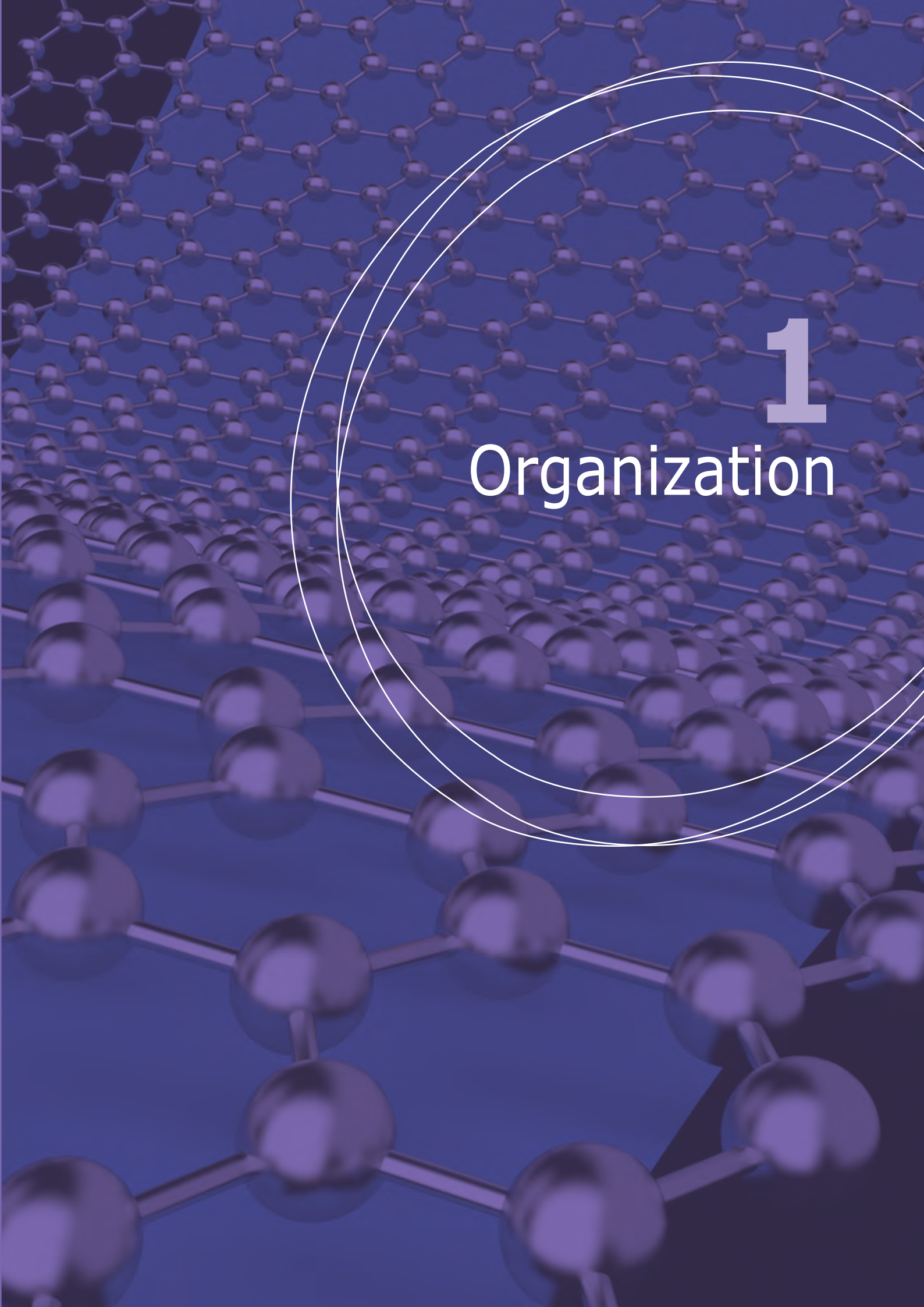
Annual Report 2013

ciberehd

Centro de Investigación Biomédica en Red
Enfermedades Hepáticas y Digestivas

INDEX



1 Organization

Letter from the Scientific Director

tuThank you so much for following the scientific activity of the Networked Biomedical Research Center in Hepatic and Digestive Diseases (CIBERehd).

CIBERehd is a public consortium the aim of which is to promote high level translational research through the interaction of the best Spanish groups. CIBERehd provides its member groups with funds to finance research and support staff, collaborative projects, common technological platforms, scientific-technical infrastructures and the development of training activities. Established on November 29th, 2006, in 2013 it is made up by 51 groups from 30 centres distributed in 9 regions.

Our mission is:

a) Execution of joint programmes of research, development and innovation in digestive and liver diseases promoting interaction and synergies among the best Spanish groups..

b) Contributing to the resolution of health care problems related to the above mentioned areas.

c) Promoting the transfer of the results of the research processes toward clinical applications and to society, especially in the biotechnological and pharmaceutical industry.

d) Promoting the participation in activities of priority research in the national sphere and in projects included in the European Framework Programmes of R+D+I.

e) Promoting the diffusion of its activities and the training of competitive researchers in the field of digestive and liver diseases.

CIBERehd is directed by the Scientific Director, appointed by the ISCIII , who assumes the responsibility of all CIBERehd actions with the assistance of the Steering Committee comprising the Manager, the Training Coordinator and the Coordinators of Research Programmes and Technological Platforms. He establishes the multiannual action plan and its budget. CIBERehd funding mostly comes (80%) from ISCIII that is basically used to cover salaries of researchers and support staff, to buy scientific-technical infrastructure and, to a lesser extent, to train research staff and to cover management and current expenses. The consorted institutions contribute with their facilities, services, and part of their staff (their staff researchers adhered to CIBERehd). Likewise, CIBERehd self-finances more than 10% of its budget.

Research Programmes

- 1. Portal hypertension
- 2. Hepatitis
- 3. Choleastasis and metabolic disorders
- 4. Immunology and liver transplantation
- 5. Liver and gastrointestinal oncology
- 6. Gastrointestinal inflammation and motility.

Technological Platforms include a Biobank, a Transcriptomic, Proteomic and Metabolomic Platform, a Pyrosequency Platform and a Bioinformatic Platform.

Steering Committee

- Scientific Director **Dr. Jaume Bosch**
- Teaching Coordinator **Dr. Joan Caballería**
- Vicedirector **Dr. Jordi Bruix.**

Program Coordinators

- Program: **Dr. Agustín Albillos**
- Program: **Dr. Juan I. Esteban**
- Program: **Dr. Juan F. Medina**
- Program: **Dr. M. Navasa**
- Program: **Dr. Jordi Bruix**
- Program: **Dr. Julián Panés**

And The General Mananger, **Manuel Sánchez**.

This year 558 articles were published in first and second quartile journals, 77 % (429) of which belong to the first quartile and 50% (218) to the first decile of their speciality. This indicates a further increase in the quantity and quality of the scientific outputs of the CIBERehd. Moreover, in 335 publications the main author or the corresponding author belonged to CIBERehd and 85 of these publications were collaborative. Finally , there were 14 publications in high impact journals.

Dr. Jaume Bosch
Scientific Director of CIBERehd

List of Groups and Institutions

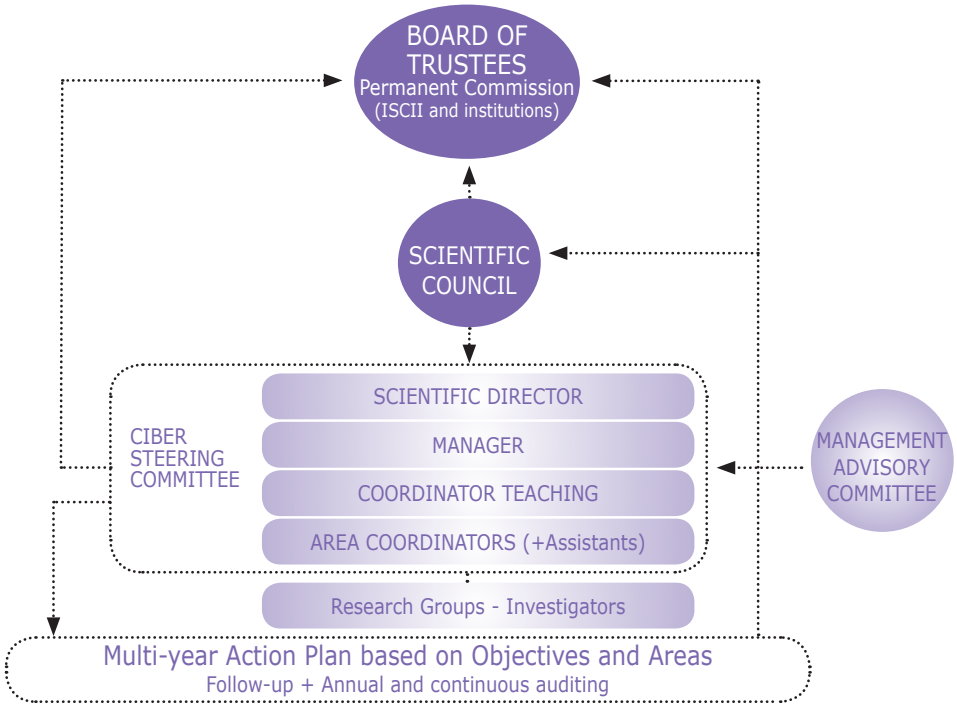
CIBERehd founded on November 29, 2006 and is currently comprised of 51 groups (1 of them being an Associate and 7 Affiliates) from 30 centres distributed throughout 9 Autonomous Communities. Its governing body and management consist of the Scientific Director, Dr. Jaume Bosch, and the Board of Trustees, formed by three representatives of the Carlos III Health Institute and an institutional representative for each of the consortium institutions.

IP	Institución
Agustín Albillos	Facultad de Medicina de Alcalá de Henares
Rocío Álvarez (Vinculado)	Hospital Virgen de la Arrixaca
Vicente Arroyo	Hospital Clínic i Provincial de Barcelona
Fernando Azpiroz	Hospital Vall d'Hebron-Institut de Recerca
Rafael Bañares	Hospital Gregorio Marañón
Marina Berenguer	Hospital La Fe
Jaime Bosch	Hospital Clínic i Provincial de Barcelona
Jordi Bruix	Hospital Clínic i Provincial
Xavier Calvet	Corporació Sanitària Parc Taulí
José V Castell	Hospital La Fe
Antoni Castells	Hospital Clínic i Provincial de Barcelona
Juan Córdoba	Hospital Val d'Hebron-Institut de Recerca
Juan Vicente Esplugues	Hospital Universitario de Valencia
Juan Ignacio Esteban	Hospital Vall d'Hebron-Institut de Recerca
Rafael Esteban	Hospital Vall d'Hebron-Institut de Recerca
José Carlos Fdez-Checa	Consejo Superior de Investigaciones Científicas
Xavier Forns	Hospital Clínic i Provincial de Barcelona
José Juan García Marín	Universidad de Salamanca USAL
Carmelo García Monzón (Vinculado)	Hospital Santa Cristina
Javier García-Samaniego	Hospital Carlos III
Eduard Cabré	Hospital Germans Trias i Pujol
Jordi Gómez	CSIC Inst Parasitología y Biomedicina López Neyra
Javier González Gallego	Universidad de León
Carlos Guarner	Hospital de la Santa Creu i Sant Pau
Francisco Guarner	Hospital Vall d'Hebron-Institu de Recerca
Angel Lanas	Instituto Aragonés de Ciencias de la Salud
Manuel de la Mata	Hospital Universitario Reina Sofía

José Mª Mato	CIC Biogune
Juan F Medina	Clínica Universitaria Navarra
Luisa García Buey	Hospital de la Princesa
Julià Panés	Hospital Clínic i Provincial de Barcelona
Albert Parés	Hospital Clínic i Provincial Barcelona
Marçal Pastor	Universidad de Barcelona
Ramon Planas	Hospital Germans Trias i Pujol
Jesús Mª Prieto	Clínica Universitaria de Navarra
Miquel Navasa	Hospital Clínic i Provincial de Barcelona
Manuel Romero	Hospital Universitario Nuestra Sra. De Valme
Fco Javier Salmerón	Hospital Universitario San Cecilio
José Such	Fund. de la Comunidad Valenciana para la Investigación
Antonio Zarzuelo	Universidad de Granada
Luis Bujanda	Hospital de Donostia
Pere Clavé	Hospital de Mataró
Javier Pérez Gisbert	Hospita de la Princesa
Belén Beltrán (Affiliate)	Hospital La Fe
Paloma Martín Sanz (Associate)	CSIC-Alberto Sols
Raul Andrade	IMABIS
Llorenç Caballeria (Affiliate)	IDIAP Jordi Gol
Maria Esteve (Affiliate)	Fundación Docencia Recerca Mutua de Terrassa
Francisco Javier Padillo (Affiliate)	Hospital Virgen del Rocío
José Luis Calleja (Affiliate)	Hospital Universitario Puerta de Hierro

Organizational Structure

The functional structure of the CIBER- Liver and Digestive Diseases is summarized in Figure 1. Two more concepts have been added to the general CIBER structure: the Management Advisory Committee (advisory body comprised of key players in the field of hepatology and gastroenterology in Spain), the Assistant Coordinators (who work with the Program Coordinators to prepare and coordinate the different lines of research in each Program).



Through the Steering Committee (body comprised of the Scientific Director, the Manager, the Teaching Coordinator and Program Coordinators), the CIBER establishes a multi-year action plan and budget. 80% of the CIBER's funding is fundamentally through ISCIII (Carlos III Health Institute) grants to cover expenses resulting from steady hiring of research staff and supporting staff, the acquisition of scientific-technical infrastructure, research staff training, running costs and management costs. Consortium institutions contribute by supplying facilities, services and some of the staff.

This structure is extremely novel, and it means that CIBERs are centres entirely managed by the investigators themselves. They establish their own needs, resources, and the temporary execution plan. Highly involved groups with long term commitment to CIBER also receive additional funding.

Budget

CIBERehd	Budget 2013
TOTAL Enterprise: CIBEREHD LIVER DISEASES AND D	4.581.311
Support to Groups	3.549.311
Group budget	3.063.000
External income, public investments	238.311
External income, private investments	248.000
Technological Platforms	230.000
CicBiogune Platform	75.000
BioBank Support	10.000
Hep. Biotechnology, (Bioinformatics)	85.000
Cancer Diagnostic Platform	60.000
Strategic actions	150.000
Agreements	135.000
Research collaboration /support agreements	50.000
Agreements with consortium inst. and others	85.000
Training	70.000
Internships abroad	40.000
Internships in CIBEReh groups	10.000
Visiting Professor Program	5.000
Participation in courses and meetings	15.000
Coordination and Management	447.000
Steering and Coordination	120.000
Management Expenses	327.000

CIBERehd Staff

Staff hired by the research groups belonging to CIBEREHD in 2013 to be on staff in the groups and equipment platforms remained stable as regards the number of hires. In 2013, CIBEREHD had an average of 125 hires. This indicates the slight adjustment occurring largely due to hiring limitations laid out by the 2013 Budget Law.

CIBEREHD staff policy is still focused on the stability offered to investigators and technicians that are hired and to the groups themselves. This allows them to focus available resources on already existing full-time indefinite job contracts.

CATEGORY	Nº. OF EMPLOYEES	PERCENTAGE
PhDs	44	35,20%
Bachelor's Degrees	43	34,40%
Research NURSE	12	9,60%
Laboratory Technician	26	20,80%
TOTAL	125	100%

2
Scientific Programs

P1. Portal Hypertension and Mechanisms of Transition to Cirrhosis

Description

CIBERehd Program num. 1, named "Portal hypertension and mechanisms of transition to cirrhosis", focuses on collaborative research on the pathogenesis, diagnosis and treatment of liver cirrhosis, portal hypertension and its complications. In particular, the cooperative translational research that holds the Program studies the pathogenic mechanisms of liver fibrogenesis and portal hypertension and seeks to develop drugs and therapeutic strategies to improve portal hypertension and its associated complications (bleeding gastroesophageal varices, ascites and renal failure, bacterial infection, hepatic encephalopathy). Research is systematized in the Program in five lines 1) hepatic fibrogenesis, 2) portal hypertension, 3) ascites / renal function and liver insufficiency, 4) infection and bacterial translocation, and 5) hepatic encephalopathy.

The Program is formed by eight groups, five located in Barcelona and led by Drs. Arroyo (Hospital Clinic), Bosch (Hospital Clinic), Genescá (Hospital Valle Hebron), Guarner (Hospital San Pablo) and Planas (Hospital Germán Trias Pujol), two in Madrid led by Drs. Albillos (Hospital Ramón y Cajal-University of Alcalá) and Bañares (Hospital Gregorio Marañón), and one in Alicante led by Dr. Such (General Hospital). In spite of its clinical origin, all the groups included in the Program have incorporated experimental research. The latter fact enables the Program 1 to cover the whole spectrum of translational research in the field of its competence, including studies of cell and molecular biology, proof of concept in patients with cirrhosis and clinical trials to evaluate different drugs and treatment strategies.

The strategic aim of CIBERehd is to promote clinical and experimental collaborative research. In this sense, the direction of CIBERehd has stimulated the development of collaborative projects among groups of Program 1, as well as with groups in other areas. The collaboration has included multicentered clinical trials, cooperation to evaluate prognostic markers and test and design strategies for diagnosis and treatment with a direct impact on clinical practice. One of the initial goals of CIBERehd was to extend this collaboration towards mechanistic basic research, using the advantages of cell and molecular biology. Cooperation in this sense has also been initiated among CIBERehd groups and is expected to continue rising in coming years.

Table describes the topics of research of the 8 groups of Program 1:

Group	Center	PI	Lines of research of each group	Number of members
1	Universidad de Alcalá-Hospital Ramón y Cajal, Madrid	Agustín Albillos	Portal hypertension Infection/Translocation	11
2	Hospital Clínic Barcelona	Vicente Arroyo	Fibrogenesis Ascites/renal function /Liver insufficiency Infection/Translocation Hepatic encephalopathy	15
3	Hospital Gregorio Marañón, Madrid	Rafael Bañares	Portal hypertension Ascitis/función renal/Insuficiencia hepática	11
4	Hospital Clínic Barcelona	Jaime Bosch	Portal hypertension Infection/Translocation	10
5	Hospital Valle de Hebrón, Barcelona	Juan Genescá	Ascites/renal function /Liver insufficiency Hepatic encephalopathy	5
6	Hospital San Pablo, Barcelona	Carlos Guarner	Portal hypertension Ascites/renal function Infection/Translocation	6
7	Hospital Germans Trías, Badalona	Ramón Planas	Portal hypertension Ascites/renal function Infection/Translocation Hepatic encephalopathy	5
8	Hospital General Universitario, Alicante.	José Such	Ascites/renal function Infection/Translocation	8

Collaborative clinical projects carried out by members of the program during 2013:

- Multicenter, randomized, double-blind, placebo-controlled study on the efficacy of beta-blockers to prevent decompensation of cirrhosis with portal hypertension. Clinical Research Project Institute of Health Carlos III EC08/00122. Code: PREDESCI. Year Started: 2008. Hospital / participating institutions: H. Santa Cruz and San Pablo, H. Clinic, H. Trias Pujol, H. Valle de Hebron, H. Ramon y Cajal-University of Alcalá, H. Gregorio Marañón, H. Puerta de Hierro Majadahonda, H. Arnau de Vilanova. Principal Investigator / Coordinator: Candido Villanueva, Hospital Santa Creu i Sant Pau, Barcelona.
- Efficacy of albumin and midodrine in the prevention of the complications of cirrhosis in cirrhotic patients in the transplantation waiting list: a double-blind, randomized, controlled study. Code: MACHT study. Year Started: 2009. Hospital / participating institutions: H. Clinic, H. Valle de Hebrón. Principal Investigator / Coordinator: Pere Ginés, Hospital Clinic, Barcelona.
- Pilot randomized study to evaluate physical exercise in cirrhotic patients and branched aminoacid supplementat.ion. Mapfre Foundation. Year started: 2010. Hospital / participating institutions: H. Santa Cruz and San Pablo, H. Valle de Hebron. Principal Investigator / Coordinator: Germán Soriano, Santa Cruz and San Pablo, Barcelona.
- Multicentered, randomized trial to evaluate the impact of weight loss on portal pressure in patients with cirrhosis and obesity/overweight. Year Started: 2011. Code: SPORTDIET study. Hospital / participating institutions: H. Clinic,

H. San Pablo, H. Valle de Hebron, H. Ramon y Cajal-University of Alcalá, H. Gregorio Marañón, H. Puerta de Hierro. This project is a strategic action of Ciberehd. Principal Investigator / Coordinator: Jaime Bosch, Hospital Clinic, Barcelona.

- Treatment of hepatorenal syndrome with terlipressin administered as continuous intravenous infusion with doses adjusted according to hemodynamic response. Code: AMELIORATE study. Year Started: 2012. Hospital / participating institutions: H. Clinic, H. Valle de Hebrón, H. del Mar, H. Sant Pau, H. Germans Trias i Pujol, H. Moises Broggi, H. Parc Taulí. Principal Investigator / Coordinator: Pere Ginès, Hospital Clinic, Barcelona.
- Treatment of hepatorenal syndrome associated with bacterial infections with terlipressin and albumin. Code: Year Started: 2012. Hospital / participating institutions: H. Clinic, H. Sant Pau. Principal Investigator / Coordinator: Pere Ginès, Hospital Clinic, Barcelona.

P2. Viral Hepatitis

Program Coordinator:

Dr. Juan Ignacio Esteban Mur

Associate Coordinators:

Drs. Xavier Forns y Manuel Romero Gómez

Description

Area 2 includes 8 research groups led by Drs. Juan Ignacio Esteban Mur (Hospital Universitari Vall d'Hebron. Barcelona), Rafael Esteban Mur(Hospital Universitari Vall d'Hebron. Barcelona), Xavier Forns Bernhardt (Hospital Clínic de Barcelona), Javier García-Samaniego Rey (Hospital Carlos III. Madrid), Jordi Gómez Castilla (CSIC Instituto Lopez Neyra. Granada), Manuel Romero Gómez (Hospital Universitario de Valme, Sevilla), Javier Salmeron Escobar (Hospital Universitario San Cecilio. Granada) and Marisa García Buey (Hospital de la Princesa. Madrid).

During 2013 the Viral Hepatitis Program groups have consolidated the collaboration efforts previously planned.

- Public HBV database named CIBERHEP, owned by Ciberehd is open to all National Health professionals willing to participate in the Project. The database coordinated by Drs. M. Buti and R. Esteban received approval in the Boletín Oficial del Estado BOE-B-2010-32871 Sept 25th 2010, and was registered in the Agencia Española de Protección de Datos (AEPD), Oct 22nd 2010. CIBERHEP is fully active and above 1000 patients have been introduced.
- The use of new technologies such as GWAS, Ultra-deep pyrosequencing (UDPS) using the 454/Roche platform and structural RNA biosensors using microarrays, have allowed to publish several papers in collaboration and open new research lines.
- A CDTI (Centro para el Desarrollo Tecnológico Industrial) project in collaboration with Roche Diagnostics and ABL granted by the MINECO IDI-20110115 has been successfully developed (Coordinated by Dr.J.I.Esteban). This project entitled "Estudios de quasiespecies de los virus de la hepatitis B y C (VHB y VHC) y de polimorfismos genómicos asociados a la respuesta al tratamiento antiviral por pirosecuenciación" started on March 1st 2010 until December 31st, 2013. The Project have involved the consortium of four Institutions: Roche Diagnostic Systems, ABL-Therapy Edge, Ciberehd, and VHIR-HUVH. The most prominent result, has been the development of an European Patent EP13382278 owner by Ciberehd, Roche and VHIR based on the HCV subtyping using massive sequencing.

- A public HCV data base named HepatiC owned by Ciberehd has been consolidated. An agreement with the AEEH (Spanish Association for Liver Disease) has been signed to open Hepatic to all National Health professionals willing to participate in the Project. The database received approval in the Boletín Oficial del Estado BOE-B-2011-20823 June 20th 2011, and was registered in the Agencia Española de Protección de Datos (AEPD). It is fully operative and more than 500 patients have been introduced during 2013.
- Another fully collaborative study, sponsored by a Ciberehd platform, still ongoing during 2013 and entitled "Secuenciación a gran escala para el diagnóstico y planificación del tratamiento de hepatitis víricas" has finally succeed and a collaborative publication has been obtained.
- IL28 polymorphism testing in chronic HCV patients has been implemented in practice in all participating Clinical Hospitals.
- We have also succeeded in using subgenomic and genomic HCV replicons to study HCV infection, replication, including the cloning of a fully replicating full-length HCV genome (Dr. X.Forns' group), and investigation of the effect of anti-viral drugs on HCV quasispecies dynamics (Drs. J.Gomez and E.Domingo).
- Non-invasive (ARFI) techniques to characterise hepatic fibrosis, including licensed software to analyse magnetic resonance images have been evaluated.
- Improvement of viral load detection of HDV is ongoing (Dr. Garcia Samaniego).
- Epidemiological studies focussed in HBV, HCV, HDV and recently in HEV infection has been reinforced including nosocomial HCV transmission studies thus supporting the National Health Spanish System. We are also studying the viral dynamics during antiviral therapy and during post-transplant recurrence and we are also involved in developing cooperative multicentre assays for antiviral treatments.
- Studies on DNA genomic polymorphisms in Interferon inducible genes (ISGs), have reported its association as independent predictive factors of response to anti-HCV treatment (Peg-IFN & Ribavirin) in chronic HCV (HCC) patients (Dr. M.García Buey). Immune response and levels of expression of host proteins have been implicated in progression to fibrosis/cirrhosis and development of hepatocarcinoma.
- A three-year multicenter study including all hepatocarcinoma cases occurring on NASH, HCV or cryptogenic cirrhosis, named FLIP (Fatty Liver: Inhibition of Progression) started in 2010 (Dr. M Romero Gomez)
- Dr. J.Salmeron's group participates in the European Project "Fatty liver: Inhibition of Progression. "Prevention and treatment of non-alcoholic fatty liver disease (NAFLD)" that started in 2010.
- A collaborative line of research involving three groups of our Area 2 and led by Dr. J.Garcia-Samaniego has been consolidated, focussing in the study of epigenetic interactions between the host's genomic DNA and HBV or HCV genomes.
- A methodology for HCV subtyping has been developed using 454/GS-Junior platform. Automation of the protocol is ongoing to be implemented in the clinical routine laboratory "Hepatitis Pathology. Biochemistry Department. Hospital Vall d'Hebron Barcelona" (Dr. R.Esteban' group).

- Most of the groups have participated in multicentre Clinical Trials with new combinations of HCV direct acting antivirals.
- Clinical trials using new antiviral strategies (lethal mutagenesis) and new inhibitors (quercetine, etc) have been proposed and will be developed in next years.

As a summary, the activity developed during 2013 in the Area 2 of Ciberehd has been successful and has increase the competitive research capability of our network. Juan I Esteban.

P3. Cholestasis, Metabolic Disorders and Hepatotoxicity

Foreword

Program Coordinator

Dr. Juan F. Medina, CIMA Universidad de Navarra

Program 3 includes ten groups, the research activities of which are mainly related to cholestasis, metabolic disorders and hepatotoxicity. A first branch in the Program is formed by three groups led by Dr. Albert Parés, Dr. Llorenç Caballería, and Dr. Juan F. Medina, respectively. These groups focus on clinical, epidemiological, and basic studies of cholestasis, and they are working towards the analysis of transport abnormalities of bile flow components and subsequent alterations in primary biliary cirrhosis and other chronic cholestatic diseases.

The other seven groups form a second branch in the program which researches metabolic disorders, and, more specifically, the study of steatohepatitis and liver toxicity. Thus, these groups conduct studies related to the mechanisms of oxidative stress and apoptosis in hepatocytes and the role of cytokines and adipocytokines in metabolic, toxicological and infectious liver disorders. Highly relevant in this regard are the activities carried out by Dr. José M. Mato and Dr. José C. Fernández-Checa's groups, which have been awarded a substantial number of projects and carry out multiple collaborations with other groups. Moreover, the groups led by Dr. Javier González Gallego, and Drs. Carmelo García Monzón and Paloma Martín Sanz maintain a close collaboration for the study of antioxidant therapies in models of hepatitis C. Finally, the groups led by Dr. Jose V. Castell and Dr. Raúl Andrade are investigating different molecular mechanisms that cause hepatotoxicity.

Program Projects and Collaborations

Cholestasis, Metabolic Disorders and Hepatotoxicity

The groups that form Program 3 have maintained collaborative networks among them (intra-Nodal collaborations) and among other external groups (inter- Nodal collaborations). Dr. José M. Mato's group, from CIC BioGUNE, has significantly potentiated these collaborations through their Genomics, Proteomics, Metabolomics and Gene Silencing Platforms, which are also available to all CIBERehd groups. Also, collaborations based on these platforms have consolidated through the organisation of formations activities such as training sessions.

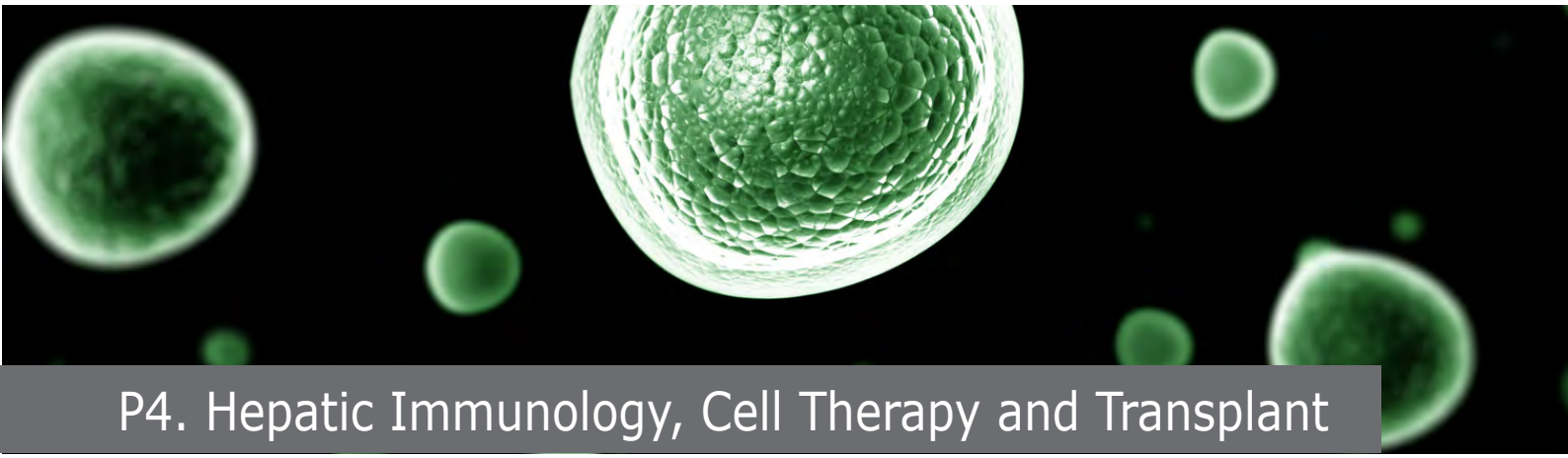
Additionally, several high-impact publications further show the high quality of current collaborations, as illustrated by the following few examples:

- Martínez-Uña M, Varela-Rey M, Cano A, Fernández-Ares L, Beraza N, Aurrekoetxea I, Martínez-Arranz I, García-Rodríguez JL, Buqué X, Mestre D, Luka Z, Wagner C, Alonso C, Finnell RH, Lu SC, Martínez-Chantar ML, Aspichueta P, Mato JM. *Excess S-adenosylmethionine reroutes phosphatidylethanolamine towards phosphatidylcholine and triglyceride synthesis*. Hepatology 2013;58:1296-305. **(IF 2012: 12.003)**.
- Guañabens N, Monegal A, Cerdá D, Muxí Á, Gifre L, Peris P, Parés A. *Randomized trial comparing monthly ibandronate and weekly alendronate for osteoporosis in patients with primary biliary cirrhosis*. Hepatology 2013;58:2070-8. **(IF 2012: 12.003)**.
- Barbero-Camps E, Fernández A, Martínez L, Fernández-Checa JC, Colell A. *APP/PS1 mice overexpressing SREBP-2 exhibit combined Aβ accumulation and tau pathology underlying Alzheimer's disease*. Hum Mol Genet 2013;22:3460-76. **(IF 2012: 7.692)**.
- Uriarte I, Fernandez-Barrena MG, Monte MJ, Latasa MU, Chang HC, Carotti S, Vespasiani-Gentilucci U, Morini S, Vicente E, Concepcion AR, Medina JF, Marin JJ, Berasain C, Prieto J, Avila MA. *Identification of fibroblast growth factor 15 as a novel mediator of liver regeneration and its application in the prevention of post-resection liver failure in mice*. Gut 2013;62:899-910. **(IF 2012: 10.732)**.

International networks are also important for Program 3. For instance:

- Vazquez-Chantada M, Gonzalez-Lahera A, Martinez-Arranz I, Garcia-Monzon C, Regueiro MM, Garcia-Rodriguez JL, Schlangen KA, Mendibil I, Rodriguez-Ezpeleta N, Lozano JJ, Banasik K, Justesen JM, Joergensen T, Witte DR, Lauritzen T, Hansen T, Pedersen O, Veyrie N, Clement K, Tordjman J, Tran A, Le Marchand-Brustel Y, Buque X, Aspichueta P, Echevarria-Uraga JJ, Martin-Duce A, Caballeria J, Gual P, Castro A, Mato JM, Martinez-Chantar ML, Aransay AM. *Solute carrier family 2 member 1 is involved in the development of nonalcoholic fatty liver disease*. Hepatology 2013;57:505-14. **(IF 2012: 12.003)**.
- Fernandez A, Matias N, Fucho R, Ribas V, Von Montfort C, Nuño N, Baulies A, Martinez L, Tarrats N, Mari M, Colell A, Morales A, Dubuquoy L, Mathurin P, Bataller R, Caballeria J, Elena M, Balsinde J, Kaplowitz N, Garcia-Ruiz C, Fernandez-Checa JC. *ASMase is required for chronic alcohol induced hepatic endoplasmic reticulum stress and mitochondrial cholesterol loading*. J Hepatol 2013;59:805-13. **(IF 2012: 9.858)**.
- Bañares R, Nevens F, Larsen FS, Jalan R, Albillos A, Dollinger M, Saliba F, Sauerbruch T, Klammt S, Ockenga J, Pares A, Wendon J, Brünnler T, Kramer L, Mathurin P, de la Mata M, Gasbarrini A, Müllhaupt B, Wilmer A, Laleman W, Eefsen M, Sen S, Zipprich A, Tenorio T, Pavesi M, Schmidt HH, Mitzner S, Williams R, Arroyo V; RELIEF study group. *Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the RELIEF trial*. Hepatology 2013;57:1153-62. **(IF 2012: 12.003)**.

- Liu JZ, Hov JR, Folseraas T, Ellinghaus E, Rushbrook SM, Doncheva NT, Andreassen OA, Weersma RK, Weismüller TJ, Eksteen B, Invernizzi P, Hirschfield GM, Gotthardt DN, Pares A, Ellinghaus D, Shah T, Juran BD, Milkiewicz P, Rust C, Schramm C, Müller T, Srivastava B, Dalekos G, Nöthen MM, Herms S, Winkelmann J, Mitrovic M, Braun F, Ponsioen CY, Croucher PJ, Sterneck M, Teufel A, Mason AL, Saarela J, Leppa V, Dorfman R, Alvaro D, Floreani A, Onengut-Gumuscu S, Rich SS, Thompson WK, Schork AJ, Næss S, Thomsen I, Mayr G, König IR, Hveem K, Cleynen I, Gutierrez-Achury J, Ricaño-Ponce I, van Heel D, Björnsson E, Sandford RN, Durie PR, Melum E, Vatn MH, Silverberg MS, Duerr RH, Padyukov L, Brand S, Sans M, Annese V, Achkar JP, Boberg KM, Marschall HU, Chazouillères O, Bowlus CL, Wijmenga C, Schrumpf E, Vermeire S, Albrecht M; UK-PSCSC Consortium; International IBD Genetics Consortium, Rioux JD, Alexander G, Bergquist A, Cho J, Schreiber S, Manns MP, Färkkilä M, Dale AM, Chapman RW, Lazaridis KN; International PSC Study Group, Franke A, Anderson CA, Karlsen TH. *Dense genotyping of immune-related disease regions identifies nine new risk loci for primary sclerosing cholangitis*. Nat Genet 2013;45:670-5. **(IF 2012: 35.209)**.



P4. Hepatic Immunology, Cell Therapy and Transplant

Coordinator:

Miquel Navasa

Assistant Coordinator:

Marina Berenguer

Description

Despite the fact that Program 4 covers various topics, its primary area of research is liver transplant. About 15,000 liver transplants are performed worldwide every year today. Transplant recipient survival rates are satisfactory. Survival is about 90% 1 year after the transplant, about 75% after 5 years, and 65% after 10 years. Nevertheless, liver transplant still presents a series of important clinical problems:

Immunosuppression: a) must be optimized to adapt to the needs of each patient in order to reduce the risk of rejection and of toxicity; b) the possibility of completely withdrawing immunosuppression in patients showing graft tolerance, who may represent a considerable proportion of transplant patients several years after the transplant, and c) suitably detecting and handling complications resulting from immunosuppressants. These aspects must be investigated in Program 4.

Pre-transplant disease recurrence, particularly hepatitis C. The importance of hepatitis C recurrence is on one hand based on the high number of patients receiving transplant due to liver diseases relating to the hepatitis C virus , and on the other hand the huge negative impact of hepatitis C recurrence on post-transplant survival due to the rapid progression of the hepatic lesion in the graft in a considerable proportion of transplant patients. The lesion mechanisms in hepatitis C recurrence and therapeutic management of patients with this complication constitute lines of research that are of great interest today, particularly in the current context of developing and marketing strong new viral agents. Program 4 therefore also preferably takes care of the research for this problem.

Disproportion between the number of organ donors and the number of patients on a liver transplant wait list. Therefore, over the past few years, on one hand a series of actions that sought to palliate this problem were implemented by means of investigating strategies that allow increasing the number of liver grafts suitable for transplant, and on the other hand, improvements were made in managing the transplant wait list. These aspects are also grounds for research for Program 4 groups.

There were three relevant aspects in 2013 that brought about important results: The research group established new therapeutic action targets based on adipocytokine modulation both in liver resections and liver transplant in marginal organs,

which may favorably affect patients subjected to liver resections or liver transplant, and on reducing liver transplant wait lists. The results obtained by the research group have further enabled participating in competitive programs intended for translating experimental results to clinical practice, which will result in patent applications and in creating a spin-off. As regards post-transplant recurrence of hepatitis C, antiviral treatment regimens have been established in liver transplant candidates and in liver transplant patients with serious recurrence of the disease. Patients with serious post-transplant recurrence of hepatitis C have also been characterized by invasive and non-invasive means. Finally, those patients with a profile indicating operational graft tolerance, which allows withdrawing immunosuppression, have been more precisely characterized.

In addition, it is very important to point out the important collaboration established with important groups dedicated to studying liver diseases, particularly with the Viral Hepatitis Group (Dr. X. Forns) and the Portal Hypertension Group (Dr. J. Bosch).

Objectives

The objectives of the Program's four projects are explained below.

PROJECT 1

Project title:

Operational tolerance and withdrawal of immunosuppressant in patients with liver transplant.

Lead Group: Navasa

Principal Investigator: A. Sánchez-Fueyo.

Collaborating Groups:

CIBEREHD Groups: Berenguer, De la Mata, Forns, Prieto, Parrilla, Bosch

International groups: Giuseppe Tisone (Roma), Jacques Pirenne (Leuven), Gavin Whitehouse (London), Frans Claas (Leiden).

Objectives:

- To determine the predictive capacity of a transcriptional tolerance test based on peripheral mononuclear blood cells to identify patients who can stop using immunosuppressant.
- To establish the clinical benefits of the withdrawal of the immunosuppressant in patients identified as tolerant based on the aforementioned transcriptional test, particularly in terms of improving renal function and various cardiovascular risk factors.
- To investigate the impact that chronic HCV infection in transplant patients with hepatitis C recurrence may have on withdrawal of the immunosuppressant.
- To analyze the gene expression profile in liver tissue to even more precisely identify patients that are tolerant to the graft.

PROJECT 2

Project Title:

Multicentre study for the validation of biomarkers of choice that reflect the individual response of solid organ transplant recipients to immunosuppressive treatment.

Lead Group: Navasa

Principal Investigator: M. Brunet

Collaborating Groups:

CIBEREHD Groups: Álvarez, Parrilla.

Objectives:

The general objective of this study consists of choosing and validating optimal pharmacodynamic biomarkers, together with pharmacokinetic parameters, which reflect the individual response to immunosuppressive treatment and are predictive of the clinical progression of solid organ transplant recipients (acute rejection, infection, toxicity).

Comment: Project in final phase, following the planed phases.

PROJECT 3

Project Title:

Control terapéutico de la diabetes en pacientes con trasplante hepático

Lead Group: Berenguer

Principal Investigator: M. Berenguer

Collaborating Groups:

CIBEREHD Groups: De la Mata, Parrilla.

Nat. Groups not related to CIBEREHD: T. Serrano (Zaragoza), JI Herrero (Pamplona)

Objective:

To evaluate the degree of therapeutic control of diabetes mellitus in liver transplant recipients and identifying the factors associated with it.

PROJECT 4

Project Title:

Biomarcadores en el diagnóstico diferencial del rechazo celular agudo y la recurrencia de la hepatitis C tras el trasplante hepático.

Lead Group: M. Navasa

Principal Investigator: M. Navasa

Collaborating Groups: X. Forns

CIBEREHD Groups: De la Mata,

National Groups not related to CIBEREHD.

Objectives:

- To evaluate a panel of serological biomarkers in differentiation between acute rejection and hepatitis recurrence after liver transplant.
- To study if any of the evaluated biomarkers allows predicting response to treatment for cellular rejection.
- To determine if these biomarkers allow early identification of patients with serious hepatitis C recurrence the liver transplant.

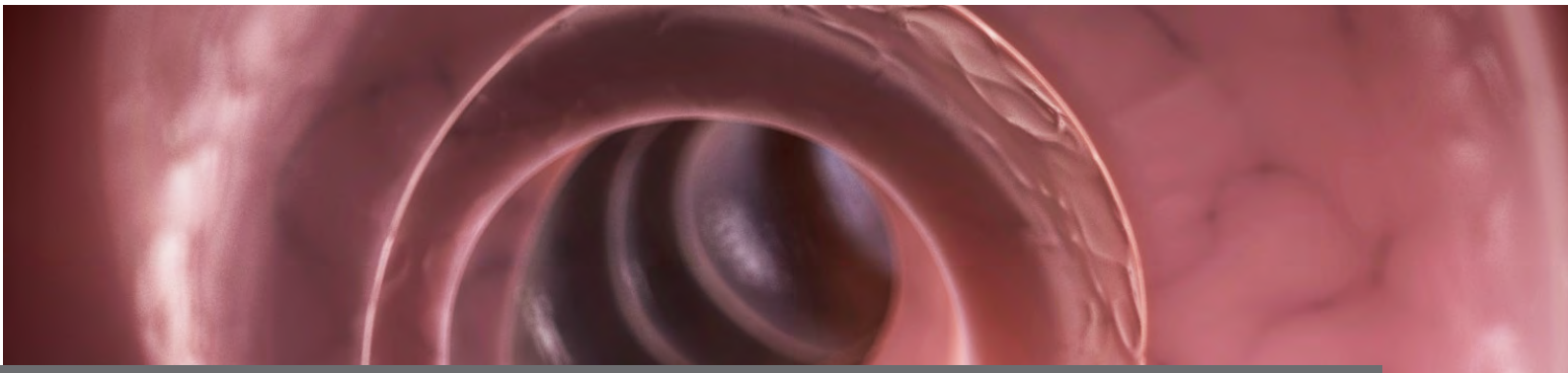
Groups Participating in the Program

Program 4 consists of the four following groups:

GROUP	CENTRE	CITY
Marina Berenguer	Hospital Universitario La Fe	Valencia
Manuel de la Mata	Hospital Universitario Reina Sofía	Córdoba
Miguel Navasa	Hospital Clínico y Provincial	Barcelona
Linked group: Rocío Álvarez	Hospital Virgen de la Arrixaca	Murcia

Descriptores de actividad de los grupos del programa 4

GROUP	ACTIVITY DESCRIPTORS
Berenguer	Hepatitis C recurrence Complications arising from immunosuppression
De la Mata	Alloimmune response and immunosuppression Lesion due to ischemia-reperfusion Hepatitis C recurrence Complications arising from immunosuppression
Navasa	Alloimmune response and immunosuppression Lesion due to ischemia-reperfusion Hepatitis C recurrence Complications arising from immunosuppression
Álvarez	Alloimmune response and immunosuppression



P5. Gastrointestinal and Hepatic Oncology

Coordinator:

Jordi Bruix

Assistant Coordinators:

José Juan García Marín, Antoni Castells

Research Groups:

1- Experimental hepatology and drug vectorization. Antitumor chemotherapy resistance. (Dr. JJ García Marín. Univ. of Salamanca)

2- Molecular Pharmacology and Experimental Therapies. (Dr. M. Pastor. Univ. of Barcelona)

3.- Gastrointestinal and Pancreatic Oncology (Dr. A Castells. IDIBAPS)

4.- Colorectal and Gastroesophageal Cancer. Peptic Acid Disease (Dr P. Parrilla. Univ. of Murcia)

5.- Hepatic Oncology (Dr. J Bruix. IDIBAPS);

6.- Experimental Hepatology and Gene Therapy (Dr. J Prieto, CUN).

Description

The research is focused on epidemiology, molecular mechanisms, diagnosis and treatment of liver cancer and cancer of the digestive system. It covers the following lines of research

1. Cellular resistance to chemotherapy and membrane transport.

The low response of liver and gastrointestinal tumors to pharmacological therapy is the result of a multifactorial phenomenon involving different mechanisms of chemoresistance (MoC). These mechanisms are classified in five groups according to whether they entail a reduction of the net amount of drug inside the cell due to a reduction in uptake (MOC-1a) or increase in efflux (MOC-1b), a reduction in metabolic activation of prodrugs or inactivation of drugs (MOC-2), changes in molecular targets (MoC-3), increase in the efficacy of processes for repairing macromolecules attacked by cytostatic agents (MOC-4) and changes in the apoptosis (MOC-5a) and survival (MOC-5b) balance. Earlier CIBERehd studies identified gene expression patterns characteristic of each type of tumor and have indicated possible targets that must be studied for therapeutic purposes.

This include membrane transporters, phase I enzymes and antiapoptotic factors. Together with changes in expression, the onset of genetic variants characteristic of the patient or arising in the tumor during the carcinogenic process can affect the function of these proteins and result in a lack of response to chemotherapy.

2. Gastrointestinal and pancreatic oncology

Gastrointestinal and pancreatic cancer is responsible for most cancer-related deaths. Reducing the number of deaths requires early detection. This is the rational basis for implementing population colorectal cancer screening programs, currently in the phase of extension and evaluation. It is important to establish which of the different existing strategies is the most effective and efficient for medium-risk population screening, as well as which groups have an increased risk of developing this tumor. Furthermore, the development and evaluation of new non-invasive biomarkers that allow increasing participation in screening and monitoring programs, increasing the diagnostic performance of strategies currently used, and reducing potential complications resulting from said strategies is fundamental. Finally, it is important to identify populations of individuals with genetic or genomic characteristics that increase their susceptibility to developing these neoplasias.

3. Hepatic oncology

Liver cancer is a neoplasia that has experienced a rise in incidence in recent years. The possibility of diagnosis in early stages of the disease and the availability of treatments that are proven effective for all stages of the disease have brought about a great deal of research activity to improve knowledge about molecular mechanisms determining their development and the most suitable diagnosis and treatment strategy.

CIBEREHD groups lead the research in genetic signatures both for the development of cancer in cirrhosis and for the progression and prognosis after treatment. The groups are designing and running international clinical trials for new drugs in phase 1-2, and in phase 3 both in first line and in second line after conventional therapy has failed. Unfortunately, results up until now have been negative. This may be because knowledge about the anomalies determining tumor progression is limited, and because the prognostic assessment and design of trials for these patients must be innovated. In addition to intervention studies, the usefulness of response markers is evaluated based on functional imaging techniques and biological peripheral blood determinations.

4. Experimental hepatology and gene therapy

This field studies the mechanisms involved in the progression from chronic liver damage to cirrhosis and hepatocarcinoma (HCC): disease markers and therapeutic relevance of hepatoprotective cytokines and growth factors. Methods based on cell therapy and gene therapy are also developed for the treatment of cirrhosis of the liver and of primary and metastatic liver tumors. Immune modulation is being investigated for possible liver cancer immunotherapy and graft tolerance in liver transplant.

Selection of large projects

Development and evaluation of methods for predicting response to chemotherapy in liver, esophageal, stomach, pancreatic and colorectal tumors.

PI: Marçal Pastor-Anglada and José J. García Marín.

The retrospective studies conducted by the CIBERehd using TLDAs have allowed identifying groups of genes involved in different MoC, the expression of which is characteristically high in hepatocarcinoma, hepatoblastoma, cholangiocarcinoma and adenocarcinoma of the colon and pancreatic cancer. Some of these genes encode proteins relating to drug uptake and expulsion by tumor cells, the main pharmacological targets, the mechanisms of drug detoxification and DNA repair, also including genes involved in cell proliferation and apoptosis. A very common feature is the drop in expression of the SLC22A1 gene which encodes for an organic cation transporter (OCT1), which is a determining factor in tumor cells absorbing cationic drugs such as sorafenib. In addition, preliminary studies have detected several inactivating mutations and aberrant splicing alternatives contributing to a lower capacity to transport the drug across the plasma membrane. The group will investigate if these changes also occur as a common characteristic in other gastrointestinal tumors. In turn, a retrospective multicentre study will be conducted to elucidate if there is a relationship between disorders in the SLC22A1 gene and the clinical response of patients to treatment with sorafenib. Furthermore, studies aimed at investigating the mechanisms of control determining changes in the genetic profile of tumors and determining the phenotype of the lack of response to antitumor chemotherapy have indicated a nuclear receptor, FXR, and its interaction with glucocorticoids as a possible control path relating to maintaining chemoprotection in healthy tissue and with the development of chemoresistance in tumor tissue. Both aspects will be analyzed in depth in the immediate development of this line of research.

Development and validation of biomarkers for the early diagnosis of colorectal cancer (EPICOLON III project)

PI: Antoni Castells and Luis Bujanda.

The progression of CRC is a complex multifactorial process involving interaction between various genetic and epigenetic events. Better understanding of these phenomena in the past decade has allowed developing molecular markers with clinical utility potential (biomarker). Until now, the most significant advancements have been made in the study of biomarkers in feces and in blood, based on genetic disorders (somatic mutations in DNA) and epigenetic disorders of tumors (aberrant DNA methylation, miRNA expression pattern disorder). However, essentially all colorectal neoplasias are different and present molecular heterogeneity, which complicates detection strategies. This is a critical consideration in developing CRC biomarkers because no biomarker available today is capable of reliably detecting all CRCs. So the development of new non-invasive biomarkers (for determination in biological fluids, such as blood or feces) with an approach that includes different types of molecules (DNA, methylation, miRNAs, proteins) in well-characterized populations, including patients with precursory lesions (particularly advanced adenoma) is fundamental.

Prospective, controlled and randomized study of colorectal cancer screening in a medium-risk population: detection of occult blood in feces by means of an immunological test every 2 years vs. colonoscopy (ColonPrev study)

PI: Antoni Castells and Luis Bujanda

Today there are various strategies accepted for colorectal cancer screening in a medium-risk population (men and women over 50 years of age, without any personal or family history of this disease). However, the most effective and efficient strategy is unknown because there are no studies comparing them directly.

Objectives

To compare the efficacy of the detection of occult blood in feces by means of biennial immunological testing with colonoscopy every 10 years in the medium-risk population (individuals over 50 years of age without any additional risk factors) in relation to: Reduction of mortality due to colorectal cancer in 10 years (primary objective) and rate of detection of advanced colorectal neoplasias (high-risk colorectal cancer and adenomas).

Translational research for integral genomic analysis of conventional fibrolamellar hepatocellular carcinoma and intrahepatic cholangiocarcinoma (CHC).

PI: Josep M. Llovet and Jordi Bruix

The prognostic assessment of patients with hepatocellular carcinoma or with cholangiocarcinoma today is based on conventional morphological criteria. Logically, tumor phenotype depends on the molecular disorders and, therefore, characterizing molecular anomalies in patients with this neoplasia and correlating them with progression must enable developing prediction models based on genetic signatures, as well as stratifying patients according to the molecular pattern that should be responsible for the response to treatment.

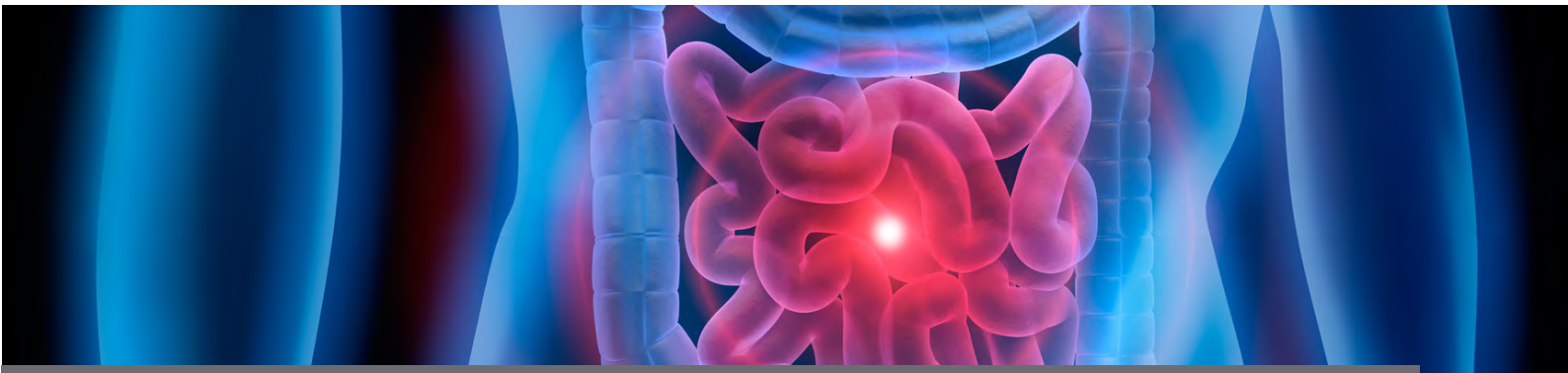
The results obtained until now have contributed to stratifying patients according to genomic patterns. This data was not generated from collections of surgically treated tumors, and the challenge today is to validate the usefulness and reproducibility of the information obtained from advanced stage tumor biopsy samples. Advanced tumor heterogeneity suggests that biopsy-based information may be limited. Therefore, studies have been designed to explore the usefulness of detecting circulating tumor cells and to obtain molecular profiles based on said studies. Colloquially speaking, this approach is referred to as "liquid biopsy".

Treatment of hepatocarcinoma by means of anti-PD1 monoclonal antibodies.

PI: Ignacio Melero y Bruno Sangro.

Advanced stage hepatocarcinoma has a very poor prognosis. Sorafenib is a biological agent that significantly increases advanced stage hepatocarcinoma patient survival.

It does this consistently in all the analyzed subgroups. In fact, it is the only systemic treatment that has demonstrated anti-neoplastic activity. There is preliminary evidence that hepatocarcinoma can be sensitive to immunotherapy strategies, including enhancement of cytotoxic T-lymphocyte response by means of anti-CTLA-4 antibodies. In addition, antibodies targeting programmed cell death receptor type 1 (PD-1) have demonstrated considerable antitumor activity in patients with lung tumors, kidney tumors or melanoma. The general objective of this project is to determine if treatment with Nivolumab, a completely humanized monoclonal antibody that is active against the PD-1 receptor, possesses antitumor action in patients with advanced hepatocarcinoma.



P6. Gastrointestinal Inflammation and Motility

The program on Gastrointestinal inflammation and motility, maintains intense networking between the groups with stable collaborations crystalizing in achievement of external funding and high standard outputs.

The area of Neurogastroenterology and Motility has further developed collaborative studies between the different groups in CIBERehd and with other international teams. The flourishing areas include the characterization of dismotility patterns and electrophysiological and ultrastructural alterations in patients with gut dysfunctions. The former aspect may provide relevant results applicable to the diagnosis and subclassification of these patients, that may facilitate their clinical management . At translational level Ciberehd promoted and endorsed the position statements of the European Society on Swallowing Disorders on best clinical practice for adult patients with oropharyngeal Dysphagia developed during the 2nd ESSD congress, October 27-27, Barcelona. The cross-task between colonic flora and the host has originated a new concept in Neurogastroenterology: the microbiotame-gut-brain axis. This new insight has been presented in an international summit (Microbiota for Health) in France. This area of research has aroused tremendous interest and has promoted the incorporation of an international multidisciplinary section within the European Society of Neurogastroenterology and Motility, led by members of CIBERehd. Furthermore, international summits on "Microbiota for Health", chaired by CIBERehd members, have been jointly organized with the American Gastroenterological Association in Evian, France (2012) and Madrid (2013.) The area of Neurogastroenterology and Motility has further developed collaborative studies on electrophysiological and ultrastructural alterations in patients with gut dysfunctions between the different groups in CIBERehd and with other international teams.

In the subprogram of acid-related diseases, the groups have been actively working integrated in 2 main collaborative areas. One of them focused on the investigation of both environmental and genetic factors linked to increased susceptibility to bleed in the GI tract in patients taking NSAIDS or antiplatelet agents. The other area deals with investigation in the treatment and management of H. pylori infection in humans, where substantial contributions has been made possible thanks to the extensive networks of hospitals leaded by investigators of this area of the CIBERehd. Both programs have provided a significant contribution in terms publications and of samples and associated high-quality clinical information for completion of ongoing genetic analysis in acid-related disease. One of the outstanding ongoing projects resulting from the intense networking an collaboration between the grupos of program 6, is the development of a multicenter project aiming at elucidating the causes of gastric cancer progression based on the characterization of clinical, histologic, microbiologic, genetic, epigenetic and epidemiologic factors, in a cohort of patients diagnosed at least 10 years previously of gastric cancer precursor lesions. This stu-

dy may provide information of high relevance for clinical practice

The research for development of cell therapies for inflammatory bowel diseases has established the option of autologous hematopoietic stem cell transplantation as a clinically accepted alternative for treatment of refractory Crohn's disease, which has been recognized in the recent guidelines of the European Bone Marrow Transplant group. Notably, the development process of another form of cell therapy, based on the administration of autologous conditioned tolerogenic dendritic cells, obtained from peripheral blood monocytes has been completed, and the production process has obtained a European patent, in which CIBERehd has a considerable participation. Furthermore, a phase I clinical trial is actively recruiting patients and will be completed in 2013.

The majority of groups integrated in the program have provided a significant contribution in terms of samples and associated high-quality clinical information for completion of a GWAS in inflammatory bowel diseases. So far, this project has led to the discovery of new susceptibility locus for Crohn's disease. This will be continued by functional characterization of the genetic susceptibility variants. The project will also take advantage of the long prospective follow-up of patients, which makes this collection unique, to establish robust genotype-phenotype associations, overcoming the limitations of previous studies with limited clinical information associated to the samples.

Studies on the gut microbiota within the European MetaHIT project have developed novel strategies to detect unknown commensal species using a high-throughput sequencing and the metagenomic species concept (groups of genes that co-vary among individuals). This strategy has unveiled a number of commensals that are missing in ulcerative colitis and Crohn's disease patients.

Collaborations between various groups have also resulted in relevant publications for development of new therapies for IBD, such as the elucidation of molecular mechanisms of resistance to corticosteroids, and optimization of current treatments such as thiopurines and anti-TNF antibodies, to get the maximum efficiency in the use of these drugs, that impose a significant cost to the public health system. In this respect, a prominent project is the identification of predictors of response to anti-TNF therapy, as well as predictors of loss of response. This is a timely initiative since it is envisiones that in the next few years other alternative therapies may be approved, and the precise prediction of responose ot each of the therapeutic options will result in improved patient care and reduced costs.

The microscopic colitis has been considered a rare disease. The collaborative effort of several groups integrated in the CIBERhed has allowed the identification of epidemiological risk factors for the disease. Advances in the diagnosis, natural history and quality of life of other forms of intestinal inflammation such as celiac disease are also under investigation in the setting of CIBERhed.

Members of the program 6 have had a high participation and international visibility on the elaboration of practice guidelines and consensus documents, in various areas including Barrett's esophagus, management of H. pylori infection, upper gastrointestinal bleeding, NSAID-related gastrointestinal complications, inflammatory bowel disease, microscopic colitis, oropharingeal dysphagia and neurogastroenterology disorders. During 2012, some of the members of the group have had tenure of presidency of international medical societies or have served as associate editors of first decile journals.

3
Horizontal Platforms

Strategic Actions and Program

One of the global objectives of CIBEREHD is to share resources and infrastructures between groups.

The platforms and strategic actions of CIBEREHD are constituted as clusters of technical-scientific equipment with a specific functionality, intended for offering top-level technological resources to CIBEREHD research groups and external groups, under the established conditions.

EFFECTS OF WEIGHT REDUCTION ON PORTAL PRESSURE IN PATIENTS WITH COMPENSATED CIRRHOSIS OF THE LIVER AND EXCESS WEIGHT/OBESITY

This strategic action was created for the purpose of studying a homogenous group of compensated cirrhosis patients who suffer excess weight and obesity of any degree. A significant weight reduction is expected to be associated with a significant portal pressure reduction, confirming that it is possible to obtain this result by means of non-pharmacological intervention.

Primary objective

To assess the effect of the weighted reduction obtained after 4 months of diet and physical exercise on portal hypertension, estimated by means of measuring GPVH in cirrhosis patients suffering excess weight or obesity.

Secondary objectives

- To assess the effect of the weighted reduction obtained after 4 months of diet and physical exercise on liver function estimated by means of indocyanine green clearance and standard liver function tests in cirrhosis patients suffering excess weight and obesity.
- To assess the effect of the weighted reduction obtained after 4 months of diet and physical exercise on fibrosis markers, endothelial dysfunction and oxidative stress and angiogenesis. This will enable better understanding the physiopathological mechanisms through which obesity affects liver disease.

The results of this project will provide new knowledge about the possibility of non-pharmacological treatment (weight loss) of portal hypertension in patients with cirrhosis of the liver and excess weight/obesity.

A professional dietician had to be hired to perform follow-up once a week for the first month and every two weeks after the second month.

BIOINFORMATICS PLATFORM

The primary objective of the Bioinformatics Platform is to provide support to research staff in this area. In current research, where a flow of data resulting from the massive data screening is obtained, this platform is a unit where any investigator that is a member of CIBERehd can have a rapid and customized solution.

The Platform works on developing and applying bioinformatics tools to analyze data from high-throughput experiments (basically microarrays) to help develop medical diagnostic kits.

Services offered by the platform:

- Development of new bioinformatics tools and applications
- File repository
- Project planning consulting and advisory services

CICBIOGUNE PLATFORM

The primary objective of this platform is to identify and validate genetic variants (for example, polymorphisms of a single nucleotide or methylation differential) involved in common complex human diseases. To that end, the complete genomes of patients and the control used on all high-throughput genotyping and sequencing techniques are studied.

Bioinformatics tools are also developed for data analysis. These tools supply a biological result interpretation by means of examining the functionality of the identified genes, and by means of investigating their involvement in the etiology of diseases and the possible mechanism of action.

Services offered by the Platform:

- SSNP genotyping and cytogenetic analysis / CNV:
- Epigenetic analysis
- Whole genome expression
- New generation sequencing

CIBERHEP PLATFORM

The CIBERHEP Platform was designed as a registry that allows studying the clinical treatment of patients with chronic hepatitis B in Spain with the following objectives:

- To study the effectiveness of the most widely used antiviral treatment options today against HVB.
- To provide users with complete and easy-to-access information for monitoring the patients that are entered.

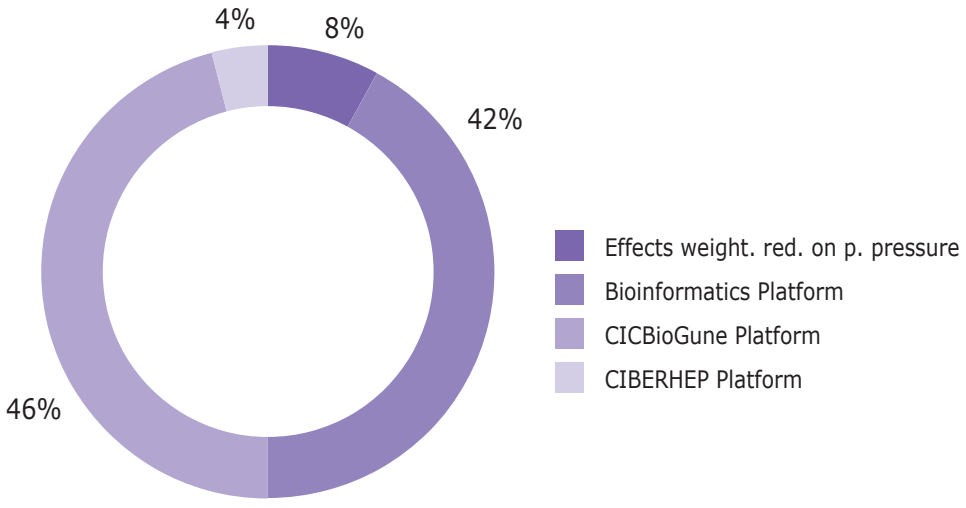
The purpose of this database is to collect the follow-up on patients undergoing treatment with first-line therapy options, i.e., Entecavir or Tenofovir (in monotherapy or combination with other antiviral agents), for at least the time that they received treatment with these drugs.

If no antiviral treatment was received prior to Entecavir or Tenofovir, it is also necessary to record the dose and the period of time during which it was received.

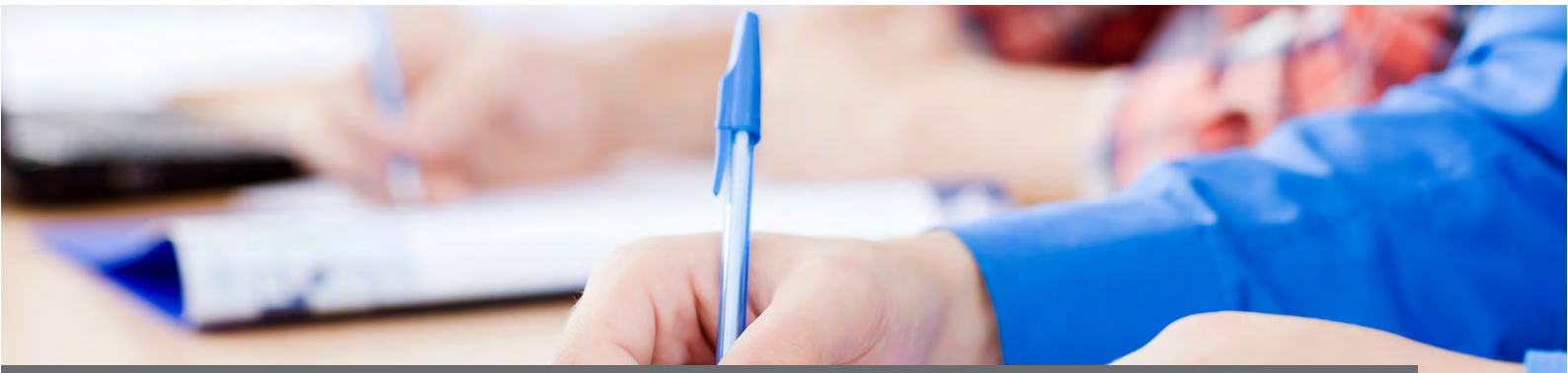
Resources used in the Platform Program

Expenses generated by hired use management staff are included, providing the necessary services to support research, as well as general item expenses and the salary and travel expenses of the platform manager.

PLATFORM	AMOUNT
Effects of weighted reduction on portal pressure	11.174 €
Bioinformatics Platform	57.150 €
CICBIOGUNE Platform	61.983 €
CIBERHEP Platform	4.902 €
TOTAL	135.209 €



4
Horizontal Programs



Training and Dissemination Plan

Training Plan

One of the goals of CIBERehd is to increase the knowledge of its components (post-docs, pre-docs, nurses and technicians) to increase the level of the research and to facilitate the interaction among the different groups. These tasks are coordinated through the training plan as a part of the annual action plan. The training plan consists on several programs: mobility (visitor professor program, stay in other CIBERehd group, and short-stays in national or international excellence centers), increase of knowledge (assistance to national or international courses, workshops and monothematic conferences), promote scientific activities organized for members of the CIBERehd (sponsor and fund workshops, symposia, post graduate courses), collaboration with the training activities of scientific societies, and virtual training activities through the web page.

In 2013, 36 grants were awarded to researchers for several activities under the program of the Training Plan. Despite the budget cuts we have been able to attend nearly all the requests. The beneficiaries of the aid were 10 investigators from CIBERehd institutions and 26 employees, of whom 6 were Post-doc, 16 Pre-doc, 1 research nurse, and 3 technicians. The activities funded were the stage of one investigator in other center CIBERehd, 4 short stays abroad (USA, Switzerland, and France), 25 training courses and activities in Spain, and 6 international ones.

Among these activities we would like to highlight the stay of Raquel González (Dr. Zarzuelo CIBERehd group) who did a stay in the University of Salamanca (Dr. Garcia Marin CIBERehd group), and the stages of Dr. Jesús Bañales (Dr. Bujanda group) and Dr. Angeles Rojas (Dr. Romero group) at the Mayo Clínic with Prof. K. Lindor and at the University of Geneve with Prof. F. Negro, respectively.

The CIBERehd through the training plan sponsored the Postgraduate Course of the Asociacón Española para el Estudio del Hígado (AEEH) and of the Asociación Española de Gastroenterología (AEG). The training plan also sponsored and funded in part the International Simposium "Control o erradicación de la hepatitis B y C" coordinated by Drs. J Quer, JI Esteban and M Buti (Barcelona, May 2013), the "XII Congreso Nacional de Virología" (Burgos, June 2013), the "Jornada de Actualización del Cáncer Colorectal", coordinated by Dr. F. Balaguer (Palma de Mallorca, June 2013), and the workshop "Translational Genomics in Biomedicine", coordinated by Dr. S. Castellvi and M. Gironella (Barcelona).

Beneficiaries of the 2013 Training Plan

Number of investigators	10
Number of employees	26
Post-doctoral	6
Pre-doctoral	16
Nurses of investigation	1
Technicians	3

activities funded in 2013

National courses	25
International courses	6
International internships	4
CIBERehd group internships	1

Dissemination Program

Annual Scientific Report

Every year CIBERehd publishes its Annual Scientific Report where it includes its most important data about the scientific activity performed, new research projects, publications in reference journals and patents under prosecution, among other milestones. The new platforms that were created and the future strategic plans of the Consortium are also published.

The annual publication of the Scientific Report is an important basis for compliance of CIBERehd in promoting and collaborating in scientific research, developing knowledge and transferring that knowledge to society

All the Scientific Reports are available on our web page.

Scientific Conferences

The purpose of the Conferences is to share challenges and advancements that are being made in the area of liver and digestive diseases, as well as to present important novel findings relating to Consortium Management and the performance of the research groups.

The meetings during the Conferences seek to highlight and promote collaboration between the groups in each Program. For this reason, the meetings particularly focus on presenting ongoing cooperative project results and on discussing new project proposals.

5 Research Groups

PROGRAMME:
Portal Hypertension and Cirrhosis

G0024

Group Members

STAFF MEMBERS

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Ubeda Cantera, María P

ASSOCIATED MEMBERS

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Llop Herrera, Elba
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Main lines of research

- Portal hypertension: advances in diagnosis and treatment of portal hypertension and their associated complications, develoment of therapeutic alternatives and study of the pathogenetic mechanisms of portal hypertension
- The immune system in cirrhosis: pathogenetic role in the progression of liver damage and the complications of portal hypertension
- Complications of portal hypertension: relevance of bacterial translocation in the triggering and progression of acute-on-chronic-liver-failure and pathogenesis of bacterial translocation

Most relevant scientific articles

- Bañares R, Nevens F, Larsen FS, Jalan R, Albillos A, Dollinger M. Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the RELIEF trial.Hepatology. 2013 Mar;57(3):1153-62.
- Ripoll C, Genescà J, Araujo IK, Graupera I, Augustin S, Tejedor M. Rebleeding prophylaxis improves outcomes in patients with hepatocellular carcinoma. A multicenter case-control study.Hepatology. 2013 Dec;58(6):2079-88.
- Lario M, Muñoz L, Ubeda M, Borrero MJ, Martínez J, Monserrat J. Defective thymopoiesis and poor peripheral homeostatic replenishment of T-helper cells cause T-cell lymphopenia in cirrhosis.J Hepatol. 2013 Oct;59(4):723-30.
- Bárcena R, Moreno A, Rodríguez-Gandía MA, Albillos A, Arocena C, Blesa C. Safety and anti-HCV effect of prolonged intravenous silibinin in HCV genotype 1 subjects in the immediate liver transplant period.J Hepatol. 2013 Mar;58(3):421-6.
- Úbeda M, Lario M, Muñoz L, Díaz D, Borrero MJ, García-Bermejo L. Systemic inflammation in absence of gut bacterial translocation in C57BL/6 mice with cirrhosis.Gut. 2013 Feb;62(2):330-1.

Highlights

TRASLATIONAL AND CLINICAL RESEARCH. The main results of the clinical research activity of the group have been:

- Study of the mechanisms involved T cell dynamics in cirrhosis. We have explained Th-cell immunodeficiency in cirrhosis by a universal defect in thymopoiesis exacerbated by splenic pooling and activation-driven cell-death induced by bacterial translocation.
- Systemic inflamation in a murine cirrhosis without bacterial translocation.
- Acute on chronic liver failure. Involvement in the studies leading to the clinical characterization of ACLF and the role of extracorporeal albumin dyalisis
- Hepatocellular carcinoma and portal hypertension. Relevance of rebleedig prevention in patients with hepatocellular carcinoma, and potential role of beta-blockers in hepatocellualr carcinoma prevention

Master in Hepatology. Organization and development of Master in Hepatology 2012/2013, as an integrated action of the Universities of Alcalá, Autónoma de Madrid, Universidad Complutense de Madrid, Sevilla y Cantabria, as well as CIBERehd.

PROGRAMME:
Immunology and Liver Transplant

G0072

Group Members

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Main lines of research

- Line 1: Transplant immunology and immune tolerance: new induction ways, maintenance and peripheral tolerance rupture (Mª Rocío Álvarez & Alfredo Minguela)
- Line 2: Cellular and molecular immunology: Regulatory and supprersor cells in transplant, and response against vaccines (Alfredo Minguela)
- Line 3: Receptor-ligand interaction in innate and specific immunology: Role in immunopathology, transplant and cancer (Mª Rocío Álvarez)
- Line 4: Immunogenetics and immunoresponse control in immunological hyperreactivity processes: Allergic and autoimmunitary diseases (Manuel Muro)
- Line 5: Immunotolerance and immunoregulation of immune response against solid tumour and hematopoietic system (José A. Campillo & Jorge A. Martínez-Escribano)
- Line 6: Primary and secondary immunodeficiencies. Regional registry and immunogenetic or functional deficits (Ana Mª García-Alonso)

Most relevant scientific articles

- Legaz I, López-Álvarez MR, Campillo JA, Moya-Quiles MR, Bolarín JM, de la Peña J et al.. KIR gene mismatching and KIR/C ligands in liver transplantation: consequences for short-term liver allograft injury.Transplantation. 2013 Apr 27;95(8):1037-44.

Highlights

The most remarkable finding of our work was the discovery that liver transplant can mediate innate immunity based on the NK cell alloreactivity, in the same way as it was previously described for hematopoietic stem cell transplantation, when this model is applied to rejection (graft versus host). Therefore, NK cell alloactivation could play a role in early acute rejection episodes in liver transplant recipients, especially when a recipient that carry either KIR2DL3 or KIR2DS4 gene, or both genes, receives a liver from a donor that poses HLA-C that does not belong to allotype C1 (when donor is a homozygote for allotype C2). This finding has led to a new way of working and prediction of the rejection based on the detection of KIR/HLA combination that could be useful for better monitoring and individual therapeutic follow-up of this transplant's recipients, in order to prevent side effects and inherent complications of the immunosuppressor therapy. Moreover, this finding could serve to demonstrate a new subtype of regulatory lymphocytes TCD8+, as well as to predict the outcome of the transplant and to define the different biological markers in the patients with cirrhosis or infected with hepatitis C virus.

PROGRAMME:
Cholestasis and Metabolic Disorders

G2008

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Main lines of research

- Spanish DILI Registry group: Epidemiological research; Caussality assessment; Identification of genetic factors and Mechanisms of toxicity.
- Cronic Viral Hepatitis: diagnostical and therapeutics aspects.
- Non-alcoholic EsteatoHepatitis (NAFLD).

Most relevant scientific articles

- Ulzurrun E, Stephens C, Crespo E, Ruiz-Cabello F, Ruiz-Nuñez J, Saenz-López P et al.. Role of chemical structures and the 1331T>C bile salt export pump polymorphism in idiosyncratic drug-induced liver injury.Liver Int. 2013 Oct;33(9):1378-85.
- Navarro-Jarabo JM, Ubiña-Aznar E, Tapia-Ceballos L, Ortiz-Cuevas C, Pérez-Aísa MA, Rivas-Ruiz F et al.. Hepatic steatosis and severity-related factors in obese children.J Gastroenterol Hepatol. 2013 Sep;28(9):1532-8.
- Andrade RJ, García-Samaniego J. [Biochemical and pharmacological features of telaprevir].Enferm Infecc Microbiol Clin. 2013 Jul;31 Suppl 3:2-6.
- Stephens C, López-Nevot MÁ, Ruiz-Cabello F, Ulzurrun E, Soriano G, Romero-Gómez M, Moreno-Casares A, Lucena MI, Andrade RJ.. HLA alleles influence the clinical signature of amoxicillin-clavulanate hepatotoxicity.Plos One. 2013;.

Highlights

- 5 PUBLIC COMPETITIVE RESEARCH PROJECTS (3 of the Sanitary Research Fund (FIS).; 1 of the Andalusian Health Service; 1 of the Ministry of Economy, Innovation and Science).
- 2 PRIVATE COMPETITIVE RESEARCH PROJECTS (AUIP grant (Asociación Universitaria Iberoamericana de postgrado) for the setting-up of an Ibero-American hepatotoxicity network. ;Grant from the University of Málaga (Research commission) for the setting-up of Thematic networks, called: "Drug-Induced Liver Injury"
- 2 CONTRACTS WITH COMPANIES (AGENCIA ESPAÑOLA DEL MEDICAMENTO; BIOIBERICA S.A.).
- 3 EUROPEAN PROJECTS (Innovative Medicines Initiative. European Union. Proposal acronym: PROTECT; Proyecto FLIP (SAS); SAFE-T INTERFACE EUROPE).

AWARDS

- 6.000 € to the project: "Support of a multicentric and multidiciplinary Ibero-American hepatotoxicity network induced by drugs and herbals products." Call of the Spanish Society of Digestive Pathology 2013.

PENDING PATENTS: 2.

- "Improved method to get meaningful data in predicting the fulminant hepatic failure in DILI patients." (Algorithm and Hy's law).

Setting-up of an Ibero-American hepatotoxicity network.

In 2013, an Ibero-American hepatotoxicity registry was created. To date, information from 114 DILI patients has been collected in Ibero-America.

Risk factors analisis that has an impact in developping the fulminant hepatic failure in DILI patients. Published and presented in national and international congresses.

Analisis of anabolic steroids' illicit use highlighting the necessity to control these compounds. Published and presented in national and international congresses.

DILI analisis of autoinmune features.

We analysed the combined effect on drug-induced liver injury (DILI) development of the ABCB11 1331T>C polymorphism and the presence of specific chemical moieties, with known BSEP inhibiting properties, in the causative drug. Published in Liver Intern. 2013, Oct;33(9):1378-85.

PROGRAMME:
Portal Hypertension and Cirrhosis

G0020

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Main lines of research

- The pathophysiological function of endothelial cells in liver disease
- Characterization of the lipid mediators in inflammation derived from the Kupffer cells.
- Translational research with liver samples from patients with chronic liver disease to study genetic expression
- Study of liver damage in experiemental models, and in genetically modified mice
- Pathogenesis, diagnosis and treatment of acute lier failure in patients with liver cirrhosis.
- Study of the pathophysiology and treatmet of complications in renal function in cirrhotic patients
- Study of the pathophysiology of hepatic encephalopathy in experimental animal models and in clinical setting.
- Bacterial infections and liver diseases.

Most relevant scientific articles

- Acevedo J, Fernández J, Prado V, Silva A, Castro M, Pavesi M. Relative adrenal insufficiency in decompensated cirrhosis: Relationship to short-term risk of severe sepsis, hepatorenal syndrome, and death.Hepatology. 2013 Nov;58(5):1757-65.
- Reichenbach V, Muñoz-Luque J, Ros J, Casals G, Navasa M, Fernández-Varo G. Bacterial lipopolyshaccaride inhibits CB2 receptor expression in human monocytic cells.Gut. 2013 Jul;62(7):1089-91.
- Pauta M, Rotllan N, Vales F, Fernández-Hernando A, Allen RM, Ford DA. Impaired liver regeneration in Ldlr-/- mice is associated with an altered hepatic profile of cytokines, growth factors, and lipids.J Hepatol. 2013 Oct;59(4):731-7.
- García-Alonso V, López-Vicario C, Titos E, Morán-Salvador E, González-Périz A, Rius B. Coordinate functional regulation between microsomal prostaglandin E synthase-1 (mPGES-1) and peroxisome proliferator-activated receptor γ (PPARγ) in the conversion of white-to-brown adipocytes.J Biol Chem. 2013 Sep 27;288(39):28230-42.
- Fagundes C, Barreto R, Guevara M, García E, Solà E, Rodríguez E. A modified acute kidney injury classification for diagnosis and risk stratification of impairment of kidney function in cirrhosis.J Hepatol. 2013 Sep;59(3):474-81.

Highlights

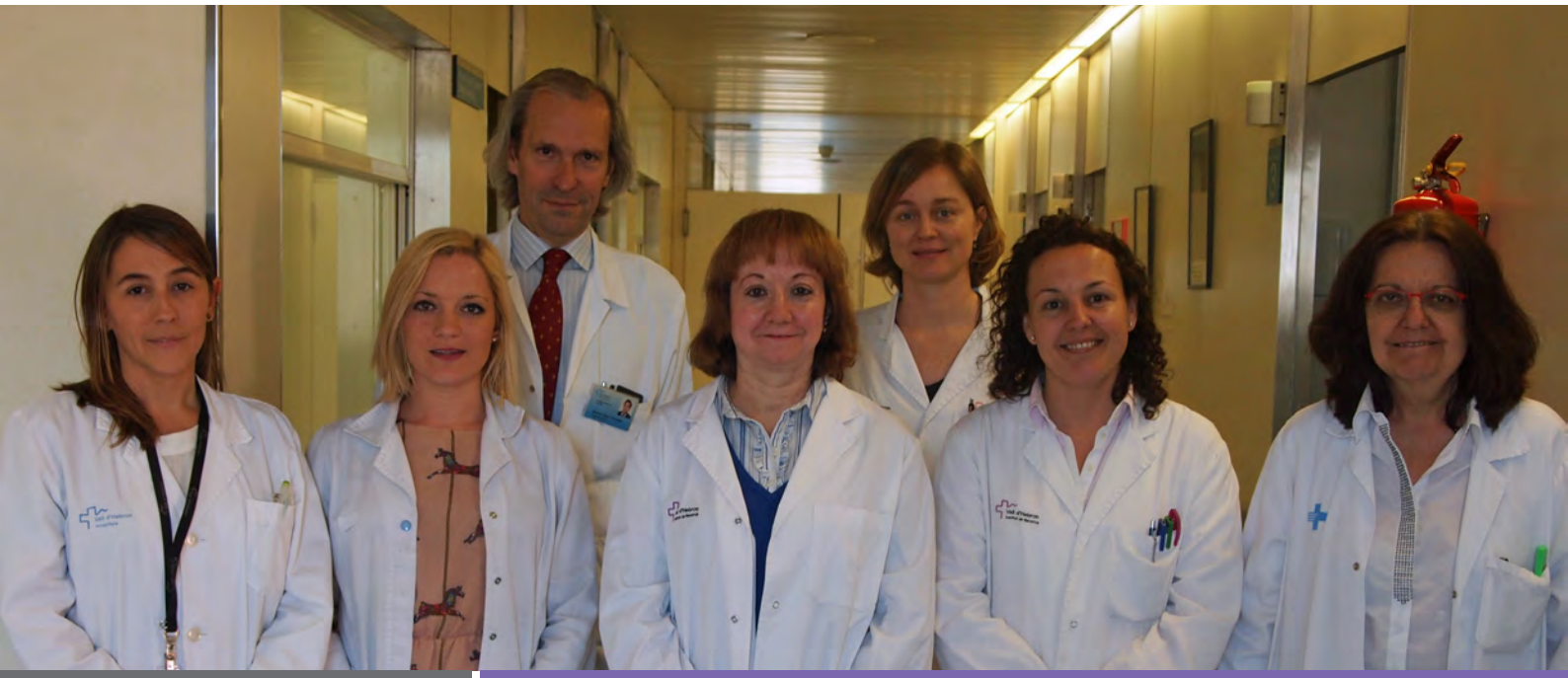
We have investigated anti-angiogenic agents with therapeutic effectiveness but which specifically inhibit hepatic pathological angiogenesis, we have also investigated the role of the receptor of low density lipoprotein in liver regeneration.

We are investigating the development of noninvasive methods that can accurately predict the early stage of the disease and fibrosis progression in time is a priority and growing medical need. Serum levels of several biochemical markers of collagen metabolism have been shown to be useful in diagnosis of liver fibrosis.

The Group is focusing on the identification of biochemical markers and their incorporation into the daily routine, which will probably replace in the near future invasive markers of liver fibrosis; consequently improving the diagnosis and treatment of patients with chronic hepatitis.

The group has actively participated in the CLIF Consortium leading the first study of the Consortium which as a result as defined Acute-on chronic Liver failure (ACLF) as a new entity, and has continued working in new aspects regarding the pathophysiology, clinical implications and prognosis of ACLF.

A further area of research has been the use of new biomarkers in the diagnosis of renal failure and its prognosis in patients with liver cirrhosis. A further line has been the evaluation of new strategies for the treatment of Hepatorenal Syndrome.



PROGRAMME:
Gastrointestinal Inflammation and Motility

G0021

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Main lines of research

- Evaluation of intestinal motility by endoluminal image analysis
- Abdominal accommodation
- Digestive, cognitive and emotive effects of meals
- Diet, microbiota, intestinal content and digestive function
- Intestinal sensory and reflex activity
- Inflammatory mediators in functional gut disorders

Most relevant scientific articles

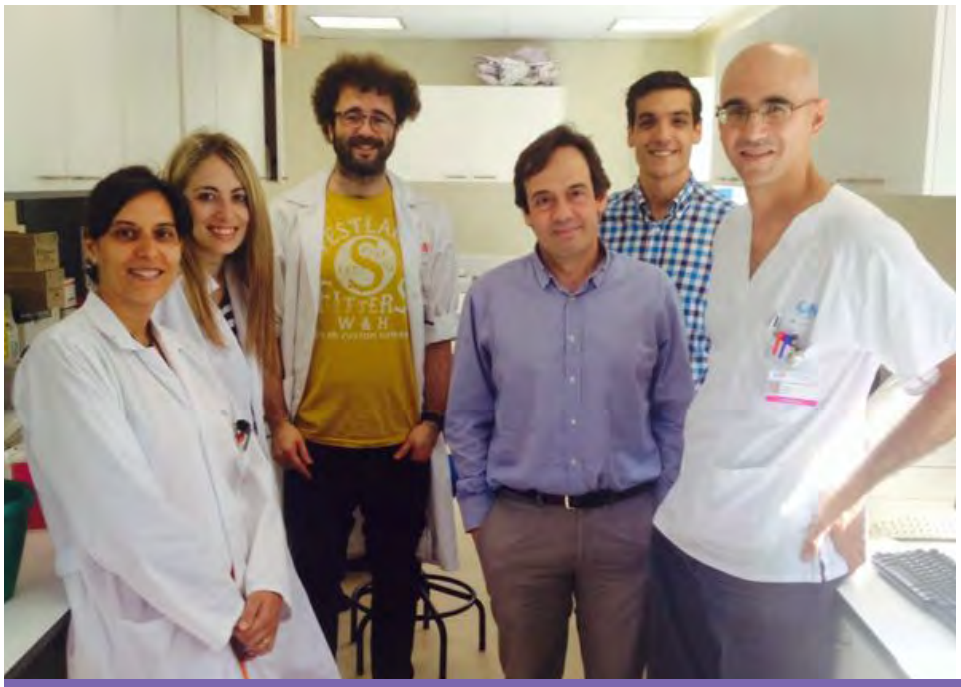
- Feinle-Bisset C, Azpiroz F. Dietary and lifestyle factors in functional dyspepsia.Nat Rev Gastroenterol Hepatol. 2013 Mar;10(3):150-7.
- Feinle-Bisset C, Azpiroz F. Dietary lipids and functional gastrointestinal disorders.Am J Gastroenterol. 2013 May;108(5):737-47.
- Martínez C, Lobo B, Pigrau M, Ramos L, González-Castro AM, Alonso C. Diarrhoea-predominant irritable bowel syndrome: an organic disorder with structural abnormalities in the jejunal epithelial barrier.Gut. 2013 Aug;62(8):1160-8.
- Burri E, Cisternas D, Villoria A, Accarino A, Soldevilla A, Malagelada JR. Abdominal accommodation induced by meal ingestion: differential responses to gastric and colonic volume loads.Neurogastroenterol Motil. 2013 Apr;25(4):339-e253.
- Barba E, Quiroga S, Accarino A, Lahoya EM, Malagelada C, Burri E. Mechanisms of abdominal distension in severe intestinal dysmotility: abdomino-thoracic response to gut retention.Neurogastroenterol Motil. 2013 Jun;25(6):e389-94.

Highlights

COLLABORATIONS AND RESULTS. The joint program with the Department of Mathematics of the University of Barcelona has implemented a system for the evaluation of intestinal motility using the endoscopic capsule, which has originated patents and is in the process of commercialization by the company Given Imaging. The collaborative program on intestinal motility with the group of Dr Clavé (Marcel Jimenez) has consolidated. Furthermore we have investigated the effects of diet on intestinal microbiota (collaboration with the group of Dr Guarner), on gut content (collaboration with the group of the robotics of the Universidad Politénica de Cataluña) and on cognitive / emotive perception (collaborations with the industry and support by Cenit program). The research line on abdominal accommodation has originated therapeutic techniques for the treatment of abdominal distention and rumination that have been applied to clinical practice.

SCIENTIFIC ACTIVITIES. During 2013 the field of intestinal microbiota has expanded tremendously. A Spanish Society for Pre-and Probiotics has been constituted (IP member of the steering committee) and an annual multidisciplinary meeting has been consolidated; during 2013 a Spanish guide on prebiotics has been developed. At the international level, within UEG a section on Intestinal Microbiota and Health has been constituted (IP chair) and a collaboration with AGA has been implemented to organize a joint annual meeting, which will take place in Barcelona every other year (IP director). UEG (IP councilor) has established Barcelona as the location for UEGW every other year. Within the Rome Foundation (IP board of directors) the process for the Rome IV meetings has been initiated and a working team for the study of the effects of diet on functional digestive symptoms has been established (IP member).

TRAINING. A European Training Program on research in Neurogastroenterology, supported by the Marie Curie program, has been established (IP director of Spanish node). UEG and ESNM organized European courses in Barcelona on functional dyspepsia and irritable bowel syndrome, respectively (IP course director).



PROGRAMME:
Portal Hypertension and Cirrhosis

G0082

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Main lines of research

- Complications of cirrhosis.
  - Study of the effect of low molecular weight heparin in cirrhosis of the liver (clinical and experimental studies).
  - Study of the mechanisms of thrombopenia in cirrhosis (clinical and experimental studies).
  - Albumin-based liver assist devices (clinical studies).
  - Complicaitions of portal hypertension (clinical and experimental studies).
- Mechanisms of liver regeneration (experimental studies).
- Inflammatory bowel disease (clinical and experimental studies).

Most relevant scientific articles

- Bañares R, Nevens F, Larsen FS, Jalan R, Albillos A, Dollinger M. Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the RELIEF trial.Hepatology. 2013 Mar;57(3):1153-62.
- Ripoll C, Genescà J, Araujo IK, Graupera I, Augustin S, Tejedor M. Rebleeding prophylaxis improves outcomes in patients with hepatocellular carcinoma. A multicenter case-control study.Hepatology. 2013 Dec;58(6):2079-88.
- Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis.Gastroenterology. 2013 Jun;144(7):1426-37, 1437.e1-9.
- Rincón D, Lo Iacono O, Tejedor M, Hernando A, Ripoll C, Catalina MV. Prognostic value of hepatic venous pressure gradient in patients with compensated chronic hepatitis C-related cirrhosis.Scand J Gastroenterol. 2013 Apr;48(4):487-95.

Highlights

From the perspective of research activity, we would like to highlight two important clinical studies that were published in 2013. The first one is the most ambitious study in the literature regarding the treatment of patients with acute-on-chronic liver disease using bio-artificial liver assist devices. This European multi-center clinical trial was coordinated by the group and involved the participation of researchers from several groups of the CIBER (Hepatology 2013).

The group also led an observational multicenter study involving the participation of several groups of the CIBER that aimed to evaluate the prognosis of patients with variceal hemorrhage and hepatocellular carcinoma (Hepatology 2013). This study provides the rationale for optimizing the treatment of this serious complication in clinical practice.

From the perspective of research facilities, it is important to highlight the profound remodelling of our group's research laboratory, which was possible due to the colaboration between the CIBEREHD and the Instituto de Investigación Sanitaria Gregorio Marañón. We hope that this improvement will generate a relevant bibliometric impact in the short term regarding experimental studies.

Our group obtained funding as IP (Luis Menchén) for a project in the line of inflammatory bowel disease and intestinal epithelial permeability in the 2013 call of the Instituto de Salud Carlos III (proyectos de investigación en salud). This circumstance reflects the capacity of several components of our group to obtain funding in competitive calls.

Finally, we directed and defended two Doctoral Thesis in the Universidad Complutense.

PROGRAMME:
Immunology and Liver Transplant

G0065

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Main lines of research

- Liver Transplantation (indications, post-transplant complications).
  - Hepatitis C and liver transplantation (clinical, virologic and immunologic studies).
  - Hepatitis B and liver transplantation (clinical and virologic studies).
  - Hepatocelular carcinoma and liver transplantation.
  - Post-liver transplantation metabolic complications.
  - Inmunosupression (efficacy, toxicity, rejection, immunologic tolerance, long-term complications).
  - Post-transplant quality-of-life.
- Viral hepatitis (HBV, HCV).
- Alcoholic and non-alcoholic fatty liver disease.
- Immunologic, virologic and molecular mechanisms associated with hepatotoxicity.
- Rare diseases (Wilson Disease).
- Non-cirrhotic portal hypertension.

Most relevant scientific articles

- Berenguer M, Roche B, Aguilera V, Duclos-Vallée JC, Navarro L, Rubín A, Pons JA, de la Mata M, Prieto M, Samuel D. Efficacy of the retreatment of hepatitis C virus infections after liver transplantation: role of an aggressive approach.LIVER TRANSPLANT. 2013;19(1):69-77.
- Berenguer M, Schuppan D. Progression of liver fibrosis in post-transplant hepatitis C: mechanisms, assessment and treatment.J Hepatol. 2013 May;58(5):1028-41.
- Giusto M, Berenguer M, Merkel C, Aguilera V, Rubin A, Ginanni Corradini S et al.. Chronic kidney disease after liver transplantation: pretransplantation risk factors and predictors during follow-up.Transplantation. 2013 May 15;95(9):1148-53.
- Rubín A, Sánchez-Montes C, Aguilera V, Juan FS, Ferrer I, Moya A et al.. Long-term outcome of 'long-term liver transplant survivors'.Transpl Int. 2013 Jul;26(7):740-50.
- Romero-Gómez M, Berenguer M, Molina E, Calleja JL.. Management of anemia induced by triple therapy in patients with chronic hepatitis C: challenges, opportunities and recommendations.J Hepatol. 2013;.

Highlights

PROJECTS: One project from the Health Spanish Society (FIS) in line with the group research (PI: Dr Victoria Aguilera, Title: Specific cellular immune response against cytomegalovirus following liver transplantation in patients with recurrent hepatitis C").

COLLABORATION WITH OTHER CIBEREHD GROUPS RELATED WITH THE PROJECTS: (1) Immunologic tolerance (PI A. Sánchez Fueyos), (2) non-cirrhotic portal hypertension (PI: JC García-Pagán); (3) Hepatotoxicity (PI: R. Andrade); (4) Hepatitis C in liver transplantation (PI: M Berenguer); (5) Post-liver transplantation metabolic complications (diabetes mellitus) (PI: M Berenguer)

PUBLICATIONS: 10 (5 original articles, 4 reviews, 1 editorial). The 5 original papers all in first quartile journals, in line with the group research main lines (long-term complications in liver transplantation, hepatitis C). International collaboration in 1 review, 1 editorial and 2 original articles. Collaboration with other Ciberehd groups: 2 publications (1 review, 1 original article)

INVITED SPEAKER: (1) M.Berenguer: in 14 Conferences/Congresses (10 international). Including 2 participations in the American Association for the Study of Liver Diseases Hepatitis Single Topic Conference: Hepatitis C treatment in special populations. Atlanta, USA. 15-16 Feb 2013): Treatment of hepatitis C in the liver transplant population, treatment of HCV-cryoglobulinemia; M. Prieto: in 2; V. Aguilera: in 2 national meetings.

OTHER ACTIVITIES (1) M. Berenguer: Associate editor in Liver Transplantation (IF: 3,944) and Journal Hepatology (IF: 9,858). Councillor of the "Asociación Española para el estudio del Hígado (AEEH)", European Society of organ transplantation (ESOT), and International Liver Transplantation Society; (2) M. Prieto: Councillor of the "Sociedad Española de Trasplante Hep??tico (SETH)"

PROGRAMME:
Portal Hypertension and Cirrhosis

G0026

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Reverter Segura, Enrique
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Vila Bellmunt, Sergi
Vilaseca Barceló, Marina

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Main lines of research

- Factors regulating hepatic microcirculation in normal and in cirrhosis, studies of liver perfusion and isolated liver sinusoidal endothelial cells.
- Post-transcriptional regulation of the activity of endothelial nitric oxide synthase(eNOS). Relevance in the treatment of portal hypertension.
- Regulation of transcription of protective genes hepatic sinusoidal endothelium: relevance to the pathophysiology of portal hypertension in liver ex vivo preservation,and complications of cirrhosis.
- Angiogenesis and portal hypertension: contribution to regulation of development of collateral circulation, hyperdynamic circulation and hepatic fibrogenesis.
- New non invasive evaluation of cirrhosis.
- Randomized clinical trials of new treatments for portal hypertension.
- Hepatic vascular disease.
- Prevention of decompensated cirrhosis.
- Diagnostic biomarker discovery and response to treatment.
- Role of sinusoidal endothelium in ischemia-reperfusion injury liver.
- Liver protection from external injury in healthy and cirrhotic livers.

Most relevant scientific articles

- Ripoll C, Genescà J, Araujo IK, Graupera I, Augustin S, Tejedor M. Rebleeding prophylaxis improves outcomes in patients with hepatocellular carcinoma. A multicenter case-control study.Hepatology. 2013 Dec;58(6):2079-88.
- Berzigotti A, Seijo S, Arena U, Abraldes JG, Vizzutti F, García-Pagán JC. Elastography, spleen size, and platelet count identify portal hypertension in patients with compensated cirrhosis.Gastroenterology. 2013 Jan;144(1):102-111.e1.
- La Mura V, Pasarín M, Meireles CZ, Miquel R, Rodríguez-Vilarrupla A, Hide D. Effects of simvastatin administration on rodents with lipopolysaccharide-induced liver microvascular dysfunction.Hepatology. 2013 Mar;57(3):1172-81.
- Gracia-Sancho J, García-Calderó H, Hide D, Marrone G, Guixé-Muntet S, Peralta C. Simvastatin maintains function and viability of steatotic rat livers procured for transplantation.J Hepatol. 2013 Jun;58(6):1140-6.
- Rosado E, Rodríguez-Vilarrupla A, Gracia-Sancho J, Tripathi D, García-Calderó H, Bosch J. Terutroban, a TP-receptor antagonist, reduces portal pressure in cirrhotic rats. Hepatology. 2013 Oct;58(4):1424-35.

Highlights

The most prominent research of the group includes the study of new mechanisms modulating the hepatic vascular tone in cirrhosis and the development of new therapeutic strategies based on those mechanisms.

During this year, in this sense, we have further characterized the use of simvastatin reducing liver vascular dysfunction in cirrhosis, and in liver protection against LPS and ischemia-reperfusion injury.

We have also shown that other drugs such as rMnSOD, Resveratrol, Terutroban, and the Leptin receptor can improve portal hypertension and fibrogenesis in cirrhosis.

Importantly, we developed new non-invasive methods to identify significant portal hypertension with compensated cirrhosis, and validated the use of transition elastography and of metabolomic markers as tools for non-invasive evaluation.

Finally we have developed a new device for hepatic cells co-culture in a sinusoidal-like environment.

PROGRAMME:
Liver Cancer and Cancer of the Digestive System

G0005

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Main lines of research

This group known as the BCLC group is devoted to clinical and translational research in liver cancer. The activity may be divided in two major fields that are tightly related: clinical research and molecular profiling. As a referral group it maintains an intense clinical activity that allows running studies including from epidemiology to diagnosis, prognosis and treatment. The creation of a tissue collection and the organization of an International Genomic Consortium with other institutions from abroad (Mount Sinai Medical School in New York, Harvard University, Institute Nationale di Tumori di Milan) has facilitated several investigations to expand the knowledge of the oncogenic mechanisms, the proposal of a molecular classification for liver cancer and the identification of potential novel targets.

The BCLC group has received wide international recognition for its work at all levels. At the clinical level the group established the relevance of hepatitis C virus infection as a risk factor for liver cancer, defined the imaging criteria for imaging diagnosis of liver cancer, defined the role of portal pressure measurement in the selection of candidates for surgery, established the benefits of ablation for early stage cancers and more importantly, demonstrated the benefit of chemoembolization and sorafenib through phase 3 randomised trials. Currently, the group leads international research in phase 1, 2 and 3, evaluating various molecular therapies in first or second line and as adjuvant after surgical resection or chemoembolization.

Furthermore, the BCLC strategy for prognosis assessment and treatment allocation has been endorsed by major scientific associations and research consortia. The BCLC contributions have laid the foundation for the development of international practice guidelines based on scientific evidence as done by EASL, AASLD, WGO, ESMO and ILCA. Indeed, most guidelines have been lead by BCLC investigators.

The activity in translational research has primed the establishment of a molecular classification of liver cancer and elucidated some of the most relevant signalling pathways involved in tumour progression. In addition, studies have identified genomic signatures associated with different outcome either due to tumor progression or to liver disease progression. As a whole, the combined clinical and translational research is paving the path for stratified medicine.

The BCLC group work has resulted, along the years, in more than 600 publications, with an Impact Factor higher than 3.000, and a total citations number higher than 36.000.

Most relevant scientific articles

- Sia D, Hoshida Y, Villanueva A, Roayaie S, Ferrer J, Tabak B. Integrative molecular analysis of intrahepatic cholangiocarcinoma reveals 2 classes that have different outcomes.Gastroenterology. 2013 Apr;144(4):829-40.
- Reig M, Rimola J, Torres F, Darnell A, Rodríguez-Lope C, Forner A. Postprogression survival of patients with advanced hepatocellular carcinoma: rationale for second-line trial design.Hepatology. 2013 Dec;58(6):2023-31.
- Nault JC, De Reyniès A, Villanueva A, Calderaro J, Rebouissou S, Couchy G et al.. A hepatocellular carcinoma 5-gene score associated with survival of patients after liver resection.Gastroenterology. 2013 Jul;145(1):176-87.
- Finn RS, Poon RT, Yau T, Klümpen HJ, Chen LT, Kang YK. Phase I study investigating everolimus combined with sorafenib in patients with advanced hepatocellular carcinoma.J Hepatol. 2013 Dec;59(6):1271-7.

Highlights

The 2013 clinical highlights include the demonstration of the correlation between tumor progression and survival. This validates time to progression as a relevant signal to detect treatment efficacy in phase 1-2 trials, but at the same time we have exposed that the pattern of progression rather than all progression types is key to predict the outcome of the patients. Design of future trials has to be modified according to our findings.

We have also shown that the development of adverse events to sorafenib are associated to a better outcome. Thus, there is need to identifying the profile of the patients that is responsible for adverse events development. Adverse event appearance has to be incorporated also in trial design. Indeed, during 2013 we have published the phase 2 of sorafenib in combination with everolimus as well as the phase 3 trial in second line assessing brivanib vs placebo. Both studies were negative, but data have helped to optimise future therapeutic studies.

At the translational level, we have published major contributions to characterize the genomic profile of hepatocellular carcinoma and cholangiocarcinoma. Our studies have allowed a consensus molecular classification of hepatocellular carcinoma with specific signatures that refine the current conventional evaluation of the patients. Similar effort has been done for the fibrolamellar variant of hepatocellular carcinoma and for intrahepatic cholangiocarcinoma.

New studies to evaluate imaging technology and novel therapeutic agents have been initiated in 2013. Also, further characterization of genetics and epigenetics in human liver cancer are under way.

International leadership has been consolidated and this has resulted in the preparation of high impact reviews in high end journals as well as clinical practice and research guidelines in the field of liver cancer.

PROGRAMME:
Liver Cancer and Cancer of the Digestive System

G1081

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Main lines of research

Cancer is the leading cause of death in men and the second in women. Colorectal cancer (CRC) has the largest incidence worldwide and the second in mortality. Our goal is to determine the best test for the early diagnosis of this disease as well as to improve its acceptance in screening programs. Other projects include the identification of genetic factors that promote its appearance, response to treatment and the adverse effects of the treatment (EPICOLON I, II EPICOLON, EPIPOLIP, EPINEO, COLONPREV, SmartHEALTH, EPICOLON III studies). Intestinal metaplasia is a precursor lesion of gastric cancer. Genetic and environmental factors associated with progression are unknown. Identifying these factors will help us to develop more effective prevention programs in these patients. Moreover, we are focused on the study of new pathogenic mechanisms in order to create new treatments and early diagnostic strategies in different gastrointestinal tumors with poor prognosis (i.e., pancreatic cancer, cholangiocarcinoma, hepatocellular carcinoma and gastric cancer). In the hepatobiliary pathophysiology, our aim is to identify the molecular mechanisms involved in: the generation and regulation of bile, the pathophysiology of the microvesicles (ie exosomes), the

role of the primary cilium of cholangiocytes, as well as the development of various hepatic chronic diseases (ie, chronic liver damage, NAFLD, hemochromatosis) and biliary diseases (ie, polycystic liver disease, primary sclerosing cholangitis, primary biliary cirrhosis).

Most relevant scientific articles

- Masyuk TV, Radtke BN, Stroope AJ, Banales JM, Gradilone SA, Huang B. Pasireotide is more effective than octreotide in reducing hepatorenal cystogenesis in rodents with polycystic kidney and liver diseases.Hepatology. 2013 Jul;58(1):409-21.
- Rodríguez-Soler M, Pérez-Carbonell L, Guarinos C, Zapater P, Castillejo A, Barberá VM. Risk of cancer in cases of suspected lynch syndrome without germline mutation. Gastroenterology. 2013 May;144(5):926-932.e1; quiz e13-4.
- Bujanda L, Lanas Á, Quintero E, Castells A, Sarasqueta C, Cubiella J. Effect of aspirin and antiplatelet drugs on the outcome of the fecal immunochemical test.Mayo Clin Proc. 2013 Jul;88(7):683-9.
- Perugorria MJ, Murphy LB, Fullard N, Chakraborty JB, Vyrla D, Wilson CL et al.. Tumor progression locus 2/Cot is required for activation of extracellular regulated kinase in liver injury and toll-like receptor-induced TIMP-1 gene transcription in hepatic stellate cells in mice.Hepatology. 2013 Mar;57(3):1238-49.
- Artal-Martínez de Narvajas A, Gomez TS, Zhang JS, Mann AO, Taoda Y, Gorman JA et al.. Epigenetic regulation of autophagy by the methyltransferase G9a.Mol Cell Biol. 2013 Oct;33(20):3983-93.

Highlights

During the last year our scientific activity and production has significantly increased due to the incorporation of two internationally recognized postdoctoral researchers through the Ikerbasque program (Dr. Bañales and Dr. Perugorria). Dr. Bañales leads the hepatobiliary area in our research group and has significant national and international collaborations as well as different research projects related to the hepatobiliary pathophysiology and oncology. Currently there are 5 pre-doctoral researchers who are developing their research projects in our group. In the gastrointestinal oncology area is important to emphasize the implementation of the EPICOLON III project, not only because of the online data collection but also for the development of projects seeking new diagnostic biomarkers in colorectal cancer. An important step during the past year has been the end of the study on precursor lesions of gastric cancer that will lead to significant advances in this field.

PROGRAMME:
Gastrointestinal Inflammation and Motility

G0034

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Main lines of research

- Pathophysiological bases of inflammatory bowel disease, its complications and therapeutic approaches.
- Functional genetics in inflammatory bowel disease.
- Biomarkers and predictive models of therapeutic response.

Most relevant scientific articles

- Julià A, Domènech E, Ricart E, Tortosa R, García-Sánchez V, Gisbert JP. A genome-wide association study on a southern European population identifies a new Crohn's disease susceptibility locus at RBX1-EP300.Gut. 2013 Oct;62(10):1440-5.
- Panés J, López-Sanromán A, Bermejo F, García-Sánchez V, Esteve M, Torres Y. Early azathioprine therapy is no more effective than placebo for newly diagnosed Crohn's disease. Gastroenterology. 2013 Oct;145(4):766-74.e1.
- Casanova MJ, Chaparro M, Domènech E, Barreiro-de Acosta M, Bermejo F, Iglesias E. Safety of thiopurines and anti-TNF-α drugs during pregnancy in patients with inflammatory bowel disease.Am J Gastroenterol. 2013 Mar;108(3):433-40.
- Mañosa M, Cabré E, Bernal I, Esteve M, García-Planella E, Ricart E. Addition of metronidazole to azathioprine for the prevention of postoperative recurrence of Crohn's disease: a randomized, double-blind, placebo-controlled trial.Inflamm Bowel Dis. 2013 Aug;19(9):1889-95.
- Lorenzo-Zúñiga V, Boix J, Mañosa M, Lezcano C, Cabré E, Moreno de Vega V. Local injection of infliximab in symptomatic isolated mucosal lesions: a novel scenario for endoscopic therapy?Inflamm Bowel Dis. 2013 Mar-Apr;19(4):E59-61.

Highlights

The scientific activity of the inflammatory bowel disease (IBD) Unit of the University Hospital and Institute "Germans Trias i Pujol" Foundation in 2013 has led to obtain 20 international publications, ten of them in the 1st quartile in the area of gastroenterology and hepatology. Of these, 3 belong to the first decile. Thus, the accumulated impact factor was 79.968 in the last year.

Three collaborative studies CIBERehd have reached the first decile, showing: a) the efficacy of thiopurines in moderate/severe flare-up in Crohn's disease (CD) (Panés, et al. Gastroenterol 2013); b) security of anti-TNF treatment during pregnancy (Casanova, et al. Am J Gastroenterol 2013); and c) a new CD susceptibility locus identification between RBX1 and EP300 (Julià et al. GUT 2013). In the last one, we contribute as corresponding author.

As in the case of the first quartile, the articles published in the second (3) and third (3) quartil aim therapeutic improvement in IBD, in line with the objectives established by CIBERehd. However, there have also been translational studies funded by governmental research programs in competitive submitting. In 2013, we manage four active projects funded by the Carlos III Health Institute (FIS), which allowed to get 58,086.05€ from public grants. In Addition, since two of them have been renewed to 2014-2016 period (PI13/02198 and PI13/02217), the line of research has gained more coherence and continuity. Other activities, such as clinical trials (6 in 2013), courses and nonprofit donations have enabled to collect 56,630.50€ from private funds. Finally, it is interesting to remark educational and formative activities such as the international course on IBD "Miquel Àngel Gassull", and a doctoral thesis on the role of intestinal axis IL10/p38MAPK in therapeutic response in ulcerative colitis.

PROGRAMME:
Gastrointestinal Inflammation and Motility

G0036

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Main lines of research

- *Helicobacter pylori* and associated diseases.
- Non-variceal upper gastrointestinal bleeding.
- Social and laboral aspects of inflammatory bowel disease.

Most relevant scientific articles

- Casanova MJ, Chaparro M, Domènech E, Barreiro-de Acosta M, Bermejo F, Iglesias E. Safety of thiopurines and anti-TNF-α drugs during pregnancy in patients with inflammatory bowel disease.Am J Gastroenterol. 2013 Mar;108(3):433-40.
- Guardiola J, García-Iglesias P, Rodríguez-Moranta F, Brullet E, Salo J, Alba E. [Management of acute lower gastrointestinal hemorrhage: position statement of the Catalan Society of Gastroenterology].Gastroenterol Hepatol. 2013 Oct;36(8):534-45.
- Megraud F, Coenen S, Versporten A, Kist M, López-Brea M, Hirschl AM. Helicobacter pylori resistance to antibiotics in Europe and its relationship to antibiotic consumption.Gut. 2013 Jan;62(1):34-42.
- Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE. Vedolizumab as induction and maintenance therapy for Crohn's disease.N Engl J Med. 2013 Aug 22;369(8):711-21.
- Gisbert JP, Calvet X, Bermejo F, Boixeda D, Bory F, Bujanda L. [III Spanish Consensus Conference on Helicobacter pylori infection].Gastroenterol Hepatol. 2013 May;36(5):340-74.

Highlights

- Has been developed the patent: container and method of storing and the extemporaneous reconstitution of a mixture of compounds in fixed proportions. Inventors: Caridad Pontes and Xavier Calvet. Patent No.:13382229.6-1651.Date of issue: 18/06/2013. European patent.
- Have been initiated new collaborative projects for the *Helicobacter pylori* treatment and several systematic reviews and studies on quality aspects, social and labor of inflammatory bowel disease, which are at different stages of development.
- Has initiated an innovation project about presentations with multiple drugs for the *H. pylori* infection treatment in children.
- Participation in multiple national and international clinical trials.

HAVE OBTAINED THE FOLLOWING GRANTS:

- 1007/C/2013. "Novel technologies as non invasive tools for prognosis / diagnosis of gastric cancer". Patronat de la Fundació la Marató de TV3. PI: Xavier Calvet. No. Scientists: 5. Coordinated study composed by three centers (Hospital de Sabadell, Department of Microbiology of the Faculty of Pharmacy and LEITAT UAB). The aim is to identify biomarkers of progression to gastric cancer in patients with H. pylori infection by means of the use of noninvasive technologies (circulating miRNA and plasma metabolomics) for the identification and pre-validation of these markers in blood.

FIS-PI10-01203 "Follow-up study on factors associated with progression of preneoplastic lesions of gastric cancer": coordinated Spanish follow-up study. This is a national project led by Dr. González-Svatetz. The project enrolls patients from 14 hospitals and has 3 analytical sub-projects: analysis of human genetic (C.Gonzalez-Svatetz, ICO), epigenetic (M.Esteller, Idibell) and H. pylori virulence factors (X. Calvet, Parc Taulí).

- Fundación Mutua Madrileña. "Cell Study to gastric cancer progression induced by Helicobacter pylori". Principal Investigator: María José Ramírez.

Other grants:

- SAF-2012-39948 "Identification of metabolomic biomarkers for the noninvasive diagnosis of digestive pathologies related to Helicobacter pylori infection.
- FIS-P12-01802 "Evaluation of non-coding RNAs as non-invasive biomarkers of precancerous gastric lesions in patients infected with Helicobacter pylori."

PROGRAMME:
Cholestasis and Metabolic Disorders

G0081

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Main lines of research

- Metabolism and hepatotoxicity of drugs: the objective is to design and validate new strategies for a more effective and safer drug development by studying, in hepatic cellular models, the metabolism of new drugs, drug-drug interactions and the molecular mechanisms of hepatotoxicity.
- Direct and indirect reprogramming of fibroblasts to hepatocytes/hepatoblasts (iHEP): the objective is to develop a human liver cell model through direct and indirect conversion of fibroblasts to iHEP. Direct conversion takes place without prior reprogramming to iPS, while indirect conversion involves first reprogramming fibroblasts to iPS cells and then their subsequent differentiation to iHEP.
- Pathogenesis of nonalcoholic fatty liver disease - transcriptional mechanisms involved: the objective is to discover new transcriptional mechanisms involved in the development and progression of nonalcoholic fatty liver disease (NAFLD) and to investigate the toxicogenomics of steatotic drugs and their mechanisms. Moreover, we are searching for specific biomarkers able to differentiate between metabolic and drug-induced steatosis.
- Metabonomics liver and chemometrics: the objective is to correlate the serum metabonome of patients who had undergone hepatocyte cell transplantation with their clinical outcome, and find changes in the level of

metabolites useful to monitor the response. Moreover, we want to clarify and define the metabonomic patterns that will predict the success of a liver before transplantation, to do this we analyze the metabonome of livers transplanted, whose post-transplant performance is known.

- Liver Cell Therapy: the goal is to apply cell therapy (hepatocyte or mesenchymal cells) for the treatment of certain liver diseases: acute liver failure, acute decompensation in chronic liver disease, primary biliary cirrhosis and congenital metabolic disorders, thus making it a therapeutic strategy that can be applied as a bridge or as an alternative to whole organ transplantation.

Most relevant scientific articles

- Serrano F, Calatayud CF, Blazquez M, Torres J, Castell JV, Bort R. Gata4 blocks somatic cell reprogramming by directly repressing Nanog.Stem Cells. 2013 Jan;31(1):71-82.
- Guzmán C, Benet M, Pisonero-Vaquero S, Moya M, García-Mediavilla MV, Martínez-Chantar ML. The human liver fatty acid binding protein (FABP1) gene is activated by FOXA1 and PPARα; and repressed by C/EBPα: Implications in FABP1 down-regulation in nonalcoholic fatty liver disease.Biochim Biophys Acta. 2013 Apr;1831(4):803-18.
- Carbajo-Pescador S, Ordoñez R, Benet M, Jover R, García-Palomo A, Mauriz JL. Inhibition of VEGF expression through blockade of Hif1α and STAT3 signalling mediates the anti-angiogenic effect of melatonin in HepG2 liver cancer cells.Br J Cancer. 2013 Jul 9;109(1):83-91.
- Tolosa L, Gómez-Lechón MJ, Pérez-Cataldo G, Castell JV, Donato MT. HepG2 cells simultaneously expressing five P450 enzymes for the screening of hepatotoxicity: identification of bioactivable drugs and the potential mechanism of toxicity involved.Arch Toxicol. 2013 Jun;87(6):1115-27.
- Blazquez M, Carretero A, Ellis JK, Athersuch TJ, Cavill R, Ebbels TM. A combination of transcriptomics and metabolomics uncovers enhanced bile acid biosynthesis in HepG2 cells expressing CCAAT/enhancer-binding protein β (C/EBPβ), hepatocyte nuclear factor 4α (HNF4α), and constitutive androstane receptor (CAR).J Proteome Res. 2013 Jun 7;12(6):2732-41.

Highlights

In late 2013 we finished two research projects funded by the Institute of Health Carlos III (ISCIII). The purpose of one of the projects has been the citomic and metabonomic study of the hepatotoxic mechanism of drugs, the prediction of their hepatotoxic potential and the transition from iatrogenic to autoimmune hepatitis. This project has achieved the development and validation of a practical and reproducible multiparametric method for evaluating and predicting drugs that are potentially hepatotoxic to humans. The other project has focused on the study of novel transcriptional mechanisms involved in the pathogenesis of nonalcoholic fatty liver disease of both metabolic and iatrogenic etiology. One of the most significant results has been the finding of a transcriptomic fingerprint able to identify new steatotic drugs.

Projects are underway in 2013 include:

- Study of the Hex-mediated activity of MYC in cell reprogramming (Ministry of Science and Innovation, 2012-2014)
- Finding a metabonomic pattern for fast pre-implantation assessment of the functional quality of the donor liver graft (ISCIII, 2012-2014).
- Innovative strategies to generate human hepatocytes for treatment of metabolic liver diseases: Tools for personalised cell therapy (InnovaLiv EU, 2011-2014).

Finally, among the projects beginning in 2013 is worth to mention a project funded by the European Union, from 2013 to 2017, and entitled "HeCaToS - Hepatic and Cardiac Toxicity Systems modelling". For this project, a new Hepatotoxicity Unit service has recently been founded in Hospital La Fe, as a result of the synergy between our Unit and the Clinical Hepatology Unit (HU), to which patients with suspected drug hepatotoxicity are referred for a detailed and personalized study.

PROGRAMME:
Liver Cancer and Cancer of the Digestive System

G0016

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Main lines of research

- Hereditary and familial forms of colorectal cancer: strategies for its identification, screening and surveillance.
- Study of molecular mechanisms involved in the development, progression and treatment-resistance of colorectal and pancreatic cancer.
- Molecular epidemiology of colorectal cancer and assessment of screening strategies.
- Diagnostic and therapeutic endoscopy and minimally invasive surgery in gastrointestinal and pancreatic oncology.

Most relevant scientific articles

- Castells A, Bessa X, Quintero E, Bujanda L, Cubiella J, Salas D. Risk of advanced proximal neoplasms according to distal colorectal findings: comparison of sigmoidoscopy-based strategies.J Natl Cancer Inst. 2013 Jun 19;105(12):878-86.
- van der Pas MH, Haglind E, Cuesta MA, Fürst A, Lacy AM, Hop WC. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial.Lancet Oncol. 2013 Mar;14(3):210-8.
- Castells A, Giardiello FM. Familial colorectal cancer screening: so close, so far.Gastroenterology. 2013 Mar;144(3):492-4.
- Gironella M, Calvo C, Fernández A, Closa D, Iovanna JL, Rosello-Catafau J. Reg3β deficiency impairs pancreatic tumor growth by skewing macrophage polarization.Cancer Res. 2013 Sep 15;73(18):5682-94.

Highlights

The research areas of our group are aimed at investigating the mechanisms involved in the development and progression of gastrointestinal and pancreatic premalignant and malignant lesions, in order to establish new diagnostic, therapeutic and/or preventive strategies. The main achievements in 2013 are those obtained in the context of cooperative projects lead by our group in the fields of colorectal cancer (CRC) screening and development of biomarkers for its early detection.

With respect to CRC screening, it is important to mention the ColonPrev project, a prospective, randomized controlled trial comparing fecal immunochemical testing and colonoscopy. After presenting the results of the first round (N Engl J Med 2012;366:697-706), we have recently published those corresponding to nested projects, including the evaluation of sigmoidoscopy as screening strategy (J Natl Cancer Inst 2013;105:878-86), the identification of factors influencing the adenoma detection rate (Gastrointest Endosc 2013;77:381-9), and the establishment of serrated lesions as risk factor for advanced neoplasia (Gastrointest Endosc 2013;78:333-41).

The development and validation of biomarkers for early diagnosis of CRC, in the context of the EPICOLON project, constitute a cross-sectional strategic action of various CIBEREHD groups. In this field, it is worth to highlight recent publications (Clin Gastroenterol Hepatol 2013;11:681-8; Gastroenterology 2013;144:926-32; Clin Gastroenterol Hepatol 2013;11:705-11), patents (PCT/US2013/028401, US61/391585 and US61/550148), and the grant from the Spanish Association against Cancer obtained by our group.

Finally, the social commitment of our group has been demonstrated by the support to the creation of the Association of Families Affected by Lynch Syndrome (www.afalynch.org) and the foundation of the Spanish Alliance for Colon Cancer Prevention (www.alianzaprevencioncolon.es).

PROGRAMME:
Gastrointestinal Inflammation and Motility

G1087

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Main lines of research

- Oropharyngeal and gastroesophageal motility. Pathophysiology, diagnosis and treatment of oropharyngeal and esophageal dysphagia. Pharmacology of swallow response. Oropharyngeal dysphagia and ageing. Neurogenic dysphagia. Brain plasticity.
- Gastrointestinal peptides, control of appetite in ageing and obesity.
- Myenteric mechanisms controlling esophageal motility.
- Intestinal, colonic and anorectal motility. Gastrointestinal pharmacology.
- Neurotransmitters in the colon, small bowel and internal anal sphincter. Purines.NO. H2S. TRPV1. PAR-2.
- Pacemaker function. Interstitial Cells of Cajal.
- Mast cell differentiation and intestinal nerve function: Role of NGF and its implication in the Irritable Bowel Syndrome (IBS) and postoperative ileus.
- Pathophysiology of intestinal dismotility in IBS and IBD.
- Pathophysiology and treatment with new pharmacological strategies of dismotility in IBS, diverticular disease, anal fissure.
- Oropharyngeal and gastrointestinal microbiota.

Most relevant scientific articles

- Rofes L, Arreola V, Martín A, Clavé P. Natural capsaicinoids improve swallow response in older patients with oropharyngeal dysphagia.Gut. 2013 Sep;62(9):1280-7.
- Rychter J, Clavé P. Intestinal inflammation in postoperative ileus: pathogenesis and therapeutic targets.Gut. 2013 Nov;62(11):1534-5.
- Almirall J, Rofes L, Serra-Prat M, Icart R, Palomera E, Arreola V. Oropharyngeal dysphagia is a risk factor for community-acquired pneumonia in the elderly.Eur Respir J. 2013 Apr;41(4):923-8.
- Gil V, Parsons S, Gallego D, Huizinga J, Jimenez M. Effects of hydrogen sulphide on motility patterns in the rat colon.Br J Pharmacol. 2013 May;169(1):34-50.
- Fernández-Blanco JA, Hollenberg MD, Martínez V, Vergara P. PAR-2-mediated control of barrier function and motility differs between early and late phases of postinfectious gut dysfunction in the rat.Am J Physiol Gastrointest Liver Physiol. 2013 Feb 15;304(4):G390-400.

Highlights

In 2013 we described two new pharmacological targets (TRPV1/TRPA1) with therapeutic effects on the oropharyngeal motor response. We designed and carried out two large clinical trials with positive results and application to clinical practice of sensory transcutaneous and intrapharyngeal electrostimulation methods to treat post-stroke dysphagia. We characterized the pharyngeal cortical sensory evoked potential and showed that patients with dysphagia present impairments in both the motor and sensory pathways, and we established the relation between oral microbiota, oropharyngeal aspirations and aspiration pneumonia in older patients and assessed the serious risk factor that dysphagia and malnutrition represent for these patients. In this area we hold an international patent PCT/EP2005/04252 and have participated in a European project (OPVK), and an international guideline (Terminology and Definitions for Texture-modified foods and thickened liquids used in dysphagia) and in the creation of a European scientific association (European Society for Swallowing Disorders). We have contributed to the description of the impairments to the permeability of the esophageal sphincter in gastroesophageal reflux disease, the mechanisms of control of peristalsis and disorders in gastric and gallbladder motility and release of postprandial gastrointestinal peptides in anorexia of frail aging patients. We have started studies on the clinical relevance of nutritional, anabolic and inflammatory disorders and the role of ghrelin in sarcopenia and frailty. We have characterized the role of mast cells in postoperative ileus following colorectal surgery in humans. The main results of the basic research were the description of the effect of PAR-2 receptors on the epithelial barrier and the role of intestinalmicrobiota in the expression of sensory innervation, new neurotransmitters (H2S) in animal models and the consolidation of the study of motility in vitro with human gastro-intestinal samples through mechanical, electrophysiological, immunohistological and molecular techniques.

PROGRAMME:
Portal Hypertension and Cirrhosis

G0007

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Main lines of research

- Hepatic encephalopathy and portal hypertension: pathogenesis, diagnosis and treatment.
- Experimental models of hepatic encephalopathy and portal hypertension.
- Preclinical assessment of new therapies for cirrhosis complications.

Most relevant scientific articles

- Simón-Talero M, García-Martínez R, Torrens M, Augustin S, Gómez S, Pereira G. Effects of intravenous albumin in patients with cirrhosis and episodic hepatic encephalopathy: a randomized double-blind study.J Hepatol. 2013 Dec;59(6):1184-92.
- Amodio P, Bemeur C, Butterworth R, Cordoba J, Kato A, Montagnese S. The nutritional management of hepatic encephalopathy in patients with cirrhosis: International Society for Hepatic Encephalopathy and Nitrogen Metabolism Consensus.Hepatology. 2013 Jul;58(1):325-36.
- Laleman W, Simon-Talero M, Maleux G, Pérez M, Ameloot K, Soriano G. Embolization of large spontaneous portosystemic shunts for refractory hepatic encephalopathy: a multicenter survey on safety and efficacy.Hepatology. 2013 Jun;57(6):2448-57.
- Ripoll C, Genescà J, Araujo IK, Graupera I, Augustin S, Tejedor M. Rebleeding prophylaxis improves outcomes in patients with hepatocellular carcinoma. A multicenter case-control study.Hepatology. 2013 Dec;58(6):2079-88.
- Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis.Gastroenterology. 2013 Jun;144(7):1426-37, 1437.e1-9.

Highlights

During 2013, it is worth noting the high number of collaborative research projects with other CIBER groups and international groups that have led to high impact publications. Also important is the NIH collaborative project on alcoholic hepatitis and 3 international contributions in clinical guidelines on complications of cirrhosis.

PROGRAMME:
Immunology and Liver Transplant

G0077

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Main lines of research

- Liver transplant. Donor-receptor matching.
- Hepatocellular carcinoma. Identification of biomarkers.
- Hepatocellular damage. Mechanisms of cytoprotection.
- Viral hepatitis.

Most relevant scientific articles

- Briceño J, Ciria R, de la Mata M. Donor-recipient matching: myths and realities. J Hepatol. 2013 Apr;58(4):811-20.
- González R, Ferrín G, Aguilar-Melero P, Ranchal I, Linares CI, Bello RI. Targeting hepatoma using nitric oxide donor strategies. Antioxid Redox Signal. 2013 Feb 10;18(5):491-506.
- Sangro B, Gomez-Martín C, de la Mata M, Iñarrairaegui M, Garralda E, Barrera P. A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C.J Hepatol. 2013 Jul;59(1):81-8.
- Rodríguez-Perálvarez M, Germani G, Darius T, Lerut J, Tsochatzis E, De la Mata M. Tacrolimus exposure after liver transplantation in randomized controlled trials: too much for too long. Am J Transplant. 2013 May;13(5):1371-2.
- Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013 Jun;144(7):1426-37, 1437.e1-9.

Highlights

It is a mixed research group formed by hepatologists, surgeons and basic researchers specializing in biomedicine, focusing investigation in liver diseases.

The main lines of research are: liver transplant, hepatocellular carcinoma and acute and chronic hepatocellular damage.

Some of the research activity in 2013 has been centered in multicentric studies:

- "CLIF: Acute on chronic liver failure in cirrhosis"
- "Inhibición of mTOR via with everolimus in patients who undergo liver transplantion due to hepatocellular carcinoma and its impact on tumor recurrence".
- " Long-term diabetes in liver transplant patients"
- "A randomized double-blind trial on patients with advanced hepatocellular carcinoma to assess the efficacy of sorafenib beyond radiological progression".
- "The value of artificial neural network in donor-receptor matching for liver transplantation.

In addition, a number a trial are in progress:

- "A phase III, randomized, double-blind, placebo- controlled study of everolimus plus best supportive care in patients with advanced hepatocellular carcinoma that progressed during or after sorafenib treatment or who are intolerant of sorafenib"
- "A randomized, double blind, multicenter phase III study of regorafenib in patients with hepatocellular carcinoma (HCC) after Sorafenib".
- "Open multicentric randomized and controlled study to evaluate the eficacy and safety of ELAD in patients with acute alcoholic hepatitis (AAH) after failure of treatment with steroids".
- "Molecular predictors of response to Sorafenib adjuvant therapy after resection of hepatocellular carcinoma"
- " Observational study of reduced immunosuppression in liver transplant patients".
- "Use of Telaprevir y Boceprevir registry in real clinical practice"
- "A clinical model to predict acute cellular rejection after liver transplantation"

PROGRAMME:
Gastrointestinal Inflammation and Motility

G0071

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Main lines of research

- Modulation of autophagy in epithelial cells by macrophages: relevance in Crohn's Disease and in non-steroidal anti-inflammatory drug-induced gastroenteropathy.
- Nitric oxide and oxygen consumption: physiological and pathophysiological implications.
- Mitochondrial dysfunction in inflammatory processes.
- Role of endothelial-mitochondrial dysfunction in obesity and gastric disorders.
- Mechanisms of toxicity, metabolic alterations, mitochondrial dysfunction and inflammation produced by antiretroviral drugs.

Most relevant scientific articles

- Apostolova N, Gomez-Sucerquia LJ, Alegre F, Funes HA, Victor VM, Barrachina MD. ER stress in human hepatic cells treated with Efavirenz: mitochondria again.J Hepatol. 2013 Oct;59(4):780-9.
- Ortiz-Masiá D, Cosín-Roger J, Calatayud S, Hernández C, Alós R, Hinojosa J. Hypoxic macrophages impair autophagy in epithelial cells through Wnt1: relevance in IBD. Mucosal Immunol. 2013 Dec 4;.
- De Pablo C, Orden S, Peris JE, Barrachina MD, Esplugues JV, Alvarez A. Profile of leukocyte-endothelial cell interactions induced in venules and arterioles by nucleoside reverse-transcriptase inhibitors in vivo.J Infect Dis. 2013 Nov 1;208(9):1448-53.
- Cosín-Roger J, Ortiz-Masiá D, Calatayud S, Hernández C, Alvarez A, Hinojosa J. M2 macrophages activate WNT signaling pathway in epithelial cells: relevance in ulcerative colitis.PLoS One. 2013;8(10):e78128.
- Hernández-Mijares A, Rocha M, Rovira-Llopis S, Bañuls C, Bellod L, de Pablo C. Human leukocyte/endothelial cell interactions and mitochondrial dysfunction in type 2 diabetic patients and their association with silent myocardial ischemia.Diabetes Care. 2013 Jun;36(6):1695-702.

Highlights

In the last year we have demonstrated the relevance of the innate immune system, in particular macrophages, in mechanisms of mucosal regeneration in inflammatory bowel disease (IBD). These cells function as a source of Wnt and Notch ligands, molecules that mediate mechanisms of epithelial regeneration. In addition, this expression seems to be associated with the macrophagic phenotype. Our results point to the pharmacological potential of modulating the macrophagic phenotype to aid mucosal recovery, one of the main objectives of current IBD therapy.

The results we have obtained about the role of the antiretroviral drug Abacavir in the genesis of inflammation, despite not yet having been published as an article, have generated considerable controversy and have led to a series of invitations to present our data in national and international meetings.

PROGRAMME:
Hepatitis Virus

G0028

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Main lines of research

TRANSLATIONAL RESEARCH:

- HCV SUBTYPING: Development of a High resolution HCV subtyping method for clinical diagnosis based on massive sequencing and molecular phylogeny 454/GS-Junior.
- HCV RESISTANCE MUTATIONS by ultra-deep pyrosequencing (UDPS) 454/GS-FLX/GS-Junior.
- Treatment of HCV infection in different clinical situations: after liver transplant, coinfection with other viruses (HIV, HBV).
- Studies of new infections by molecular phylogeny. Outbreaks and Nosocomial transmission.

BASIC RESEARCH:

- HCV Quasispecies variability and progression of Liver Damage in different clinical situations (liver transplantation...)
- HCV and Immune Response. Restoration of immune response in chronic infection.
- Study of HCV Superinfection after Liver Transplantation by UDPS.
- HCV in Liver transplantation.

CLINICAL RESEARCH:

- Epidemiology of HCV infection.
- Development of a National HCV Data Base. HepatiC.

Most relevant scientific articles

- Ramírez C, Gregori J, Buti M, Tabernero D, Camós S, Casillas R. A comparative study of ultra-deep pyrosequencing and cloning to quantitatively analyze the viral quasispecies using hepatitis B virus infection as a model.Antiviral Res. 2013 May;98(2):273-83.
- Cubero M, Gregori J, Esteban JI, García-Cehic D, Bes M, Perales C. Identification of host and viral factors involved in a dissimilar resolution of a hepatitis C virus infection. Liver Int. 2013 Oct 17;.
- Gregori J, Esteban JI, Cubero M, García-Cehic D, Perales C, Casillas R. Ultra-deep pyrosequencing (UDPS) data treatment to study amplicon HCV minor variants.PLoS One. 2013;8(12):e83361.
- Sapisochin G, Castells L, Dopazo C, Bilbao I, Minguez B, Lázaro JL. Single HCC in cirrhotic patients: liver resection or liver transplantation? Long-term outcome according to an intention-to-treat basis.Ann Surg Oncol. 2013 Apr;20(4):1194-202.
- Marco A, Esteban JI, Solé C, da Silva A, Ortiz J, Roget M. Hepatitis C virus reinfection among prisoners with sustained virological response after treatment for chronic hepatitis C.J Hepatol. 2013 Jul;59(1):45-51.

Highlights

PROJECTS

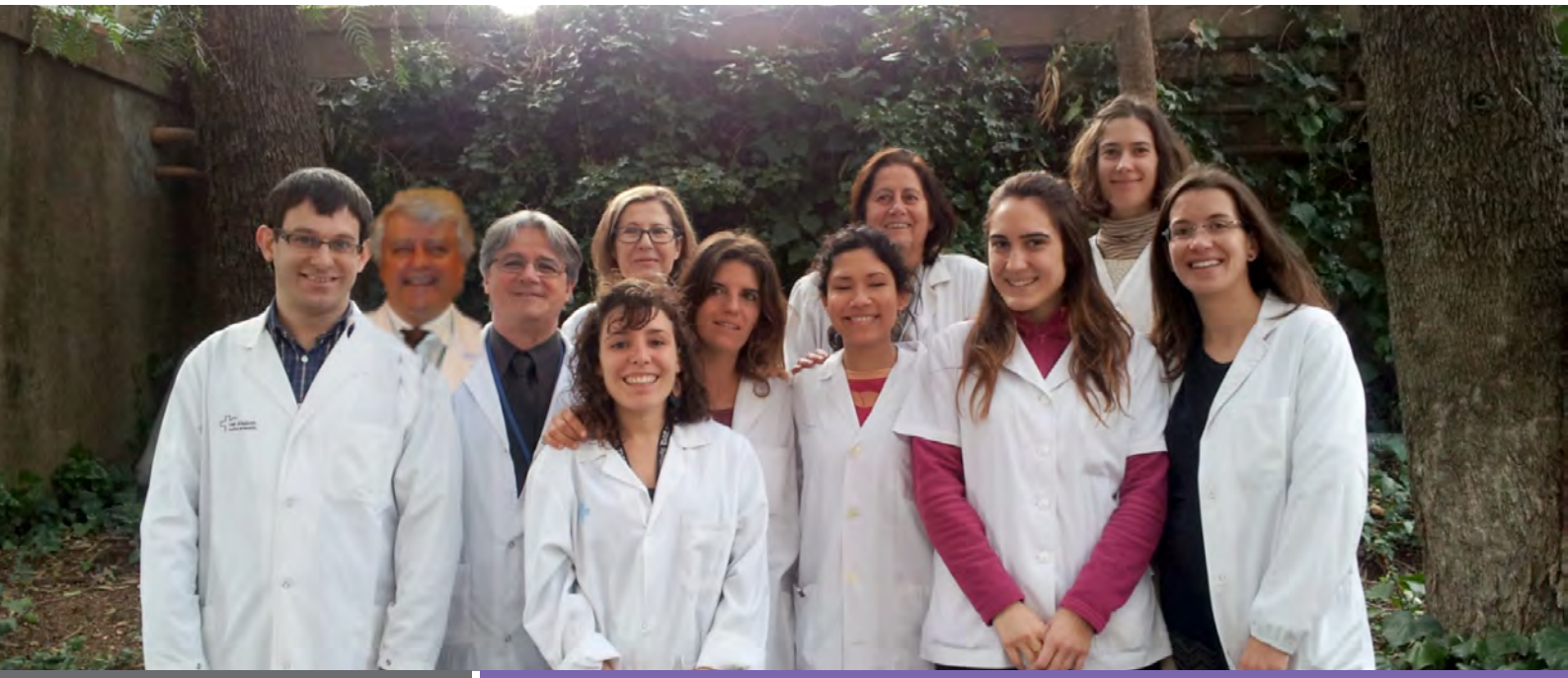
- Quasispecies study of HCV and HBV and genomic polymorphisms associated with antiviral resistance using ultra-deep pyrosequencing. Centro para el Desarrollo Tecnológico Industrial (CDTI). MINECO. Ref. IDI-20110115. 2010-2013. JI. Esteban.
- Expansion/restauration of functional CD4 NS3-specific autologous cells to prevent VHC post-transplant hepatic recurrence: Protocol optimization for clinical use. FIS. PI10/01505. 2011-2014. JI. Esteban.
- HBV quasispecies complexity on X, precore and core regions: Association with severity of infection. FIS. PI12/01893. 2013-2015. F. Rodríguez-Frías.
- Prospective study to analyze the role of gut microbiota with fast evolution of hepatic transplant. Proyecto interno VHIR-HUVH. 2013-2015. I. Bilbao.
- Network 2009 SGR 383. Unitat de recerca en Malalties hepatobiliars. AGAUR. Generalitat de Catalunya. 2010-2014. J. Genescà.
- Anti-HBc antibody prevalence in blood donors from high risk HBV geographic areas. Proyecto interno VHIR-HUVH PR(BS)128/2013. M. Piron.
- Performance evaluation Elecsys HTLV I/II CIM RD001837/A13P004". VHIR-HUVH PR(BS)324/2013. S. Sauleda.
- Prevalence of HEV markers (anti-IgG/IgM and HEV RNA) in Catalonian blood donors. VHIR-HUVH PR(BS)100/2013. S. Sauleda.
- Pilot study Elecsys CHAGAS on Elecsys study. VHIR-HUVH PR(BS)325/2013. M. Piron.
- Association of IL-28B polimorphism rs12979860 with ocult HBV infection. VHIR-HUVH PR(BS)95/2013. 2013. M. Bes.
- Analysis of the role of suppressor mieloide cells in HCV infection. VHIR-HUVH PR(IR)297/2013. 2013. J. Barquinero.
- Determination of specificity and sensitivity of ELISA kits for the screening of blood against infectious diseases. Cession of serum/plasma samples from blood donors for validation of ELISA kits. VHIR-HUVH PR(BS)46/2013. 2013. S. Sauleda.

PATENTS

- Appl.number: EP13382278. Primers and methods for detecting Human Hepatitis C Virus (HCV) variants in an isolated sample. Country of priority: ESPAÑA. Priority data: 05Julio2013. Entity priority: VHIR, CIBEREHD, ROCHE. Extension countries: EU. NATIONAL HCV SPANISH DATA BASE. HepatiC.

CLINICAL TRIALS

EudraCT: 2010-024247-32. Oscar Len / EudraCT: 2013-001191-38. Ramón Charco / EudraCT: 2013-002802-30. María Buti / Exp: JIE-VHC-2012-01. Lluis Castells / EPA(AG)42/2012(3426). Lluís Castells / EudraCT: 2012-003463-22. J.I.Esteban.



PROGRAMME:
Hepatitis Virus

G0025

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Main lines of research

- Platform to collect clinical data from patients with chronic hepatitis B (CIBERHEP).
- Study of hepatitis B virus (HBV) quasispecies using ultradeep pyrosequencing:
  - Study of nucloside / nucleotide analogs treatment and immune system escape variants.
  - Study of genomic regulatory regions.
- Applying ultradeep pyrosequencing based on the GS-Junior platform (available to our group) to clinical practice:
  - High-resolution hepatitis C virus (HCV) subgenotyping
  - Detection of HBV and HCV variants resistant to antiviral treatment.
- Study of the replication of different HBV genomes "in vitro".
- Hepatitis D Virus (HDV) infection.
  - Study of HDV quasispecies by ultra-deep pyrosequencing
  - Collaboration with the database from hepatitis delta international network

- Collaboration in the preparation of a "clean" HDV-RNA standard for its real-time PCR quantification.
- Hepatitis E Virus (HEV) infection.
- New strategies for the treatment of chronic hepatitis B and C.
- Pharmacoeconomics.

Most relevant scientific articles

- Sulkowski MS, Poordad F, Manns MP, Bronowicki JP, Rajender Reddy K, Harrison SA. Anemia during treatment with peginterferon Alfa-2b/ribavirin and boceprevir: Analysis from the serine protease inhibitor therapy 2 (SPRINT-2) trial.Hepatology. 2013 Mar;57(3):974-84.
- Fried MW, Buti M, Dore GJ, Flisiak R, Ferenci P, Jacobson I. Once-daily simeprevir (TMC435) with pegylated interferon and ribavirin in treatment-naïve genotype 1 hepatitis C: the randomized PILLAR study.Hepatology. 2013 Dec;58(6):1918-29.
- Zeuzem S, Soriano V, Asselah T, Bronowicki JP, Lohse AW, Müllhaupt B. Faldaprevir and deleobuvir for HCV genotype 1 infection.N Engl J Med. 2013 Aug 15;369(7):630-9.
- Ramírez C, Gregori J, Buti M, Tabernero D, Camós S, Casillas R. A comparative study of ultra-deep pyrosequencing and cloning to quantitatively analyze the viral quasispecies using hepatitis B virus infection as a model.Antiviral Res. 2013 May;98(2):273-83.
- Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study.Lancet. 2013 Feb 9;381(9865):468-75.

Highlights

During 2013 we have made progresses in standardizing ultra-deep pyrosequencing and implementing it to clinical practice in viral hepatitis B and C. In this sense we have continued our collaboration in the CDTI project (IDI - 20110115), which has been completed in 2013, within which have been developed primers and methods for the study of HCV quasispecies of which a patent is being processed (patent request EP13382278). Also we have started to apply this technology to the study of quasispecies of hepatitis D and E viruses.

In line with the study of hepatitis D virus, we have continued international collaborations with groups of doctors Petersen and Dandri (Hamburg , Germany) and Roggendorf (Munich, Germany) and have established a new partnership with the hepatitis delta international network (HDIN) to include clinical data into its data base. It is also remarkable our collaboration with the German network for excellence in the treatment of viral hepatitis (Hep-Net).

Nationally, we coordinate and manage the platform for collecting clinical data of chronic hepatitis B (CIBERHEP) which have collected data from nearly 1,000 patients with chronic hepatitis B, most of them under antiviral treatment with tenofovir or entecavir (first-line treatment options against chronic hepatitis B). The analysis of part of the data collected in this platform was accepted for oral presentation at the 39th annual meeting of the AEEH (2014).

We have also continued to participate in clinical trials of new direct action antiviral treatments against hepatitis C. These studies have led to publications in high impact factor journals, some of which are listed among the 5 publications that we have selected this year.

PROGRAMME:
Cholestasis and Metabolic Disorders

G0035

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Main lines of research

- Functional relationship between methionine metabolites, acid sphingomyelinase and phosphatidylcholine in steatohepatitis.
- Development of non-invasive diagnostic methods for diagnosis and prognosis in alcohol-induced liver disease.
- Ischemia-reperfusion hepatocellular damage mechanisms and their regulation based on antioxidant and antiinflammatory strategies.
- Sphingolipid and mitochondrial oxidative-stress regulation of cell death.
- Contribution of sphingolipids and autophagy to lipid metabolism and non-alcoholic steatohepatitis.
- Regulation of cholesterol homeostasis in patients and experimental models of non-alcoholic steatohepatitis and ischemia-reperfusion injury.
- Mechanisms responsible for cholesterol transport to the mitochondria.
- Role of cholesterol in hepatocellular carcinoma response to chemotherapy
- Parenchyma-stroma interaction in cancer and ischemia/reperfusion-induced liver damage: lipid therapies.
- Role of cholesterol and the mitochondria in disease.
- Contribution of TNF receptors and cathepsins to fibrosis and inflammation of the liver.

Most relevant scientific articles

- Fernández A, Matias N, Fucho R, Ribas V, Von Montfort C, Nuño N et al.. ASMase is required for chronic alcohol induced hepatic endoplasmic reticulum stress and mitochondrial cholesterol loading.J Hepatol. 2013 Oct;59(4):805-13.
- Barbero-Camps E, Fernández A, Martínez L, Fernández-Checa JC, Colell A. APP/PS1 mice overexpressing SREBP-2 exhibit combined Aβ accumulation and tau pathology underlying Alzheimer's disease.Hum Mol Genet. 2013 Sep 1;22(17):3460-76.
- García-Ruiz C, Fernández-Checa JC. To binge or not to binge: binge drinking disrupts glucose homeostasis by impairing hypothalamic but not liver insulin signaling.Hepatology. 2013 Jun;57(6):2535-8.
- Marí M, Morales A, Colell A, García-Ruiz C, Kaplowitz N, Fernández-Checa JC. Mitochondrial glutathione: features, regulation and role in disease.Biochim Biophys Acta. 2013 May;1830(5):3317-28.
- García-Ruiz C, Baulies A, Mari M, García-Rovés PM, Fernández-Checa JC. Mitochondrial dysfunction in non-alcoholic fatty liver disease and insulin resistance: cause or consequence?Free Radic Res. 2013 Nov;47(11):854-68.

Highlights

Our recent work, *ASMase is required for chronic alcohol induced hepatic endoplasmic reticulum stress and mitochondrial cholesterol loading* (J Hepatol. 2013), highlighted in Nature Reviews Gastroenterology&Hepatology, provides evidence for ASMase as a therapeutic target in alcoholic liver disease (ALD). ALD is a major health concern of alcohol abuse and a leading cause of liver-related morbidity and mortality. ALD pathogenesis still remains poorly understood what has greatly limited the availability of efficient therapeutic options. Our data provided evidence that acid sphingomyelinase (ASMase) links alcohol consumption to endoplasmic reticulum (ER) stress, a key mechanism of ALD determining hepatic steatosis and liver injury, independently of alcohol-mediated hyperhomocysteinemia. Another key finding was that alcohol-induced ASMase-mediated ER stress triggers the induction of StARD1, a cholesterol-transporting polypeptide that regulates mitochondrial cholesterol trafficking. Consequently, ASMase knockout mice or wild type mice after pharmacological ASMase inhibition were insensitive to alcohol-induced mitochondrial cholesterol loading and subsequent mitochondrial GSH depletion, which in turn sensitized to circulating and cell-bound TNF susceptibility and liver injury. Moreover, increased expression of ASMase, StARD1 and ER stress markers were seen in liver biopsies of patients with acute alcoholic hepatitis, providing a rationale to ASMase targeting as applicable in human ALD treatment.

A mechanistically related study, *APP/PS1 mice overexpressing SREBP-2 exhibit combined Aß accumulation and tau pathology underlying Alzheimer's disease* (Hum Mol Genet, 2013), highlights the role of cholesterol in the development of Alzheimer's disease. Our data shows that that increasing cholesterol accelerates and worsens different pathological manifestations of the disease and cognitive deficits. Moreover, the increase of total cholesterol is associated with decreased mitochondrial glutathione (GSH) fraction, and in vivo administration of GSH ester significantly reduced neural degeneration. These results, in line with our previous results in liver, demonstrate the importance of preserving mitochondrial antioxidant defense as a therapeutic strategy in Alzheimer's disease.

PROGRAMME:
Hepatitis Virus

G0004

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Main lines of research

- Impact of antiviral treatment in patients with hepatitis C recurrence after liver transplantation and in the natural history of chronic hepatitis C.
- Evaluation of new hepatitis C treatments.
- Study of host factors in relation to the natural history and treatment response among patients with chronic hepatitis C.
- Validation of non-invasive diagnostic methods of liver fibrosis in chronic hepatitis C and liver transplantation.
- Identification of serum markers of liver fibrosis using metabolomic tools.
- Evaluation of early histological markers of fibrosis progession in liver transplant recipients with hepatitis C recurrence.
- Genetic evolution of hepatitis C virus in the liver transplantation setting using ultra-deep pyrosequencing.
- Characterization of hepatitis C virus life cycle using in vitro cell culture models.
- Development of diagnostic tools for the detection of hepatitis C antigens in liver tissue.

Most relevant scientific articles

- Mensa L, Pérez-del-Pulgar S, Crespo G, Koutsoudakis G, Fernández-Carrillo C, Coto-Llerena M. Imaging of hepatitis C virus infection in liver grafts after liver transplantation.J Hepatol. 2013 Aug;59(2):271-8.
- Mariño Z, Crespo G, D'Amato M, Brambilla N, Giacovelli G, Rovati L. Intravenous silibinin monotherapy shows significant antiviral activity in HCV-infected patients in the peri-transplantation period.J Hepatol. 2013 Mar;58(3):415-20.
- Pedersen J, Carlsen TH, Prentoe J, Ramirez S, Jensen TB, Forns X. Neutralization resistance of hepatitis C virus can be overcome by recombinant human monoclonal antibodies.Hepatology. 2013 Nov;58(5):1587-97.
- Crespo G, Carrión JA, Coto-Llerena M, Mariño Z, Lens S, Pérez-Del-Pulgar S. Combinations of simple baseline variables accurately predict sustained virological response in patients with recurrent hepatitis C after liver transplantation.J Gastroenterol. 2013 Jun;48(6):762-9.
- Schepis F, Vukotic R, Berzigotti A, Carrión JA, Forns X, Abraldes JG. Hemodynamic response to propranolol in patients with recurrent hepatitis C virus-related cirrhosis after liver transplantation: a case-control study.Liver Transpl. 2013 Apr;19(4):450-6.

Highlights

TREATMENT OF CHRONIC HEPATITIS C: 1) Participation in clinical trials for the evaluation of the efficacy and safety of new antiviral molecules in immunocompetent patients and 2) leadership, coordination and design of clinical studies using new direct acting antivirals in special populations: decompensated cirrhotics, cirrhotics awaiting liver transplantation and liver transplant recipients.

DETECTION OF HCV ANTIGENS IN LIVER BIOPSIES: We have established an immunohistochemical assay to detect HCV antigens in formalin-fixed paraffin-embedded liver tissue from HCV-infected liver transplant patients. The system has been validated by assessing HCV antigens using confocal microscopy and we have been able to confirm our results in samples provided by other transplant centers. This method might be helpful for the diagnosis of severe hepatitis C recurrence after liver transplantation in cases where the histopathological findings are not conclusive.

HCV MASSIVE SEQUENCING: We have consolidated an active collaboration with our CIBERehd partners at Institut de Recerca de l'Hospital Vall d'Hebron (Barcelona) to study HCV genetic evolution in the liver transplantation setting by ultra-deep pyrosequencing (UDPS). In particular, we have performed a very detailed analysis of HCV quasispecies dynamics and the competition of hepatitis C viral strains in HCV-infected patients who underwent liver transplantation and received a liver from an HCV-infected donor.

R & D COMPETITIVE PROJECTS: In January 2013 began the implementation of the European project entitled "Human monoclonal antibody therapy to prevent hepatitis C virus reinfection of liver transplants: advancing lead monoclonal antibodies into clinical trial" (Ref. 305500, HepaMAb). The main objectives of this project are: 1) the preclinical development of two monoclonal antibodies capable of blocking HCV entry into hepatocytes and 2) the development of a proof of concept clinical trial for the prevention of graft infection after liver transplantation.

PROGRAMME:
Hepatitis Virus

G0048

Group Members

STAFF MEMBERS

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ASSOCIATED MEMBERS

García Buey, Luisa Consuelo
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Main lines of research

- Angiogenesis in chronic liver disease
- Hepatic Fibrosis in chronci liver diseases
- Viral and cellular determinants in hepatic C virus infection
- Hepatitis B Virus X protein in hepatocellular carcinoma
- Identification of genetic and serum prognostic markers of chronic liver diseases progression

Most relevant scientific articles

- Poynard T, Bruix J, Schiff ER, Diago M, Berg T, Moreno-Otero R. Improved inflammatory activity with peginterferon alfa-2b maintenance therapy in non-cirrhotic prior non-responders: a randomized study.J Hepatol. 2013 Mar;58(3):452-9.
- Rodríguez-Muñoz Y, Martín-Vílchez S, López-Rodríguez R, Hernández-Bartolomé Á, García-Buey L, Borque MJ. Preliminary evidence of sustained expression of angiopoietin-2 during monocyte differentiation in chronic hepatitis C.Liver Int. 2013 Jul;33(6):864-70.
- López-Rodríguez R, Hernández-Bartolomé Á, Borque MJ, Rodríguez-Muñoz Y, Martín-Vílchez S, Trapero-Marugán M. Polymorphisms in histone deacetylases improve the predictive value of IL-28B for chronic hepatitis C therapy.Genes Immun. 2013 Jul-Aug;14(5):317-24.
- Trapero-Marugán M, Moreno-Otero R. Letter: impact of mild alcohol consumption in chronic hepatitis C treatment.Aliment Pharmacol Ther. 2013 Jun;37(11):1118-9.
- Hernández-Bartolomé A, López-Rodríguez R, Rodríguez-Muñoz Y, Martín-Vílchez S, Borque MJ, García-Buey L. Angiopoietin-2 Serum Levels Improve Noninvasive Fibrosis Staging in Chronic Hepatitis C: A Fibrogenic-Angiogenic Link.PLoS One. 2013;8(6):e66143.

Highlights

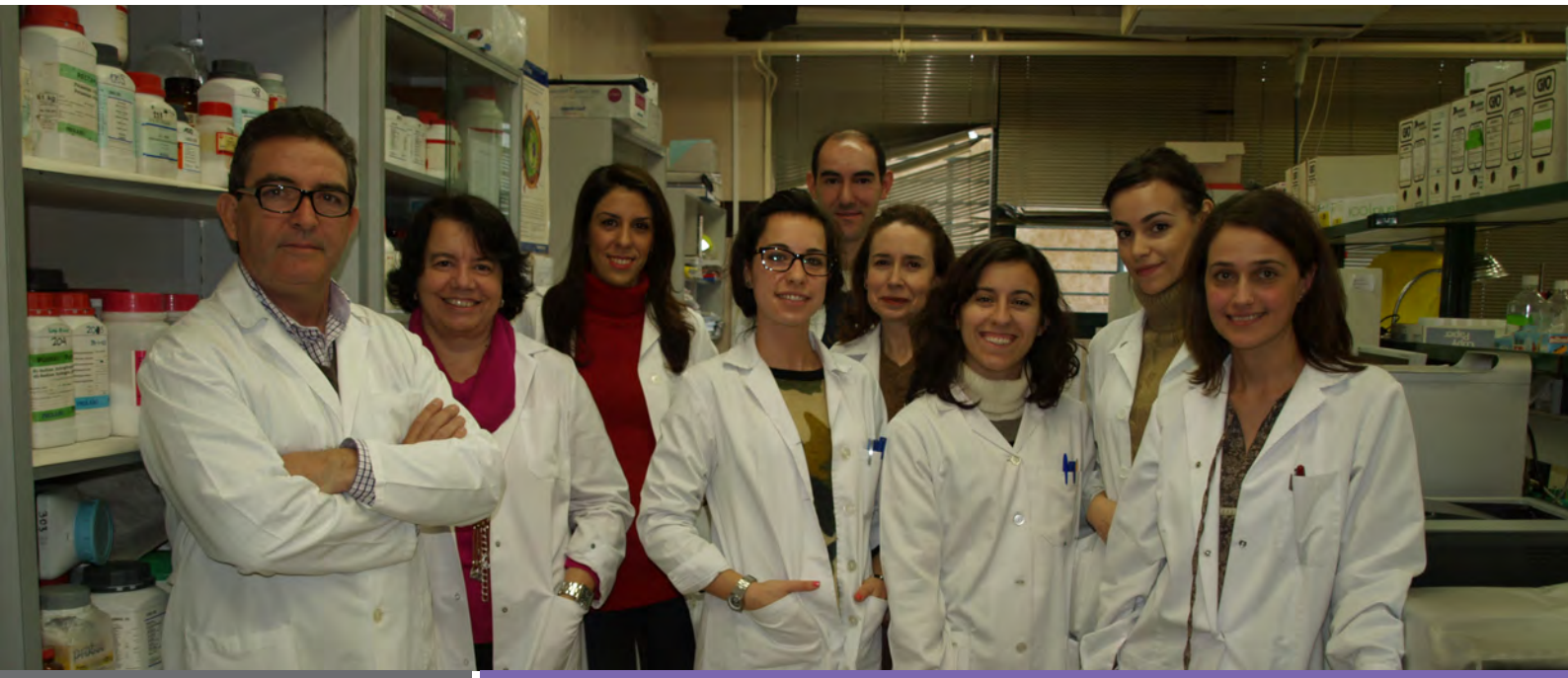
During last years our research group has been particularly focused on identifying useful non-invasive prognostic biomarkers of chronic hepatitis C (CHC) progression to cirrhosis and hepatocellular carcinoma (HCC). We are also interested in understanding how the hepatitis C virus (HCV) interacts with target cells, with particular emphasis on the role of the cellular factors implicated in different steps of the viral life cycle.

The altered expression of multiple angiogenic and fibrogenic-related factors during the course of CHC provides a valuable tool for the non-invasive assessment of liver fibrosis, clue for clinical decision-making. Among other clinical and demographic variables, peripheral levels of angiopoietins correlated significantly with hepatic fibrosis. Such finding allowed us to develop a novel index for non invasive evaluation of liver fibrosis, AngioScore, which was further validated in an independent series of patients with CHC.

Monocytes, essential precursors of antigen-presenting cells, notably contribute to the pathogenesis of chronic inflammatory diseases and cancer. Interestingly, we detected in the peripheral blood of CHC patients a significant increment of a subtype of monocytes with marked proangiogenic properties but notable immunosuppressive nature able to express the angiopoietin receptor Tie2, highlighting the relevant role of Angiopoietin/Tie-2 axis on the regulation of inflammatory response during the progression of chronic liver diseases.

In addition, we have characterized the significance of certain genetic variants of ISGs and HDACs for the optimization of IL28B predictive value of therapeutic response of CHC patients; interestingly some of them were markedly related to fibrosis progression (Patents: ES-2422874_A1 and ES-2423154_A1).

Regarding HCV infection in vitro, our studies have demonstrated that HCV promotes structural and functional alterations of intercellular junctions and that occludin, a tigh junction associated protein, plays an essential role in HCV infection. We have also described a novel use of Matrigel-embedded hepatocytes cultures supporting the entire HCV infection cycle.



PROGRAMME:
Liver Cancer and Cancer of the Digestive System

G0023

Group Members

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Main lines of research

- Bile acids in physiology, pathology and pharmacology. Cholestasis.
- Mechanisms of chemoresistance in liver and gastrointestinal cancer.
- ABC Proteins: Their role in resistance to chemotherapy.
- Biotechnology applied to overcome tumor chemoresistance.
- Drug targeting through membrane transporters.
- Role of the nuclear receptor FXR in chemoprotection and chemoresistance. Hepatocarcinogenesis and cholangiocarcinogenesis.

Most relevant scientific articles

- Herraez E, Lozano E, Macias RI, Vaquero J, Bujanda L, Banales JM et al.. Expression of SLC22A1 variants may affect the response of hepatocellular carcinoma and cholangiocarcinoma to sorafenib.Hepatology. 2013 Sep;58(3):1065-73.
- Uriarte I, Fernández-Barrena MG, Monte MJ, Latasa MU, Chang HC, Carotti S. Identification of fibroblast growth factor 15 as a novel mediator of liver regeneration and its application in the prevention of post-resection liver failure in mice.Gut. 2013 Jun;62(6):899-910.
- Marin JJ, Hernández A, Revuelta IE, González-Sanchez E, González-Buitrago JM, Pérez MJ. Mitochondrial genome depletion in human liver cells abolishes bile acid-induced apoptosis: Role of the Akt/mTOR survival pathway and Bcl-2 family proteins.Free Radic Biol Med. 2013 Apr 16;61C:218-228.
- Vaquero J, Briz O, Herraez E, Muntané J, Marin JJ. Activation of the nuclear receptor FXR enhances hepatocyte chemoprotection and liver tumor chemoresistance against genotoxic compounds.Biochim Biophys Acta. 2013 Oct;1833(10):2212-9.
- Papacleovoulou G, Abu-Hayyeh S, Nikolopoulou E, Briz O, Owen BM, Nikolova V et al.. Maternal cholestasis during pregnancy programs metabolic disease in offspring.J Clin Invest. 2013 Jul 1;123(7):3172-81.

Highlights

The Laboratory of Experimental Hepatology and Drug Targeting (HEVEFARM) is a multidisciplinary team directed by Dr. Jose Juan Garcia Marin, which is composed by members of the Departments of Physiology and Pharmacology and of Biochemistry and Molecular Biology, University of Salamanca and University Hospital of Salamanca. The group belongs to the National Biomedical Research Centre for the Study of Liver and Digestive Diseases (CIBERehd), Institute of Health Carlos III, and is part of the Institute of Biomedical Research of Salamanca (IBASL).

Several of its components are members of the Spanish (AEEH) and European (EASL) Associations for the Study of the Liver, the Spanish Society of Digestive Pathology (EDPS), the Spanish Society of Biochemistry and Molecular Biology (SEBBM), the Spanish (SECF), British (PS) and American (APS) Societies of Physiology, the American Society for Pharmacology and Experimental Therapeutics (ASPET) and the Federation of American Societies for Experimental Biology (FASEB).

During the last 15 years the research group, recognized as Group of Excellence by the Castilla and Leon Government, has been dedicated to the study of issues related to Biochemistry, Physiology, Pathophysiology and Pharmacology of the liver.

The HEVEFARM coordinates a Doctoral Programme (Pathophysiology and Pharmacology; http://www.usal.es/webusal/en/node/30186) and a University Master (Master in Cellular and Molecular Pathophysiology and Pharmacology; http://www.hevefarm.com/en).

The HEVEFARM has 4 patents (submitted plus obtained).

The HEVEFARM has participated in the development of a clinical guideline for the management of patients with gestational cholestasis.

The HEVEFARM regularly carries out analysis by HPLC-MS/MS of metabolomics (bile acids, flavonoids, steroid hormones, melatonin, sorafenib and other drugs) in biological fluids, tissues and cell cultures for numerous international and national laboratories within and outside the CIBERehd.

Bibliometric parameters of HEVEFARM:

Publications: >250

Impact Factor accumulated (last 5 years): >200

Cited Received: >2400

H Index: 29

PROGRAMME:
Cholestasis and Metabolic Disorders

G0009

Group Members

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Main lines of research

The main research line of the group headed by Dr. Carmelo García-Monzón focus on the characterization of the epidemiology and molecular mechanisms involved in the pathogenesis of nonalcoholic fatty liver disease, which is commonly associated with obesity and diabetes mellitus type 2 as well as with metabolic syndrome and, therefore, being considered as the more frequent chronic liver disease in the developed world.

Most relevant scientific articles

- Solute carrier family 2 member 1 is involved in the development of nonalcoholic fatty liver disease. Vazquez-Chantada M, González-Lahera A, Martínez-Arranz I, García-Monzón C, Regueiro MM, García-Rodríguez JL, Schlangen KA, Mendibil I, Rodríguez-Ezpeleta N, Lozano JJ, Banasik K, Justesen JM, Joergensen T, Witte DR, Lauritzen T, Hansen T, Pedersen O, Veyrie N, Clement K, Tordjman J, Tran A, Le Marchand-Brustel Y, Buque X, Aspichueta P, Echevarria-Uraga JJ, Martín-Duce A, Caballeria J, Gual P, Castro A, Mato JM, Martínez-Chantar ML, Aransay AM. Hepatology 2013;57:505-14.
- Increased soluble CD36 is linked to advanced steatosis in non-alcoholic fatty liver disease. García-Monzón C, Lo Iacono O, Crespo J, Romero-Gómez M, García-Samaniego J, Fernández-Bermejo M, Domínguez-Díez A, Rodríguez de Cía J, Sáez A, Porrero JL, Vargas-Castrillón J, Chávez-Jiménez E, Soto-Fernández S, Díaz A, Gallego-Durán R, Madejón A, Miquilena-Colina ME. Eur J Clin Invest 2013 Oct 17. doi: 10.1111/eci.12192.

Highlights

Regarding the scientific production of the group during 2013, it is important to note the collaborations with other groups from the CIBEREHD leading to the characterization of soluble fatty acid translocase CD36 as a serum marker for the noninvasive diagnosis of nonalcoholic fatty liver disease (Eur J Clin Invest, 2013) and to the identification of a polymorphism in the SLC2A1 gene associated with the development of nonalcoholic fatty liver (Hepatology, 2013).

On the other hand, a relevant hit for our group was that a research project for the next three years (2014-2016) aimed to assess the impact of intermitent chronic hypoxia on the pathogenesis of nonalcoholic fatty liver disease was granted by the Instituto de Salud Carlos III, with a total budget of 116,160 €.

PROGRAMME:
Hepatitis Virus

G0083

Group Members

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Main lines of research

- Epigenetic modifications analysis induced by HCV and HBV infections and their role in the hepatic damage oprogression.
- Study of predictive markers of antiviral response in chronic hepatitis C patients treated with direct antiviral agents.
- Study of predictive markers of fibrosis progression and hepatocellular carcinoma in patients with chronic hepatitis C.
- Design of novel HCV quantification and genotyping methods in point-of-care for non development countries.
- Analysis of genetic and epigenetic risk factors of development of hepatocellular carcinoma in non-treated patients with chronic hepatitis B.
- Optimization of management and treatment of patients with chronic viral hepatitis coinfected with HIV.

Most relevant scientific articles

- Romero-Gómez M, Planas R, Ampuero J, Solà R, García-Samaniego J, Diago M, Crespo J, Calleja JL, Turnes J.. Meta-analysis: pegylated interferon α-2a achieves higher early virological responses than α-2b in chronic hepatitis C.Aliment Pharmacol Ther. 2013;.
- Rivas P, Herrero MD, Poveda E, Madejón A, Treviño A, Gutiérrez M. Hepatitis B, C, and D and HIV infections among immigrants from Equatorial Guinea living in Spain.Am J Trop Med Hyg. 2013 Apr;88(4):789-94.
- García-Samaniego J, Romero M, Granados R, Alemán R, Jorge Juan M, Suárez D. Factors associated with early virological response to peginterferon-α-2a/ribavirin in chronic hepatitis C.World J Gastroenterol. 2013 Mar 28;19(12):1943-52.
- Andrade RJ, García-Samaniego J. [Biochemical and pharmacological features of telaprevir].Enferm Infecc Microbiol Clin. 2013 Jul;31 Suppl 3:2-6.
- Turnes J, Romero-Gómez M, Planas R, Solà R, García-Samaniego J, Diago M. Pharmacoeconomic analysis of the treatment of chronic hepatitis C with peginterferon alfa-2a or peginterferon alfa-2b plus ribavirin in Spain.Gastroenterol Hepatol. 2013 Nov;36(9):555-64.

Highlights

FINANCIAL SUPPORT.

- Public research projects.

  - Identification of treatment-resistant HCV variants against telaprevir or boceprevir therapy by using cold-PCR technique. Application in monitoring antiviral response. PI: Javier García-Samaniego. FINANCING SOURCES: FISS PI12/02146.

- Private financing research projects.

  - Genetic and epigenetic analysis of asymptomatic HBV carriers. Implications in the therapeutic decisions. PI: Antonio Madejón. FINANCING SOURCES: Gilead S.A.

  - Performance evaluation of a qPCR based point-of-care test (POCT) for blood-borne viral infections: HCV, HIV and HTLV. PI: Antonio Madejón, Berta Rodes and Carlos

MOST RELEVANT PARTICIPATIONS IN COLABORATIVE PROJECTS.

- Epigenetic mechanisms induced by hepatitis C virus; involvement in the evolution of fibrosis and development of hepatocellular carcinoma. PI: Javier García-Samaniego. CIBERehd GROUPS: Dr. Esteban Domingo. EXTERNAL COLABORATORS: Dr. Sánchez-Pacheco (Medicine Faculty, Biochemistry Department, UAM).
- Automate High-resolution HCV subtyping and detection of resistant mutations and translate into a routine diagnostic laboratory. IPs: J.Quer, F.Rodríguez-Frias. CIBER GROUPS: JI.Esteban, R.Esteban, X.Forns, J.Garcia-Samaniego.
- Epigenetic modulation of chronic hepatitis c progression to hepatocellular carcinoma: role of histone deacetylases genetic variants. PI: Paloma Sanz Cameno. CIBERehd GROUPS: Dr. Salmerón, Dr. García-Samaniego.
- Identification and validation of angiogenic biomarkers of chronic hepatitis c progression to cirrhosis and hepatocellular carcinoma. PI: Dr. Paloma Sanz Cameno. CIBERehd GROUPS: Dr. Salmerón, Dr. García-Samaniego, Dr. Forns, Dr. Pérez del Pulgar.
- HeapiC-based Nationwide point-of-care concerted action for HCV screening and "treatment as prevention and cure". PI: Dr. J.I.Esteban. PARTICIPATING GROUPS: All groups of the CIBEREHD-VHP, ABL.
- Pharmacogenomics in triple therapy: Genome Wide Association Study (GWAS) in Hepatitis C patients treated with peginterferon + ribavirin + protease inhibitor: Safety and Efficacy. PI: Dr. Manuel Romero-Gómez. PARTICIPATING GROUPS: All groups of the CIBEREHD – Viral hepatitis program

CLINICAL TRIALS.

Dr. Javier García-Samaniego is the principal investigator of 18 active cluinical trials in the Hospital carlos III.

PROGRAMME:
Hepatitis Virus

G0086

Group Members

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Main lines of research

Dr. Jordi Gómez Lab has been involved in : characterization of the RNA structure of messenger RNA coding for the interferon alfa 5, which expression is liver specific, and to characterize its molecular mimicry with the genomic RNA of the Hepatitis C virus; (2) the RNA structure of the 5' genomic region of HCV RNA in the presence of the liver specific microRNA miR-122; (3) in collaboration with Drs, Esteban Domingo (CBM-SO) and Juan Ignacio Esteban (Hosp. Vall d' Hebron) we have evaluated the mutagenic effects of ribavirine on the the 5' genomic region of HCV, in cell culture, and also evaluated the mutagenic effects on viral RNA recognition by stereospecifc factors, and (4) a collaboration with Dr. Carlos Briones, is described in the following paragraph.

During 2013, the group of Dr. Carlos Briones at the Centro de Astrobiología (CSIC-INTA) continued the investigation of the structure/function relationships in the genomic RNA of hepatitis C virus (HCV). We have deepened into the structural characterization of the long-range interaction between the 5' and 3' ends of the HCV genome, and an article was published (online version in September 2013 and paper in January 2014) in collaboration with the group of Dr. Alfredo Berzal (IPBLN, CSIC) [1]. In parallel, we have extended a collaborative study with Dr. Jordi Gómez (IPBLN, CSIC) in which a magnesium-induced RNA conformational switch was described at the internal ribosome entry site (IRES) of HCV genome, thanks to the combined use of atomic force microscopy (AFM) and molecular biology techniques [2]. Additionally, in 2013 Dr. Briones was the Chairman of the Organizing and Scientific Committees of the XII National Congress of Virology (Burgos, June 9-12), in which the plenary session 'Hepatitis B and C: from basic virology to clinical practice' was organized in collaboration with the CIBERehd [http://cab.inta-csic.es/congresovirologiasev2013/index.php/en.html].

[1] C. Romero-López, A. Barroso-del Jesús, A. García-Sacristán, C. Briones y A. Berzal-Herranz. 'End-to end cross-talk within the Hepatitis C virus genome mediates the conformational switch of the 3'X-tail region'. Nucleic Acids Research 2014, 42: 567-582.

[2] A. García-Sacristán, E. López-Camacho, A. Ariza-Mateos, M. Moreno, R.M. Jáudenes, J. Gómez, J.A. Martín-Gago y C. Briones. 'A magnesium-induced RNA conformational switch at the internal ribosome entry site of hepatitis C virus genome visualized by atomic force microscopy'. Artículo en revisión en una revista de biología molecular del primer cuartil.

In Esteban Domingo's lab the main interest is to understand how quasispecies dynamics allows adaptation of RNA viruses to changing environments, and to explore antiviral treatments that counteract the adaptive capacity of viruses.

We follow clinical developments concerning anti-HCV treatments, as part of CIBERehd (a Spanish network on hepatic diseases), with the objective of applying our conclusions with model systems in cell culture to the improvement of antiviral treatments.

Most relevant scientific articles

- Perales C, Beach NM, Gallego I, Soria ME, Quer J, Esteban JI et al.. Response of hepatitis C virus to long-term passage in the presence of alpha interferon: multiple mutations and a common phenotype.J Virol. 2013 Jul;87(13):7593-607.
- Ortega-Prieto AM, Sheldon J, Grande-Pérez A, Tejero H, Gregori J, Quer J et al.. Extinction of hepatitis C virus by ribavirin in hepatoma cells involves lethal mutagenesis. PLoS One. 2013;8(8):e71039.
- Gregori J, Esteban JI, Cubero M, García-Cehic D, Perales C, Casillas R. Ultra-deep pyrosequencing (UDPS) data treatment to study amplicon HCV minor variants.PLoS One. 2013;8(12):e83361.
- Cubero M, Gregori J, Esteban JI, García-Cehic D, Bes M, Perales C. Identification of host and viral factors involved in a dissimilar resolution of a hepatitis C virus infection. Liver Int. 2013 Oct 17;.
- Arias A, Isabel de Ávila A, Sanz-Ramos M, Agudo R, Escarmís C, Domingo E. Molecular dissection of a viral quasispecies under mutagenic treatment: positive correlation between fitness loss and mutational load.J Gen Virol. 2013 Apr;94(Pt 4):817-30.

Highlights

- Development of nucleic acid-based biosensors for RNA virus genotyping and for the structural characterization of their genomic RNA. FUNDING AGENCY: Spanish Ministry of Science and Innovation, Plan Nacional de I+D+I BIO2010-20696. PRINCIPAL INVESTIGATOR: Carlos Briones CAB (CSIC/INTA). PERIOD: 1.1.2011-31.12.2014
- Characterization of a new ribozymic activity within the internal ribosome entry site of Hepatitis C virus. FUNDING AGENCY: Spanish Ministry of Science and Innovation, Plan Nacional de I+D+I. BFU2012-35898 PRINCIPAL INVESTIGATOR: Jordi Gómez IPBLN (CSIC). PERIOD: 1.1.2012-31.12.2014
- Antiviral design based on lethal mutagenesis. FUNDING AGENCY: Spanish Ministry of Science and Innovation, Plan Nacional de I+D+IBFU-2011-23604. PRINCIPAL INVESTIGATOR: E. Domingo (CSIC-SO). PERIOD: 01.01.2012 -31.12.2014

PROGRAMME:
Cholestasis and Metabolic Disorders

G0013

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Main lines of research

- Development and validation of experimental models of liver and digestive disease
- Role of oxidative stress and inflammation in liver and gastrointestinal diseases
- Molecular mechanisms involved in development of steatosis in liver chronic diseases

Most relevant scientific articles

- Tuñón MJ, San-Miguel B, Crespo I, Laliena A, Vallejo D, Álvarez M. Melatonin treatment reduces endoplasmic reticulum stress and modulates the unfolded protein response in rabbits with lethal fulminant hepatitis of viral origin.J Pineal Res. 2013 Oct;55(3):221-8.
- Mauriz JL, Collado PS, Veneroso C, Reiter RJ, González-Gallego J. A review of the molecular aspects of melatonin's anti-inflammatory actions: recent insights and new perspectives.J Pineal Res. 2013 Jan;54(1):1-14.
- Carbajo-Pescador S, Steinmetz C, Kashyap A, Lorenz S, Mauriz JL, Heise M. Melatonin induces transcriptional regulation of Bim by FoxO3a in HepG2 cells.Br J Cancer. 2013 Feb 5;108(2):442-9.
- Carbajo-Pescador S, Ordoñez R, Benet M, Jover R, García-Palomo A, Mauriz JL. Inhibition of VEGF expression through blockade of Hif1α and STAT3 signalling mediates the anti-angiogenic effect of melatonin in HepG2 liver cancer cells.Br J Cancer. 2013 Jul 9;109(1):83-91.
- Guzmán C, Benet M, Pisonero-Vaquero S, Moya M, García-Mediavilla MV, Martínez-Chantar ML. The human liver fatty acid binding protein (FABP1) gene is activated by FOXA1 and PPARα; and repressed by C/EBPα: Implications in FABP1 down-regulation in nonalcoholic fatty liver disease.Biochim Biophys Acta. 2013 Apr;1831(4):803-18.

Highlights

OUTPUTS:

Publications 1st decil: 2 / Publications 1st quartile: 6 / Publications 2nd quartile: 1

Total IF: 35.9 / Competitive projects: 3

Public/private funding: 56,004€/62,886€

Multicentric Clinical trials: 5

Collaborations: José V Castell (Hospital Universitario La Fe, Valencia); Ricardo Moreno (Hospital de la Princesa, Madrid); Jesús Mª Prieto Clínica (Universitaria de Navarra); José María Mato (CIC BioGUNE, Vizcaya)

PROJECTS:

- "Papel del receptor nuclear LXRa y de los principales genes lipogénicos e inflamatorios en el desarrollo y evolución de esteatosis en modelos in vitro de hepatitis C. Efecto de un tratamiento con quercetina". Plan Nacional de I+D+i. 2011-2013. 25.108€.
- "Eficacia de la glutamina en la prevención de enteritis rádica aguda y su efecto sobre el estrés oxidativo". Gerencia Regional de Salud de Castilla y León. 2011-2014. 14.000€.
- "Estudios de pauta de administración y análisis de mecanismos del uso de la cardiotrofina-1 humana en un modelo animal de fallo hepático fulminante de etiología vírica". Digna Biotech. 2011-2013. 11.934€.
- "Estudio del papel de diversos factores de transcripción en la carcinogénesis hepática". Fundación Investigación Sanitaria en León. 2012-2013. 21.793€.
- "Estudio de los efectos de la administración de glutamina en patologías gastrointestinales". Fundación Investigación Sanitaria en León. 2011-2013. 12.203€.
- "Efecto de moléculas antioxidantes sobre la progresión de NAFLD a hepatocarcinoma". Fundación Investigación Sanitaria en León. 2013-2014. 16.956€.
- "Extracción y purificación de compuestos bioactivos presentes en hongos comestibles. Evaluación de su actividad inmunomoduladora y/o antibacteriana, in vitro e in vivo". Plan Nacional de I+D+I 2013-2015. 2013-2015. 16.896€.

THESIS:

- "Efecto de la melatonina sobre la proliferación, apoptosis y angiogénesis en un modelo in vitro de hepatocarcinoma". Sara Carbajo Pescador. Directores: Javier González-Gallego y José Luis Mauriz. Sobresaliente "Cum Laude" (Mención Europea). 3/10/2013.
- "Análisis in vitro del efecto oncostático de la melatonina en hepatocitos tumorales de la línea HepG2". Andrés García Palomo. Directores: José Luis Mauriz y Javier González-Gallego. Sobresaliente "Cum Laude". 7/6/2013.

PROGRAMME:
Portal Hypertension and Cirrhosis

G0030

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Main lines of research

EXPERIMENTAL RESEARCH:

- Experimental rat model of cirrhosis and ascites.
- Mechanisms and prevention of bacterial translocation in rats with cirrhosis.
- Experimental model of spontaneous and induced bacterial peritonitis: physiopathology and treatment.

CLINICAL INVESTIGATION:

- Physiopathology, diagnosis, treatment and prevention of bacterial infections, ascites and hepatorenal syndrome in cirrhosis.
- Diagnosis and treatment of hepatic encephalopathy in cirrhosis.
- Physiopathology, diagnosis, treatment and prevention of digestive haemorrhage due to portal hypertension of non-varicose origin.

Most relevant scientific articles

- Villanueva C, Colomo A, Bosch A, Concepción M, Hernández-Gea V, Aracil C. Transfusion strategies for acute upper gastrointestinal bleeding.N Engl J Med. 2013 Jan 3;368(1):11-21.
- Laleman W, Simon-Talero M, Maleux G, Pérez M, Ameloot K, Soriano G. Embolization of large spontaneous portosystemic shunts for refractory hepatic encephalopathy: a multicenter survey on safety and efficacy.Hepatology. 2013 Jun;57(6):2448-57.
- Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis.Gastroenterology. 2013 Jun;144(7):1426-37, 1437.e1-9.
- Bellot P, Welker MW, Soriano G, von Schaewen M, Appenrodt B, Wiest R. Automated low flow pump system for the treatment of refractory ascites: a multi-center safety and efficacy study.J Hepatol. 2013 May;58(5):922-7.
- Soriano G, Guarner C. Probiotics in cirrhosis: do we expect too much?Liver Int. 2013 Nov;33(10):1451-3.

Highlights

During 2013 the Research Group CIBERehd of the Hospital de la Santa Cruz y Sant Pablo (EHD 25) , led by Dr. Carlos Guarner, has developed a large scientific activity both by the own team and in collaboration with other groups of CIBERehd.

In this period we have published 18 articles, all but two in international journals. Publications are 13 originals, 2 reviews , 2 letters and an article by consensus. Eight of the publications are of our team, that means made under the direction of any member of our group and 10 are collaborative studies with other groups. Of the 8 own publications, five are articles, 4 of the first quartile and one of the first decile. It is important to highlight our publication in New England Journal of Medicine "Transfusion strategies for acute upper gastrointestinal bleeding", which merited an editorial comment and letters, and has now been cited in 73 articles .

Of the 10 articles with other collaborative groups of the CIBERehd 7 have been published in journals of the first decile.

Currently, we have 7 state grants on hepatic encephalopathy, fragility in cirrhosis, translocation in cirrhosis evaluated by pyrosequencing, preventing the development of portal hypertension in cirrhosis and application of prostheses in patients with esophageal variceal bleeding.

We are collaborating in 8 multicentric clinical trials on complications of cirrhosis and 9 unrelated to our area (chronic viral hepatitis).

The industry is funding 3 projects of basic research on the prevention of bacterial translocation and its consequences by probiotics.

Eva Román has read her doctoral thesis, obtaining a maximum assessment, entitled "Fallen in patients with liver cirrhosis. Relationship between cognitive impairment and quality of life. "The two collaborators hired by the CIBERehd are finalizing their doctoral thesis.

PROGRAMME:
Gastrointestinal Inflammation and Motility

G0062

Group Members

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Main lines of research

- Investigation of complex microbial communities by high-thruput sequencing and bioinformatics
- Host-microbe interactions at the mucosal immune system
- Quality of life in chronic gastrointestinal diseases
- Epidemiology of chronic pancreatitis: genetic and environmental factors
- Experimental models of pancreatic cancer

Most relevant scientific articles

- Le Chatelier E, Nielsen T, Qin J, Prifti E, Hildebrand F, Falony G. Richness of human gut microbiome correlates with metabolic markers.Nature. 2013 Aug 29;500(7464):541-6.
- Guarner F, Hooper LV, Núñez G. Understanding the microbiota in the midst of Renaissance architecture and olive groves.Nat Immunol. 2013 Feb;14(2):101-5.
- Sunagawa S, Mende DR, Zeller G, Izquierdo-Carrasco F, Berger SA, Kultima JR. Metagenomic species profiling using universal phylogenetic marker genes.Nat Methods. 2013 Dec;10(12):1196-9.
- Casellas F, Ginard D, Vera I, Torrejón A, GETECCU. Development and testing of a new instrument to measure patient satisfaction with health care in inflammatory bowel disease: the CACHE questionnaire.Inflamm Bowel Dis. 2013 Mar;19(3):559-68.
- Nikolaou C, Bermúdez I, Manichanh C, García-Martínez J, Guigó R, Pérez-Ortín JE. Topoisomerase II regulates yeast genes with singular chromatin architectures.Nucleic Acids Res. 2013 Nov 1;41(20):9243-56.

Highlights

In 2013, we dedicated special efforts to the analysis of data generated by the European MetaHIT project, which obtained novel information about the gut microbial communities, not only regarding diversity, but also providing a novel view of genetic potential and functional networks in the community. These tasks implicated a special effort in developing bioinformatic tools for the analysis of massive datasets, and turned in a successful outcome in terms of publications with a high impact factor.

Our collaboration with the pharma industry aimed at developing novel drugs able to stimulate proliferation of T regulatory cells in human intestinal mucosa. Our organ-culture studies with human intestinal tissues have provided encouraging results. Such drug could become a powerful treatment for immuno-inflammatory disorders.

Our membership to the Guidelines Committee of the World Gastroenterology Organization has resulted this year in an important contribution to the production of a new guideline of common digestive disorders (WGO practice guideline of 2013)

PROGRAMME:
Gastrointestinal Inflammation and Motility

G0066

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Main lines of research

DISEASES OF THE DIGESTIVE TRACT ASSOCIATED WITH ACID INHIBITION OF COX OR H. PYLORI INFECTION

- Identification of environmental and genetic risk factors for injuries and complications of gastro-intestinal mucosa, development of prevention and treatment strategies.
- Biological and molecular mechanisms of neoplastic progression in Barrett's esophagus: identification of new biomarkers and therapeutic targets for chemoprevention.
- Identification of effective bactericide compounds against *Helicobacter pylori* infection.

GENETIC AND ENVIRONMENTAL DETERMINANTS INVOLVED ON INFLAMMATORY OR TUMOUR PROCESSES OF THE DIGESTIVE TRACT

- Genetic susceptibility and Helicobacter pylori infection associated with the development and prognosis of gastric cancer.
- Study of the genetic basis of susceptibility to hereditary and familial colon cancer.
- Diagnostic and Therapeutic Targets.

STEM CELLS AND CELL THERAPY FOR DIFFERENT DIGESTIVE AND LIVER GASTROINTESTINAL DISEASES.

- Identification, separation and molecular characterization of cancer stem cells in esophageal cancer .
- Optimization of isolation and culture of human hepatocytes to be used for cell therapy source. Investigation of the role of bone marrow stem cells in liver regeneration in different human models of disease.
- Bioengineering of organs and tissues (hepatic and pancreatic). Cellular therapies are being developed in patients, in a clinic level just like expansion of human stem cells of fetal and adult liver.

IDENTIFICATION OF BIOACTIVE COMPOUNDS AGAINST PROTEIN TARGETS RELATED WITH DIGESTIVE PATHOLOGIES. Transport and selective release by using multifunctional nanoparticles and nanosphere/nanoaggregated polymers

- Selected targets are associated with colon cancer (BFT), pancreatic cancer (NUPR1), Clostridium difficile infection (DPC) and viral hepatitis C (HCV NS3 protease). We work with gold nanoparticles (NP) as nanospheres /nanoclusters of polymers for drug transport and release.

Most relevant scientific articles

- Lanas A, Boers M, Nuevo J. Gastrointestinal events in at-risk patients starting non-steroidal anti-inflammatory drugs (NSAIDs) for rheumatic diseases: the EVIDENCE study of European routine practice.Ann Rheum Dis. 2013 Dec 18;.
- Bujanda L, Lanas Á, Quintero E, Castells A, Sarasqueta C, Cubiella J. Effect of aspirin and antiplatelet drugs on the outcome of the fecal immunochemical test.Mayo Clin Proc. 2013 Jul;88(7):683-9.
- Lanas A, Polo-Tomás M, Casado-Arroyo R. The aspirin cardiovascular/gastrointestinal risk calculator--a tool to aid clinicians in practice.Aliment Pharmacol Ther. 2013 Apr;37(7):738-48.
- Lanas A. Compliance with prescriptions of appropriate therapy for nonsteroidal anti-inflammatory drug users: is the glass half empty or half full?Clin Gastroenterol Hepatol. 2013 May;11(5):505-6.
- Gomollón F, Gisbert JP. Current management of iron deficiency anemia in inflammatory bowel diseases: a practical guide.Drugs. 2013 Nov;73(16):1761-70.

Highlights

PROJECTS

- Angel Lanas. Evaluation of the effectiveness of flavodixin inhibitors in the eradication of helicobacter pylori infection in an experimental animal model in m. gerbils. PI11/02578
- Asunción García. PS09/00213. Relevance of DNA repair gene polymorphisms as genetic markes of susceptibility and /or prognosis of gastric adenocarcinoma.. Their interaction with environmental factors and Helicobacter pylori infection.
- Elena Piazuelo. PI11/02089. Epigenetic changes in the progression of Barrett's esophagus to esophageal adenocarcinoma: aplication to the identification of high risk patients
- Angel Ferrández. PI10/02934. Follow-up study of factors associated with progressión of preneoplastic lesions of gastric cancer.
- Fernando Gomollón. European project. Inflammatory Bowel Disease CHARACTERization by a multi-modal integrated biomarker study. Project acronym: IBD-CHARACTER, Grant agreement no: 305676.

CLINICAL TRIALS

- Clinical Pharmacology of enteric-coated aspirin in healthy subjects. Angel Lanas. Phase I.
- Melatonin associated to acid inhibition for chemoprevention in BE:a pilot study. Angel Lanas. Phase IV.
- A Multi-centre, Phase II, Double-blind, Randomised, Placebo-controlled, Parallel Group, Dose-ranging Study in Patients With Faecal Incontinence; to Evaluate the Efficacy, Safety and Tolerability of Locally Applied NRL001 Over an 8 Week Treatment Period. Federico Sopeña. Phase II.

TOOL WITH INTELECTUAL PROPERTY OF CLINIC USE

http://www.asariskcalculator.com

CLINICAL GUIDELINES

- [Safe prescription recommendations for non steroidal anti-inflammatory drugs: Consensus document ellaborated by nominated experts of three scientific associations (SER-SEC-AEG)]. Lanas A, et al. . Gastroenterol Hepatol. 2014 Mar;37(3):107-27
- [Recommendations of the Spanish Working Group on Crohn's Disease and Ulcerative Colitis on the use of anti-tumor necrosis factor drugs in inflammatory bowel disease]. Cabriada JL, ..., Gomollón F; (GETECCU). Gastroenterol Hepatol. 2013 Mar;36(3):127-46.
- [III Spanish Consensus Conference on Helicobacter pylori infection]. Gisbert JP, ... Gomollón F, Lanas Á, et all. Gastroenterol Hepatol. 2013 May;36(5):340-74..
- Therapeutic guidelines on ulcerative colitis: a GRADE methodology based effort of GETECCU. Gomollón F, et all. Gastroenterol Hepatol. 2013 Feb;36(2):104-14

PROGRAMME:
Cholestasis and Metabolic Disorders

G0017

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Main lines of research

At present, the aim of our work is to study metabolic alterations as a tool and target for the detection, prevention and treatment of nonalcoholic steatohepatitis (NASH) including its progression to liver cirrhosis and cancer. To this end, we utilize state-of-the-art metabolomic, proteomics, genomic, structural biology and molecular imaging technologies together with biological systems of increasing complexity, including cellular systems, genetic engineered mouse models and human prospective studies. The specific areas of research are:

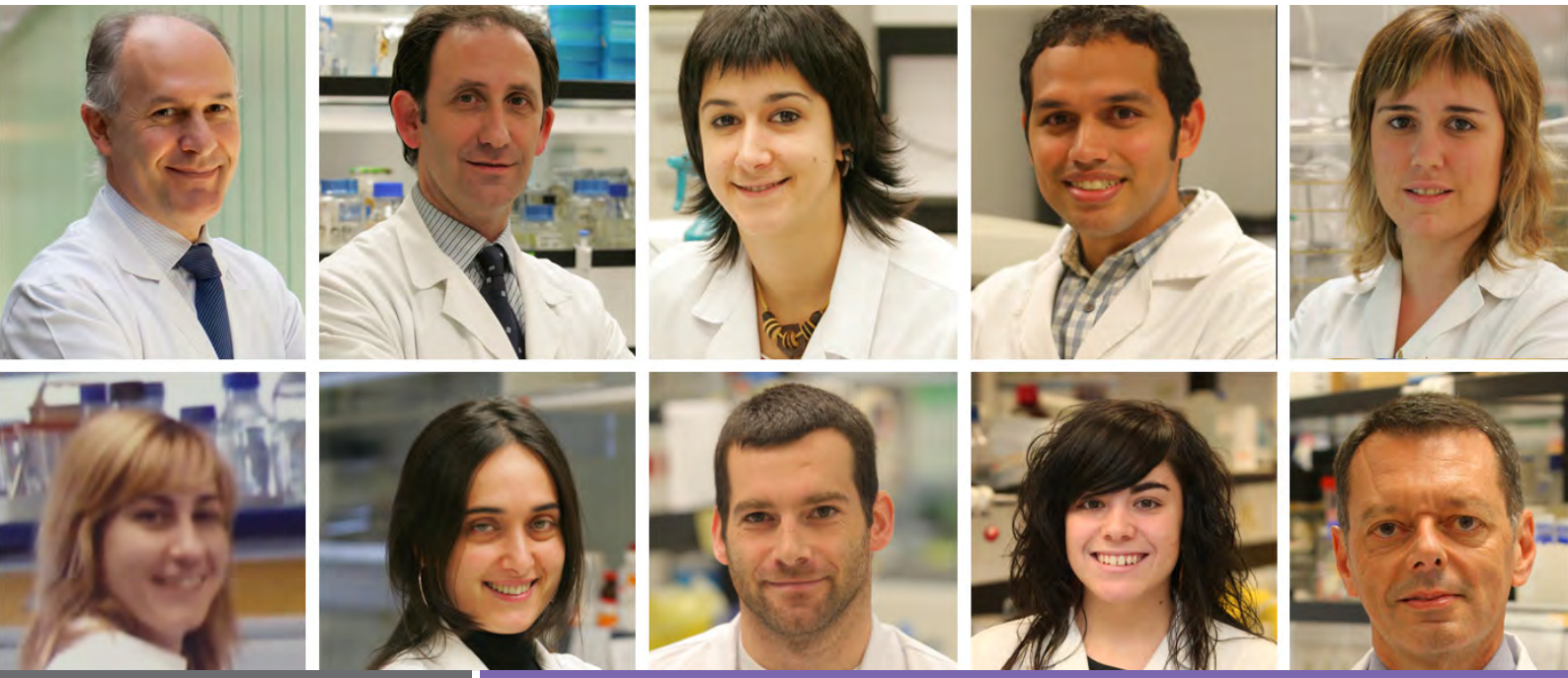
- We investigate the regulation of S-adenosylmethionine (SAMe) biosynthesis in mammalian cells and the function of SAMe in fatty liver disease, liver cirrhosis, and cancer.
- New molecular mechanisms in the development and progression of nonalcoholic fatty liver disease (NAFLD) to liver cancer: unraveling the impact of the post-translational modifications.
- Application of "omics" technologies to the study of the composition and function of hepatic exosomes: application to the identification of new non-invasive biomarkers of liver diseases.
- Structural virology of envelope and lipid-containing viruses: host-recognition and assembly.
- We offer state-of-the-art technological services in genomics, proteomics and metabolomics to all members of CIBERehd.

Most relevant scientific articles

- Martínez-Uña M, Varela-Rey M, Cano A, Fernández-Ares L, Beraza N, Aurrekoetxea I, Martínez-Arranz I, García-Rodríguez JL, Buqué X, Mestre D, Luka Z, Wagner C, Alonso C, Finnell RH, Lu SC, Martínez-Chantar ML, Aspichueta P, Mato JM. Excess S-adenosylmethionine reroutes phosphatidylethanolamine towards phosphatidylcholine and triglyceride synthesis.Hepatology (Baltimore, Md.). 2013;58(4):1296-305.
- Vazquez-Chantada M, González-Lahera A, Martínez-Arranz I, García-Monzón C, Regueiro MM, García-Rodríguez JL, Schlangen KA, Mendibil I, Rodríguez-Ezpeleta N, Lozano JJ, Banasik K, Justesen JM, Joergensen T, Witte DR, Lauritzen T, Hansen T, Pedersen O, Veyrie N, Clement K, Tordjman J, Tran A, Le Marchand-Brustel Y, Buque X, Aspichueta P, Echevarria-Uraga JJ, Martín-Duce A, Caballeria J, Gual P, Castro A, Mato JM, Martínez-Chantar ML, Aransay AM. Solute carrier family 2 member 1 is involved in the development of nonalcoholic fatty liver disease.Hepatology (Baltimore, Md.). 2013;57(2):505-14.
- Yang H, Zheng Y, Li TW, Peng H, Fernández-Ramos D, Martínez-Chantar ML, Rojas AL, Mato JM, Lu SC. Methionine adenosyltransferase 2B, HuR, and sirtuin 1 protein cross-talk impacts on the effect of resveratrol on apoptosis and growth in liver cancer cells.The Journal of biological chemistry. 2013;288(32):23161-70.
- Seijo S, Lozano JJ, Alonso C, Reverter E, Miquel R, Abraldes JG. Metabolomics discloses potential biomarkers for the noninvasive diagnosis of idiopathic portal hypertension. Am J Gastroenterol. 2013 Jun;108(6):926-32.
- Peralta B, Gil-Carton D, Castaño-Díez D, Bertin A, Boulogne C, Oksanen HM, Bamford DH, Abrescia NG. Mechanism of membranous tunnelling nanotube formation in viral genome delivery.PLoS biology. 2013;11(9):e1001667.

Highlights

In 2013 thirty-seven people, including principal investigators and post-doctoral researchers, laboratory technicians and PhD students, integrated the research force of CIC bioGUNE-CIBERehd. Our work has been mainly integrated in Program No. 2 on Cholestasis, Metabolic Diseases and Hepatotoxicity of CIBERehd's Strategic Plan, although it is relevant to indicate our activity in Programs No. 5 on Gastrointestinal and Hepatic Oncology and No. 2 on Viral Hepatitis. It is also important to emphasize our commitment with the development of new Omics technologies, and with the provision of services in genomics, proteomics and metabolomics to other CIBERehd researchers. Our activity in this area is not limited to the simple provision of services, but includes other aspects as the analysis of the quality of the data and the statistic interpretation of the results. In 2013 our group published 27 research articles, several of them in top journals such as J Clin Inves, PLoS Biol, Gastroenterology and Hepatology. In 2013 we also obtained a US patent, N0. 8,563,318 B2. This patent protects a noninvasive method for the serum diagnostic of nonalcoholic steatohepatitis (NASH) based on a metabolic profile. This method is presently commercialized by OWL Metabolomics, a spin off of our group. Our research team is presently funded by the MINECO, through the Plan Nacional de I+D+i, the INNPACTO program, the ISCIII-CIBER (CIBERehd) and the ISCIII-FIS, and the Ramón y Cajal and FPI programs. We are also funded by Basque Government through the ETORTEK program of the Department de Economic Development and Competitiveness, the Ikerbasque Foundation, and the Departments of Health and Education; and by the National Institutes of Health (NIH), the COST program of the European Union, the Asociación Española Contra el Cáncer (AECC), and Abbott Laboratories.



PROGRAMME:
Cholestasis and Metabolic Disorders

G0067

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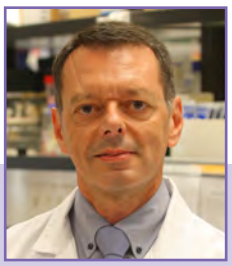

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Main lines of research

- Molecular genetics of intrahepatic cholestasis; the role of the AE2 anion exchanger in the etiopathogenesis of primary biliary cirrhosis; ursodeoxycholic acid and AE2.
- Analysis of hepatic and immunologic phenotypes of the Ae2-deficient mice (in collaboration with Dr. Oude Elerink, AMC, Amsterdam).
- Role of NO species for the choleretic effect of ursodeoxycholic acid and other bile salts.
- Involvement of bile acids in liver regeneration.
- Effects of IGF-I on an animal model of primary sclerosing cholangitis.
- Analysis of the purinome in the biliary tree (in collaboration with Dr. M. Pastor-Anglada, CIBERehd).

Most relevant scientific articles

- Uriarte I, Fernández-Barrena MG, Monte MJ, Latasa MU, Chang HC, Carotti S. Identification of fibroblast growth factor 15 as a novel mediator of liver regeneration and its application in the prevention of post-resection liver failure in mice.Gut. 2013 Jun;62(6):899-910.
- Hohenester S, Beuers U, Medina JF, Elferink RP. Antimitochondrial antibodies may be insufficiently specific to define primary biliary cirrhosis-like disease in mouse models. Hepatology. 2013 Aug;58(2):828-30.
- Reboredo M, Chang HC, Barbero R, Rodríguez-Ortigosa CM, Pérez-Vizcaíno F, Morán A. Zolmitriptan: a novel portal hypotensive agent which synergizes with propranolol in lowering portal pressure.PLoS One. 2013;8(1):e52683.
- Lucena JF, Alegre F, Martínez-Urbistondo D, Landecho MF, Huerta A, García-Mouriz A et al.. Performance of SAPS II and SAPS 3 in intermediate care.PLoS One. 2013;8(10):e77229.
- Sokolović A, Rodríguez-Ortigosa CM, Bloemendaal LT, Oude Elferink RP, Prieto J, Bosma PJ. Insulin-like growth factor 1 enhances bile-duct proliferation and fibrosis in Abcb4(-/-) mice.Biochim Biophys Acta. 2013 Jun;1832(6):697-704.

Highlights

PROJECTS

- "Studies of the immunological alterations in the Ae2a,bdeficient mice, an animal model of PBC, and validation in conditional Ae2 knockouts". Ref. SAF2012-35455. Spanish "Ministerio de Ciencia e Innovación". PI: Juan F. Medina. Team Members: Carlos M. Rodríguez-Ortigosa, Nicolás García, María López, Alejandro Ferrer, Ion Celay Leoz, Axel Concepción, Ronald P. J. Oude-Elferink. Period: 2013-2015. Amount: €165,000
- "Mechanisms of the therapeutic action of IGF-I in cirrhosis and hepatocarcinoma: Studies in experimental cirrhosis, cell lines and human liver." Ref. PI13/01989, Spanish "Ministerio de Sanidad y Consumo" PI: Jorge Quiroga. Team Members: Carlos M. Rodríguez-Ortigosa, Ion Celay Leoz, Maite G. Fernández de Barrena, Delia Davola, Nerea Juanarena. Period: 2013-2015. Amount: €94.985. This project is related to a clinical trial with IGF-I

PROGRAMME:
Immunology and Liver Transplant

G0011

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Main lines of research

- Aloimmune response and immunosuppression
- Ischemic reperfussion injury
- Hepatitis C recurrence
- Complications of immunosuppression

Most relevant scientific articles

- Benítez C, Londoño MC, Miquel R, Manzia TM, Abraldes JG, Lozano JJ. Prospective multicenter clinical trial of immunosuppressive drug withdrawal in stable adult liver transplant recipients.Hepatology. 2013 Nov;58(5):1824-35.
- Mariño Z, Crespo G, D'Amato M, Brambilla N, Giacovelli G, Rovati L. Intravenous silibinin monotherapy shows significant antiviral activity in HCV-infected patients in the peri-transplantation period.J Hepatol. 2013 Mar;58(3):415-20.
- Peralta C, Jiménez-Castro MB, Gracia-Sancho J. Hepatic ischemia and reperfusion injury: effects on the liver sinusoidal milieu. J Hepatol. 2013 Nov;59(5):1094-106.
- Sánchez-Cabús S, Fondevila C, Calatayud D, Ferrer J, Taurá P, Fuster J. Importance of the temporary portocaval shunt during adult living donor liver transplantation.Liver Transpl. 2013 Feb;19(2):174-83.
- Crespo G, Carrión JA, Coto-Llerena M, Mariño Z, Lens S, Pérez-Del-Pulgar S. Combinations of simple baseline variables accurately predict sustained virological response in patients with recurrent hepatitis C after liver transplantation.J Gastroenterol. 2013 Jun;48(6):762-9.

Highlights

Three aspects have been relevant and have produced the most important results in 2013: The research group has established new targets for therapeutic action based on the modulation of the resections both adipocytokins and transplantation of liver in marginal organs, which may impact favorably on the quality of life of patients undergoing resections or transplant and a reduction in liver transplant waiting lists. The results obtained by the research group have allowed further participation in competitive programs for the translation of the experimental results to clinical practice, which will derived in clinical trials and in the creation of a spin-off. With regard to the recurrence of hepatitis C post, antiviral treatment regimens have been established in candidates for liver transplantation and in those with severe recurrence of the disease. It has been established the use of invasive a non-invasive methods to evaluate the severity of hepatitis C recurrence after transplantation. Finally, patients with operational tolerance to the graft have been better characterized, doing the elimination of immunosuppressant therapy safer. Works for development of ex-vivo, normothermic perfusion liver machine are in progress.

It is important to remark the collaboration established with important groups that are working in liver disease like Viral Hepatitis Group (Dr. X. Forns) and Portal Hypertension Group (Dr. J. Bosch).

PROGRAMME:
Gastrointestinal Inflammation and Motility

G0018

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Main lines of research

The research group on inflammatory bowel diseases at Hospital Clínic de Barcelona concentrates research activities on aspects of pathophysiology, diagnosis and therapy of Crohn's disease and ulcerative colitis. Research on disease pathophysiology is oriented to discovering aspects that may have a direct therapeutic value. Thus, projects are directed to characterization of differential patterns of immune response in early and late CD that may help personalize treatments based on immune characteristics, and the identification of molecular factors that maintain remission in these inflammatory disorders. In the area of diagnostics the group is leading initiatives on the use of magnetic resonance imaging for evaluation of inflammatory lesions in the intestine, and in the area of therapeutics the main focus of the group is the development of innovative forms of cell therapy for human IBD including the use of hematopoietic stem cells in a program of transplant for refractory Crohn's disease, tolerogenic dendritic cells, and epithelial stem cells.

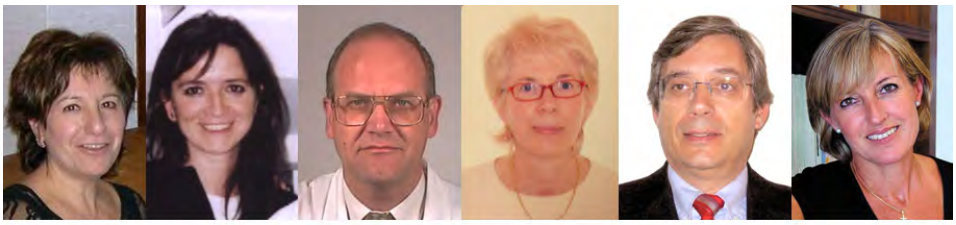
Most relevant scientific articles

- Planell N, Lozano JJ, Mora-Buch R, Masamunt MC, Jimeno M, Ordás I. Transcriptional analysis of the intestinal mucosa of patients with ulcerative colitis in remission reveals lasting epithelial cell alterations.Gut. 2013 Jul;62(7):967-76.
- Panés J, López-Sanromán A, Bermejo F, García-Sánchez V, Esteve M, Torres Y. Early azathioprine therapy is no more effective than placebo for newly diagnosed Crohn's disease. Gastroenterology. 2013 Oct;145(4):766-74.e1.
- Cleynen I, González JR, Figueroa C, Franke A, McGovern D, Bortlík M. Genetic factors conferring an increased susceptibility to develop Crohn's disease also influence disease phenotype: results from the IBDchip European Project.Gut. 2013 Nov;62(11):1556-65.
- Julià A, Domènech E, Ricart E, Tortosa R, García-Sánchez V, Gisbert JP. A genome-wide association study on a southern European population identifies a new Crohn's disease susceptibility locus at RBX1-EP300.Gut. 2013 Oct;62(10):1440-5.
- Ordás I, Rimola J, García-Bosch O, Rodríguez S, Gallego M, Etchevers MJ. Diagnostic accuracy of magnetic resonance colonography for the evaluation of disease activity and severity in ulcerative colitis: a prospective study.Gut. 2013 Nov;62(11):1566-72.

Highlights

The research Group on IBD from Hospital Clínic de Barcelona has provided relevant contributions in the area of IBD pathophysiology, and particularly in ulcerative colitis. Using transcriptomic analysis, corroborated by other analytical techniques, we have shown that when achieving endoscopic and histologic remission the intestinal mucosa does not revert to a healthy condition from a functional point of view, but shows a potent activation of anti-inflammatory mechanisms, which may be the basis for the development of new therapies. The group has provided a relevant contribution to completing the first genome wide association scan in a Spanish population of ulcerative colitis patients that has identified new susceptibility genes. The group has also made highly relevant contributions in the area of diagnostics in IBD, particularly in cross-sectional imaging. We have characterized the value of magnetic resonance imaging for assessment of activity and severity in ulcerative colitis, and as a continuation of previous work in Crohn's disease we have shown the value of magnetic resonance imaging for assessment of the therapeutic response. The group has also provided significant contributions to intramural CIBERehd projects lead by other research groups in the area of IBD.

The research capacity of the members of the group is demonstrated also by the fact that in addition to the group coordinator (JP) two other members of the group (AS, DB) lead respective national competitive research projects. In addition, the group has established important contracts for research projects on basic science with pharmaceutical industries aimed at determining mechanisms of action, proof of concept and identification of new therapeutic targets.



Colestasis y Patología Ósea

PROGRAMME:
Cholestasis and Metabolic Disorders

G0015

Group Members

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Main lines of research

- Epidemiology, natural history and therapeutic response of chronic cholestatic diseases in adults.
- Development of new prognostic models in primary biliary cirrhosis.
- Pathogenic mechanisms of osteoporosis and development of fractures in primary biliary cirrhosis and in other chronic cholestatic diseases.
- Pathogenesis of pruritus of chronic cholestasis and treatment response to albumin dialysis.
- Efficacy and safety of the different procedures in a bioarticial liver.

Most relevant scientific articles

- Guañabens N, Monegal A, Cerdá D, Muxí Á, Gifre L, Peris P et al.. Randomized trial comparing monthly ibandronate and weekly alendronate for osteoporosis in patients with primary biliary cirrhosis.Hepatology. 2013 Dec;58(6):2070-8.
- Bañares R, Nevens F, Larsen FS, Jalan R, Albillos A, Dollinger M. Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the RELIEF trial.Hepatology. 2013 Mar;57(3):1153-62.
- Liu JZ, Hov JR, Folseraas T, Ellinghaus E, Rushbrook SM, Doncheva NT et al.. Dense genotyping of immune-related disease regions identifies nine new risk loci for primary sclerosing cholangitis.Nat Genet. 2013 Jun;45(6):670-5.
- Dubreuil M, Ruiz-Gaspà S, Guañabens N, Peris P, Alvarez L, Monegal A et al.. Ursodeoxycholic acid increases differentiation and mineralization and neutralizes the damaging effects of bilirubin on osteoblastic cells.Liver Int. 2013 Aug;33(7):1029-38.
- Martínez-Ferrer A, Blasco J, Carrasco JL, Macho JM, Román LS, López A et al.. Risk factors for the development of vertebral fractures after percutaneous vertebroplasty.J Bone Miner Res. 2013 Aug;28(8):1821-9.

Highlights

The group has launched a new research project aimed at knowing the metabolomic profile of pruritus of cholestasis, and continues with the project that assesses the role of bile acids and bilirubin as well as the protective effect of ursodeoxycholic acid in the pathogenesis of osteoporosis in cholestatic diseases. As specific achievements has presented the main results in the domestic and international congresses of Hepatology and Metabolic Bone Diseases. The team has continued collaborating with other groups CIBERehd, and with international groups on cholestatic diseases, specifically the Global PBC study group and the IPSCSG. Likewise the team has been invited to take part into the International Autoimmune Hepatitis group. Regarding outputs the group has published articles identifying new genes involved in the pathogenesis of primary sclerosing cholangitis, and the protective role of ursodeoxycholic acid on the harmful effects of bile acids and bilirubin in model human osteoblasts in culture. A clinical trial comparing the effects of alendronate and monthly ibandronate for the treatment of osteoporosis in primary biliary cirrhosis has been published, showing that both regimens are safe and increase bone mass after two years of treatment. Another paper defined the risk factors for presenting new fractures in osteoporotic patients treated with vertebroplasty. In cooperation with other CIBERehd groups, a trial assessing the effect of albumin dialysis in patients with decompensated liver cirrhosis compared with standard therapy has been published. Two of these papers are especially important since they have been accompanied by an editorial. Other aspects to point out are the invitation of members of the team to give lectures in international courses and symposia, as well as the appointment as associate editor for Bone, a journal specialized in metabolic bone diseases.

PROGRAMME:
Liver Cancer and Cancer of the Digestive System

G1092

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Main lines of research

- Progression of Barrett esophagous to adenocarcinoma
- Inflammation and cancer
- Poly(ADP-ribose) polymerases and cancer
- Liver regeneration and liver tumours
- Liver transplantation

Most relevant scientific articles

- Revilla-Nuin B, Parrilla P, Lozano JJ, Martínez de Haro LF, Ortiz A, Martínez C, Munitiz V, Bermejo J, Molina J, Cayuela ML, Yélamos J. Predictive value of microRNAs in the progression of Barret´s esophagus to adenocarcinoma in a long-term follow-up studyANN SURG. 2013;257(3):413-418.
- Farrés J, Martín-Caballero J, Martínez C, Lozano JJ, Llacuna L, Ampurdanés C, Ruiz-Herguido C, Dantzer F, Schreiber V, Villunger A, Bigas A, Yélamos J. Parp-2 is required to maintain hematopoiesis following sublethal γ-irradiation in mice-BLOOD. 2013;122(1):44-54.
- Frutos MD, Abrisqueta J, Lujan J, Abellan I, Parrilla P.. Randomized prospective study to compare laparoscopic appendectomy versus umbilical single-incision appendectomy.ANN SURG. 2013;257(3):413-418.
- Baroja-Mazo A, Barberà-Cremades M, Pelegrín P.. P2X7 receptor activation impairs exogenous MHC class I oligopeptides presentation in antigen presenting cells. PLOS ONE. 2013;8(8):E70577.
- Berenguer M, Roche B, Aguilera V, Duclos-Vallée JC, Navarro L, Rubín A, Pons JA, de la Mata M, Prieto M, Samuel D. Efficacy of the retreatment of hepatitis C virus infections after liver transplantation: role of an aggressive approach.LIVER TRANSPLANT. 2013;19(1):69-77.

Highlights

The main results obtained by our group during 2013 are related to (i) Barrett esophagous, (ii) inflammation, and (iii) Poly(ADP-ribose) polymerases.

Barrett esophagous (BE) is a premalignant condition associated with the development of esophagous adenocarcinoma (EAC), the prevalence of which has increased dramatically over the past three decades in the western world. Therefore, great interest surrounds the identification of molecular biomarkers which contribute to the pathogenesis of BE and its progression to EAC. We have performed a high-throughput screening and qRT-PCR validation studies of miRNAs expression in NE, BE, HGD and EAC and we have validated the selected miRNAs in BE samples from patients that have developed EAC vs those that have not developed EAC after a long-term follow-up of disease evolution. Our data suggest that measurement of the expression of a modest number of miRNA in metaplasia biopsies could identify the BE patients at high risk for developing EAC. Therefore, it would constitute a robust diagnostic test to predict the progression of BE to EAC.

By using mice models, we have shown that genetic inactivation of Parp-2, but not of Parp-1, resulted in bone marrow failure in response to sublethal ?-irradiation dose, providing the first evidence for an important and non-redundant role of Parp-2 protein to properly maintain haematopoietic system homeostasis.

P2X7 receptors (P2X7Rs) are present on the plasma membrane of APCs to sense the extracellular danger signal adenosine-5′-triphosphate (ATP). P2X7R activates the inflammasome and the release of IL-1ß in macrophages and other immune cells to initiate the inflammatory response.

PROGRAMME:
Liver Cancer and Cancer of the Digestive System

G0063

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Main lines of research

- Analysis of the cellular transportome and its role on oncogenesis in liver and gastrointestinal tumors.

  We will dissect the interactome of membrane proteins whose expression is known to be altered in tumors. This project combines the "transceptor" concept with the analysis of the protein networks incorporating these membrane proteins. We anticipate that these networks are relevant to oncogenesis.

- Molecular pharmacology and pharmacogenetics of drug transporters.

  We will study drug-transporter interactions and the impact of genetic variability on transporter functionl. The ultimate goal is to understand how transporter expression patterns determine drug responsiveness.

- Generation of preclinical models to study newly developed anticancer drugs.

  - Genetic engineering of cellular models for the preclinical assay of drug bioavailability.

  Based upon the increasing interest of the pharmaceutical companies and regulatory agencies to establish preclinical assays of drug-transporter interaction, we are developing epithelial barrier models to anticipate pharmacokinetics interactions among drugs.

  - New animal models for the study of new drugs against pancreatic adenocarcinoma.

  The MPET laboratory has a platform of orthotopic models derived from human pancreatic adenocarcinomas, suitable for the preclinical assessment of novel antitumor therapies.

- Role of the cell purinome and the transportome on liver and gastrointestinal pathologies.

  - Study of the biliary purinome.

  We will study the purinergic regulation of cholangiocytes implicating P1 receptors. Knowledge on the cholangiocyte purinome is scarce but might be relevant to bile duct physiology and pathophysiology. This is a CIBER EHD intramural collaboration.

- Study of the purinome and the transportome in inflammatory bowel disease.

  We will functionally characterize changes in the purinome and the transportome contributing to inflammatory bowel disease, by combining the use of animal models and samples from Crohn patients. This is also an intramural CIBER EHD collaboration.

Most relevant scientific articles

- Pérez-Torras S, Vidal-Pla A, Cano-Soldado P, Huber-Ruano I, Mazo A, Pastor-Anglada M. Concentrative nucleoside transporter 1 (hCNT1) promotes phenotypic changes relevant to tumor biology in a translocation-independent manner. Cell Death Dis. 2013 May 30;4:e648.
- Cárdenas A, Toledo C, Oyarzún C, Sepúlveda A, Quezada C, Guillén-Gómez E. Adenosine A(2B) receptor-mediated VEGF induction promotes diabetic glomerulopathy. Lab Invest. 2013 Jan;93(1):135-44.
- Medina-Pulido L, Molina-Arcas M, Justicia C, Soriano E, Burgaya F, Planas AM. Hypoxia and P1 receptor activation regulate the high-affinity concentrative adenosine transporter CNT2 in differentiated neuronal PC12 cells. Biochem J. 2013 Sep 15;454(3):437-45.
- Pastor-Anglada M. Transporter pharmacogenetics: do we need function? Do we need motion? Pharmacogenomics. 2013 Oct;14(13):1537-40.

Highlights

During 2013, we published the first evidence of hCNT1 being a transceptor protein whose loss in normal cells could contribute to oncogenesis. This study involved both cell models as in vivo models of pancreatic adenocarcinoma. Using both it was shown that hCNT1 restoration resulted in cell cycle arrest, cell death and significant inhibition of tumor growth. We are now undertaking a high throughput analysis of hCNT1 in correctal carcinoma, pancreatic cancer and hepatocarcinoma, in an attempt to clinically correlate hCNT1 loss with tumor stage and progression. This publication had impact in the media. On the other hand the role CNT2 and CNT3 might play as modulators of extracellular adenosine levels and, hence, on purinergic regulation via P1 receptors (previously shown by us to occur in hepatocytes), was further addressed in other cell types under the framework of inter-CIBER/REDES collaborations. Basically, it seems that CNT2 is an ubiquitous modulator of purinergic responses. Also in 2013 an innovative and comprehensive monography on "Pharmacogenomics of Human Drug Transporters: Clinical Impacts", was published by John Wiley & Sons. Chapter 11, devoted to "Nucleoside transporters (SLC28 and SLC29) families" was contributed by members of the MPET laboratory. This monography was highlighted on the webpage of the Spanish Society of Pharmacogenetics and Pharmacogenomics. Also in this context, the PI of the group was invited by the journal "Pharmacogenomics" to write a critical editorial paper on the mid-term challenges of drug transporter pharmacogenetics. Within this same framework, researchers from different CIBER were involved in the organization of the international meeting of the Purine and Pyrimidine Society, held in Madrid, June 2013.

PROGRAMME:
Gastrointestinal Inflammation and Motility

G1088

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Main lines of research

Focuses on the understanding and management of *Helicobacter pylori* infection and Inflammatory Bowel Disease (IBD). Clinical and epidemiological projects are performed coordinating networks of gastroenterologists from over 30 Spanish hospitals.

Traslational research lines:

- Gastric *H. pylori* induced proliferation/apoptosis

  Effect of infection status, bacterial strain, patients' genotype and the type and severity of gastric lesions; Comparison pre and post eradication; Genetic and epidemiological factors in the progression of pre-cancerous lesions

- Angiogenesis and lymphangiogenesis in IBD

  Ulcerative colitis vs. Crohn's disease; Correlation with clinical and disease course variables; Effect of the therapy (immune suppressors and biologic treatments)

- Immunity in IBD

  Vaccination optimization in IBD patients; Immunological alterations after Hepatitis B virus (HBV) vaccination; Predictive variables to HBV vaccination response; Mechanisms of production of antibodies against anti-TNF treatments, and their relation with treatment response

- New diagnostic methods

  Serologic diagnosis of Duodenal Ulcer; Diagnosis of *H. pylori* infection with novel monoclonal fecal kits; Clinical utility of biological markers like fecal calprotectin and lactoferrin as well as azathioprine metabolites; Genetic/Pharmacogenetics and individualized medicine in IBD; Improved diagnosis of concomitant diseases in IBD

- New therapies

  Routine-data-based studies on the efficacy and safety of novel and traditional treatments on *H. pylori* eradication; New antibiotic combinations and formulations (hydrogels) for *H. pylori* treatment; New antibiotic indications for *H. pylori*; Photodynamic therapy applied to the inactivation of *H. pylori*; Identification of new therapeutic targets in IBD

Most relevant scientific articles

- Casanova MJ, Chaparro M, Domènech E, Barreiro-de Acosta M, Bermejo F, Iglesias E. Safety of thiopurines and anti-TNF-α drugs during pregnancy in patients with inflammatory bowel disease.Am J Gastroenterol. 2013 Mar;108(3):433-40.
- Chaparro M, Ordás I, Cabré E, García-Sanchez V, Bastida G, Peñalva M. Safety of thiopurine therapy in inflammatory bowel disease: long-term follow-up study of 3931 patients.Inflamm Bowel Dis. 2013 Jun;19(7):1404-10.
- Molina-Infante J, Romano M, Fernández-Bermejo M, Federico A, Gravina AG, Pozzati L. Optimized nonbismuth quadruple therapies cure most patients with Helicobacter pylori infection in populations with high rates of antibiotic resistance.Gastroenterology. 2013 Jul;145(1):121-128.e1.
- Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE. Vedolizumab as induction and maintenance therapy for Crohn's disease.N Engl J Med. 2013 Aug 22;369(8):711-21.
- Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ et al.. Vedolizumab as induction and maintenance therapy for ulcerative colitis.N Engl J Med. 2013 Aug 22;369(8):699-710.

Highlights

In 2013 the group has focused on increasing its activity in European and international contexts:

- Coordinates the 'Pan-European Registry on Helicobacter pylori infection management' in which 300 gastroenterologists from 31 European countries participate, making it the largest study on an infectious agent.
- The United European Gastroenterology has granted this team a long-term educational and research project entitled 'Optimal H. pylori management in Primary Care' aiming to improve the knowledge and implementation of the 'Maastricht IV European Consensus on Helicobacter pylori infection' in 9 European countries.
- The group is represented by its members in several international organizations such as the European Helicobacter Study Group, the European Crohn's and Colitis Organization, the United European Gastroenterology, the American Gastroenterology Association, the Iberoamerican Network for the Study of Helicobacter and the Cochrane Collaboration.

The Group has also coordinated the following educative actions and transfer activities (Clinical Guides):

- Actualización de Gastroenterología Aplicada (Summary of the most relevant works presented at the USA Digestive Disease Week congress). Accredited by the Spanish Continuing Medical Education Council. Endorsed by the AEG.
- Post-ECCO Congress (Summary of the most relevant works presented at the European Crohn's and Colitis Organization Congress). Endorsed by the AEG and GETECCU.
- ECCO Anaemia Consensus. European Consensus on the management of anaemia in IBD. Dr. Gisbert has been the coordinator of the Prevention of iron deficiency anaemia Working Group. Endorsed by the European Crohn's and Colitis Organization
- III Spanish Consensus Conference on H. pylori infection. Dr. Gisbert was the general coordinator. Endorsed by the AEG and the SEPD.

National or international publications: 81

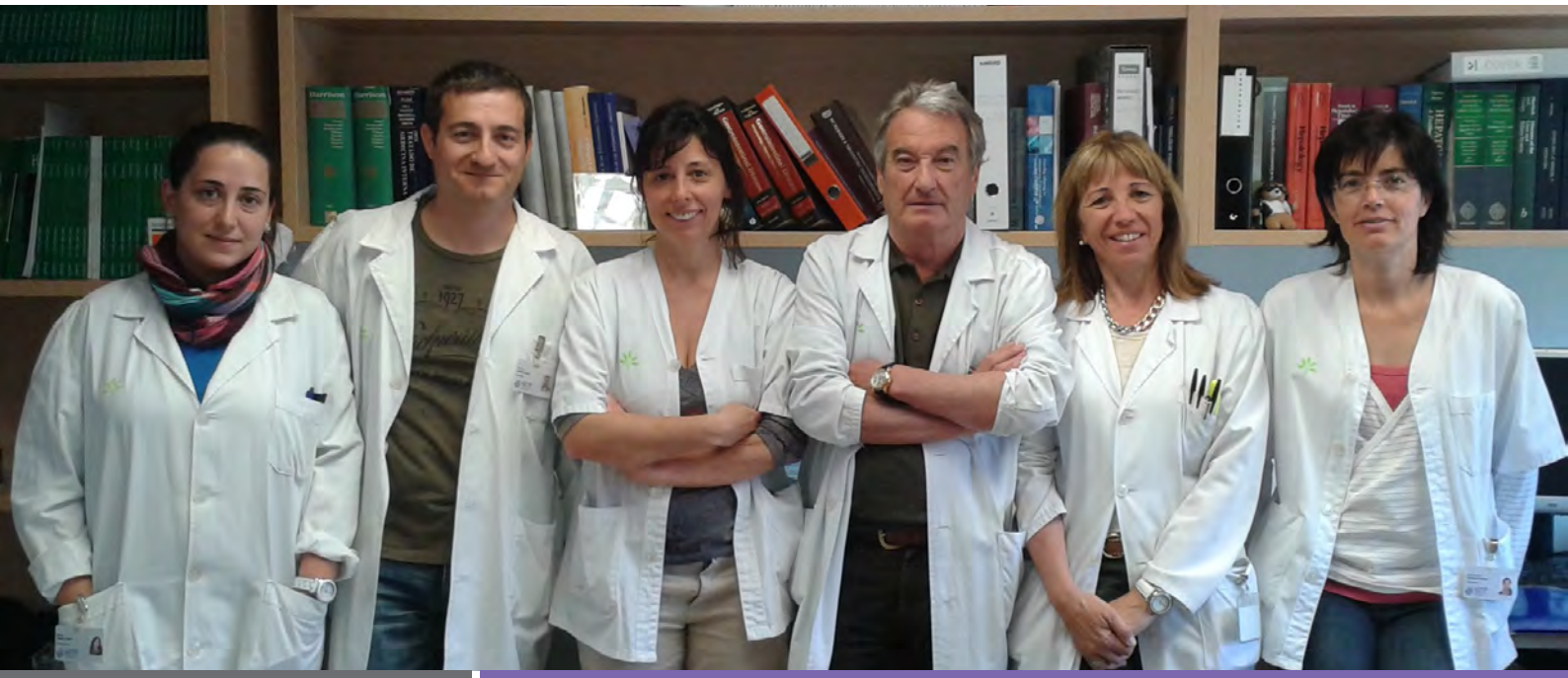
1st decile publications: 17

1st quartile publications: 46

Ongoing proyects: 26

Defended dissertations / thesis: 5

Dissertations / thesis in preparation: 10



PROGRAMME:
Portal Hypertension and Cirrhosis

G0033

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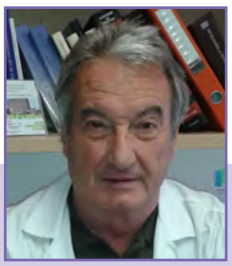

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Main lines of research

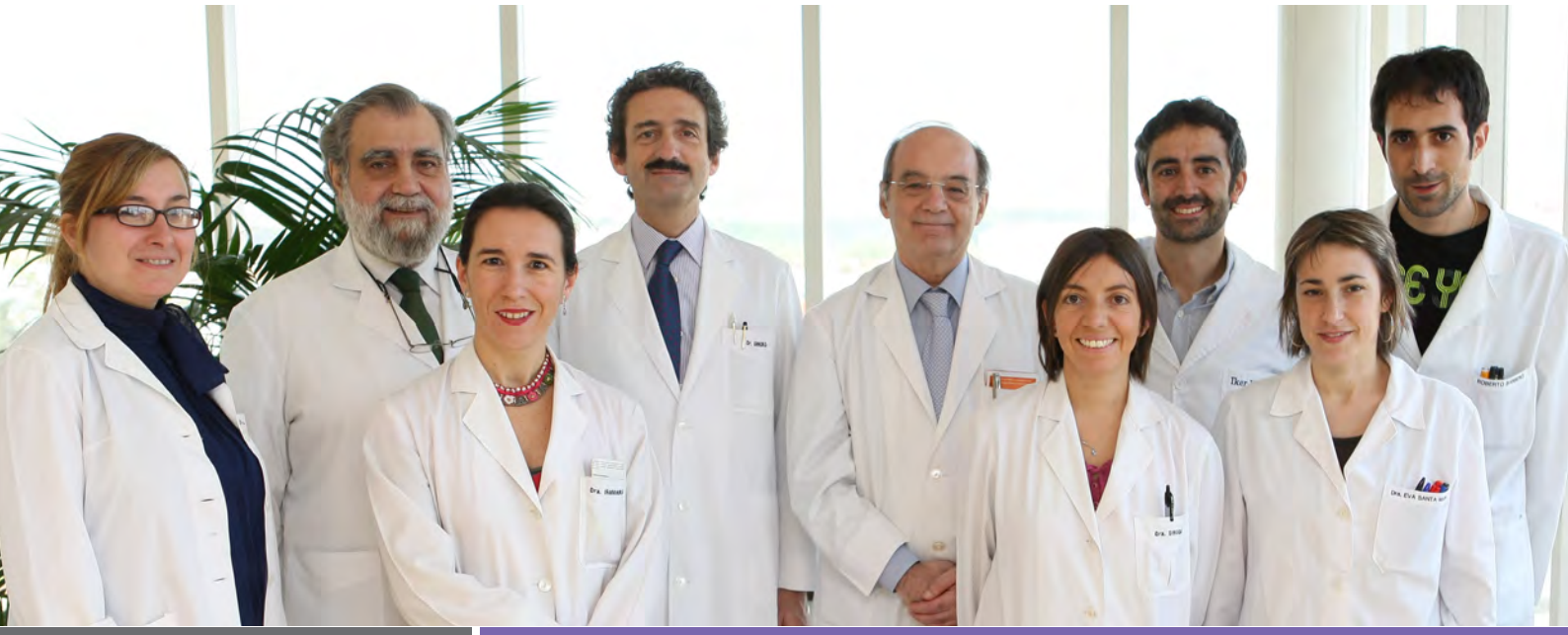
- Complications of cirrhosis: portal hypertension, ascites and hepatorenal syndrome in cirrhosis and associated infections. Pathophysiology and therapeutic strategies.
- Hepatitis C Virus: Optimization of therapies and new therapeutic strategies.
- Hepatoblastoma and hepatocellular cancer. Proteomic studies. Identification of diagnostic and prognostic markers.
- Progression of liver fibrosis. Mechanisms. Role of the endocannabinoid system.

Most relevant scientific articles

- Ripoll C, Genescà J, Araujo IK, Graupera I, Augustin S, Tejedor M. Rebleeding prophylaxis improves outcomes in patients with hepatocellular carcinoma. A multicenter case-control study.Hepatology. 2013 Dec;58(6):2079-88.
- Armengol C, Bartolí R, Sanjurjo L, Serra I, Amézaga N, Sala M. Role of scavenger receptors in the pathophysiology of chronic liver diseases.Crit Rev Immunol. 2013;33(1):57-96.
- Saludes V, Bascuñana E, Jordana-Lluch E, Casanovas S, Ardèvol M, Soler E. Relevance of baseline viral genetic heterogeneity and host factors for treatment outcome prediction in hepatitis C virus 1b-infected patients.PLoS One. 2013;8(8):e72600.
- Saludes V, González-Candelas F, Planas R, Solà R, Ausina V, Martró E. Evolutionary dynamics of the E1-E2 viral populations during combination therapy in non-responder patients chronically infected with hepatitis C virus subtype 1b.Infect Genet Evol. 2013 Jan;13:1-10.
- Urquijo JJ, Diago M, Boadas J, Planas R, Solá R, Del Olmo JA. Safety and efficacy of treatment with pegylated interferon alpha-2a with ribavirin in chronic hepatitis C genotype 4.Ann Hepatol. 2013 Jan-Feb;12(1):30-5.

Highlights

The group has developed its activity in the scientific research program on portal hypertension and mechanisms of transition to cirrhosis, viral hepatitis, liver cancer and liver immunology. In 2013, the group has led five competitive projects from the National Health Institute CarlosIII , FIS (PI 09/ 00751 , PI10/08082 , PI11/00187 , PI10/01565 and PI10/1656) and participated in another project(PI10/00132) . We also led a regional project (2009SGR00738, Generalitat de Catalunya). Also, during 2013 we have obtained 4 new projects (PI13/01906, PI13/02340, PI13/02217, and one "Marato de TV3"). As a result of scientific activity, the group has generated a total number of 11 international publications and one book chapter (total impact factor of 36.57). Likewise, there have been seven communications to international congresses and 16 national conferences, as well as invitations to 57 national and international conferences. Three doctoral theses supervised by members of the group were presented during 2013. The group has organized and coordinated, in conjunction with other Ciber groups, clinical courses in the field of gastroenterology and hepatology. The number of active clinical trials this year has been 14, most of them in collaboration with other Ciber, and international groups. Moreover, several group members are part of the editorial board of several journals, also a member of the group coordinates the Spanish Study Group of childhood liver tumors SEOHP. Finally, the total public funding during 2013 (FIS, SGR) amounted to € 122,329 and private funds (clinical trials, agreements, grants) have been raised € 219,000.



PROGRAMME:
Liver Cancer and Cancer of the Digestive System

G0006

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Main lines of research

- Study of the cellular and molecular mechanisms of liver response to acute and chronic injury, and hepatocarcinogenesis .
- Design of hepatoprotective strategies against situations of injury/acute liver failure and identification of therapeutic targets to slow the progression of chronic liver disease and its malignant transformation.
- Development of hepatoprotective therapies including insulin-like growth factor type 1 (IGF1) and cell therapy with endothelial cell progenitors.
- Characterization of the effects of amino-terminal protein modifications and their implications for the development of hepatocellular carcinoma and liver regeneration, and development of inhibitors of these enzymes as novel anti-tumor molecules.
- Clinical development of new agents with specific therapeutic targets.
- Immunotherapy with immunological checkpoint inhibitors and universal and personalized peptide vaccines.
- Improved procedures and materials for intra-arterial therapy of liver tumors: radioembolization and chemoembolization .
- Improvement of the procedures and results of the surgical treatment of liver cancer including liver transplantation and surgical resection in patients with and without cirrhosis

Most relevant scientific articles

- Sangro B, Gomez-Martín C, de la Mata M, Iñarrairaegui M, Garralda E, Barrera P. A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C.J Hepatol. 2013 Jul;59(1):81-8.
- Uriarte I, Fernández-Barrena MG, Monte MJ, Latasa MU, Chang HC, Carotti S. Identification of fibroblast growth factor 15 as a novel mediator of liver regeneration and its application in the prevention of post-resection liver failure in mice.Gut. 2013 Jun;62(6):899-910.
- Santamaria M, Pardo-Saganta A, Alvarez-Asiain L, Di Scala M, Qian C, Prieto J. Nuclear α1-antichymotrypsin promotes chromatin condensation and inhibits proliferation of human hepatocellular carcinoma cells.Gastroenterology. 2013 Apr;144(4):818-828.e4.
- Gil-Alzugaray B, Chopitea A, Iñarrairaegui M, Bilbao JI, Rodríguez-Fraile M, Rodríguez J. Prognostic factors and prevention of radioembolization-induced liver disease. Hepatology. 2013 Mar;57(3):1078-87.
- Golfieri R, Bilbao JI, Carpanese L, Cianni R, Gasparini D, Ezziddin S. Comparison of the survival and tolerability of radioembolization in elderly vs. younger patients with unresectable hepatocellular carcinoma.J Hepatol. 2013 Oct;59(4):753-61.

Highlights

In immunotherapy of hepatocellular carcinoma we presented the first trial showing signs of activity and security of tremelimumab, an anti-CTLA4 monoclonal antibody, paving the way for clinical research on immune checkpoint inhibitors, and we have identified in preclinical models other strategies such as the use of EDA (endogenous ligand of TLR4) that targets antigens to dendritic cells; a triple fusion protein combining Apo AI, IL15, and the sushi domain of IL15Ra that increases the effectiveness of IL-15; and the combination of three monoclonal antibodies anti-CD137, anti-OX40 and anti-B7-H1.

In radioembolization we have presented a modified treatment protocol that reduces liver complications without altering the efficacy and have confirmed the good tolerability in elderly patients and the reversibility of gastrointestinal toxicity.

In carcinogenesis and regeneration we have identified two molecules with therapeutic potential in hepatocellualr carcinoma: alpha1antichemotrypsin, that controls cell proliferation and its overexpression has antitumor activity in animal models ; FGF15, a key factor in preventing liver injury during liver regeneration and makes animal models tolerate subtotal hepatectomies. Furthermore, we have described that MMP10 is involved in tissue repair and described a new way in which SULF2 regulates tissue regeneration partly through the activation of a new pathway Wnt-GLI1-Cyclin D1.

In liver transplantation we have provided new data on patient selection for immunosuppression withdrawal, fully laparoscopic living donation, use of everolimus to improve renal failure, utility of screening for lung cancer and preclinical demonstration of the utility of cardiotrophin 1 to reduce ischemia- reperfusion injury.

We have finally made further progress in the development of gene therapy adeno-associated vectors for liver diseases by studying their safety in nonhuman primates.

PROGRAMME:
Hepatitis Virus

G0047

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Main lines of research

The research group at Valme Hospital is focused on two main lines: Hepatitis C and Non-alcoholic fatty liver disease (NAFLD). The development of hepatocellular carcinoma from these diseases also currently represents a priority area of research for the group. On the other hand, several projects deal with other areas within the liver and digestive diseases (complications of cirrhosis, hepatic encephalopathy, Helicobacter pylori infection and inflammatory bowel disease).

Regarding hepatitis C, our projects aimed to identify elements (genes and/or proteins) that may represent new therapeutic targets. To achieve this goal we perform two complementary approaches: one is based on an association analysis of the entire genome (GWAS), and the other in the study of molecular interactions between viral and host, with special emphasis on proteins related with the insulin-signaling pathway.

Most relevant scientific articles

- Romero-Gómez M, Planas R, Ampuero J, Solà R, García-Samaniego J, Diago M, Crespo J, Calleja JL, Turnes J.. Meta-analysis: pegylated interferon α-2a achieves higher early virological responses than α-2b in chronic hepatitis C.Aliment Pharmacol Ther. 2013;.
- Romero-Gómez M, Berenguer M, Molina E, Calleja JL.. Management of anemia induced by triple therapy in patients with chronic hepatitis C: challenges, opportunities and recommendations.J Hepatol. 2013;.
- Romero-Gómez M, Del Campo JA.. Insulin resistance, telaprevir, and virological response in hepatitis C: the debate must go on.Hepatology. 2013;.
- Burger D, Back D, Buggisch P, Buti M, Craxí A, Foster G, Klinker H, Larrey D, Nikitin I, Pol S, Puoti M, Romero-Gómez M, Wedemeyer H, Zeuzem S.. Clinical management of drug-drug interactions in HCV therapy: challenges and solutions.J Hepatol. 2013;.
- Wedemeyer H, Jensen D, Herring R Jr, Ferenci P, Ma MM, Zeuzem S, Rodríguez-Torres M, Bzowej N, Pockros P, Vierling J, Ipe D, Munson ML, Chen YC, Najera I, Thommes J; PROPEL Investigators.. PROPEL: a randomized trial of mericitabine plus peginterferon alpha-2a/ribavirin therapy in treatment-naïve HCV genotype 1/4 patients.Hepatology. 2013;.

Highlights

The group ended last year FLIP project, funded by the EU FP7, which has succeeded in developing a non-invasive tool for the diagnosis of liver fibrosis based on MRI image processing. Several collaborations with other CIBERehd groups has allowed the publication of results in high-impact journals, emphasizing the management of anemia in patients with triple therapy (J.Hepatol) and the analysis of the interaction of HCV with lipid metabolism.

PROGRAMME:
Hepatitis Virus

G0044

Group Members

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Main lines of research

The main lines of research are conducted in our research group are detailed below:

- Viral hepatitis in children and adults: analysis of viral factors and host in relation to sustained virological response, rational basis for obtaining a therapeutic vaccine, mother-children transmission.
- Hepatocellular carcinoma: study of new therapies, development nanoparticles
- Colon Cancer: cancer stem cells in colorectal cancer markers.
- Drug hepatotoxicity.
- Obesity and liver disease in children and adults.

Most relevant scientific articles

- Ruiz-Extremera A, Muñoz-Gámez JA, Abril-Molina A, Salmerón-Ruiz MA, Muñoz-de-Rueda P, Pavón-Castillero EJ. Variation of transaminases, HCV-RNA levels and Th1/Th2 cytokine production during the post-partum period in pregnant women with chronic hepatitis C.PLoS One. 2013;8(10):e75613.
- López-Rodríguez R, Hernández-Bartolomé Á, Borque MJ, Rodríguez-Muñoz Y, Martín-Vílchez S, Trapero-Marugán M. Polymorphisms in histone deacetylases improve the predictive value of IL-28B for chronic hepatitis C therapy.Genes Immun. 2013 Jul-Aug;14(5):317-24.
- Viota JL, Carazo A, Munoz-Gamez JA, Rudzka K, Gómez-Sotomayor R, Ruiz-Extremera A. Functionalized magnetic nanoparticles as vehicles for the delivery of the antitumor drug gemcitabine to tumor cells. Physicochemical in vitro evaluation.Mater Sci Eng C Mater Biol Appl. 2013 Apr 1;33(3):1183-92.
- Pavón-Castillero EJ, Muñoz-de-Rueda P, López-Segura R, Gila A, Quiles R, Muñoz-Gámez JA. Importance of IL-10 and IL-6 during chronic hepatitis C genotype-1 treatment and their relation with IL28B.Cytokine. 2013 Feb;61(2):595-601.
- Muñoz-Gámez JA, Salmerón J. Prevalence of hepatitis B and C in Spain - further data are needed.Rev Esp Enferm Dig. 2013 May;105(5):245-248.

Highlights

During the year 2013 has been granted us two projects, one national and other autonomic:

- Title: Circadian regulation of cancer stem cells in Colorectal Cancer markers. Exp: PI-0677 - 2013. Principal investigator: Josefa Leon Lopez. Funding: Consejería de Salud, Igualdad y Políticas Sociales, Junta de Andalucía. Duration: 3 years.
- Title: Study of tracking (TV) transmission of the virus of hepatitis C (HCV) and hepatitis B (HBV): analysis of factors involved. Exp: PI13-01925. Funding: Instituto de Salud Carlos III (FIS). Duration: 3 years. PRINCIPAL investigator: Angeles Ruiz Extremera.

The number of active competitive projects carried out this year is a total of 4, including an Intrasalud project, one of the Excellence of the University of Granada, a FIS and one of the Consejería de Salud de Andalucía. The results have given rise to a large number of communications: 12 in national congresses and 9 in international congresses. Two national communications received the award for the best poster of liver (LXXII annual Congress of the EDPS) communication and the best clinical oral communication (XXXVIII annual Congress of the AEEH).

On the other hand, at the end of 2013 was presented a patent which has been accepted at the beginning of the year 2014 (P-06781), whose name is "Polimorfismos para predecir o pronosticar la respuesta al tratamiento antiviral". Our Group collaborated with other members of the CIBER (Dr. Manuel Romero Gomez, Dr. Manuel de la Mata and Dr. Raúl Andrade) and the Hospital de la Princesa of Madrid, Dr. Ricardo Moreno Otero and Clinic of Barcelona, Dr. José Luis Martín Ruiz, (Study CROMO).

In addition the Dr. Ángeles Ruíz Extremera has published with the University of Granada publishing the book entitled: Pediatrics in Sciences of health, ISBN: 9788433854810.

PROGRAMME:
Portal Hypertension and Cirrhosis

G0041

Group Members

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Main lines of research

- Clinical aspects of bacterial translocation in cirrhosis.
- Immunology of bacterial translocation in cirrhosis.
- Intestinal microbiota and homeostasis in cirrhosis.
- Pharmacology and hepatotoxicity in cirrhosis.
- Inflammasome in cirrhosis

Most relevant scientific articles

- Sánchez E, Francés R, Soriano G, Mirelis B, Sancho FJ, González-Navajas JM. Modulation of inflammatory response in a cirrhotic rat model with induced bacterial peritonitis. PLoS One. 2013;8(3):e59692.
- Bellot P, Welker MW, Soriano G, von Schaewen M, Appenrodt B, Wiest R. Automated low flow pump system for the treatment of refractory ascites: a multi-center safety and efficacy study.J Hepatol. 2013 May;58(5):922-7.
- Moratalla A, Gomez-Hurtado I, Santacruz A, Peiró G, Zapater P, González-Navajas JM, Gimenez P, Such J, Sanz Y, Frances R.. Protective effect of Bifidobacterium pseudocatenulatum CECT7765 against induced bacterial antigen translocation in experimental cirrhosisLIVER INT. 2013;.
- Bellot P, Frances R, Such J. Pathological bacterial translocation in cirrhosis: pathophysiology, diagnosis and clinical implicationsLIVER INT. 2013;:31-9.
- Tapia-Abellan A, Ruiz-Alcaraz AJ, Hernández-Caselles T, Such J, Frances R, García-Peñarrubia P, Martínez-Esparza M. Role of MAP kinases and PI3K-Akt on the cytokine inflammtory profile of peritoneal macrophagues from the ascites of cirrhotic patients-LIVER INT. 2013;:552-60.

Highlights

- 7 international publications (1st quartil)
- 2 new national research grants (ISCIII)
- 1 oral communication in international meetings (best oral communication award, UEG 2013, Berlin)
- 2 oral communications in national meetings (AEEH 2013, Madrid; Congreso nacional de Farmacología 2013, Alicante).
- 2 poster communications in international meetings (EASL 2013, Amsterdam)
- 3 poster communications in national meetings (AEEH 2013, Madrid; AEG 2013, Madrid)

PROGRAMME:
Gastrointestinal Inflammation and Motility

G0042

Group Members

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Main lines of research

- Novel therapeutic approaches to inflammatory bowel disease, specially via the use of natural products.
- Pathophysiological alterations in inflammatory bowel disease.
- Targeting obesity and metabolic syndrome: influence of intestinal microbiota.
- Alterations of intestinal barrier in acute pancreatitis.

Most relevant scientific articles

- Garrido-Mesa N, Algieri F, Rodríguez Nogales A, Gálvez J. Functional plasticity of Th17 cells: implications in gastrointestinal tract function.Int Rev Immunol. 2013 Oct-Dec;32(5-6):493-510.
- Algieri F, Zorrilla P, Rodríguez-Nogales A, Garrido-Mesa N, Bañuelos O, González-Tejero MR. Intestinal anti-inflammatory activity of hydroalcoholic extracts of Phlomis purpurea L. and Phlomis lychnitis L. in the trinitrobenzenesulphonic acid model of rat colitis.J Ethnopharmacol. 2013 Apr 19;146(3):750-9.
- Rosales R, Romero MR, Vaquero J, Monte MJ, Requena P, Martínez-Augustin O. FXR-dependent and -independent interaction of glucocorticoids with the regulatory pathways involved in the control of bile acid handling by the liver.Biochem Pharmacol. 2013 Mar 15;85(6):829-38.
- Daddaoua A, Martínez-Plata E, Ortega-González M, Ocón B, Aranda CJ, Zarzuelo A. The nutritional supplement Active Hexose Correlated Compound (AHCC) has direct immunomodulatory actions on intestinal epithelial cells and macrophages involving TLR/MyD88 and NF-κB/MAPK activation.Food Chem. 2013 Feb 15;136(3-4):1288-95.
- Garrido-Mesa N, Zarzuelo A, Gálvez J. Minocycline: far beyond an antibiotic.Br J Pharmacol. 2013 May;169(2):337-52.

Highlights

Last year, the Research Group has carried out different projects supported by either private funding from contracts with Pharmaceutical Companies or public money from Junta de Andalucía and Spanish Ministry of Economy and Competitively. All the current projects are financed with over one million euros. Regarding the publications, the group has published 13 articles, including 3 reviews, in indexed scientific journal that mostly belong to the first quartile. Some of the publications are the result of different collaboration with other groups of the CIBER and the Heracles network. The research has further investigated the anti-inflammatory properties of some antibiotics with immune-modulatory capacities, discovered new plant extracts with intestinal anti-inflammatory activity, investigated the beneficial properties of pre and probiotics as well as other nutritional complements and drugs.

PROGRAMME:
Cholestasis and Metabolic Disorders

G1069

Group Members

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Main lines of research

- Dual role of COX-2 in liver pathology. IIBM, CSIC-UAM.
- Role of caveolin in proliferation and liver regeneration. IIBM, CSIC-UAM. Universidad de California, San Diego, UCSD.
- Autophagic flux and endoplasmic reticulum stress during development of NAFLD. IIBM, CSIC-UAM, Instituto de Investigación Sanitaria Princesa y Ciberdem.

Highlights

During 2013 we have focused on studying the role of cyclooxygenase 2 (COX-2) after liver damage, either in situations of hepatocellular carcinoma (HCC) or in situations of hyperglycemia. In these cases we found that while the COX-2 has no implications on liver tumor progression, overexpression of COX-2 protects the hepatocyte against apoptosis induced by hyperglycemia in type 1 diabetes models. We have completed the study with other enzymes in the pathway of synthesis and degradation of prostaglandins, suggesting that the 15 -hydroxyprostaglandina dehydrogenase (15-PGDH) could function as a relevant tumor suppressor in HCC.

On the other hand, our group has also focused its work on studying the role of macrophages in the pathophysiology of major organs. In 2013, we have highlighted that prostaglandin E2 (PGE2) selectively impairs pyrimidine receptors P2Y Ca2+ mobilization. This inhibition involves the activation of nPKCs and PKD, providing new clues to understand the resolution phase of inflammation, when accumulation of PGE2 anti-inflammatory and proresolving mediators occurs. We have also provided evidence for a new mechanism by which the 15 -epi- lipoxin 4 contributes to inflammation resolution, consisting of the reversion of LPS effects on voltage-dependent potassium channels Kv and Kir in macrophages.

Finally, we have characterized a new variant of the 6-fosfofructo-2-quinasa/fructosa-2,6-bisphosphatase in fetal liver that controls the atypical regulation of glucose metabolism in this stage of development.

PROGRAMME:
Cholestasis and Metabolic Disorders

G00V1

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Main lines of research

Group established in 2006 first as an emergent and from 2013 as consolidated by the Institute for Research in Primary Care IDIAP Jordi Gol. Our lines of work have been and are the study of nonalcoholic fatty liver disease, early detection of chronic liver disease, detection of hidden C virus, alcoholic and non-invasive diagnosis of liver fibrosis.

Most relevant scientific articles

- Fabrellas N, Alemany M, Urquizu M, Bartres C, Pera G, Juvé E et al.. Using transient elastography to detect chronic liver diseases in a primary care nurse consultancy.Nurs Res. 2013 Nov-Dec;62(6):450-4.
- Caballería L, Arteaga I, Pera G, Rodríguez L, Alumà A, Auladell MA et al.. [Risk factors associated with non-alcoholic fatty liver disease: a case-control study].Med Clin (Barc). 2013 Sep 21;141(6):233-9.

Highlights

Second year of FIS PI11/02657 project. We followed the recruitment and at the end of 2013 we had 1470 patients in 3460 provided. We generated two publications listed in the previous section. 5 members of the group are pursuing doctorate through the projects generated by the group. It has also begun analysis results given Grant Calvo Gonçal during 2013.

PROGRAMME:
Gastrointestinal Inflammation and Motility

G00V2

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Main lines of research

- COELIAC DISEASE (CD): The group has become a reference in Spain in the research of celiac disease (CD) in adults. Several projects are on going: Project of the Carlos III Institute PI13/02499 and PI13/00413.
- MICROSCOPIC COLITIS AND CHRONIC DIARRHEA: Our group leads the research on microscopic colitis in Spain (registry of microscopic colitis through the ENEIDA project as a follow-up of the initial RECOMINA project.
- INFLAMMATORY BOWEL DISEASE (IBD): Projects on pathophysiology, clinical and therapeutics are also developing in this field. The group is leading several aspects related to the opportunistic infection and endoscopic treatments (PI13/01226) in IBD.
- COLON CANCER: Achievement of a grant of the TV3 Marató 2012 dedicated to prediction of advanced Colonic Neoplasia.

Most relevant scientific articles

- Fernández-Bañares F, de Sousa MR, Salas A, Beltrán B, Piqueras M, Iglesias E. Impact of current smoking on the clinical course of microscopic colitis.Inflamm Bowel Dis. 2013 Jun;19(7):1470-6.
- Fernández-Bañares F, de Sousa MR, Salas A, Beltrán B, Piqueras M, Iglesias E. Epidemiological risk factors in microscopic colitis: a prospective case-control study.Inflamm Bowel Dis. 2013 Feb;19(2):411-7.
- Carrasco A, Mañe J, Santaolalla R, Pedrosa E, Mallolas J, Lorén V. Comparison of lymphocyte isolation methods for endoscopic biopsy specimens from the colonic mucosa.J Immunol Methods. 2013 Mar 29;389(1-2):29-37.
- Panés J, López-Sanromán A, Bermejo F, García-Sánchez V, Esteve M, Torres Y. Early azathioprine therapy is no more effective than placebo for newly diagnosed Crohn's disease. Gastroenterology. 2013 Oct;145(4):766-74.e1.
- Julià A, Domènech E, Ricart E, Tortosa R, García-Sánchez V, Gisbert JP. A genome-wide association study on a southern European population identifies a new Crohn's disease susceptibility locus at RBX1-EP300.Gut. 2013 Oct;62(10):1440-5.

Highlights

- CELIAC DISEASE: Publications 2013: Monzon H. World J Gastroenterol 2013. Projects: "Immunopatogenesis of lymphocytic enteritis due to gluten sensitive enteropathy: Diagnostic and physiopathological assessment" and "OMIC" analysis for lymphocytic enteritis diagnosis secondary to gluten-sensitive enteropathy (PI10/00892 y PI13/02499, PI:FFernández- Bañares), "Natural history of celiac disease: longitudinal long term study to assess the evolution of serological markers of CD and histology in children 1 to 4 years old"(PI13/00413; PI: M Mariné).
- MICROSCOPIC COLITIS: Publications 2013 leaded by our group: RECOMINA project: Fernández- Bañares F et al. inflamado Bowel Dis 2013; 19:1470-6 y Fernández - Bañares F et al. Inflam Bowel Dis 2013; 19: 411-7) and international clinical trials Münch A, Fernandez-Bañares F, Munck LK. Azathioprine and mercaptopurine in the management of patient with chronic, active microscopic colitis. Aliment Pharmacol Ther 2013; 37:795-8).
- INFLAMMATORY BOWEL DISEASE (IBD): Publications 2013 leaded by our group: Carrasco A. J Immunol Methods. 2013;389:29-37. Projects: "Role of interleukin Il -10 to the pathophysiology of drug refractoriness in Crohn's disease. Relationship between apoptosis of T and B lymphocytes" (PI:MEsteve, BFU - BFI 2010-19888) and "Multicenter prospective randomized comparative study of endoscopic treatment of strictures in Crohn's disease: self-expanding metal stents vs dilation" (PI:C.Loras, PI13/01226). Collaborative Publications: (ENEIDA and INNP-BMK-IMID projects): Nunes T. Aliment Pharmacol Ther 2013; 38: 752-60; Panés J. Gastroenterology 2013;145:766-74; Mañosa M. Inflamm Bowel Dis 2013;19:1889-95; Chaparro M. Inflamm Bowel Dis 2013;19:1404-10; Zabala W. Pharmacogenomics 2013;14:631-40; Casanova MJ. Am J Gastroenterol. 2013; 108: 433-40; Julià A. Gut. 2013; 62:1440-5; Cabriada JL. Gastroenterol Hepatol 2013;36:127-46.

PROGRAMME:
Liver Cancer and Cancer of the Digestive System

G00V4

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Main lines of research

- REGULATION OF CELL DEATH AND PROLIFERATION AND THEIR RELATION WITH THE THERAPEUTIC EFFICACY IN HEPATOCARCINOMA. ROLE OF P53 GENE FAMILY MEMBERS AND OXIDATIVE/NITROSATIVE STRESS
  We investigate the alteration of cell death and proliferation signaling during treatment with Sorafenib and immunosuppressive agents (Everolimus vs Sirolimus). The project includes a descriptive follow-up study of patients with hepatocellular carcinoma, as well as various experimental in vitro and in vivo using established hepatoma cell lines. In particular, the role of p53 gene family members, the degree of tumor differentiation and oxidative/nitrosative stress will be associated with the antitumor activity of the treatments.
- GENETIC AND FUNCTIONAL CHARACTERIZATION OF PANCREATIC CANCER. CLINICAL AND EXPERIMENTAL MODELS.
  The project investigates the involvement of PTEN/PI3K/AKT/mTOR signaling pathways in pancreatic cancer. Different experimental cellular models, as well as tumor implantation in nude mice will be developed in order to evaluate the role of several Ras-related therapeutic strategies in the induc-

tion and progression of pancreatic cancer. The effect of various inhibitors of the signaling pathway is studied in pancreatic tumor cells.

- LIVER REGENERATION BY INFUSION OF STEM CELLS IN THE LIVER. CLINICAL AND EXPERIMENTAL MODELS.
  The project investigates the functional impact of the infusion of bone marrow stem cells in patients undergoing extended liver resection. Different clinical parameters of tissue regeneration, as well as the presence of stem cells in liver and peripheral blood with characteristics of hepatocellular differentiation will be assessed.

Most relevant scientific articles

- González R, Ferrín G, Aguilar-Melero P, Ranchal I, Linares CI, Bello RI. Targeting hepatoma using nitric oxide donor strategies.Antioxid Redox Signal. 2013 Feb 10;18(5):491-506.
- Castaño D, Larequi E, Belza I, Astudillo AM, Martínez-Ansó E, Balsinde J. Cardiotrophin-1 eliminates hepatic steatosis in obese mice by mechanisms involving AMPK activation.J Hepatol. 2013 Dec 19;.
- Mobasher MA, González-Rodríguez A, Santamaría B, Ramos S, Martín MÁ, Goya L, Rada P, Letzig L, James LP, Cuadrado A, Martín-Pérez J, Simpson KJ, Muntané J, Valverde AM. Protein tyrosine phosphatase 1B modulates GSK3β/Nrf2 and IGFIR signaling pathways in acetaminophen-induced hepatotoxicityCell Death & Disease . 2013;4:e626.
- Vaquero J, Briz O, Herraez E, Muntané J, Marin JJ. Activation of the nuclear receptor FXR enhances hepatocyte chemoprotection and liver tumor chemoresistance against genotoxic compounds.Biochim Biophys Acta. 2013 Oct;1833(10):2212-9.
- Vaquero J, Monte MJ, Dominguez M, Muntané J, Marin JJ. Differential activation of the human farnesoid X receptor depends on the pattern of expressed isoforms and the bile acid pool composition.Biochem Pharmacol. 2013 Oct 1;86(7):926-39.

Highlights

During 2013 we have developed a research project to identify the alteration of cell death and proliferation signaling by Sorafenib and immunosuppressants (everolimus vs sirolimus) (CTS- 6264, Consejería de Economía, Innovación, Ciencia y Empleo) and three research projects related to cell therapy in the context of liver regeneration in large resections (CMMO/RH/2009, Instituto de Salud Carlos III; PI-0540/2010, Consejería de Salud), promoting immunosupression in liver transplantation (PI-0385/2010, Consejería de Salud) and the treatment of anal fistulas in Crohn's disease without concomitant therapy with second-line drugs (EC11-450, Instituto de Salud Carlos III). Twenty five articles have been published including original and reviews, comprising all scientific areas in which the group is involved. Also, there were presented two patents " Kit for the decommissioning of large cutaneous wounds after abdominal surgery " (P- 06165) and "Effectiveness of nitric oxide to treat differentiated, but not poorly differentiated, liver cancer cells" (FISEVI-13007).

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