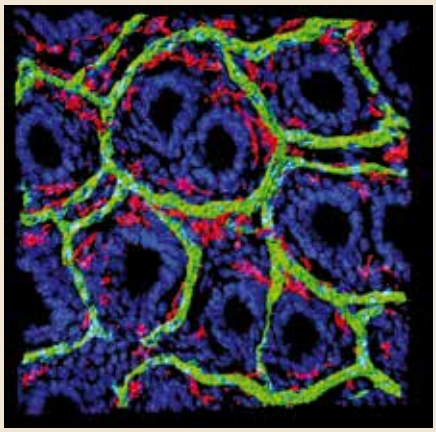
One of the cardiologists at Mount Sinai responsible for ensuring the smooth running of the agreement is Spaniard **Javier Sanz.** He explains that the program has a certain sentimental importance for him because "the intimate relationship between the imaging programs at Mount Sinai and the CNIC" bring so many experts from Spain to spend long periods furthering their training in the Big Apple, and many firm friendships have been formed between the two teams.

Sanz believes that the CNIC "has much to offer Mount Sinai and its Medical Faculty from an academic perspective." The reason is that the CNIC has the resources to conduct research projects spanning the most basic aspects to large translational studies with small and large animal models. "Mount Sinai investigators have access to world leading facilities at the CNIC and a range of resources and experience," Sanz points out. This link also represents benefits for the Spanish center: "Mount Sinai offers the facets of biomedical research closer to the patient, because of the large number of patients we see and the numerous procedures practiced here that make this center a recognized leader in almost every aspect of cardiovascular medicine."

Sanz emphasizes that although Mount works with other European centers, it does not have such lasting connections with other institutions, nor the "reciprocal exchange of investigators", as it has with the CNIC. "Our relationship with the CNIC is extremely valuable and rewarding."

In *Circulation Research*

IDENTIFICATION OF A MUTATION ASSOCIATED WITH THE RISK OF ANEURYSM



The CNIC is at the vanguard once again. This time with the identification of a mutation affecting the protein MMP17 and that is associated with the risk of aneurysm. But the good news doesn't stop there. **Alicia García Arroyo**'s work also opens the way toward possible gene-therapy-based treatments for hereditary aneurysm.

Public impact

A MUTATION TURNS EXERCISE INTO A LIFE-THREATENING ACTIVITY

No one would dispute that exercise is healthy, least of all a cardiologist. But as with anything else there are exceptions, and one of them is described in this study by **Borja Ibáñez** and **Juan Antonio Bernal.** The study concludes that carriers of the mutation R735X in the human gene Pkp2 should not participate in competitive sports.

European project

€6 MILLION TO ANALYZE THE EFFECT OF THE POLYPILL

The efficacy and security of the polypill have been demonstrated in numerous studies, and this has led to the approval of this medication, developed by the CNIC and Ferrer Laboratories. Now the European Union has awarded €6 million to the SECURE project, to quantify the reduction in events with this treatment and the consequences on the mortality rate. Great news.

Epigenetic changes

A PROTEIN PROTECTS HEART CELLS AGAINST AGING

One of the goals of science is to challenge established theories. This is the case of a study by **Susana Gonzalez,** who has shown that dilated cardiomyopathy can develop as a result of epigenetic changes (alterations to chromatin folding) that don't affect the DNA sequence but do affect the gene expression level.

agenda...

4th- 5th SEPTEMBER 2015
CICERONE Workshop

This group of lectures provides a general introduction to cardiovascular research in Spain, and also gives participants the chance to question key researchers and opinion leaders in the field. Since 2012, the Cicerone Meeting has been run in collaboration with the Fundación Interhospitalaria para la Investigación Cardiovascular (FIC) and takes place in the Hospital Clínico San Carlos, Madrid.

The CICERONE Workshop is intended for Medical professionals undertaking the first three years of their resident specialization internship (MIR: R1, R2, R3) in Cardiology or Cardiovascular Surgery.

OPEN UNTIL 16th OCTOBER 2015
RES@CNIC Program

The aim of the RES@CNIC program is to offer medical professionals, during the first years of their specialization period as resident interns, the opportunity to learn about and become familiar with the latest techniques in biomedical research being used in the CNIC's laboratories, under the guidance of a CNIC scientist. Residents participating in RES@CNIC program also receive training in theoretical aspects of cardiovascular research through a taught module run by experts.

The Program also seeks to create links and partnerships so that these professionals, when they complete their MIR specialization period, will have the chance to undertake research projects in their National Health System centers in collaboration with the CNIC.

The duration of the stay will be a maximum of 9 consecutive weeks.

Requirements for applicants:

- Be a profesional Doctor, of any nationality, in period of specialization in the MIR Program at any Hospital in the Spanish territory.
- Specializing in Cardiology or Cardiovascular Surgery.

27th NOVEMBRER 2015
CNIC PhDay

CNIC PhDay is designed not only provide a forum for undergraduates, graduate students, lab technicians and postdoctoral researchers to present an original poster, but also as an opportunity for young researchers to gather and exchange scientific ideas while networking.

For the Second edition more than 100 people are expected to attend and will focus on:

- Negative results, retractions and quality science
- Solving interpersonal problems, team working and coaching/mentoring
- Public speaking, writing a paper, and making poster, etc. (scientific communications)
- Outreach strategies and divulgation initiatives.
- How to apply for scholarships, writing grants and patents, etc.

11th -12th DECEMBER 2015
Cardiovascular Pathophysiology Course

Jointly organized by the CNIC and the Sociedad Española de Cardiología (SEC), the course in Cardiovascular Pathophysiology (from Symptom to Gene) offers a translational vision of cardiology to medical specialists by introducing them to the study of pathophysiology and basic research. Participants are given an overview of the molecular and genetic factors that underlie cardiac diseases and gain a modern vision of cardiac physiology.

This course is intended to Medical professionals during their MIR specialization internship.

FROM HIGH-SCHOOL GRADUATES TO PHYSICIANS... AT THE CNIC

Julio César García Rubio and **Eliú David Pérez Nogales** first met at the CNIC back in 2007 and ran into each other again at the same center in 2015. In these eight years, they have gone from being high-school seniors, graduating with the maximum grade average (10) in the Spanish *bachillerato* program, to practicing physicians in their first residency year. As they have grown in years and wisdom, both have retained a shared conviction: their admiration for the CNIC and its training programs, in which they have participated at various stages.

Eliú, from Gran Canaria, remembers how he came to participate in Acércate—the CNIC program aimed at the brightest school leavers with an interest in research—almost by accident. "I started a course option at school called 'Science through Experiment'. It was a total flop because hardly any students took the course. But the course teacher told me about the Acércate program and suggested I apply." What most impressed him about the selection process was the telephone interview in English. "In those days this was how they selected among the applicants who all had an overall grade 10 in the *bachillerato;* nowadays they do it by raffle draw."

The telephone interview is something that also sticks in **Julio**'s mind. He received his call in his native Gijón, where he is now training as a cardiologist. This career path wasn't planned back in 2007. "I was pretty clear that I wanted to work in research, and it was here at the CNIC that I changed my thinking and veered more toward the clinic." When he first came to the CNIC he was planning to study Biotechnology rather than Medicine.

Eliú already had a clear vocation for medicine, but as yet didn't have a clear idea of what area he would specialize in, and it was precisely at the CNIC that he set his heart on cardiology. But neither of the two was content to follow the standard training path, which is to say that neither of them has respected the traditional dichotomy between research and clinical practice.

Julio acknowledges that "when you first hang a stethoscope around your neck, it changes your outlook, you start to treat patients and what you really enjoy is the work in the clinic." Precisely because he saw this happening, he decided to return to the CNIC in 2011, on the Cicerone program. "I had completed my fourth year and joined **Ignacio Flores**'s lab to do basic research; I wanted to rediscover something of the spirit of enquiry that seemed to have got lost during my degree studies."

And, in effect, this return started him anew on that path. But neither **Julio** nor **Eliú** think that there should be such a stark choice between the bench and the clinic. **Julio** affirms that "ideally it should be straightforward to combine both elements, and one thing I'm clear about is that I don't want to leave the clinic to work exclusively in research; I don't want to give up anything, and even though I realize that achieving this professionally means giving up on free time, I think it's time well invested."

This chimes with **Eliú**'s view. "I knew from the start that I needed to do many things at the same time and that I would have to get into research of some kind, if not basic research then clinical research with patients. But I do want to combine both activities, and I'm prepared to give time up to do that."

And it is precisely this commitment to getting the most out of both worlds that drove these two medics and future cardiologists to apply for another CNIC fellowship, eight years after the first, and in **Julio**'s case four years after the second.

Having lost contact over the years, the one-time Acércate participants are once more training together at the CNIC, as physicians enrolled on the RES@CNIC program. The nine intense weeks of this program have demonstrated that their dream is not impossible. **Julio** explains that "the program is also building the foundations for future multicenter studies, because graduates of the program are dispersed in centers throughout Spain. This is going to make it easier to recruit study participants from all over the country, because we and our fellow RES@CNIC graduates are more than ready to work in partnership with the CNIC. This is one of the key ideas of the program, to form lasting and direct links with hospitals in the Spanish health system."

Collaboration is also what **Eliú** most valued about the program. "The program equips you with a great many tools to take back with you to your hospital, and these tools enable you to advance with your work in ways that otherwise would not have been possible."

Julio defines RES@CNIC as a special program. "You arrive here with a clinician's perspective, but in just a short time this perspective is changed. You leave with the conviction that a physician can also do research, something that seems difficult for colleagues in other specialties. With this program you realize that the two activities are compatible."

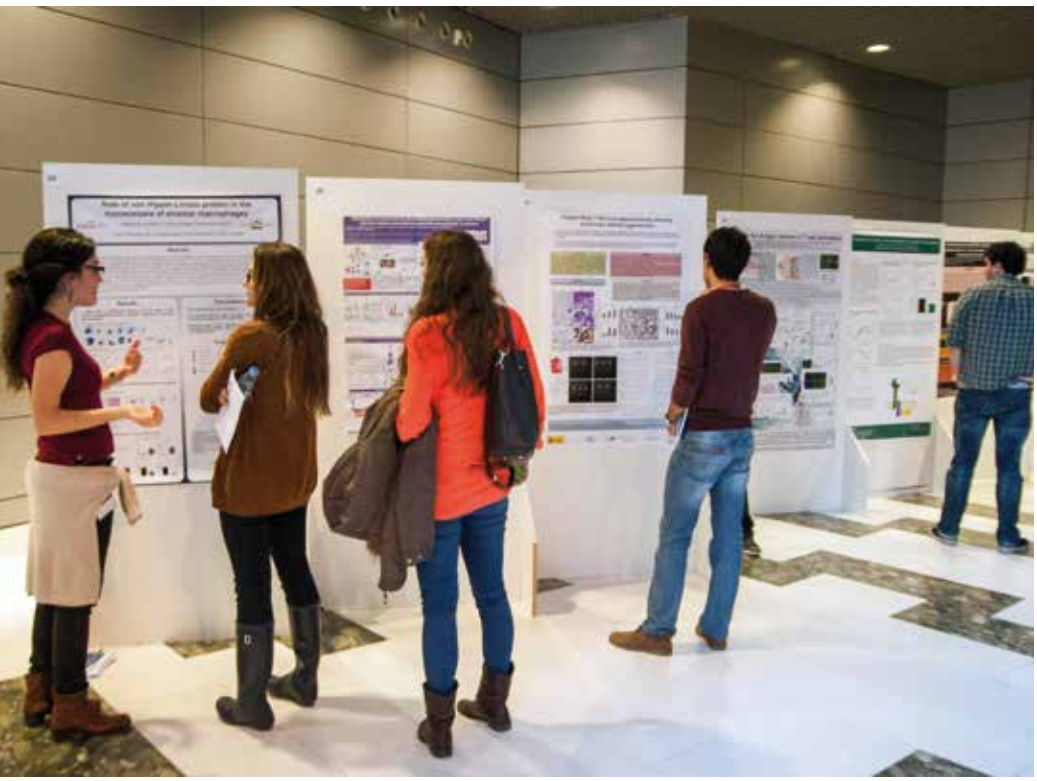
THE 'LITTLE ONES' TAKE CHARGE

The importance of their work is undeniable, but we seldom hear about them. They are the predoctoral researchers, as well as those who already have their PhD title in their pocket but don't yet have their own research group. However, last December 1, these 'juniors', who are set to be a major talking point, organized an event at the CNIC, the PhDay, that would have not been out of place at any leading international conference. It was the first such event at the Center and was such a success that it will be repeated this coming November 27.

Bárbara González Terán, a researcher in **Dr. Guadalupe Sabio**'s lab, was the main organizer of this event, together with her colleague **Daniel Torralba,** from **Francisco Sánchez-Madrid**'s group. Although Bárbara feels that she is privileged to receive "so much technical training" at the CNIC, where she is working toward her PhD thesis, she feels that improvements could be made in other areas. In particular, she mentions the stress of giving presentations, the need to develop skills in networking through researcher networks, and writing and publishing scientific articles.

Bárbara points out that there is generally better provision of training in these areas in universities in the United States, where postrgraduates have to present their projects regularly and receive training in communication skills.

So from the earliest planning stages of the PhDay it was clear that there were many issues to be addressed, and this ambitious goal made the design of the program challenging. But even before this, the first task was to get approval from the CNIC. The Direction gave the project the green light after a presentation given by two representatives of the predoctoral researchers. With this approval, the team began planning the conference, an event organized in its entirety by pre- and postdoctoral researchers and masters students; for once, the group



The quality of the presentations was comparable with any more traditional meeting. Researchers working in Spain and abroad tackled key themes in the training of tomorrow's scientific leaders.

leaders would be out of the spotlight, both as presenters and participants. "Part of our aim was to create a forum in which early stage researchers would be disinhibited from speaking," comments **González Terán.**

There was just one exception to this rule. In a demonstration of the Center's approval of the initiative, the inaugural presentation was given by CNIC General Director **Dr. Valentín Fuster,** who was delighted to have this opportunity to show support for young researchers, one of the core missions of the CNIC.

The quality of the presentations was comparable with any more traditional meeting. Researchers working in Spain and abroad tackled key themes in the training of tomorrow's scientific leaders.

Scientific themes were presented in a series of 15 minute talks, and dealt with subjects such as the regulation of genome architecture during heart development. In addition, the meeting dedicated time to more general issues, such as motivation in the laboratory, the ways in which basic research discoveries can be converted into successful businesses, and the links between basic and clinical research.

In an event that emphasized enterprise, business initiatives derived from research carried particular weight. There was a dedicated session called *Beyond the bench, where ideas become reality.* "We invited people who are driving their own projects, to show participants that there are many alternatives after the doctorate," **González Terán.**

And to motivate the participants in their scientific career, who better than **Dr. Joan Guinovart,** whose presentation was called *Everything I wanted to know about science but was afraid to ask.* **Dr. Guinovert,** like all the invited speakers, participated in the PhDay for free.

The level of satisfaction of the participants was in direct proportion to the effort put in by the organizers. In a post event survey, 100% of attendees expressed their enthusiasm for future PhDays, and many people expressed an interest in organizing the next event.

Plans for the second edition are already underway, and it promises to surpass even the high quality of the first meeting. In a preview of upcoming innovations, **González Terán** spoke of the intention to include Elevator Pitches, a feature of many congresses in the US. These competitions consist of short conversations, about the duration of an elevator ride, in which a young investigator tries to convince a group leader of the validity of an idea or project.

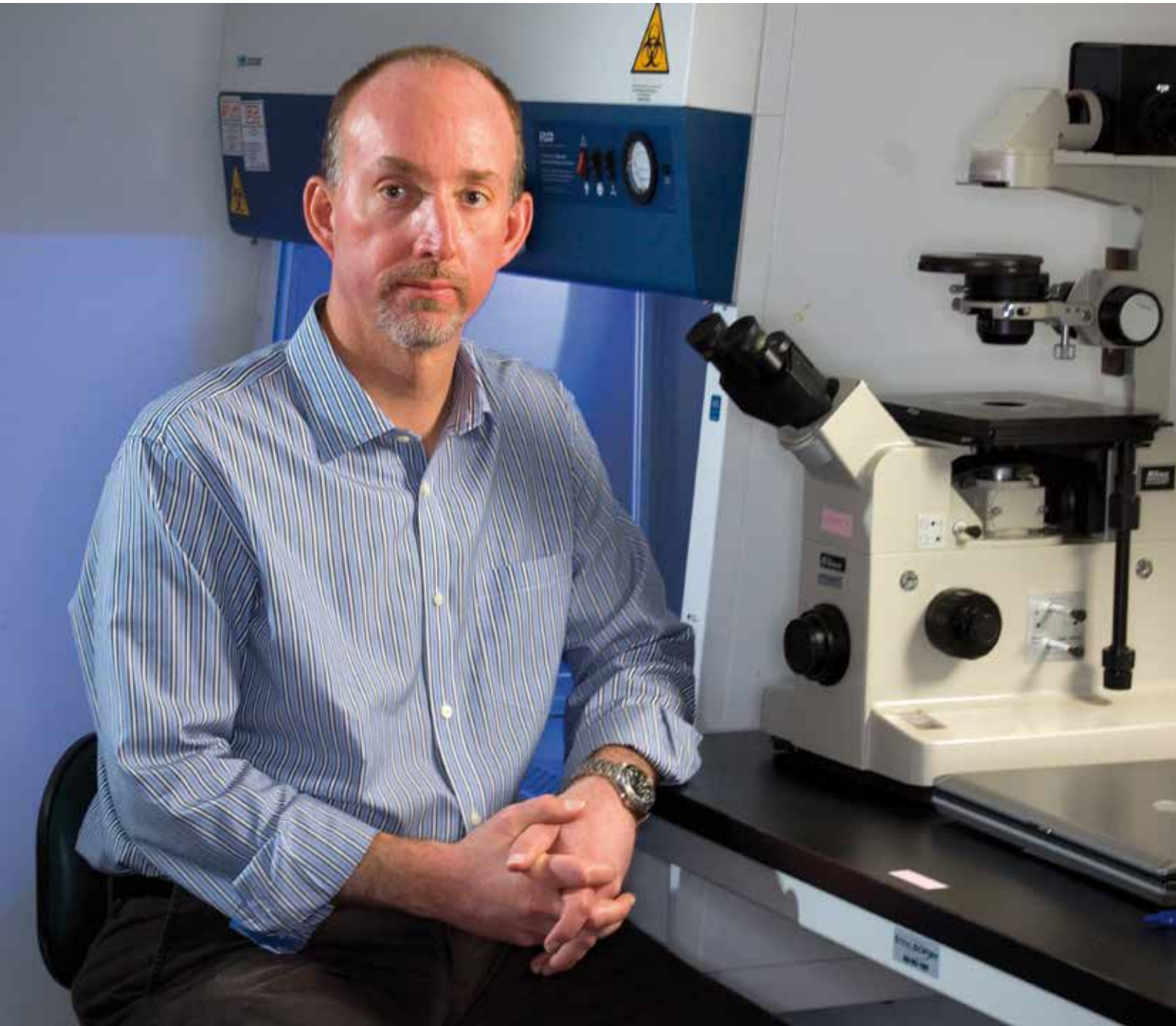
Another goal is to include more presenters from outside Spain, and the team is working on several other ideas to make the meeting even more attractive.

Like all good scientific meetings, the PhDay included a poster session, and prizes were awarded to the three judged to be the best. On this occasion, the prize winners were **Irene Rubio-Ferrera** of the Universidad Autónoma de Madrid, for her poster *The role of scribble and daschshund in segmental specification of neuronal subtypes,* **Alberto Hidalgo** of the Universidad Complutense de Madrid, for his poster *Biophysical evaluation of pulmonary surfactant as a drug delivery system,* and predoctoral CNIC researcher **Víctor Fanjul Hevia,** for his poster *Hutchinson-Gilford Progeria Syndrome as a model to study heart disease in aging.*

SCIENTIFIC DIRECTOR OF THE PENN INSTITUTE FOR REGENERATIVE MEDICINE

Edward Morrisey

"WE ARE STILL A SEVERAL YEARS AWAY FROM MAKING CELL REPLACEMENT THERAPY A REALITY"



In 2012, the Japanese scientist Shinya Yamanaka received the Nobel Prize for Medicine for his pioneering research on stem cells. Yamanaka's achievement was to obtain pluripotent stem cells from adult cells (induced pluripotent stem cells; iPSC) by manipulating a small set of transcription factors. Although the method has proved to be effective, it has yet to lead to the ultimate goal: the regeneration of organs from adult stem cells. Teams of researchers across the world are working toward this goal, and their findings promise significant advances.

Leading stem-cell researcher Edward Morrisey visited the CNIC recently to deliver his seminar on the development and regeneration of the cardiovascular system. Dr. Morrisey is optimistic that the goal of regenerative medicine will be achieved, and sees several opportunities for partnership with the CNIC.

In 2011, you published a paper in Cell Stem Cell about a new way of making induced pluripotent stem cells without the standard four transcription factors. How has this work developed in the time since then?

Since that paper there have been many excellent advances that have increased the efficiency of iPSC generation. We decided to focus on the role of miR302-367 in tissue-specific stem/progenitor cells. Our iPSC Core at Penn has been generating iPSCs using the Sendai virus method, which we have found to be the most efficient of the methods we have tried.

The ultimate goal of making iPSCs is regenerative medicine, but we still seem to be a long way from clinical applications. What would you say are the next steps and when do you envisage that regenerative medicine will become a reality for patients?

While the innovation of iPSC technology has increased our access to pluripotent stem cells, there is still much that is unknown about how these cells can be differentiated into useful cell lineages. Most of the cell lineages derived from ES/iPSCs are immature, and in many cases this seems to limit their utility for regenerative therapies. Moreover, our ability to engraft into tissues such as the heart is still very primitive and inefficient. Cell replacement therapy is likely several years away and for some tissues may not be the ideal way to promote regeneration.

During your visit to the CNIC you talked about the development and regeneration of the cardiopulmonary system. Do you think that this is the most important area where regenerative medicine could be applied?

The 2 tissues that form the cardiopulmonary system (cardiovascular and pulmonary) utilize very different mechanisms to respond to injury. The mammalian heart has a limited repertoire of responses to acute ischemic injury and chronic injury. In mammals, there are no truly robust mechanisms to replace lost myocardium. In contrast, the lung is a truly regenerative organ, and lost tissue can be regenerated in vivo through various mechanisms, including activation of regional stem/progenitor cells followed by proliferation and differentiation. While different, these two tissues are involved in most morbidity and mortality in the Western world. So understanding how they respond to injury and defining mechanisms to promote repair and regeneration are of paramount importance.

Which diseases do you think would most benefit from regenerative medicine?

My bias would be toward the heart and lungs given their predominance in causing human disease. However, there are other organs in which regeneration could be improved by a better understanding of the in vivo mechanisms, such the liver and pancreas.

What can you tell us about the molecule miR302-367?

This is actually a cluster of microRNAs that is highly expressed during early development. They promote cell proliferation while inhibiting differentiation. miR302-367 molecules act in part by inhibiting the Hippo signal transduction pathway.

Do you think that regenerative medicine receives enough funding?

As new discoveries refine our understanding of tissue regeneration, allocation of resources to the most promising avenues of research will be important. At least in the US, there is a growing crisis because of insufficient funding for basic science while there is an increased emphasis on trying to translate current knowledge into new therapies. While generating new therapies is the ultimate goal of what we do, many of the funding agencies are pushing too hard on that end of the discovery spectrum. This is causing an imbalance of priorities at a time when there are incredible opportunities to explore the basic understanding of disease processes.

What is your impression of the CNIC? Do you see opportunities for joint projects?

I was impressed by the full spectrum of research being performed at the CNIC. This type of resource balancing is important and the CNIC provides an excellent model of how to do it. The core facilities are incredible and the organization is something that we in the US could learn from. As for collaborations, there were several areas of interest, including the basic understanding of how developmental pathways are re-utilized during tissue regeneration and the possibilities of using large animals to explore translational opportunities for cardiac regeneration.

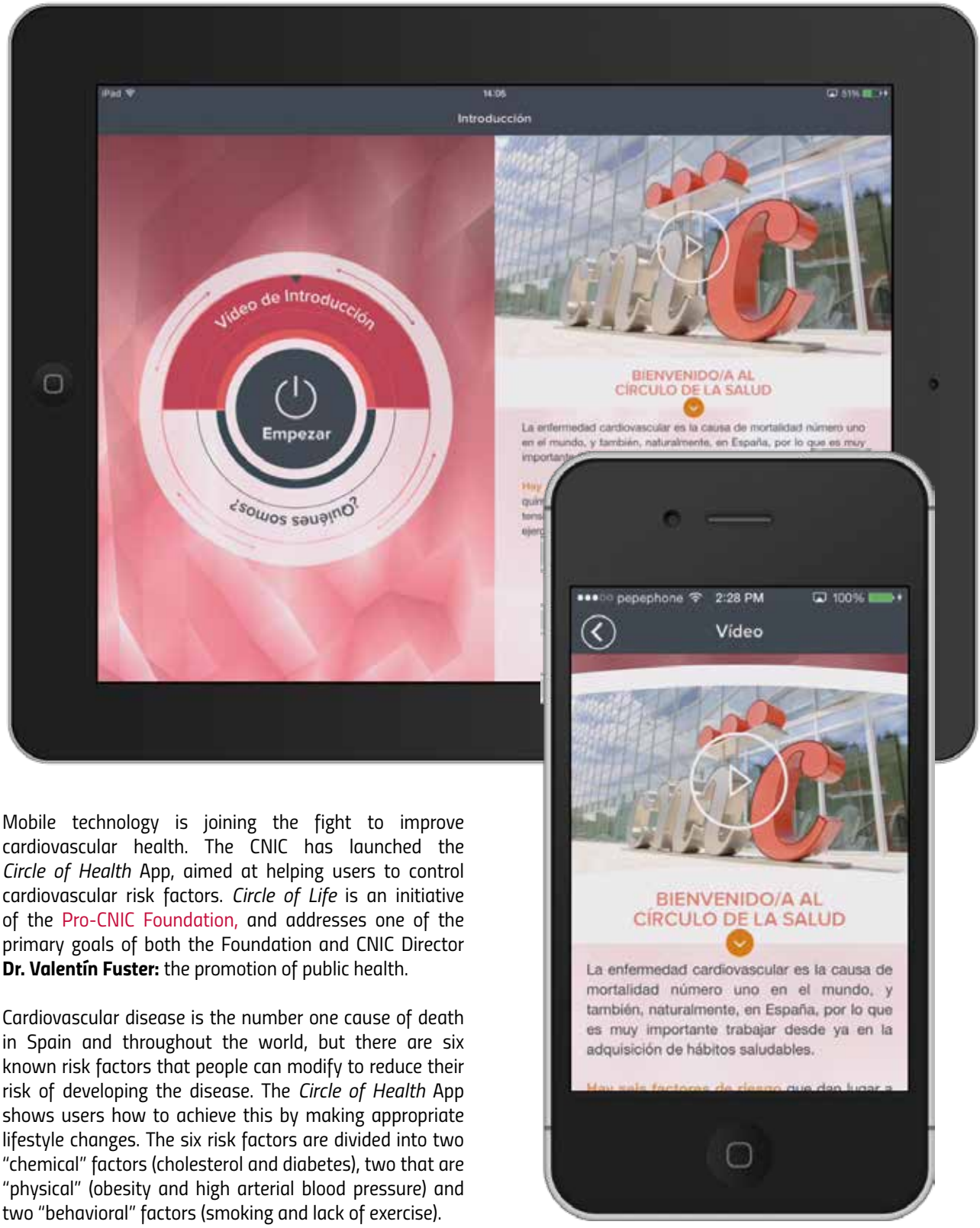
21st September 2015
CNIC Invited Seminar
Duojia Pan
Howard Hughes Medical Institute
Johns Hopkins University School of Medicine
Baltimore
USA

5th October 2015
CNIC Invited Seminar
Mathias Gautel
New Hunt's House
King's College London
UK

19th October 2015
CNIC Invited Seminar
"Cardiac PET: from research tool to clinical hybrid imaging"
Juhani Knuuti
Turku PET Centre
University of Turku and Turku University Hospital
Turku
Finland

26th October 2015
CNIC Invited Seminar
James Eberwine
PENN Genome Frontiers Institute
University of Pennsylvania
Philadelphia
USA

THE CNIC SIGNS UP FOR M-PREVENTION



Mobile technology is joining the fight to improve cardiovascular health. The CNIC has launched the *Circle of Health* App, aimed at helping users to control cardiovascular risk factors. *Circle of Life* is an initiative of the Pro-CNIC Foundation, and addresses one of the primary goals of both the Foundation and CNIC Director **Dr. Valentín Fuster:** the promotion of public health.

Cardiovascular disease is the number one cause of death in Spain and throughout the world, but there are six known risk factors that people can modify to reduce their risk of developing the disease. The *Circle of Health* App shows users how to achieve this by making appropriate lifestyle changes. The six risk factors are divided into two "chemical" factors (cholesterol and diabetes), two that are "physical" (obesity and high arterial blood pressure) and two "behavioral" factors (smoking and lack of exercise).

The App explains the nature of each of these risk factors through videos presented by **Dr. Fuster:** "The message is that all of us can do a lot to stay healthy, and the introduction of this new tool is great news for society."

The App is divided into several stages. In the first stage, *Evaluation,* users learn about their individual state of cardiovascular health by responding to a set of simple questions that reveal the factors that present most risk. The results of this assessment are not intended to be definitive, and users are advised of the importance of consulting a specialist, especially if the result is negative.

Next up is the *Information* stage, where users are presented with key information about the significance of the risk factors and how to minimize their impact through videos and other interactive tools.

One of the most important stages is *Motivation,* which teaches users how to abandon unhealthy habits and acquire new one that are more beneficial to health. This stage is based on the principles expounded by **Dr. Fuster** in his recent book *The motivation cycle,* in which he speaks of the four tasks and four actions (the 4 T's and the 4 A's), vital tools for achieving motivation and changing habits to promote health.

The final stage is *Activation,* which includes a set of recommended actions, grouped into weekly challenges to help users improve their health. Users can also share their progress with friends and family.

Circle of Health, free to download from Google Play and the Apple Store, provides the keys to averting the most significant risks of cardiovascular disease and in this way aims to promote public health through an attractive interface and a comprehensive multimedia content.

The App, developed by WakeApp Health, was launched at an event at the CNIC presided over by Spanish health minister **Alfonso Alonso. Alonso** reminded those attending that "health is a constitutional obligation that the Spanish consider a right." But that right, as this App emphasizes, requires individuals to make a commitment to monitoring their personal health.

THE *MUJERES POR EL CORAZÓN* CAMPAIGN BUS TOURS MADRID

The Fundación Mapfre, the Pro-CNIC Foundation, and the Madrid regional government joined together to launch the *Mujeres por el corazón* campaign last October. The purpose of the campaign is to inform women about the importance of recognizing the early signs of cardiovascular disease and the need to maintain a healthy lifestyle to reduce the impact of this disease, the main cause of death in women as well as in men

Several months in, the campaign is as active as ever, and the campaign bus has now visited 11 boroughs in the Madrid region. At each stop, the team provides rapid and free medical tests and also gives information to women about the risks associated with a heart attack.

The tests offered include measurement of the waist circumference, a more reliable indicator of risk than body-

mass index, and that shouldn't be more than 82 cm. Other tests include blood pressure and cholesterol, which need to be kept under control to avoid cardiovascular risk, and measures of height and weight. Excess body fat, another important risk factor for heart disease, is closely related to overeating and lack of physical exercise.

Visitors to the campaign bus also receive a leaflet explaining that although chest pain and discomfort are the main symptoms of a heart attack in women and men, women generally also experience other symptoms, such as shortness of breath, nausea, vomiting and pain in the back and jaw. The leaflet provides guidance on learning to control stress, as this will help to protect the cardiovascular system, and also emphasizes the importance of taking regular exercise and avoiding tobacco, since smoking can cause blood clots, thrombosis, stroke and heart attack.

To coincide with the campaign bus visits, each borough council holds public events featuring contributions from the sponsoring organizations and the Spanish Heart Foundation.

The *Mujeres por el corazón* campaign includes a practical guide to cardiovascular health for women, called *Cuídate, Corazón* (Looking after your heart). This guide was developed in partnership with the magazine *Women's Health* and can be downloaded from the campaign website: www.mujeresporelcorazon.org. This site also includes a promotional advertisement under the slogan "Make no mistake, recognizing the symptoms could save your life." In the advert the actress Elena Martín attributes her symptoms to other causes until finally deciding to call the emergency services.

At each stop, the team provides rapid and free medical tests and also gives information to women about the risks associated with a heart attack.