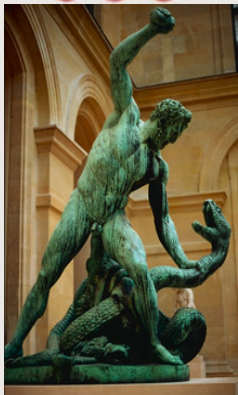




RIC

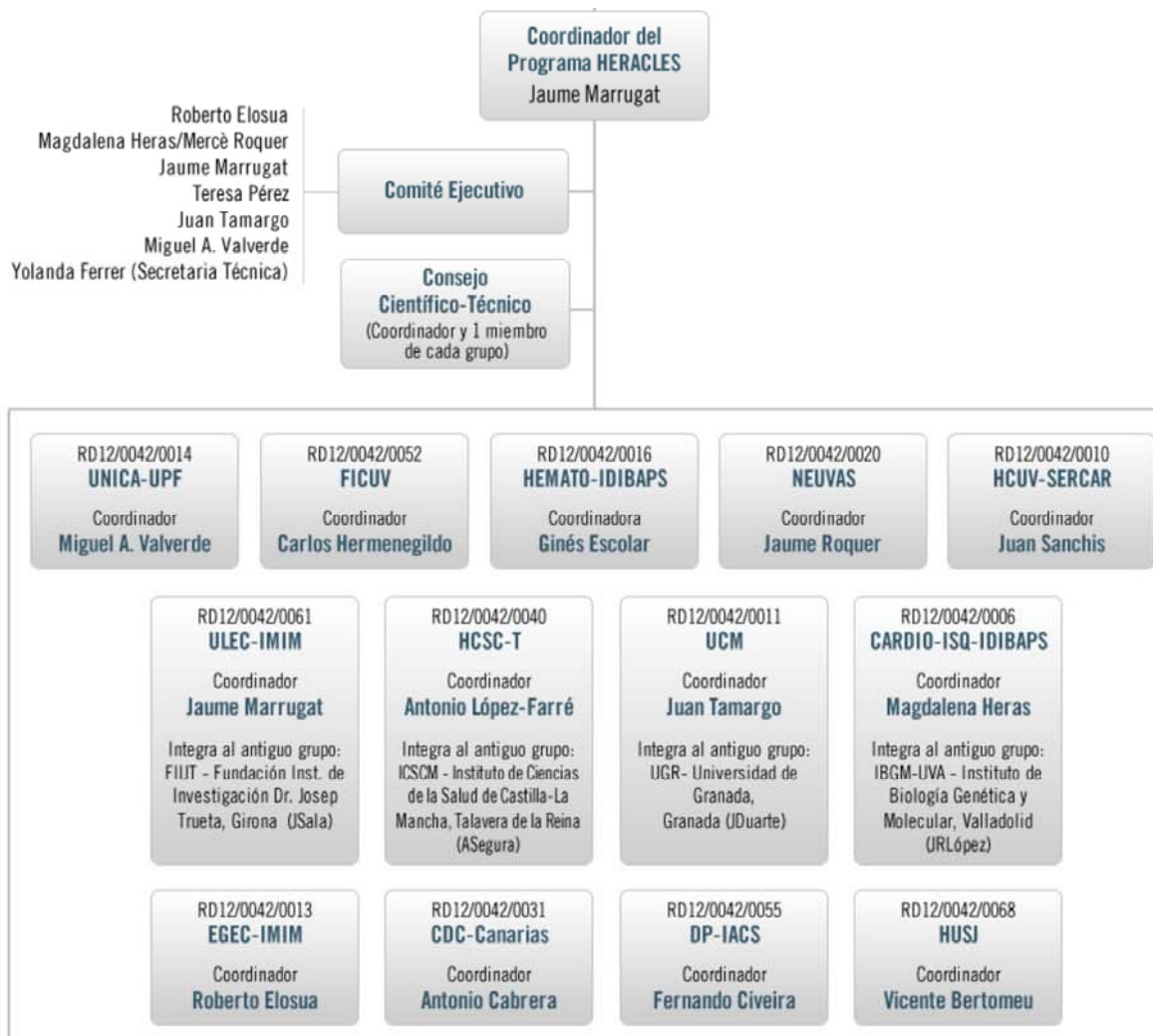
red de investigación cardiovascular

Scientific Program 7 Cardiovascular Prevention & Mechanisms of Hypertension



HERACLES (*Hipertensión Esencial: Red de Análisis de Canales iónicos y Ligandos de Estrógenos Sintéticos*)

Cardiovascular Prevention & Mechanisms of Hypertension



Background for primary prevention of coronary heart disease

- Greatest cause of death in developed countries. In ~35% of cases its onset symptom is sudden death.
- Most cases are related to lifestyle & other modifiable factors, whose improvement results in reduced CHD incidence.

Background: cardiovascular consequences of hypertension

- More than 30% of general population aged 25 to 74 years suffer hypertension (HT) in Spain
- After 74 years of age the prevalence of HT is even higher
- HT is associated to increased morbidity from
 - Coronary disease (Attributable risk: 15%)
 - Stroke (Attributable risk: 50%)
 - Congestive Heart Failure
 - Target organ damage

Background: cardiovascular consequences of hypertension

- More than 90% of hypertension is of unknown origin
- Less than 25% of hypertension patients have a blood pressure under control
- More than 40% of patients are unaware of their hypertension
- Some risk factors are known, but genetic and molecular mechanisms remain to be disentangled

Under pressure: the search for the essential mechanisms of hypertension

Thomas M Coffman^{1,2}

High blood pressure, or hypertension, is a very common disorder with a substantial impact on public health because of its associated complications. Despite the high prevalence of essential hypertension and years of research, the basic causes remain obscure. Here I review recent advances in understanding the pathophysiology of hypertension. I present a general overview of the field and, by necessity, use broad strokes to portray recent progress and place it in context. For this purpose, I use illustrative examples from the large number of important developments in hypertension research over the last five years. The intent of this review is to provide a sense of where the field is progressing, with an emphasis on work that sheds light on pathogenic mechanisms and that is therefore likely to inform new translational advances.

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Coffman TM. Nature Genetics 2011; 17: 1402.

HERACLES Vision of CV diseases

- Objective year 2100 medicine:
 - **Predict** with no error in healthy population
 - **Prevent** 100% of future cases when accessible
 - **Cure** clinical cases
 - **Revert** subclinical cases
- Medicine in a closer future (the four “**P**”)
 - **P**redictive, **P**reventive, **P**ersonalized & **P**articipative

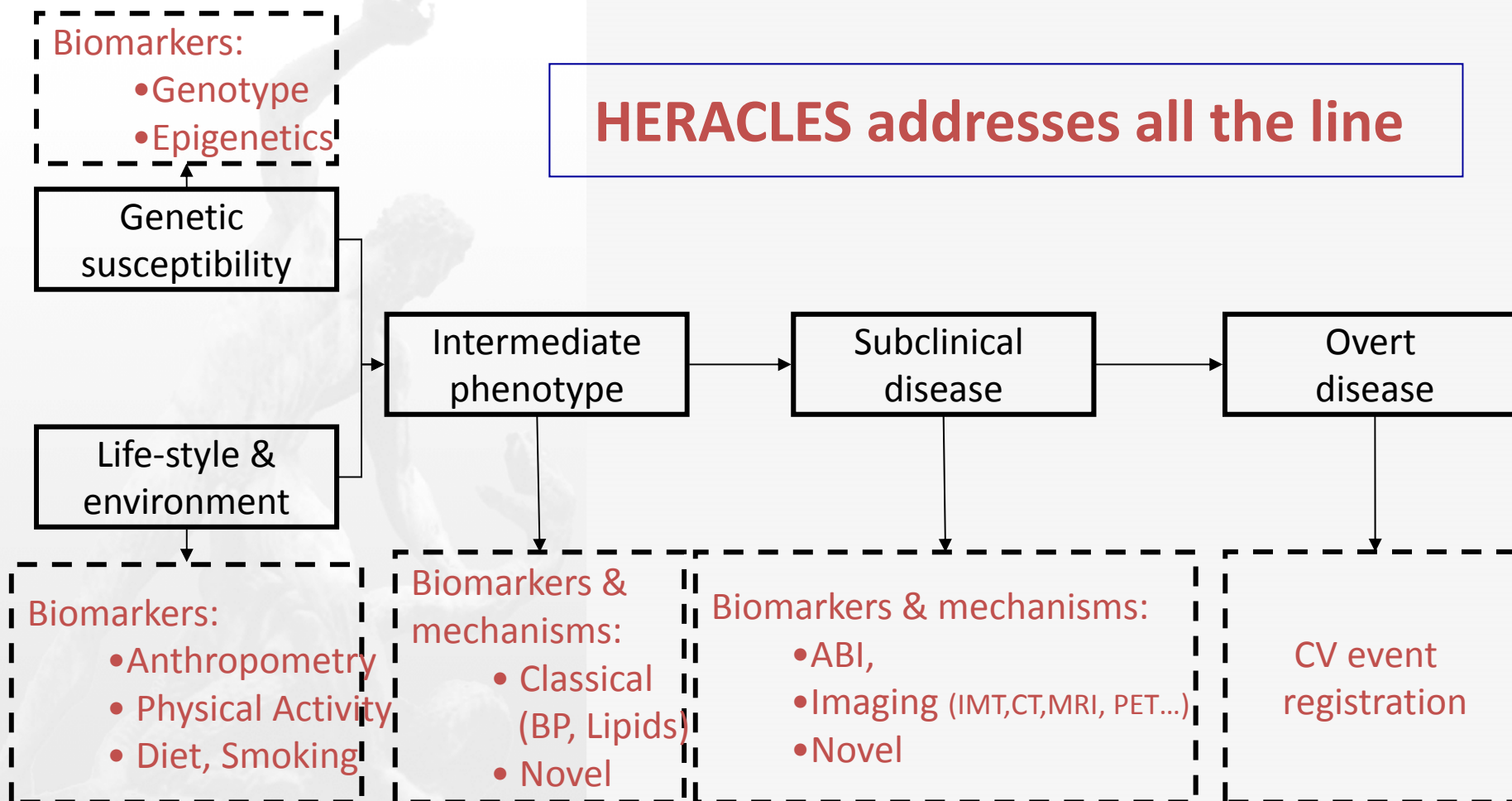
FOCUSed Vision of CV research

In HERACLES we look for

- **Feasibility** (technologic, know-how, economic),
- **Oportunity** (novelty, originality, patentability),
- **Causality** (mechanisms, function),
- **Utility** (translation, innovation, development),
- **Simplicity** (cost-effectiveness, platforms use)

of the work-packages & projects involved in our objectives.

Cardiovascular disease risk line



Prevention of cardiovascular diseases & study of hypertension mechanisms

General Objective

To study the mechanisms of hypertension in the development of atherosclerosis and related cardiovascular diseases.

WP1: Scientific coordination

Objetives

1. Improvement of cardiovascular risk functions for primary prevention.

WP2: Analysis of cardiovascular disease biomarker predictive and reclassification capacity in cohort studies & mendelian randomization trials. **R Elosua**

WP2 Projects

1. Improvement of CVD risk function in primary prevention of CVD. J Marrugat.
2. Genetic and environmental determinants of blood pressure. R Elosua
3. Contribution of epigenetic modification to senescence, hypertension and atherosclerosis. Ginés Escolar.

Objetives

2. Development of new predictive functions of prognosis of acute coronary syndrome (ACS), stroke & congestive heart failure (CHF)

WP3: Biomarker & other prognostic factors in ACS, stroke & CHF patients. **M Heras/M Roquer**

WP3 Projects

1. Biomarkers of prognosis for ACS without ST elevation (NSTEACS). J Sanchis
2. Predictive function & biomarkers for patients with cerebrovascular diseases: The BASICMAR Registry. Project. J Roquer

Objetives

3. Analysis of the metabolic pathways involved in the impact of hypertension on atherosclerosis & related CVD

WP4: Studying endothelial function and myocyte regeneration. **J Tamargo**

WP5: Vascular smooth muscle cell and cardiac myocytes in hypertension & cardiovascular diseases. **M Valverde**

WP4 Projects

1. Endothelial progenitor cell biomarkers for endothelial repair after CVD. G Escolar
2. Renal graft and endothelial dysfunction by levels of endothelial cell microparticles & inflammation biomarkers. C Hermenegildo
3. Study of the mechanisms for menopause- and diet-associated endothelial dysfunction. C Hermenegildo
4. Impact of aging on vascular inflammation. J Tamargo

WP5 Projects

1. Electrical remodeling associated with atrial fibrillation and the hypertensive phenotype. J Tamargo
2. Ion channels and Ca²⁺ signals in CVD. M Valverde


Strategic objectives

- To design projects that involve other RIC Programs.
- To use the COLMAH collection of human artery samples.
- To share the high throughput DNA extraction system with all RIC groups.
- To exploit the population cohort studies available in HERACLES.

HERACLES Renewed & RIC-adapted web site

www.redheracles.net


Castellano
Login Contact Links



PROGRAMA HERACLES
Red de Investigación Cardiovascular (RIC)

About us Research groups Work Packages Publications Services Patents and tech transfer Professional development Study-related forms Heart health info


Services



High Throughput Nucleic Acid Extraction and Normalization

A high throughput DNA extraction service is available to all researchers in Europe.


[More >>](#)




Human Artery Samples (COLMAH-HERACLES)

The HERACLES Network places its collection of human arterial samples at the disposition of HERACLES Network researchers and others for expression studies and functional studies, through collaboration and service agreements.


[More >>](#)



COLLABORATIVE PROJECTS



TRANSLATIONAL AND TRANSFER ACTIVITIES



COLLABORATIVE PROJECTS

News

Reunión Científica Programa HERACLES 2013

Estamos preparando la Reunión Científica HERACLES 2013 que tendrá lugar el día 30 de Mayo de 2013 en Girona, coincidiendo con la celebración del 35º Aniversario del estudio REGICOR.

Ampliar información, programa de la jornada y formulario de inscripción (+)

La función de riesgo cardiovascular REGICOR-Framingham aterriza en las plataformas móviles para que sus usuarios puedan disponer de todas sus ventajas


Descarga nuestra aplicación para móviles, más cerca, más fácil.

Seguramente ya conoces la función de riesgo coronario adaptada de REGICOR que se utiliza en diversas comunidades autónomas actualmente. Posiblemente te interesará saber


Descarga nuestra versión para Iphone del GRANMO

Como novedad te presentamos también la versión para Iphone del GRANMO, que es un programa para calcular el tamaño muestral necesario para las pruebas estadísticas que se utilizan en la investigación biomédica, y cada vez que se requiere un cálculo del tamaño muestral para asegurar una potencia estadística en particular.


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FEDER



IMIM

COLMAH Platform

WHAT IS COLMAH?



COLMAH[®] is the biobank of human arterial tissue collected by the HERACLES[®] Program of the Spanish Cardiovascular Research Network, linked to a cross-referenced database with advanced search capacity. The goal is to offer an exceptional tool for basic, applied and translational research on the epidemiology, pathophysiology, diagnosis and treatment of cardiovascular diseases.

KEY CHARACTERISTICS

- The largest collection in Spain of human vascular samples, from a wide variety of vascular beds.
- Pertinent clinical data from all tissue donors.
- Rigorous protocols.
- State-of-the-art technologies, including:
 - Cryopreservation of arterial rings for morphometric & immunohistochemical studies.
 - RNeasy[®] storage of arterial tissues for sequential extraction of RNA, DNA & proteins from endothelial or vascular smooth muscle cells.
 - Extraction of primary cell lines from endothelial & smooth muscle explants for use in expression & functional studies.

WHY COLMAH IS UNIQUE

COLMAH develops primary cultures from endothelial and vascular smooth muscle cells from healthy donors and from patients with vascular diseases. These cells are expanded, cryopreserved and identified with a barcode that links each sample to donor characteristics in a regularly updated central database. This powerful, searchable combination of tissue and data holds enormous potential for research in the field of vascular physiology and pathophysiology.

*COLMAH: Colección de Muestras Arteriales Humanas
 †Human Artery Samples collection
 ‡HERACLES: Herencias Estratégicas. Red de Análisis de Cerebro Vascular de la musculatura Liza arterial y su Explicación Impulsora Sistémica. (Essential Hypertension Analysis of Liza Channels Mechanisms in Arterial Smooth Muscle and Their Systemic Therapeutic Applicability).

COLMAH AT A GLANCE



- Patients
- Organ donors
- Umbilical cords

DONORS



- DNA
- RNA & proteins
- Frozen tissue
- Cell lines
- Clinical data (patients, healthy donors, newborns)

SAMPLES & DATA



- High-capacity freezers for sample storage
- Database management
- Statistical analysis
- Coordination of secure sample shipment

STORAGE ANALYSIS & COORDINATION



- Basic biomedical sciences
- Genetic expression
- Phenotype-genotype correlations
- Diagnostic & treatment biomarkers
- New therapeutic targets and drugs
- Personalized medicine

BIOMEDICAL RESEARCH APPLICATIONS

COLMAH
HUMAN ARTERY SAMPLE COLLECTION



Unión Europea

Fondo Europeo de Desarrollo Regional
"Una manera de hacer Europa"

High throughput DNA extraction platform

DNA extraction

Human Artery Samples

High Throughput Nucleic Acid Extraction and Normalization - RICAD-CARIN and RICAD-EGEC Research Groups Laboratory -



The RICAD-CARIN and RICAD-EGEC Research Groups molecular biology laboratory offers automated or manual high-throughput human genomic DNA extraction from:

- ▶ Fresh or frozen whole blood (initial volume of 2 ml to 10 ml)
- ▶ Buffy coat (volume of 1 ml to 2 ml)

After extracting the DNA, the RICAD-CARIN and RICAD-EGEC Research Groups Laboratory offers the following additional procedures:

- ▶ DNA purification to eliminate protein
- ▶ DNA aliquotating
- ▶ Quantification of DNA concentration
- ▶ DNA normalization
- ▶ Sample preparation for quantitative PCR

Contact us about the availability of these procedures:

- ▶ RNA extraction from several tissues
- ▶ RNA extraction from internal cheek swab

Take advantage of our experience and technology:

- ▶ Excellent service and fast turnaround for a large volume of samples
- ▶ Cost savings from our know-how and equipment
- ▶ Complete sample tracking with any barcode system
- ▶ Quotation for various sample types tailored to your needs

ISO/IEC 17025: 2005 for assay and calibration laboratories

- Design & Implementation of a Quality System based on that International Standard since 2009
- Internal Audit passed on June 2012
- Independent audit by ENAC of our quality system performed on 15/05/2013

ISO/IEC: International Standard Organization/ International Electrotechnical Commission

ENAC: *Entidad Nacional de Acreditación*

Group participation in HERACLES work-packages & projects

HERACLES Programme 7 of RIC

WORK PACKAGE	1	2	3	4	5	6	7	8	9	10	11	12	13
	ULEC-IMIM	UNICA	FCIUV	CARDIO ISQ IDIBAPS	HEMATO IDIBAPS	HCSC-T	NEUVAS	UCM	HCIUV-SERCAR	EGEC-IMIM	CANARIAS CDC	DPIACS	HUSJ
WP1 Project coordination. Jmarrugat IMIM	XX	X		X				X		X			
WP2 Analysis of predictive and reclassification capacity of CVD biomarkers in cohort studies & mendelian randomization trials. WP2 Coordinator: R Elosua	X	X			X	X	X			XX	X	X	
SP1 Improvement of CVD risk function in primary prevention of CVD. Project coordinator: J Marrugat.	XX					X				X	X	X	
SP2 Genetic and environmental determinants of blood pressure. Project coordinator: R Elosua	X	X				X	X			XX	X	X	
SP3 Contribution of epigenetic modification to senescence, hypertension and atherosclerosis. Project coordinator: Ginés Escolar.					XX		X			X	X		
WP3 Biomarkers & other prognostic factors in ACS, stroke & CHF patients. WP3 Coordinator: M Heras	X	X		XX	X	X	X		X	X			X
SP1 Predictive functions & Biomarkers of prognosis for ACS without ST elevation (NSTEMACS). Project coordinator: J Sanchis	X			X	X	X			XX	X			X
SP2 Predictive function & biomarkers for patients with cerebrovascular diseases: The BASICMAR Registry. Project coordinator: J Roquer	X	X					XX			X			
WP4 Endothelial function and vascular regeneration. WP4 Coordinator: J Tamargo	X		X	X	X	X	X	XX	X	X	X		X
SP1 Endothelial progenitor cells as biomarkers for endothelial repair after CVD. Project coordinator: G Escolar.		X	X	X	XX		X		X				X
SP2 Renal graft and endothelial dysfunction by levels of endothelial cell microparticles and inflammation biomarkers. Project coordinator: C Hermenegildo	X		XX		X					X			
SP3 Study of the mechanisms for menopause- and diet-associated endothelial dysfunction. Project coordinator: C Hermenegildo	X		XX	X	X						X		
SP4 Impact of aging on vascular inflammation. Project coordinator: J Tamargo			X	X		X		XX			X		
WP5 Ion channels in the vasculature and CVDs. WP5 Coordinator: Miguel A Valverde		XX		X	X		X	X	X				
SP1 Electrical remodelling associated with atrial fibrillation and the hypertensive phenotype. Project coordinator: J Tamargo		X		X				XX	X				
SP2 Ion channels and Ca ²⁺ signals in CVD. Project coordinator: M Valverde		XX		X	X		X						

Deliverables Programme 7 HERACLES

DELIVERABLES Programme 7		2013												2014												2015												2016											
		september	october	november	december	january	february	march	april	may	june	july	august	september	october	november	december	january	february	march	april	may	june	july	august	september	october	november	december	january	february	march	april	may	june	july	august	september	october	november	december								
WP2 - J Marrugat Project 1	D1	Baseline descriptive analysis of pooled database by sex and cohort																																															
	D2	Lifestyle effect on CVD/hypertension occurrence																																															
	D3	Biomarker effect on CVD/hypertension occurrence (Case-cohort substudy)																																															
	D4	Report on AROC and reclassification capacity of all new biomarkers tested																																															
WP2 - R Elosua Project 2	D1	Report baseline descriptive analyses by sex and cohort of the pooled database and flow-chart of the 10-year follow-up																																															
	D2	Report the role of interaction of genetic & environmental factors on BP & stroke risk																																															
	D3	Report on hypertension & risk/protective factor interaction on CVD development																																															
WP2 - G Escobar Project 3	D1	Report of potential epigenetic biomarkers associated with cardio- and cerebrovascular risks																																															
	D2	Description of the effect of biomarker and epigenetic modifications in micro-macrovascular models																																															
	D3	Report on potential preventive / modifying strategies																																															
WP3 - J Sanchis Project 1	D1	Report on efficacy, safety and effectiveness of invasive management in patients with NSTEMI and comorbidities																																															
	D2	Report on EDM numbers, proteomic maps, drug response by platelet-derived megakaryocytes proteomic maps																																															
WP3 - J Roquer Project 2	D1	Report baseline descriptive analysis of the pooled database and flow-chart																																															
	D2	Report of analyses of clinical and neuroimaging data, nutrition habits and genetic information on stroke recurrence and prognosis																																															
	D3	Creation of predictive models for stroke risk and outcome																																															
WP4 - G Escobar Project 1	D1	Report of acute events patient data																																															
	D2	Evaluation of EPC functionality																																															
	D3	Report on possible correlations between biomarkers analysed, CVD risk and rates of ventricular remodelling																																															
WP4 - C Hermenegildo Project 2	D1	Report on the recipients' baseline characteristics																																															
	D2	Report on donor's endothelial cell behavior when exposed to recipient's serum																																															
	D3	Final report with follow-up and laboratory data																																															
WP4 - C Hermenegildo Project 3	D1	Mechanisms for vascular reactivity in females rodent models																																															
	D2	Analysis of endothelial cell pathways modified by sex hormones																																															
	D3	Report on effects of dietary intervention.																																															
WP4 - J Tamargo Project 4	D1	Report on the different vascular responses produced by endothelial mediators under an inflammatory status derived from aging in SAM																																															
	D2	Report on biomarkers of endothelial dysfunction and inflammation produced by aging and menopause in cultured cells and SAM																																															
	D3	Report on the influence of age in protein expression related to inflammation and energetic metabolism in human arteries and on protein biomarkers in platelet and plasma from patients with CVD																																															
	D4	Report on the effects of ageing on biomarkers of endothelial function, vascular antioxidant systems and vascular structure and function, and their modulation by dietary (polyphenols, probiotics) and pharmacological (PPAR α agonists) interventions																																															
WP4 - J Tamargo Project 1	D1	Report on the characterization of Na ⁺ , Ca ²⁺ and K ⁺ channels in atrial myocytes from patients in sinus rhythm and in AF and their endogenous and pharmacological modulation																																															
	D2	Report on the identification of ion channel expression patterns in VSMC associated to the hypertensive phenotype																																															
	D3	Report on the ORMDL1-3 channel expression in healthy and hypertensive vascular tissue																																															
WP5 - M Valverde Project 2	D1	characterization of the role of K ⁺ channels in ischemic conditions and smooth muscle proliferation																																															
	D2	molecular regulation of TRPV4 and P/Q calcium channels																																															
	D3	analysis of the impact of ORMDL proteins in calcium signalling																																															
	D4	identification and characterization of modulators of K ⁺ channels																																															

Milestones Programme 7 HERACLES

MILESTONES		2013			2014					2015					2016														
		september	october	november	december	january	february	march	april	may	june	july	august	september	october	november	december	january	february	march	april	may	june	july	august	september	october	November	December
WP2 - Marrugat Project 1	M1	Basal characteristics data pooled																											
	M2	Biological sample distributed to labs																											
	M3	10-year follow-up completed																											
	M4	Lab tests completed																											
WP2 - R Elosua Project 2	M1	Basal characteristics data pooled																											
	M2	Biological sample standardized and prepared																											
	M3	10-year follow-up completed																											
	M4	Genotyping completed																											
WP2 - G Escolar Project 3	M1	Completion of the inventory of potential epigenetic biomarkers in cardiometabolic disease																											
	M2	Completion of in vitro models of disease																											
WP3 - J Sanchis Project 1	M1	Basal characteristics analysis completed.																											
	M2	Invasive or conservative management completed.																											
	M3	1-year follow-up completed.																											
	M4	Lab tests completed.																											
WP3 - J Roquer Project 2	M1	Case and matched controls phenotype data collected;																											
	M2	Patient neuroimaging & examination completed;																											
	M3	Laboratory determinations completed;																											
	M4	Completion of the follow-up of cohort																											
WP4 - G Escolar Project 1	M1	Clinical and laboratory characteristics of populations studied;																											
	M2	Laboratory tests;																											
	M3	Establishment of cell cultures and evaluation of cell viability.																											
	M4	Image analysis of ventricular remodelling																											
WP4 - C Hermenegildo Project 2	M1	cohort completion;																											
	M2	laboratory analyses completion;																											
	M3	Follow-up completion																											
WP4 - C Hermenegildo Project 3	M1	Cohort completion;																											
	M2	laboratory analyses completion;																											
	M3	Follow-up completion																											
WP4 - J Tamargo Project 4	M1	Completion of experiments on vascular responses to endothelial mediators in aged vascular systems in SAM.																											
	M2	Completion of experiments on biomarkers of endothelial dysfunction and inflammation induced by aging and menopause																											
	M3	Completion of experiments on protein expression pattern produced by inflammation in human arteries and biomarkers of platelet dysfunction in patients with CDV																											
	M4	Completion of the experiments on characteristics of the antioxidant defence system, proinflammatory genes and vascular structure and function at different ages and their modulation by diet and drugs																											
WP4s- J Tamargo Project 1	M1	Characterization of AF-induced electrical remodelling.																											
	M2	Quantitative description of the VSMC electrical activity associated with hypertension.																											
	M3	Localization of ORM DLs within the vascular tissue.																											
WP5 - M Valverde Project 2	M1	Completion of K ⁺ channel activity experiment in smooth muscle proliferation and under ischemic conditions, overexpression and knockdown of ORM DL proteins experiment																											
	M2	Completion of TRPV4 regulation and voltage-gated Ca ²⁺ channel experiment.																											
	M3	completion of overexpression and knockdown of ORM DL proteins experiment																											

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Celebramos el 35º Aniversario
del estudio REGICOR el día
31 de Mayo de 2013
en Girona



**La verdadera grandeza de la ciencia
acaba valorándose por su utilidad.**

***The true value of science ends up being
credited by its applicability.***

Gregorio Marañón