

## The HERACLES Cardiovascular Network

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In 2002, a group of researchers in the fields of cell electrophysiology, cardiology, population genetics, epidemiology, proteomics, molecular biology, bioinformatics, and statistics decided to take up the challenge of investigating the mechanisms and genetics of arterial hypertension (AH). Mechanisms related to ion channel regulation of arterial smooth muscle function were identified. The HERACLES (Hipertensión Esencial: Red de Análisis de Canales iónicos de la musculatura lisa arterial y su Explotación terapéutica Sistemática) network was honored with a distinguished mention in the 2005 evaluation, and was strengthened by the incorporation of new research groups in 2007. The work of the HERACLES network is characterized as much by the transfer of knowledge "from bedside to bench" as by its converse: "from bench to bedside."

The current objectives of the HERACLES network are: *a*) to study the Ca<sup>2+</sup>-dependent K<sup>+</sup> channels, the transient receptor potential (TRP) cation channels, and the Ca<sup>2+</sup>-dependent Cl<sup>-</sup> channels that are involved in vascular physiology; *b*) to study protein expression maps in plasma and cardiovascular tissue and their significance for drug treatment; *c*) to study the effect of flavonoids on ion transport and responses to oxidative stress; and *d*) to identify biomarkers of risk, prognosis, and treatment responses in extreme AH phenotypes.

Our project includes a number of lines of research coordinated within cross-sectional programs based on centralized facilities, which are used by them. The HERACLES network has published more than 60 articles (available from: <http://www.redheracles.net>), funding has been received for more than 90 projects in competitive submissions to Spanish and 6 international bodies, and there is a DNA Biobank.

**Key words:** Hypertension. Multidisciplinary. Ion channels. Arterial smooth muscle.

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### Red cardiovascular HERACLES

En 2002, un grupo de investigadores en electrofisiología celular, cardiología, genética de poblaciones, epidemiología, proteómica, biología molecular, bioinformática y estadística decidió afrontar el reto de analizar los mecanismos y la genética de la hipertensión arterial (HTA). Se identificaron mecanismos relacionados con la regulación de la función de la musculatura lisa arterial por canales iónicos. La Red HERACLES (Hipertensión Esencial: Red de Análisis de Canales iónicos de la musculatura lisa arterial y su Explotación terapéutica Sistemática) fue calificada con mención Excelente en la evaluación de 2005, y se ha consolidado con la incorporación de nuevos grupos en la convocatoria 2007. Las actividades de la red se enmarcan en la transferencia de conocimiento del *bedside-to-bench*, así como su inversa, *bench-to-bedside*.

Los objetivos actuales de la red son: *a*) estudio de canales de K<sup>+</sup> dependientes de Ca<sup>2+</sup>, canales catiónicos TRP y canales de Cl<sup>-</sup> dependientes de Ca<sup>2+</sup> que participan en la fisiología vascular; *b*) estudio de los mapas de expresión proteínica en plasma y tejido cardiovascular y su relevancia en el tratamiento farmacológico; *c*) estudios del efecto de los flavonoides en el transporte iónico y la respuesta al estrés oxidativo, y *d*) identificación de marcadores biológicos de riesgo, pronóstico y respuesta al tratamiento en fenotipos de HTA extremos.

Nuestro proyecto incluye un conjunto de líneas de investigación coordinadas con programas horizontales basados en plataformas centrales, que las sirven. La red ha publicado más de 60 manuscritos (disponibles en: <http://www.redheracles.net>) y ha recibido financiación para más de 90 proyectos en convocatorias competitivas nacionales y 6 internacionales, y un Biobanco ADN.

**Palabras clave:** Hipertensión. Multidisciplinario. Canales iónicos. Músculo liso arterial.

## INTRODUCTION

In the Spanish Health Research Fund's (Fondo de Investigación Sanitaria) first call for applications from its investigation networks in 2002, a group of researchers interested in studying cardiovascular disease from different aspects of scientific disciplines decided to take up the challenge of working together to investigate arterial hypertension (AH), which is a chronic disease with one of the highest morbimortality rates in Spain. The disease is easy to diagnose clinically and yet not much is known in terms of its etiopathology, therapeutic management and cardiovascular repercussions, such as coronary and cerebrovascular disease.

For this purpose, they decided on a multidisciplinary approach (pathophysiology, cardiology, population genetics, epidemiology, proteomics, molecular biology, bioinformatics, and statistics) enabling them to study the lesser known mechanisms of essential hypertension and vascular damage associated with the ion channel regulation of arterial smooth muscle.

The HERACLES Network was therefore created (Essential Hypertension: Network for the Analysis of Ion Channels in Arterial Smooth Muscle and Systematic Therapeutic Management). The network was financed as a network of groups from the previous and first call for applications from the Spanish Research Fund (G03/045) and was honoured with a distinguished mention in the December 2005 evaluation. The HERACLES Network received new funding in the second official call for applications from networks, and consolidated its position in this new phase with the incorporation of new groups and established new and even more ambitious objectives.

## BACKGROUND AND JUSTIFICATION

### Social and Health Importance of Arterial Hypertension and Ischaemic Heart Disease

In Spain, cardiovascular disease was the cause of 33.3% of all deaths in 2004 and is the primary cause of mortality in women (38%) and the second in men (29%).<sup>1</sup> Ischaemic heart disease is the primary specific cause of mortality in men and the second cause in women, after stroke.<sup>1</sup> Despite the fact that the incidence of such diseases appears stable, the ageing population and fall in the death rate has led to increased prevalence and pressure on the health services.<sup>2</sup>

AH affects approximately 30% of the Spanish population aged between 25 and 74, however this percentage significantly increases with age.<sup>3</sup> AH is a cardiovascular risk factor which increases mortality due to heart failure, heart disease, and stroke, among others.<sup>4</sup> In Spain in 2005, approximately 75% of hypertensive patients (arterial pressure [AP]  $\geq$ 140/90 mm Hg) knew about their condition (known AH) and of these,

approximately 50% received pharmacological treatment (treated AH). However, it is significant that 60% of the hypertensive patients treated did not have their AP under control (below 140/90 mm Hg).<sup>5,6</sup>

One of the network's groups has the largest biobank in Spain accredited by the Spanish National DNA Bank, with more than 20 000 DNA samples from healthy individuals and patients with ischaemic heart disease, cerebrovascular, and other cardiovascular diseases. This facilitates rapid studies on the prevalence and impact of any genetic variant in the ion channels of the smooth muscle in case studies and controls. Likewise, the know-how on cellular electrophysiology from other groups enables the 2-way transfer of information between groups, which therefore enables confirmation of whether the genetic variants detected in genome-wide scan association studies present any changes in their cell culture function.

### Multifactorial Pathophysiology of Essential Arterial Hypertension

Barely 10% of AH cases have a known cause and 90% of the remainder are included under the term essential AH.<sup>5</sup> As a result, research into the specific causes of AH is a necessity as well as a challenge. This is even more apparent in light of the encouraging advances in the fields of genomics, proteomics, pharmacogenomics, and pharmacoproteomics, since the management of essential AH (90% of hypertensives) would probably be more effective if the mechanisms and therapeutic targets at a molecular level were known.

Despite the fact that numerous genetic mutations seem to be involved in some types of hypertension associated with abnormalities of the bioavailability of mineral corticosteroids, this is not so clear in a large majority of patients with essential hypertension. In such cases, it is quite possible that genetic abnormalities associated with hypertension result in subtle changes which have a negative impact on elements which are crucial to the regulation of arterial resistance. Of course, in addition to these genetic factors, the influence of environmental factors must be also considered. The following genetic factors associated with AH (hereditary and constitutional), which are therefore non-changeable, are to be highlighted: family history of AH, age (which is the most significant predictor of AP in developed countries), male sex (even more significant up to the age of 45), and black race. Environmental factors, salt intake, nutritional factors, obesity, and alcohol consumption, etc, are all modifiable.

### Ion Channels and Regulation of Vascular Tone

The regulation of resistance to blood flow is directly dependent on the diameter of the vessels, in particular the small arteries and arterioles. The dynamics of

regulating vessel diameter are governed by the contractile force of smooth muscle fibres which form the vascular wall. The contraction of the smooth muscle is regulated by increases in intracellular  $\text{Ca}^{2+}$  concentration.

$\text{K}^+$  channels, such as MaxiK and  $\text{Kv}$ , as well as other more recently described channels, such as TRP, are key regulators of vascular tone. It is for this reason that the detection of possible mutations in genes which encode these proteins may have a huge significance on understanding the molecular pathophysiology of essential AH and consequently ischaemic heart disease and cerebrovascular disease. This new approach provides a different slant to that traditionally maintained, which established the study of renal function and its associated mechanisms as an almost exclusive priority in investigating the causes of AH. Results from the network itself confirm this theory, since they have shown that a variant of a MaxiK channel beta subunit presenting with a gain-of-function protects against diastolic AH at a population level.<sup>7</sup>

### Interaction Between the Endothelium and Vascular Smooth Muscle

Endothelial dysfunction is caused by a lack of vasodilator response through the nitric oxide system (NO),<sup>8</sup> which is generated in the endothelium by endothelial nitric oxide synthase enzyme activity (eNOS). Nitric oxide is what causes endothelium dependent vasorelaxation. Nitric oxide exercises its vasodilator action by stimulating soluble guanylyl-cyclase in the vascular smooth muscle next to the endothelium. The activity of the soluble guanylyl-cyclase generates cyclic guanosine monophosphate (GMP), which in turn stimulates a series of intracellular responses which finally result in the opening of the calcium-dependent  $\text{K}^+$  channels and therefore the relaxation of the muscle cell.<sup>9</sup> Direct activation of NO in the calcium-dependent  $\text{K}^+$  channels in the vascular smooth muscle, independent of cyclic GMP, has also been shown.<sup>10</sup> Various groups within the HERACLES Network are investigating these channels, dysfunctions of which would seem to partly explain essential AH.

### Role of Oestrogen In the Regulation of Endothelial Function and Vascular Tone

Oestrogen undoubtedly has a clear influence on endothelial function and vascular tone. The differences between men and women in terms of morbidity and mortality associated with cardiovascular disease have mainly been attributed to the differences in the quantities of sex hormones between both sexes.<sup>11</sup> It is well documented that the menopause and subsequent suppression of oestrogen increases the risk of cardiovascular disease in women. However, the impact

of hormone replacement therapy in vascular disease is not so clear.<sup>12</sup> Replacement therapy does not influence the incidence of ischaemic heart disease in postmenopausal women, however it clearly increases the risk of ischaemic stroke<sup>13</sup> and cognitive deterioration.<sup>14</sup>

### STRUCTURE/ORGANOGRAM. MANAGEMENT BODIES WITHIN THE HERACLES NETWORK

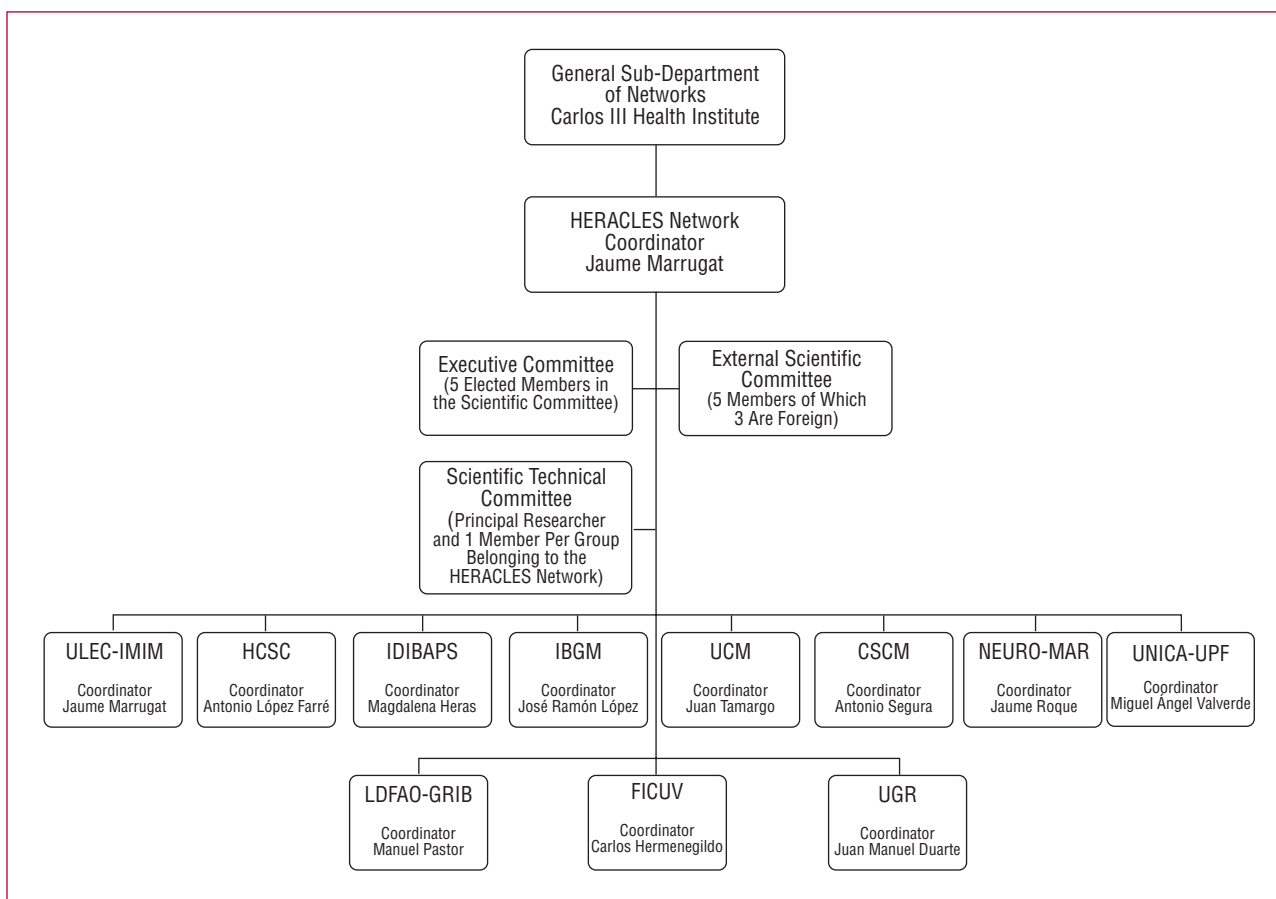
The coordination structure aims to make all of the network's activities both operational and efficient. The elements forming the structure are as follows: a Network Coordinator, who is the main contact for the General Sub-Department of Networks (Subdirección General de Redes); an Executive Committee formed by 4 researchers and the Coordinator, elected by the heads of each of the participating Groups; and a Scientific-Technical Council formed by 1 or 2 representatives of each Group belonging to the network, 1 of which should be the principal researcher. When it was created the network appointed an External Scientific Council, formed by 5 researchers of international renown and prestige, 3 of which are foreign (the members appear at the end of the list of HERACLES researchers). The Network's Coordination structure is outlined in Figure 1. The network's research project is conceived as a set of interrelated and coordinated research lines, managed by a line coordinator. Each group contributes its field of knowledge, experience and resources, some of which are made available to the network to help achieve the project objectives. A series of horizontal programmes based on the central platforms and structures have been made available to the different coordinated research lines.

### OBJECTIVES

The configuration of the HERACLES Network in its second phase has been developed with the objective of strengthening, on the one hand, the presence of groups whose main research area focuses on ion channels in the cardiovascular region and, on the other, that of groups involved in cardiovascular epidemiology and population genetics, with the largest biobank in Spain. The network now includes new groups involved in basic research within the field of the endogenous and pharmacological regulation of vascular function, as well as new clinical groups, thus facilitating a transfer of knowledge from bedside-to-bench and its reverse, bench-to-bedside.

The network's central scientific objective is the study of the genetics and function of different molecules which play a key role in regulating vascular tone and in situations directly related to AH: the myocardial response to ischaemic and hypertensive situations, cardiac arrhythmia, and stroke.

The central objective has been broken down into 4 types of strategic action:



**Figure 1.** Coordination Structure for the HERACLES Network. Abbreviations in Table.

1. The study of 3 large families of ion channels, whose participation in vascular physiology has been proven, whether by one of the groups belonging to the network or other researchers.

–  $\text{Ca}^{2+}$  (KCNN) and voltage (kV) dependent  $\text{K}^+$  channels, both of which play an important role in the

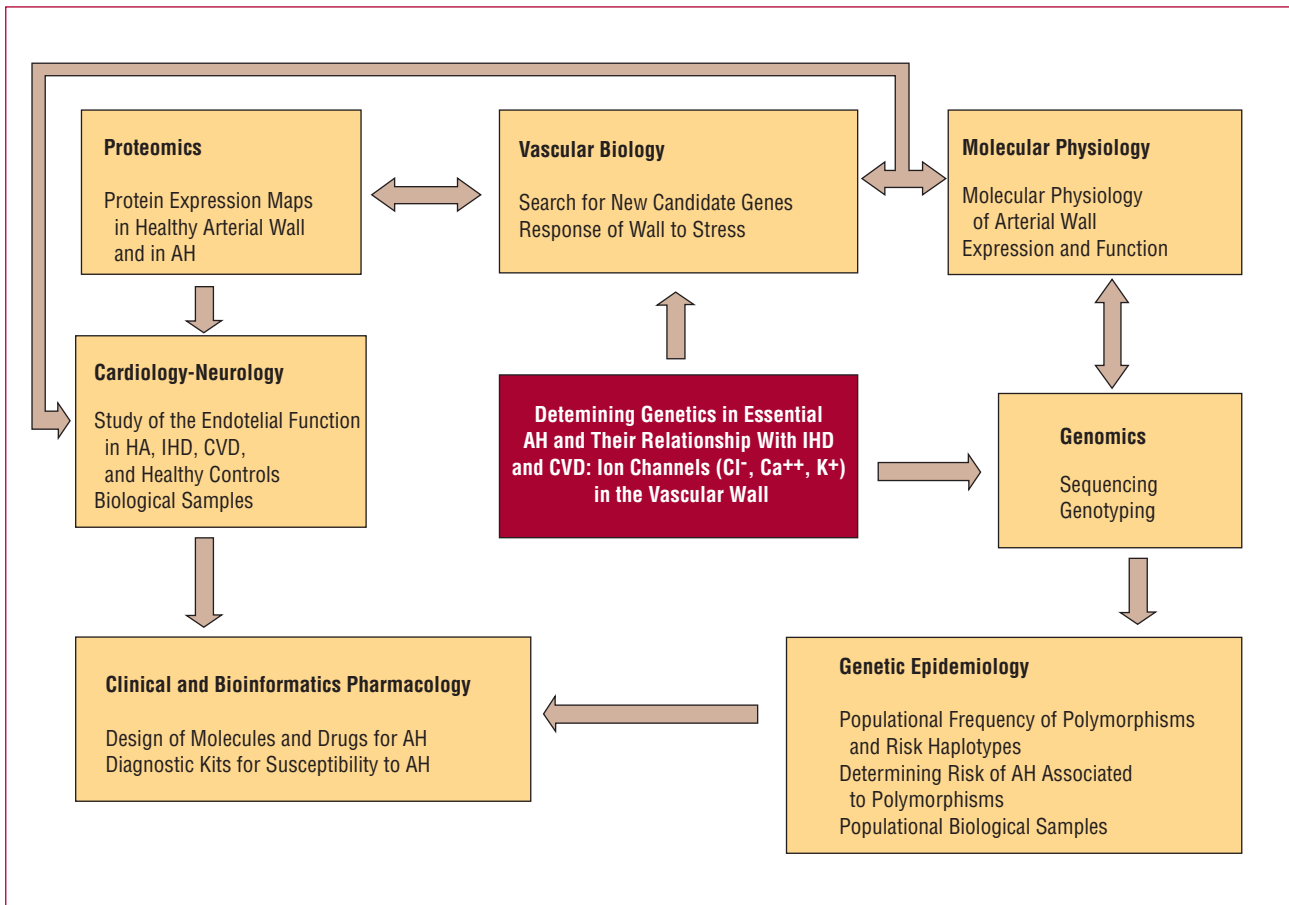
hyperpolarisation of the membrane's potential and therefore in reducing the excitability and tone of the arterial smooth muscle

– TRP cation channels. TRP channels have recently acquired huge significance in intracellular  $\text{Ca}^{2+}$  regulation. Their involvement in the physiology of the endothelium (where they are involved in releasing relaxation factors)

**TABLE. List of Groups Participating in the HERACLES Network In 2007 and Their Principal Researchers**

Group and Autonomous Community	Acronym	Principal Researcher
Unitat de Lípids i Epidemiologia Cardiovascular, Institut Municipal d'Investigació Mèdica, Barcelona, Catalonia	ULEC-IMIM	Jaume Marrugat
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Universidad Complutense, Madrid	UCM	Juan L. Tamargo
Servicio de Neurología, Hospital del Mar, Barcelona, Catalonia	NEURO-MAR	Jaume Roquer
Unidad de Canalopatías-Universidad Pompeu Fabra, Barcelona, Catalonia	UNICA-UPF	Miguel Ángel Valverde
Laboratorio de Diseño de Fármacos Asistido por Ordenador-Unitat de Recerca en Informàtica Biomèdica, Catalonia	GRIB	Manuel Pastor
Fundación Investigación del Clínico y Universidad de Valencia, Valencia	FICUV	Carlos Hemenegildo
Universidad de Granada, Andalucía	UGR	Juan Manuel Duarte
Instituto de Ciencias de la Salud de Castile-La Mancha, Talavera de la Reina, Castile-La Mancha	ICSCM <sup>a</sup>	Antonio Segura

<sup>a</sup>Associated Clinical Group.



**Figure 2.** Outline of interaction between the HERACLES network's different collaborative, multidisciplinary, and coordinated actions, based on the central theme of the mechanisms of essential AH. IHD indicates ischaemic heart disease; CVD, cardiovascular disease; AH, arterial hypertension.

and the vascular smooth muscle (where they are involved in contraction and proliferation) are of particular interest to this project

–  $\text{Ca}^{2+}$  dependent  $\text{Cl}^-$  channels. These channels participate in the depolarisation (and subsequent contraction) of the smooth muscle in response to different agonists. Unlike other channels, whose modular bases are well known, only 2 candidates,  $\text{ClCa}$  and bestrophin, are known to contribute to the molecular architecture of these channels

2. Study of protein expression maps in plasma and cardiovascular tissue, both in healthy individuals, as well as patients with different cardiovascular conditions, and their relevance in pharmacological treatment.

3. Studies of the effect and mechanisms of the action of organic substances (flavonoids) in the vascular targets involved in the transport of ions and response to oxidative stress.

4. Identification of extreme clinical phenotypes and search for biological risk markers, prognosis and response to treatment.

Figure 2 outlines the interaction between the HERACLES Network's different collaborative,

multidisciplinary and coordinated actions, based on the central theme of the mechanisms of essential AH.

In order to optimise the material and human resources available and make the network's actions function, a group of horizontal programmes have been developed to provide a service to all groups within the network and help achieve the general objectives of the strategic plan, based on the main research lines. Of course these general objectives are established in more detail within the specific projects in which the groups involved in this line of research participate, for which they have requested financing from bodies who award grants for independent research, in Spain, Europe or Internationally.

## RESULTS

The HERACLES Network was originally created in 2003 and was formed by different research groups. It was associated with a research project and scientific production in which the contribution of financing for the network was significant. Since its formation, the network's work has led to the publication of more than 60 articles in prestigious international periodicals<sup>6,7,14-70</sup> (which can be accessed via <http://www.redheracles.net>), the financing

of more than 90 national competitive projects (of which the grant awarded to the network for the DNA Biobank by the Spanish National DNA Bank is to be noted) and participation in 6 international projects.

### Ion Channels

In its first phase the network worked successfully on studying the genetics and functioning of the 2 subunits which form the MaxiK<sup>+</sup> Potassium Channel. The project was able to establish that a genetic characteristic of this channel was associated to a lower probability of developing hypertension.<sup>7</sup> The network's contribution on the characterisation of the contractile and proliferating phenotype of the arterial smooth muscle and the role of the Kv potassium channels in this process has also been related to the functioning of the channels in the membrane of the arterial smooth muscle.<sup>16</sup>

A genetic analysis of a representative population of almost 4000 individuals in the province of Girona identified a genetic polymorphism, which was present in 20% of the people studied. This polymorphism caused a mutation in the human  $\beta_1$  subunit (KCNMB1) of the MaxiK<sup>+</sup> channel (a glutamic acid to lysine substitution at position 65, E65K), which is associated to a lower risk of moderate and severe diastolic hypertension among the population studied. This functional analysis shows that the E65K polymorphism leads to increased sensitivity to CA<sup>2+</sup> and voltage in the MaxiK<sup>+</sup> channel (gain-of-function), which favours arterial relaxation and may explain the protective action against moderate to severe diastolic hypertension.<sup>7</sup> A subsequent study showed that the protective action of the E65K polymorphism against diastolic hypertension was regulated by age and sex: the results indicate that the association of the E65K polymorphism with a reduced risk of moderate-severe diastolic hypertension is only observed in women of a more mature age (possibly menopausal). However, functional studies show that this age-related sexual dimorphism of the protective action of the E65K mutation against hypertension is independent of the acute modulation of the MaxiK<sup>+</sup> channel activity by oestrogen, both directly (due to the union of oestrogen to the channel) and indirectly (via the phosphorylation of the channel by cyclic GMP dependent protein kinase). In addition, clinical monitoring of the study population over 5 years also indicates the clear protective action of the E65K polymorphism against cardiovascular disease (myocardial infarction and stroke).<sup>16</sup> The study is currently being continued with the characterisation of new genetic variants identified in the *KCNMA1* gene (which encodes the alpha subunit of the MaxiK<sup>+</sup> channel) and their association with cardiovascular disease.

Also of particular interest in the physiology of the vascular smooth muscle is the characterisation of the expression pattern of Kv channels in human uterine arterial smooth muscle cells, both in messenger RNA

and proteins, and their functional contribution to cellular excitability via electrophysiological and pharmacological studies. The results indicate the existence of a significant change both in the profile expression of Kv channels and in the electrophysiological properties of the cells in response to the phenotype change. It is to be noted that dedifferentiation is associated to an increase in the expression and functional contribution of Kv3.4. Moreover, the blocked expression of this channel leads to a reduction in the speed of cellular proliferation. These results indicate that the Kv3.4 channel may be a factor involved in the proliferation of vascular smooth muscle, and may therefore constitute a therapeutic target for the treatment of disease related to intimal hyperplasia such as arteriosclerosis, AH and restenosis following angioplasty.<sup>17</sup>

### Endothelial Dysfunction

Studies have been carried out on cytotoxicity mediated by oxidative stress with amyloid beta peptide (ABP) and hydrogen peroxide in different cell types of the human vasculature. Toxicity induced by both toxics in the vascular endothelium was completely reversed in the presence of a soluble vitamin E analogue. This toxicity was reversed with beta-estradiol in vascular myocytes and neurons, but not in the endothelium. The lack of endothelium protection seems to be due to the increased production of NO and subsequent nitrotyrosination of cellular proteins in the presence of estradiol and a pro-oxidant situation.

The MERCED study (Menopause and Raloxifene in Ischaemic Heart Disease: Effect on Endothelial Dysfunction) is a phase IV multi-centre and national clinical study aimed at analysing the effect of treatment with raloxifene on endothelial function in the peripheral blood flow and the biological markers of inflammation and thrombotic risk. The administration of raloxifene did not induce any significant effect on endothelium-dependent or independent vasodilatation. In terms of thrombosis markers, raloxifene led to changes in the quantity of fibrinogen and the generation of thrombosis and fibrinolysis. Likewise, changes in the quantity of CD40 were also observed. An increase in fibrinolytic activity was observed in women with the K allele of the E65 polymorphism in the *KCNMB1* gene. In general, treatment with raloxifene changes the thrombotic risk profile in a population of menopausal women with high risk heart disease.

### Proteomics

Another important research area for the HERACLES Network is the development of a protein map in patients suffering from acute coronary syndrome, as well as the study of the effect of oestrogen on the protein map of the endothelium and vascular smooth muscle exposed to situations of oxidative stress.<sup>17,18</sup>

## Patents

It is worth noting that as a result of the network's work, the first international patent has been granted for a possible diagnostic kit related to the findings in the publication of the polymorphism in the *KCNMB1* gene,<sup>7</sup> "Método y kit para la detección del riesgo de padecer hipertensión/Method and Kit for Detecting the Risk of Hypertension" (patent application presented on March 29 2004; application No. 200400883). The patent includes the method for prognosing or diagnosing essential hypertension in humans, including the detection of the presence or absence of the polymorphism in the *KCNMB1* gene. The patent includes methods, equipment and kits for diagnosing and prognosing essential hypertension in humans.

## CONCLUSIONS

The identities of genetic variants that are potentially involved in the development of essential AH are still unknown. This is particularly important since understanding the molecular mechanisms of hypertension may provide new and more specific pharmacological tools, in addition to significantly helping the early diagnosis of a disease that affects more than 30% of the adult population in Spain. Such approaches would help establish individualised anti-hypertensive treatments contributing to the reduction of the risk of morbimortality due to cardiovascular disease.

In any case, the study of candidate genes and genome-wide scan association related to the mechanisms proposed by the HERACLES Network is one of the leading approaches to studying the factors determining abnormally high AP. For several years, the primary focus has been on loci responsible for regulating the Na<sup>+</sup> ion. However, more recently, new functional data on angiotensinogen has provided specific evidence of the role of aldosterone and sodium channels in regulating AP. All of the above represent small advances in explaining essential hypertension, which is one of the main causes of ischaemic heart disease and stroke.

The study of genes operating in the walls of the arteries which determine resistance to blood flow and, ultimately, vascular tone is the main objective for creating this network of research groups. The starting point for this work is the fact that there is sufficient documentation stating that some ion channels (the MaxiK<sup>+</sup> channels) have a significant regulating function in vasomotor tone. The inclusion of the molecular study of other ion channels involved in vascular tone in the present project, as well as the possible role of genetic factors related to the expression of oestrogen receptors, significantly increases the number of potential candidates for participation in the pathogenesis of essential hypertension. In this way, the characterisation of possible genetic variants that modify the proper functioning of these channels represents

a significant advance in terms of knowledge of the molecular bases of the physiology of hypertension. These molecules are also very susceptible to interaction with oestrogen and, possibly, pharmacological and environmental factors, which significantly increases the scope of interest in such molecules.

Proteomics is another important area in helping develop knowledge of the molecular mechanisms involved in creating and developing conditions such as AH, myocardial ischaemia and atrial fibrillation or even discovering how the proteome is modified in a population according to their cardiovascular risk factors or lifestyles.

It is also important to highlight the role of pharmacoproteomics within this area, since this enables the identification of changes to the protein expression map in plasma or different cells following pharmacological treatment in patients. For example, this provides information on the pleiotropic mechanisms of drugs. An example of this is a project carried out in collaboration between three of the network's groups, in which they identified modifications in the plasma proteome in patients with moderate hypercholesterolemia following treatment with statins<sup>19</sup>. Pharmacoproteomics also helps identify biomarkers for a better or worse pharmacological response. For example, in the same year the network identified a biomarker to predict the response to the inhibition of platelet activity using aspirin in patients with established myocardial ischaemia.<sup>21</sup>

Within the HERACLES Network, the generation of new knowledge is strengthened by the possibility to apply this knowledge in the development of genetic screening and new anti-hypertensive drugs in collaboration with companies from the pharmaceutical sector. The relationship between companies and the academic world within the field of pharmacology and the design of new drugs is a priority in developed countries wanting to maintain competitiveness in their economies. This relationship promotes translational research, which facilitates the incorporation of technological innovation into companies, thus increasing their competitiveness. This will help make the most of researchers' efforts in applied research via patents.

In summary, the HERACLES Cardiovascular Network has sufficient resources for a multidisciplinary approach to a complex and significant health problem such as essential AH: cardiologists, neurologists, vascular biologists, molecular physiologists, epidemiologists, biochemists, and geneticists, who work together to identify genes and proteins related to the ion channels. Their objective is to develop new pharmacological strategies for patients with AH and diseases associated with this condition, such as ischaemic heart disease and cerebrovascular disease. Moreover, pharmacogenomics and proteogenomics enable the identification of selective anti-hypertensive treatment, which is more efficient and has fewer adverse effects and may be adjusted to the genetic characteristics of each patient.

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