SCIENTIFIC MEETING
HERACLES PROGRAMME 2013

Girona, May 30, 2013

Centre Cultural La Mercè
Pujada de la Mercè, 12
17004 - GIRONA

AGENDA

Thursday, May 30

08:00 10:15	**Monograph MEETINGS**		**2h 15min**
08:00 08:45	**PROCELL** Study Room: **SALA POLIVALENT**		45 min
08:45 09:30	**MOSCA** Study Room: **SALA POLIVALENT**		45 min
09:30 10:15	**COLMAH** Study Room: **SALA POLIVALENT**	**XUE** Study Room: **SALA DE REUNIONS**	45 min

10:15 11:00	**COFFEE / WELCOME** Room: **CLAUSTRE**	45 min

11:00 12:00	MEETING OF THE HERACLES PROGRAMME **SCIENTIFIC COMMITTEE** Room: **AULA 1**	MEETING OF THE **HERACLIDES** young INVESTIGATORS Carla Lluis / Óscar Díaz Room: **SALA POLIVALENT**	60 min

12:00 12:25	**The new CV Network** **The new HERACLES programme** **J Marrugat.** Room: **AUDITORI**	25 min

Thursday, May 30 (2)

12:25 12:30	Introduction to the new HERACLES groups and platforms, by J Marrugat Room: **AUDITORI**	5 min

12:30 12:40	Group **EGEC-IMIM**, R Elosua	10 min
12:40 12:50	Group **CANARIAS CDC**, A Cabrera	10 min
12:50 13:00	Group **DP IACS**, F Civeira	10 min
13:00 13:10	Group **HUSJ**, V Bertomeu	10 min

UPDATING HERACLES PLATFORMS

13:10 13:15	The high throughput **DNA** extraction platform**,** R Elosua	5 min
13:15 13:20	The **Luminex** platform**,** M Fitó (IMIM-Institut de Recerca Hospital del Mar & CIBERobn)	5 min
13:20 13:25	The **COLMAH** human artery collection, T Pérez/C Hermenegildo	5 min

PROJECTS NETWORKING & COORDINATION

13:25 14:10	WP2. Analysis of predictive and reclassification capacity of CVD biomarkers in cohort studies & mendelian randomization trials Room: **AULA 1** WP3. Biomarkers & other prognostic factors in ACS, stroke & CHF patients Room: **SALA DE REUNIONS** WP4. Endothelial function and vascular regeneration WP5. Ion channels in the vasculature and CVDs Room: **SALA POLIVALENT**	45 min

14:10 **15:00**	**FINGER BUFFET** Room: **CLAUSTRE**	50 min

15:00 15:30	**INVITED LECTURE: PREDIMED Study final results** **MI Covas** (IMIM-Institut de Recerca Hospital del Mar & CIBERobn) Room: **AUDITORI**	30 min

Thursday, May 30 (3)

15:30 16:00	**ENDOTHELIAL DYSFUNCTION PANEL** Moderator: Juan Tamargo	
	15:30 -15:45 **1) Evidence of endothelial dysfunction in major depression patients, and its modulation during antidepressive treatment with a selective serotonin reuptake inhibitor (SSRI) -** Irene López-Vilchez Several lines of evidence have pointed out the existence of a relationship between depression and cardiovascular risk. More recently inflammation has been recognized as an additional mechanism to induce endothelial dysfunction. It has been postulated that depression may be associated to an inflammatory state, which could contribute negatively to the increased rates of cardiovascular events observed in these patients. Our present studies have evaluated the pro-inflammatory state and level of endothelial dysfunction in patients with major depression before starting treatment (P0), and after 24 weeks (P24) of antidepressive treatment with the SSRI escitalopram. Results were compared with those obtained in healthy donors (CON). We found statistically significant increases in the levels of circulating endothelial cells (CEC), soluble VWF and VCAM-1, and in vitro expression of ICAM-1 in cultured endothelial cells exposed to sera pools from patients with major depression, at P0 vs. CON. Treatment with a SSRI for 24 weeks resulted in normalization of these markers showing statistical significance in the CEC levels. Our results confirm the existence of endothelial dysfunction related to major depression, and indicate that treatment with a SSRI could modulate the pro-inflammatory state in these patients.	10+5 min
	15:45-16:00 **2) Senescence exacerbates neointimal formation and increases vascular smooth muscle proliferation: potential role of Akt and RhoA mediated signaling pathways -** Ana Paula Dantas Vascular senescence is associated to number of physiological and morphological changes that alter functioning and increases cardiovascular risk. Among physiological changes, we have described - using a murine model of accelerated senescence (senescence accelerated mice - SAM) - diminished endothelial relaxation and increase in contractile responses to several agonists. Besides, we have observed morphological changes including wall thickening and alterations of matrix substances deposition, ultimately leading to greater arterial stiffening (reduced compliance). Our most recent data reveals increased neointimal formation in SAM prone mice (SAMP) subjected to wire injury of femoral artery in comparison to SAM resistant (SAMR). Histological analysis of femoral arteries sections showed increased expression of the protein kinases Akt and RhoA in the neointimal and medial areas of injured artery in comparison to the collateral uninjured femoral artery in both SAMR and SAMP. However, western blot analysis revealed an increased expression of these kinases in the vasculature of SAMP vs SAMR. Vascular smooth muscle cells (VSMC) from SAMP display a greater proliferative profile than cells from non-senescent mice SAMR, which was significantly diminished by Akt and Rho kinases inhibitors (Wortmannin and GSK269962). Our data suggest that senescence exacerbates neointimal formation by a mechanism that involves increased expression of Akt and RhoA kinases.	10+5 min

Thursday, May 30 (4)

16:00 16:30	**MOLECULAR MECHANISMS OF ARTERIAL HYPERTENSION PANEL** Moderator: Miguel Ángel Valverde	
	16:00-16:15 **3) Novel potent small molecule modulators of coronary endothelial KCa2 and KCa3.1 channels -** Ralf Kohler KCa3.1 and KCa2, small-conductance Ca2+-activated K+ channels, are expressed in the coronary artery endothelium where they enable endothelium-derived hyperpolarization(EDH)-mediated vasodilation. Thus, small molecule activators of the channels could be of therapeutic utility to treat cardiac ischemia. We report on novel KCa3.1/KCa2 activators(positive gating modulator), SKA-31 and SKA-111 that produce strong hyperpolarizing K+-currents in native porcine coronary endothelium and strongly counteracted serotonin-induced coronary contraction and potently amplify bradykinin-induced relaxation in a selectivity profile-dependent manner. A novel phenolic negative-gating modulator of KCa3.1/KCa2, 13b, antagonized these effects, and promoted vasoconstriction. In conclusion, potent gating modulators of cardiovascular KCa are of potential therapeutic utility to treat ischemic disease.	10+5 min
	16:15-16:30 **4) Does metabolic syndrome provide additional valuable information on vascular risk beyond that of individual risk factors? A genetic approach -** Carla Lluis BACKGROUND: Hypertension is one of the main components of metabolic syndrome (MetS) which also includes other cardiovascular risk factors and seems to be driven by obesity. This constellation of risk factors increase the risk of developing cardiovascular events, but there is discussion regarding whether MetS provides additional valuable information on vascular health beyond the mere addition of risk factors. Genetic profile associated with each of the risk factors defining MetS could be used to shed light on this debate. OBJECTIVE: To evaluate whether genetic risk scores (GRS) associated with the individual cardiovascular risk factors that define MetS present more than an additive association with myocardial infarction (MI) risk. METHODS: We included 2,967 cases of early onset MI and 3,075 controls from the MIGen study. We selected genetic variants identified in recent meta-GWAs for the following risk factors: blood pressure, obesity, HDL cholesterol, LDL cholesterol, triglycerides and type 2 diabetes. We weighted each genetic variant according to its effect on the risk factor and calculated the total weighted genetic load of each individual for each separate risk factor phenotype. Then we tested for association between each GRS and MI. Finally, we performed a test for interaction between each pair combination of GRS on MI risk. RESULTS: The GRS for obesity, blood pressure, HDL cholesterol, LDL cholesterol and triglycerides were associated with MI risk. After correcting for multiple comparisons (p-value to be considered as statistically significant <0.001) there was no statistically significant interaction between any of the combinations of GRS on MI risk. However, the interaction between the GRS of obesity and the GRS of LDL was marginally non statistically significant (p-value=0.0085). CONCLUSIONS: These results need to be replicated in an independent population to completely discard the possible interaction. Although there was no statistically significant interaction between the GRSs on MI risk, it seems plausible that a true interaction between obesity and LDL in modulating MI risk exists. The lack of association between the GRS for diabetes and MI is unforeseen and question the causal association between diabetes and MI.	10+5 min

Thursday, May 30 (5)

16:30 17:00	**CLINICAL AND INFLAMMATION RESEARCH PANEL** Moderator: Teresa Pérez	
	16:30-16:45 **5) Resistin is a marker of coronary disease in the general population -** Antonio Cabrera de León Aims: The aim was to explore the association between resistin and the incidence of ischemic heart disease in the general population. Methods and Results: Follow-up study of 6636 adults recruited randomly from the general population. Serum resistin concentration was higher in women (6.1±2.4) than in men (5.6±2.2 ng/mL, P<0.001). Individuals in the 5th quintile or higher of resistin (R≥Q5) were younger (P<0.001) and had a lower prevalence of hypertension (P<0.001), abdominal obesity (P<0.001), diabetes (P<0.013) and dyslipidemia (P=0.026). Cardiovascular risk estimated with the Framingham function was also lower in the R≥Q5 subgroup (P<0.001); however, the prevalence of smoking was higher (P<0.001), as was the prevalence of low HDL cholesterol (P=0.001). After 3.5 years of follow-up, the R≥Q5 subgroup had a higher incidence of acute myocardial infarction (AMI, RR=1.9; 1.01-3.54; P=0.048). In the population without diabetes, the R≥Q5 subgroup had a higher risk of AMI (RR=2.4 [1.10-5.17], P=0.029), and the risk of AMI was highest in women in this group (4.97 [1.33-18.57], P=0.026). The risk levels were significant in Cox models adjusted for age, sex and smoking; and in the sample matched by sex and smoking, the hazard ratio was 3.2 for AMI (1.60-6.00, P<0.001). Conclusions: Resistin is a risk marker for ischemic heart disease in the general population. Serum resistin concentration is higher in women, and the associated increase in risk of AMI is also higher in women than in men.	10+5 min
	16:45-17:00 **6) Expert system for predicting unstable angina based on Bayesian networks -** Juan Sanchis We have developed a Clinical Decision Support Systems (CDSS) that predicts unstable angina in patients presenting to the hospital with acute chest pain of uncertain origin, i.e., normal ECG and troponin levels. This CDSS is based on a Bayesian Network, which takes 17 patient-related inputs from the clinical history. We have validated the CDSS on two datasets of patients presenting to the emergency department with acute chest pain of uncertain origin from two different hospitals (Hospital Clinic Barcelona and Hospital Clinic València). Due to the different management policy in each hospital, there were significant differences in risk profile between both patient populations. The decision boundaries of the CDSS can be traded-off between a high sensitivity and a good specificity, but not both. The system achieves a 90% negative predictive value (NPV) on the València dataset, and a 98% NPV on the Barcelona dataset. Finally, we have developed a web application to help clinicians to use the CDSS in a fast an easy web from any Internet-enabled device. The application stores an anonymized database of all the queries, so that they can be validated a posteriori in order to improve the model.	10+5 min

Thursday, May 30 (6)

17:00 17:45	**GENDIAG** AWARDS CEREMONY Room: **AUDITORI** - **Best Publication** HERACLES 2011-2012. Presentation – 15 min - **Best HERACLIDES (young investigator) Publication**, HERACLES 2011-2012. Presentation – 15 min	**45 min**

17:45	**Concluding remarks**, by J Marrugat

20:15 21:15	**Girona Historic Centre Tour**	
21:15	**HERACLES – REGICOR DINNER** Restaurant DIVINUM Carrer Albereda 7 GIRONA	