Dr. Christopher O’Donnell
Framingham Heart Study
The HERACLES Cardiovascular Research Network

www.RedHERACLES.net

Hipertensión Esencial: Red de Análisis de Canales iónicos y Ligandos de Estrógenos Sintéticos
The Spanish Biomedical Research Networks

- In 2003 a call of the Instituto de Salud Carlos III encouraged Spanish researchers from different disciplines to collaborate in thematic Networks.
- In 2006 a new call homogenized the type of networks: 3 CV research networks approved
- HERACLES network started in 2003 around the study of new vascular mechanisms of hypertension and endothelium dysfunction
Strategic Objectives of the Spanish Research Networks

- To develop the priorities of the Spanish National Plan of Investigation, development and innovation
- To promote and facilitate translational research
- To stimulate multidisciplinary research
- To encourage collaborative research
- To develop “research & development” (patents, Spin-off, etc…)
Objectives of the Spanish Biomedical Research Network organization

- To provide stable funding for:
  - Investigator personnel,
  - Technicians,
  - Administrative personnel,
  - Platforms for common use,
  - Mobility and training,
  - Meeting and courses organization
The 8 HERACLES Groups 2003

- **ULEC-IMIM**
  Population cardiovascular Epidemiology & genetics.

- **USC-UPF**
  Cell & molecular physiology of vascular ion channels.

- **IDIBAPS**
  Effect of estrogens on vascular reactivity.

- **LIC-FJD**
  Vascular biology and proteomics.

- **ICSCM**
  Population epidemiology of cardiovascular risk factors

- **IBGM-CSIC**
  Molecular bases & regulation of VSMC K channels & their reaction to hypoxia.

- **CARDIO-TRUETA**
  CHD population CHD registries and prevalence of risk factors

- **CARDIO-SONDURETA**
  CHD population CHD registries and prevalence of risk factors
The 15 HERACLES Groups 2009

- **URLEC-IMIM (2003)**
  Unitat de Recerca en Lípids i Epidemiologia Cardiovascular, REPICA
  IMIM-Hospital del Mar, Barcelona.

- **ICSCM * (2003)**
  Instituto de Ciencias de la Salud de Castilla-La Mancha, Talavera de la Reina.

- **UNICA-UPF (2003)**
  Unidad de Canalopatías, Universitat Pompeu Fabra, Barcelona.

- **FICUV (2008)**
  Fundación de Investigación del Hospital Clínico Universitario de Valencia

- **UGR (2008)**
  Universidad de Granada

- **CARDIO-IDIBAPS (2003)**
  Servei de Cardiologia, Institut d’Investigacions Biomèdiques August Pi i Sunyer, Barcelona.

- **LDFAO-GRIB (2007)**
  Laboratorio de Diseño de Fármacos Asistido por Ordenador, Unitat de Recerca en Informàtica Biomèdica, Universitat Pompeu Fabra, Barcelona.

- **UCM (2007)**
  Universidad Complutense de Madrid

- **HCSC (2003)**
  Hospital Clínico San Carlos, Madrid

- **IBGM-UVA (2003)**
  Instituto de Biología y Genética Molecular, Universidad de Valladolid y CSIC

- **NEURO-MAR (2007)**
  Servei de Neurologia, Hospital del Mar

- **HCUV-SERCAR (2008)**
  Servicio de Cardiología Hospital Clínico Universitario de Valencia

- **HEMATO-IDIBAPS (2008)**
  Servei d’Hematologia, Institut d’Investigacions Biomèdiques August Pi i Sunyer, Barcelona.

- **FIIJT * (2003 & 2008)**
  Servei de Cardiologia, Fundació Institut d’Investigació Dr. Josep Trueta, Girona.

- **NKRI-IMIM (2008)**
  NK cell Receptors and Infection.
  REPICA, Immunologia, IMIM-Hospital del Mar Barcelona

*Clinical Associated member*
Distribution of HERACLES centres over Spain
Organization in HERACLES 2008

Subdirección General de Redes

HERACLES Network Coordinator
Jaume Marrugat

Technical Secretariat
Yolanda Ferrer

Executive Committee
(5 members elected among Scientific Board)

External Advisory Board
(4 members, at least 2 foreigners)

Scientific Board
(II + 1 member / HERACLES Group)

* Associated Clinical Group
Provides: Coordination, biobank, DNA extraction platform, hypertension clinical, epidemiology and cardiovascular genetics know-how, population databases, human artery, and DNA and serum and plasma samples to the biobank.

Receives: Opportunities for research stemming from multidisciplinary environment of HERACLES, that allows us to test hypothesis on hypertension mechanisms based on gene variants observed in population studies.
**Primary prevention: REGICOR risk factor functions**

### TABLAS DE FRAMINGHAM calibradas para la población española

#### Hombres

<table>
<thead>
<tr>
<th>Edad</th>
<th>No fumadores</th>
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<tr>
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<tr>
<td>140-159/90-99</td>
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#### Instucciones

Estas tablas se han adaptado a las características de la población española mediante un proceso de calibración bien contrastado (1-4) y se encuentran en proceso de validación. Permiten estimar el riesgo de un acontecimiento coronario (angina, infarto de miocardio silente o con síntomas, mortal o no) a 10 años.

Para estimar el riesgo debe seleccionarse la tabla correspondiente a la presencia o ausencia de diabetes, al sexo y la edad del/a paciente y buscar la intersección de su presión sistólica y diastólica con su colesterol total buscando la columna de valor central ≥ 20 mg/dL (≥ 0.5 mmol/L) que incluya el valor deseado. El valor inscrito en la casilla hallada por este procedimiento indica el riesgo a 10 años, y el fondo pertenece al código de colores cuya leyenda se encuentra al pie de las tablas.
Carrying out of population studies on cardiovascular risk factors and cardiovascular disease + Biobank of serum & DNA.

Talavera de la Reina (Toledo)
Phenotypically well characterized population cohorts in Talavera de la Reina, as well as the biobank of serum, plasma & DNA for clinical, epidemiological, proteomic and genetic studies on hypertension and CHD

Contribution of HERACLES to our group...

...allows us to share our epidemiological and clinical data and biobank with other groups in the network working in other disciplines. We collaborate with different groups of the network on epidemiological studies in cardiovascular risk, genetics epidemiology, proteomics epidemiology, clinical complications prediction.
I CSCM collaborations

- NEURO MAR
- LDFAO GRI B
- HEMATO IDI BAPS
- FI CUV
- UGR
- UNICA UPF
- HCUV SERCAR
- CARDIO IDI BAPS
- UBG M UVA
- UCM

- FIII T
- NKRI IMIM
- I CSCM
- URLEC IMIM
- HCSC

- Basic Sc
- Clínical-Basic
- Clinical
- Clinical-Epidemiological
- Bio-informatics
DESCRIPTION: Our research focuses on ion channels and the cellular responses to oxidative and mechanical stress.

THE FUTURE GOAL of our lab is to evaluate the relationship of Ca\textsuperscript{2+} transport systems (including intracellular Ca\textsuperscript{2+} stores, TRP and voltage-gated channels) with four common diseases: hypertension, asthma, migraine and Alzheimer disease.

PI M Valverde
We have provided the know-how to identify and select target genes for the study of hypertension and to functionally analyze the mutated proteins. Our contribution also relates to the study of the endothelial response to stress and its impact on cardiovascular diseases.

HERACLES has provided the framework and the funding to initiate and maintain a collaboration with cardiovascular epidemiologists and clinicians to tackle the genetic analysis of ion channels in hypertension. The funding has been essential to incorporate two talented researchers to the group.
Our translational research is focused on the **vascular effects of sex hormones**, in different models: cultured endothelial cells, animal models and postmenopausal women.

**Group:**
- Dr. Carlos Hermenegildo (PI)
- Dr. Elena Monsalve
- Dr. Juan J. Tarín
- Dr. Susana Novella*
- Dr. Pilar J. Oviedo
- Agua Sobrino
- Andrés Laguna
- Begoña Pineda*

* Contracted by HERACLES
Our role in HERACLES:

- Our group joined HERACLES as a basic research group in 2007, without any previous contact with its groups.
- We have started research collaborations with several HERACLES groups.

Contribution of HERACLES to our group:

- To get stable funds for paying researchers. In our group, HERACLES contracted persons represent 25% of our research team.
- To establish research collaborations with basic and clinical groups of excellence.
- To improve and to increase the objectives and the perspectives of our research, by applying our expertise to different samples and different clinical and basic questions.
FICUV
Fundación Hospital Clínico Universitario de Valencia

Scientific relationship with other HERACLES’ groups:

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>RESEARCH PROJECTS</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARDIO-IDIBAPS, NEUROMAR, HCUV-SERCAR, HEMATO-IDIBAPS</td>
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<tr>
<td>Hospital Clínico de San Carlos</td>
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<td>* CARDIO-IDIBAPS (Ana Paula Dantas)</td>
<td>A.P. 074/2009 (C. Sanitat, GV)</td>
<td>1</td>
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</table>

* Applied, waiting for resolution.

<table>
<thead>
<tr>
<th>HERACLES TRAVEL FUNDS</th>
<th>ORIGIN LAB</th>
<th>HOSTING LAB</th>
</tr>
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<tbody>
<tr>
<td>Eva García-Ramallo</td>
<td>NEUROMAR</td>
<td>FICUV</td>
</tr>
<tr>
<td>Susana Novella del Campo</td>
<td>FICUV</td>
<td>Kings College (London, UK)</td>
</tr>
<tr>
<td>Susana Novella del Campo</td>
<td>FICUV</td>
<td>HEMATO-IDIBAPS</td>
</tr>
</tbody>
</table>
Preventive strategies in hypertensive endothelial dysfunction
PI J Duarte
1. Heracles contributions to our group

- Incorporation of 1 doctor
- Stability of the group
- Interchange of research aims

2. Publications with Heracles collaborations

• Mechanisms of intimal hyperplasia

• Acute Coronary Syndromes: Pathophysiology Prognosis

• Estrogen, vascular biology and aging

Magda Heras Amadeo Betriu
Mercè Roqué José Luís Pomar
Xavier Bosch Ana Paula Dantas
Marta Sitges
CONTRIBUTIONS TO HERACLES NETWORK:
• Collection and shipment of uterine arteries
• Training biologists in the murine model of intimal hyperplasia
• Organization of 2 International Symposium on Antithrombotic Treatment

ADVANTAGES FROM HERACLES NETWORKING:
• Interaction with basic scientists
• Facilitation in recruiting patients and controls to clinical studies
• Access to biobanks
• The funding allows the recruitment of pre-doc and research nurse
INTERACTIONS with:

- **ULEC/IMIM.** Recruitment of controls, access to DNA biobank, statistician support
- **FICUV.** Characterisation of EPC function and apoptosis
- **LDFAO-GRIB.** Computation of equine estrogen with estradiol receptors
- **IBGM-UVA:** Studies in a murine model on the regulation of intimal hyperplasia. Identification of the Kv 1.3 channel as a therapeutic target to prevent restenosis. *This has resulted in a patent*
- **NEURO-MAR:** Coordinated study funded by FIS. Role of EPCs and CECs in acute stroke and myocardial infarction
- **HCUV-SERCAR:** Coordinated study funded by FIS. Role of EPCs and CECs in acute stroke and myocardial infarction. Studies on prognosis of ACS
- **HEMATO-IDIBAPS:** Identification and measure EPCs and CECs in AMI. Studies on thrombosis and ACS
Computer-Aided Drug Design Laboratory -2007-

PI
Manuel Pastor

Mission
Development and application of computational methods in the field of drug discovery and development
Group contribution to the network
Provide expertise in drug discovery to explore any potential exploitation of the research results in terms of novel targets or novel drugs.

Network contributions to the group
Incorporation of a postdoc (Jana Selent).
Coverage of travel expenses allowed more contacts with international groups.
Group contribution to the network
Started contacts and initiated joint research with two groups:
IDIBAPS (Ana Paula Dantas)
Unidad de Canalopatías (Miguel Valverde)
The Hospital Clínico San Carlos node is a multidisciplinary group focused in both the proteomic study of cardiovascular diseases and the changes induced in the proteome of cardiovascular involved cells i.e. platelets, mononuclear cells and the vascular wall cells by pharmacological treatment.

A new research area in which our group is at present interested is the genetic identification of mutations in both ionic channels and structural cardiac proteins involved in cardiac pathologies related to sudden cardiac death (Collaboration with Dr. Tamargo´s node). For this purpose, José Zamorano León spent a training period in Prof. Silvia Priorí´s labs supported by Heracles Research Network.
We have provided to the Heracles network the possibility to perform proteomic studies. In this regard, we have published a collaboration paper with other Heracles’ member in one of the most prestigious journal of proteins, i.e. J Proteome Research. At present, we have several collaborations with three different groups within HERACLES network and these collaborations are supported by both competitive grants and grants from pharmacological industry.

In addition, our Heracles group has obtained a grant from the Science and Technology Minister to develop a clinical trial that aims to compare by proteomics changes in the expression of proteins in plasma and platelets from patients treated with different anti-thrombotic drugs and in order to know if there are proteins in either plasma and platelets that could be associated with a different platelet response to these antithrombotic drugs. Finally, our contributions also included the organization of a Symposium focused in the medical prevention in the sports (2008 and 2009 with the participation of cardiologists and European and American researchers) and an International Meeting about Actualization in Cardiological Research (2008 and 2009).

CONTRIBUTION OF HERACLES TO OUR GROUP

We have obtained from Heracles network professional stability of two researchers which it is very important for the group. In addition, we have opened two important collaborative research lines: the first one is in collaboration of Dr. Tamargo’s group; and the other one is with Antonio Segura. The collaboration with Dr. Tamargo has reached two different publications in cardiovascular disease and it has opened a new research area in the group about functional and genetic alterations of ionic channels associated with cardiac sudden death. In addition, we have obtained plasma samples from an important number of patients from Dr. Antonio Segura’s collaboration for proteomics analysis to perform an epidemiological study in a population of 1100 patients from a specific area in Spain (Talavera de la Reina).
HOSPITAL CLINICO SAN CARLOS

• COLLABORATIVE PUBLICATIONS

- Cardiovasc Res 2006
- J Proteome Res 2006
- Proteomics 2008
- Cardiovasc Res 2008

• COLLABORATIONS WITH OTHER HERACLES NODES

- FICUV node (Dr. Hermenegildo)
- UCM node (Dr. Tamargo)
- UGR node (Dr. Duarte)
- NEW COLLABORATION 2009

- HCSC node
- ICSCM node (Dr. Segura)

Editorial
NeuroMar - 2007 -

Members:

Jaume Roquer, MD PhD. PI
José E. Martínez Rodríguez, MD PhD.
Ana Rodríguez Campello, MD.
Angel Ois Santiago, MD.
Jordi Jiménez Conde, MD PhD.
Elisa Cuadrado Godia, MD.
Eva García-Ramallo, Biologist.
Gemma Romeral, Nurse.

Research in stroke: “From the clinical to the biomarkers”
**NeuroMar contributions to Heracles**

We are the only neurological group of HERACLES network and we contribute through several actions:

1. - We have an ongoing comprehensive **registry of consecutive stroke cases** admitted to the Hospital del Mar (the only hospital in two districts of Barcelona: 350,000 inhabitants).
2. - We have an ongoing collection of **blood samples for genetic and biomarker** studies (more than 2,000 stroke cases).
3. - We have an ongoing **carotid tissue biobank** (more than 100 samples).

**Heracles contributions to NeuroMar**

HERACLES allows us to working together with some first line basic and epidemiological investigator teams and facilitates us to reach a true translational research.

**Relationships with other Heracles’ Groups**

**Collaborative ongoing projects:**

- Endothelial progenitors in atherosclerotic disease:
  - CARDIO-IDIBAPS
  - HCUV-SERCAR
  - FICUV
- NK receptors in stroke and neuroimmunological diseases:
  - NKRI-IMIM
- Diet, lipids and stroke:
  - URLEC-IMIM
1.- Clinical research on stroke:
   Epidemiology and natural history
   Vascular risk factors
   Diet and Stroke

2.- Genetics and stroke:
   KCNMB1 polymorphisms and cerebral hemorrhage (1)
   Copy number variants and stroke subtypes (2)
   GWS studies in cerebral hemorrhage (1)

3.- Oxidative stress, biomarkers and stroke:
   Endothelial progenitors cells
   Protein nitrotyrosination
   Antioxidant capacity and stroke
   MICA and stroke

4.- Immunology and stroke:
   NK Cell Receptors, infection and stroke (3)

(1) Collaboration with the “Centre for Human Genetic Research.” Massachusetts General Hospital, Boston.
(2) Collaboration with CRG. PRBB.Barcelona.
(3) Collaboration with NK-RI-IMIM.
Physiopathology of ion channels in vascular smooth muscle cells (VSMC) function -2003-
1. Role of ion channels in vascular tone control (ESSENTIAL HYPERTENSION)

Model: BPN/BPH mice

Screening: TaqMan® Low Density Array

Functional validation:
- Electrophysiology of isolated VSMCs
- Myography of isolated vessels

Identification of hypertension-related changes studying 96 ion channel genes of VSMCs from several vascular beds
2. Role of ion channels in vascular remodelling (INTIMAL HYPERPLASIA)

- Screening (TaqMan® Low Density Array) of proliferation-induced changes in two models
  - *in vivo* (endoluminal lesion)
  - *in vitro* (cultured VSMCs)

- Functional expression of the channels involved in the phenotypic switch:
  - Immunohistochemistry and immunocytochemistry
  - Functional studies (Electrophysiology)

- Functional contribution of the channels to the phenotypic switch:
  - Migration and proliferation studies
HERACLES contribution to the group:

• “Technology Transfer" from our original field of research (arterial chemoreceptors) into VSMC

• Growth of the group, by hiring personnel to complete and reinforce the group

• Establishment of cooperation with applied research and clinical groups
Main interest of the group: Cardiac Cellular Electrophysiology

To analyze the mechanisms involved in the endogenous and/or pharmacological regulation of cardiac ion channels in the context of cardiac arrhythmias, particularly, atrial fibrillation (AF).
Contribution of our group to HERACLES

We contribute with our expertise on cardiovascular basic and clinical pharmacology and on cellular cardiac electrophysiology.

Molecular Biology

- Action potentials in cardiac muscles
- Ionic currents in human atrial myocytes

Human cloned channels transfected in cell lines

Ion channel molecular modeling

- Macroscopic currents
- Single channel
- Site-directed mutant channels

Con
SNAP
DEANO

S-NO Kv4.3
Kv4.3

Control
50 μM 4-AP
4-AP + 200 μM SNAP

250 pA
2 s

Kv4.3+R99H KCNE3

500 pA
100 ms
Contribution of HERACLES to our Group

HIRED WITH HERACLES FUNDS:
A. Ferret
I. Amorós
A. Barana

INSTITUTO DE CC. DE LA SALUD TALAVERA DE LA REINA

Evaluation of several cardiovascular risk markers in hypertensive and non-hypertensive patients

HOSPITAL CLÍNICO SAN CARLOS MADRID

Human atrial samples for electrophysiological and proteomic analysis coming from patients with and without atrial fibrillation.
Access to the atrial tissue bank and the mass spectrometry facilities.

GROUP: UCM

Ariadna Ferret
Irene Amorós
Juan Tamargo
Eva Delpón
Ricardo Caballero
Ricardo Gómez
Lourdes Osuna
Adriana Barana
Servei Cardiologia.  
Hospital Clínic Universitari. València -2008-  
Research into ischemic heart disease and heart failure
Contribution of Heracles to our Group:

1. Possibility of hiring collaborators
2. Possibility of interaction with other groups in multicenter multidisciplinary projects
3. Access to techniques not available in our center
Implementation of the clinical risk score described by our group on patients with chest pain in other hospitals

Original Contribution

Limitations of risk score models in patients with acute chest pain

Alex F. Manini MDa,*, Nina Dannemann BSb, David F. Brown MDc, Javed Butler MD, MPHd, Fabian Bamberg MDa, John T. Nagurney MD, MPHc, John H. Nichols BAe, Udo Hoffmann MD, MPHb on behalf of the Rule-Out Myocardial Infarction using Coronary Artery Tomography (ROMICAT) Study Investigators

*Harvard Affiliated Emergency Medicine Residency, Boston, MA, USA
bCardiac MR PITT CT Program, Harvard Medical School, Boston, MA, USA
cDepartment of Emergency Medicine at Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA


Abstract

Objectives: Cardiac multidetector computed tomography (CMCT) has potential to be used as a screening test for patients with acute chest pain, but several tools are already used to risk-stratify this population. Risk models exist that stratify need for intensive care (Goldman), short-term prognosis (Thrombolysis in Myocardial Infarction, TIMI), and 1-year events (Sanchis). We applied these cardiovascular risk models to candidates for CMCT and assessed sensitivity for prediction of in-hospital acute coronary syndrome (ACS). We hypothesized that none of the models would achieve a sensitivity of 90% or greater, thereby justifying use of CMCT in patients with acute chest pain.

Methods: We analyzed TIMI, Goldman, and Sanchis in 148 consecutive patients with chest pain, nondiagnostic electrocardiogram, and negative initial cardiac biomarkers who previously met inclusion and exclusion criteria for the Rule-Out Myocardial Infarction Using Coronary Artery Tomography Study. ACS was adjudicated, and risk scores were categorized based on established criteria. Risk score agreement was assessed with weighted k statistics.

Results: Overall, 17 (11%) of 148 patients had ACS. For all risk models, sensitivity was poor (range, 35%-51%), and 95% confidence intervals did not cross above 77%. Agreement to risk-classify patients was poor to moderate (weighted k range, 0.16-0.43). Patients categorized as "low risk" had nonzero rates of ACS using all 3 scoring models (range, 8%-9%).

Conclusions: Available risk scores had poor sensitivity to detect ACS in patients with acute chest pain. Because of the small number of patients in this data set, these findings require confirmation in larger studies.

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Ginés Escolar, PhD, MD (PI)
- Servicio Hemoterapia Hemostasia.
- Haemostasis. Thrombosis.

Aleix Cases, PhD, MD (PI)
Servicio Nefrología.
Uraemia. Endothelial Dysfunction.

Ana M. Galán, PhD (PI)
Servicio Hemoterapia Hemostasia.
Haemostasis. Serotonergic System.

Dolors Tàssies, PhD, MD (PI)
Servicio Hemoterapia Hemostasia.
Haemostasis. Molecular Genetics.

Maribel Díaz-Ricart, PhD (PI)
Servicio Hemoterapia Hemostasia.
Haemostasis. Endothelial Dysfunction.

Joan Carles Reverter, PhD, MD (PI)
Servicio Hemoterapia Hemostasia.
Haemostasis. Thrombosis.

Irene López-Vilchez, PhD (contracted by HERACLES, Post-Doc)
Servicio Hemoterapia Hemostasia.
Haemostasis. Serotonergic System.
CONTRIBUTIONS HERACLES-GROUP

CONTRIBUTIONS OF OUR GROUP TO HERACLES
• Models of endothelial dysfunction, analysis of circulating endothelial cells and corresponding progenitor in blood.
• Technological support with perfusion systems with human blood. Physiological useful approach to evaluate both inflammation and the contribution of platelets to thrombotic processes.
• Access to patients with abnormalities in coagulation.
• Understanding of the hemostasis mechanisms and genetics.

CONTRIBUTIONS OF HERACLES TO OUR GROUP
• Establishment of close relationships with other groups with clinical and epidemiological expertise in Cardiology.
• Enhanced presence in the research on atherothrombosis.
• New areas of interest on the involvement of serotonergic mechanisms in cardiovascular risk and endothelial dysfunction.
• Participation in scientific sessions on subjects of mutual interest.
• Preparation of collaborative grants.
• Mutual feedback that should result in further alliances.
• Incorporation of a new member to our research group (Post-Doc contracted by HERACLES), who would strengthen our scientific production.
HERACLES COLLABORATIONS

GRANTS: Direct participation in two coordinated FIS grants from two HERACLES groups, CARDIO-IDIBAPS (coord: Magda Heras) and LDFAO-GRIB (coord: Jaume Roquer). Project entitled “Células endoteliales circulantes y células progenitoras endoteliales en la enfermedad cardiovascular aguda. Correlación con la función endotelial y la evolución clínica”.

SHARING KNOWLEDGE: We have shared our knowledge on the detection and analysis of circulating endothelial cells and endothelial progenitor cells in blood, with Susana Novella from the Group FICUV (coord: Carlos Hermenegildo).

Associated Clinical Group

**Contributions to HERACLES:**
Large population databases
>12000 samples to the Biobank.
Clinical approach (Cardiology & family practice) for translational research

**HERACLES contribution to FIJT:**
Personnel stabilization.
Participation in multicenter multidisciplinary projects.
Mobility.
IMMUNOLOGY IMIM (NKRI-IMIM) -2008-

PI M López-Botet

IMIM-Hospital del Mar

University Pompeu Fabra (DCEXS)

IDIBAPS
Research lines and HERACLES collaborations (I)

Team I: Miguel López-Botet (IMIM-HMAR /UPF) and Ana Angulo (IDIBAPS)

- Role of NK cell receptors in the immune response to human cytomegalovirus (HCMV) infection. Involvement in chronic inflammatory disorders (ML-B)

- Role of major immediate early components on CMV growth and pathogenesis (AA)

HCMV infection and immunity in atherosclerosis
N. Romo J. Marrugat, M. Fitó, J. Sala, R. Masiá (HERACLES)
Research lines and HERACLES collaborations (II)

Team II : Cristina López-Rodríguez and José Aramburu, UPF

• Regulation of immune cell function by the transcription factor NFAT5 (CL-R)

• Signalling pathways involved in the activation of NFAT5 in leukocytes and other cell types (JA)

Role of NFAT proteins in inflammation-induced myocardial disease. E. Roig, M Batlle, JL Pomar (HERACLES), JM Redondo (CNIC / RECAVA)
Essential Hypertension molecular (e.g., ion channels), immunologic & other determinants, therapy, & its relationship with CHD, stroke & endothelial function

**PROTEOMICS**
- HCSC
  - Protein expression mapping in arterial wall

**VASCULAR BIOLOGY**
- IBGM, HCSC, UNICA-UPF, HEMATO-IDIBAPS, NKRI-IMIM, CARDIO-IDIBAPS
  - Endoteliun-muscle interaction
  - Muscle excitability

**CELL PHYSIOLOGY**
- UNICA-UPF, IBGM
  - Expression & function
  - Molecular Interactions

**GENOMICS**
- IMIM-ULEC, UNICA-UPF
  - DNA extraction
  - Sequenciation
  - Genotyping

**GENETIC EPIDEMIOLOGY**
- IMIM-ULEC, ICSCM, CARDIO-FIIJT, SERCAR-HCUV
  - Population genetics
  - Hypertension risk associated to HT
  - Population biological samples

**CLINICAL PHARMACOLOGY & BIOINFORMÁTICS.**
- IMIM-ULEC, CARDIO-FIIJT, ICSCM, UCM, LDFAO-GRIB, SERCAR-HCUV, USC-UPF, CARDIO-IDIBAPS
  - New drug for HT design
  - Diagnostic & susceptibility Kits for HT.

**CARDIOLOGY & NEUROLOGY**
- CARDIO-IDIBAPS, NEURO-MAR, HCSC, CARDIO-FIIJT, HCUV-SERCAR, ICSCM.
  - Endothelial function in HT, CHD, stroke & healthy controls
  - Biological samples

**VASCULAR BIOLOGY**
- IBGM, HCSC, UNICA-UPF, HEMATO-IDIBAPS, NKRI-IMIM, CARDIO-IDIBAPS
  - Endoteliun-muscle interaction
  - Muscle excitability

**CELL PHYSIOLOGY**
- UNICA-UPF, IBGM
  - Expression & function
  - Molecular Interactions

**GENOMICS**
- IMIM-ULEC, UNICA-UPF
  - DNA extraction
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**GENETIC EPIDEMIOLOGY**
- IMIM-ULEC, ICSCM, CARDIO-FIIJT, SERCAR-HCUV
  - Population genetics
  - Hypertension risk associated to HT
  - Population biological samples

**CLINICAL PHARMACOLOGY & BIOINFORMÁTICS.**
- IMIM-ULEC, CARDIO-FIIJT, ICSCM, UCM, LDFAO-GRIB, SERCAR-HCUV, USC-UPF, CARDIO-IDIBAPS
  - New drug for HT design
  - Diagnostic & susceptibility Kits for HT.

**CARDIOLOGY & NEUROLOGY**
- CARDIO-IDIBAPS, NEURO-MAR, HCSC, CARDIO-FIIJT, HCUV-SERCAR, ICSCM.
  - Endothelial function in HT, CHD, stroke & healthy controls
  - Biological samples

**VASCULAR BIOLOGY**
- IBGM, HCSC, UNICA-UPF, HEMATO-IDIBAPS, NKRI-IMIM, CARDIO-IDIBAPS
  - Endoteliun-muscle interaction
  - Muscle excitability

**CELL PHYSIOLOGY**
- UNICA-UPF, IBGM
  - Expression & function
  - Molecular Interactions

**GENOMICS**
- IMIM-ULEC, UNICA-UPF
  - DNA extraction
  - Sequenciation
  - Genotyping

**GENETIC EPIDEMIOLOGY**
- IMIM-ULEC, ICSCM, CARDIO-FIIJT, SERCAR-HCUV
  - Population genetics
  - Hypertension risk associated to HT
  - Population biological samples

HT: hypertension, CHD: coronary heart disease, SMC: Smooth muscle cell
Current research lines in HERACLES

Genetics, proteomics, molecular mechanisms, epidemiology, and clinical and treatment approaches to essential hypertension and cardiovascular diseases.

Inflammatory, cellular and molecular factors in vascular remodelling and new therapeutic options.

Physiopathology of endothelial dysfunction and clinical and therapeutic implications in arterial hypertension and cerebrovascular and coronary heart disease
HERACLES Organization

1- *Know-how and shared knowledge*

- Cell physiology
- Molecular biology
- Population proteomics and genetics
- Translational Research (clinical, basic & epidemiology investigation, animal models and clinical pharmacology)
- Epidemiology, prevention, and biostatistics.
- Bioinformatics.
HERACLES Organization

- **2- Platforms**
  - Biobank (15000 participant DNA, serum & human artery samples) & shared data bases.
  - High throughput DNA Extraction & genotyping
  - Coordination of the HERACLES Network
    - **Technical secretariat:** biobank registry, sample transportation, minutes, administrative support
    - Web site [www.redheracles.net](http://www.redheracles.net)
  - Training and mobility of investigators program.
HERACLES achievements

Project-driven cardiovascular research Network of 8 Groups between 2003 and 2006. Enlarged up to 15 Groups so far. Since 2003:

- 76 original cooperative papers (out of a total of 607)

- HERACLES was scored with the highest qualification in the international evaluation in 2006
Original collaborative articles in HERACLES (76 papers)
Gain-of-function mutation in the KCNMB1 potassium channel subunit is associated with low prevalence of diastolic hypertension

José M. Fernández-Fernández,1 Marta Tomás,2 Esther Vázquez,1 Patricio Orio,3 Ramón Latorre,3 Mariano Sentí,1,2 Jaume Marrugat,2 and Miguel A. Valverde1

The $\beta_1$ subunit of the $\text{Ca}^{2+}$-sensitive $\text{K}^+$ channel protects against hypertension

Mark T. Nelson and Adrian D. Bonev

Department of Pharmacology, University of Vermont, Burlington, Vermont, USA.

Previous animal studies have demonstrated that the loss of the $\beta_1$ subunit of the large-conductance $\text{Ca}^{2+}$-activated $\text{K}^+$ (BK) channel leads to hypertension. A new study (see the related article beginning on page 1032) demonstrates that a gain in $\beta_1$ subunit function is associated with protection against diastolic hypertension in humans, underscoring the importance of the $\beta_1$ subunit and the BK channel in the regulation of vascular resistance.
Descubierta una mutación que reduce el riesgo de hipertensión

Strategias farmacológicas
El tratamiento de la hipertensión arterial se basa en el uso de medicamentos que reducen el riesgo de enfermedad cardiovascular. Entre ellos, los inhibidores de la enzima convertidora de la angiotensina (IECA) y los antagonistas del receptor de la angiotensina II (ARAII) son los más utilizados.

La mutación genética descubierta se ha asociado con un menor riesgo de hipertensión arterial. La mutación se encuentra en el gen que codifica la enzima convertidora de la angiotensina (ACE), la cual regula la producción de la hormona angiotensina II, una molécula que aumenta la presión arterial.

La mutación conocida, denominada ACE2, presenta una versión más activa que la versión normal, lo que puede explicar la reducción del riesgo de hipertensión. La mutación se ha observado con mayor frecuencia en personas de origen asiático y africano.

La mutación genética se asocia con un menor riesgo de enfermedades cardiovasculares, incluido el riesgo de enfermedad cardiovascular. Sin embargo, es importante tener en cuenta que la mutación genética no es la única causa de la presión arterial y que el estilo de vida también juega un papel importante en el control de la hipertensión arterial.

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Letter to the Editor

Novel mutation (H402R) in the S1 domain of KCNH2-encoded gene associated with long QT syndrome in a Spanish family

José J. Zamorano-León a, Sergio Alonso-Orgaz a, Javier Moreno b, Rafael Cíntra b, María J. García-Torrent e, Nicasio Pérez-Castellano b, Julián Pérez-Villate b, Carlos Macaya a, Antonio J. López-Farré a, c

a Cardiovascular Research Unit, Unit of the Cardiology Department, Cardiovascular Institute, Hospital Clinic, San Carlos, Madrid, Spain
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Received 30 June 2008; accepted 29 November 2008

Abstract

Long QT syndrome is a congenital cardiac disease resulting in ventricular arrhythmias and sudden death. Genetic mutations in two protein ion-channels, genes KCNQ1 and KCNH2. The mutations position is stage geographical additional information about the evaluation of the risk-stratification. In a Spanish family in whom previous reports of syncpe, episodes, sudden death and pathological prolongation of the QT interval were documented, a novel intron-exon mutation in the KCNH2 gene (A1218->G) was identified. This mutation leading to amino acid substitution H402R in the S1 transmembrane domain of KCNH2. The new A1218->G mutation in the KCNH2 gene detected in this Spanish family causes arrhythmia manifestation in the cardiac.

Keywords: KCNQ1; KCNH2; Long QT syndrome; Atrioventricular block

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1. Introduction

LQTS is characterized by prolonged ventricular repolarization leading to a prolongation of the QT interval and a variable clinical course with arrhythmia-related syncope and sudden death [1].

Mutations in the potassium channel-generating genes KCNQ1 and KCNH2, are responsible for the most frequent forms of the long QT syndrome known as forms 1 and 2 respectively and both genes explain the 60-70% of the diagnosed cases [2].

Asymptomatic patients and gene-defect carriers with normal or borderline QTC values are not uncommon in LQTS families. Therefore, it is probable of clinical importance to detect both the genetic defect and the carriers within a family. The present study reports a Spanish family in which initially one member was clinically diagnosed with LQTS, and showed a novel missense mutation (H402R) in the S1 domain of the KCNH2-encoded gene.

2. Materials and methods

2.1. Clinical evaluation

The study family comprised 4 members in two-generations (Fig. 1A). The proband (patient Ia) was a 42-year-old woman diagnosed with LQTS in the Arrhythmia Unit of Hospital Clinic San Carlos, Madrid, Spain. The relatives (IIa, IIb and IIIc) were subjected to clinical examination including 12-lead electrocardiography (ECG) where QT intervals were measured. Long QT affected individuals were defined according to Priori et al., as QTC>440 ms for males and >460 ms for females [3].
Genome-wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants


Established Genome-wide Association Study Consortium*

A genome-wide association study testing single nucleotide polymorphisms (SNPs) and copy number variants with early-onset myocardial infarction (MI) controls. We carried out replication analysis with an effective sample size of nine loci reached genome-wide significance in the discovery phase. These loci include 2q12 near 6p24 in PHACTR1 and 2q33 in LRRTM1 and 2p13 in CXCL12, 1q41 in 1p32 near PCSK9. We tested other polymorphisms (>1% allele frequency) in these loci, but this approach did not identify additional loci with robust evidence. Structural variation, however, may account for myocardial infarction traits that are not included in the current analysis. Of these, O.E.D. 7800

Structural variation, however, may account for myocardial infarction traits that are not included in the current analysis. Of these, O.E.D. 7800

Halladas las nuevas claves del infarto precoz
Un estudio con 25.000 voluntarios y participación española halla las mutaciones genéticas que comparten las personas con predisposición a sufrir un ataque cardíaco

Metges gironins troben nous gens que incrementen el risc d'infart

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Barcelona. (EFE). Un consorcio de investigadores europeos y norteamericanos ha descubierto tres nuevas características genéticas relacionadas con el infarto agudo de miocardo —prima causa de mortalidad y muerte en los países desarrollados— y ha confirmado otras seis ya identificadas en estudios anteriores.

Los investigadores han determinado en una primera fase del proyecto, 2,5 millones de características genéticas (también llamadas polimorfismos) en cerca de 3.000 personas que han sufrido un infarto agudo de miocardo antes de los 60 años, y han comparado con los de otras 3.000 personas sanas que han actuado de control.

M. Pennati

MADRID. Al menos tres nuevas características del genoma que aumentan el riesgo de padecer un infarto agudo de miocardo, además de la edad y la familia, han sido descubiertas por un consorcio europeo de investigación. Estas características se encuentran en los genes responsables de enfermedades de transmisión familiar, y pueden ser útiles para predecir el riesgo de enfermedad cardiovascular en individuos que no tienen antecedentes familiares de esta afección.

Los hallazgos servirán para desarrollar nuevos fármacos y métodos diagnósticos que permitan prever el riesgo de enfermedad cardiovascular en individuos que no tienen antecedentes familiares de esta afección.

El estudio, financiado por la Fundación de Investigación Cardiovascular de la Comunidad de Madrid y la Fundación Carlos III de Investigación Sanitaria, ha analizado la genómica de más de 2.500 pacientes con infarto agudo de miocardo, así como de 3.000 personas sanas. Los investigadores han comparado los datos genéticos de estos grupos para identificar posibles características genéticas que aumenten el riesgo de enfermedad cardiovascular.

La característica genética más importante identificada hasta ahora es un polimorfismo en el gen PCSK9, que se relaciona con una mayor predisposición a la enfermedad cardiovascular. Otros polimorfismos implicados son los en los genes SMAD3, IL1B y TLR4, que están asociados con el riesgo de desarrollar enfermedades cardiovasculares.
Weather as a Trigger of Stroke

Daily Meteorological Factors and Incidence of Stroke Subtypes


*Unit of Neurovascular Research, Neurology Department, Institut Municipal d’Investigació Mèdica, Hospital del Mar, Department of Medicine, Universitat Autònoma de Barcelona, Spain

Los cambios en la presión atmosférica pueden ser el detonante de un ictus

En el trabajo, coordinado por Jordi Jiménez-Conde, se estudió la relación entre los ictus y los fenómenos atmosféricos, con el objetivo de determinar si existe una correlación entre la ocurrencia de ictus y los cambios en la presión atmosférica. Se analizaron datos de 1.286 pacientes con ictus atendidos en el Hospital del Mar entre 2001 y 2003. Se observó una correlación significativa entre la presión atmosférica y la ocurrencia de ictus, lo que sugiere que los cambios en la presión atmosférica pueden ser un factor de riesgo para el desarrollo de ictus.
HERACLES achievements

- **Patents:**
  - “Método y kit para la detección del riesgo de padecer hipertensión” (29 marzo 2004). Nº de registro: P200400883; Solicitud Internacional: P200400883
  - Second patent presented in October 2008 (nº 08105518.8)
HERACLES achievements

- 70 arterial samples or cell cultures for the biobank
- Maintenance of a specific DNA biobank (>15,000 muestras)
- Contracts for R-D with private sector
- 92 projects funded in competitive calls: 14 are ongoing or completed collaborative projects
HERACLES. Colaboraciones en PROYECTOS
HERACLES achievements

- 7 investigators awarded with mobility and training funds
- 4 new Groups incorporated in 2008
- The most powerful high throughput DNA extraction platform operative by the end of 2009
- 11 courses/conferences/workshops/symposia promoted or sponsored
HERACLES achievements
a permanent call for mobility and

CONVOCATORIA DE AYUDAS DE FORMACIÓN Y MOVILIDAD
RED HERACLES

AYUDAS PARA ESTANCIAS EN CENTROS DE LA RED DE INVESTIGADORES 2007

Antecedentes: Las bases de la convocatoria de redes 2006 (BOE núm 19 junio 2006, RESOLUCIÓN de 13 de junio de 2006,) preven que el centro coordinador de las redes disponga de fondos para movilidad y formación para los miembros de la red. Para llevar a cabo esta misión el centro coordinador de la Red HERACLES convoca las presentes ayudas.

Plazo de presentación: convocatoria abierta durante todo el año 2007.

Objeto:
Favorecer la adquisición e intercambio de conocimientos y técnicas de laboratorio u otros, el contacto, la preparación de proyectos y de publicaciones y el intercambio científico entre grupos de investigación mediante la financiación de estancias de investigadores en centros de la Red Heracles, y excepcionalmente en otros centros, y para la participación en cursos.
Core Platform for DNA extraction

2008: Robot Tecan: sample distribution and replication of plaques. Normalization of samples

2008: 2 technicians

2008 Quality control Nanodrop & picogreen

Infraestructure FIS 2009
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A Sample of Scientific meetings and courses promoted by HERACLES 2007-2009

- **Beyond Frontiers: Atherosclerosis and Air Pollution**, International Conference & Workshop, Barcelona, 24 y 25 de Abril de 2008, PRBB de Barcelona

- **I Simposio de Prevención en el Fútbol**, Nuevos retos en el avance del conocimiento científico de la medicina en el fútbol. Madrid, 24 y 25 de Abril de 2008, Hospital Clínico San Carlos

- **X Simposio Internacional Actualización en el Tratamiento Antitrombótico**, ¿Qué hemos aprendido en los últimos 10 años? Barcelona, 9 de Mayo de 2008. Hotel Fira Palace


- **Reunión Científica HERACLES.** Madrid, 26 y 27 de Junio de 2008. Hospital Clínico San Carlos

- **CURSO: Las Dimensiones de las Enfermedades Cardiovasculares en España.** De la etiopatogenia a la prevención. Barcelona, 15,16 y 17 de septiembre de 2008, PRBB

- **CURSO: Enfermedades cardiovasculares: de los mecanismos moleculares a la prevención.** Universidad de Talca, Chile, 25 y 26 de septiembre, 2008)
Some challenges for HERACLES to face

- Improve the web site and translate it into English.
- To keep on deepening mutual trust.
- To further exploit the advantages of collaborating under multidisciplinary approach.
- Persist in applying to competitive calls for research projects.
- To focus on Europe and US to search new partners and calls for projects.
Some challenges for HERACLES to face

- To work out the relationships with the private sector (R+D+I):
  - Look for industry interested in R+D+I to promote collaborative projects (PETRI, CEDETI, CIDEM…)
  - To patent selectively
  - To organize Spin-offs whenever possible

- Bench-to-bed translation of research results

- Bed-to-bench feedback for important issues to be solved
The HERACLES teams
www.redheracles.net

Founding HERACLES
Barcelona, IMIM 2003

Continuing/enlarging HERACLES
Valladolid, IBGM 2007

Further enlargement HERACLES
Madrid, HCSC-UM 2008