ANNUAL REPORT 2014

ciberehd

Centro de Investigación Biomédica en Red
Enfermedades Hepáticas y Digestivas

Index

1. ORGANISATION

Letter from the Scientific Director

Dr. Jaume Bosch.
Scientific Director
CIBEREHD

Thank you so much for following the scientific activity of the Centro de Investigación Biomédica en Red en Enfermedades Hepáticas y Digestivas (Networking Biomedical Research Centre in Hepatic and Digestive Diseases) (CIBEREHD).

CIBEREHD is one of the eight subject areas of research in the CIBER public consortium. Our goal is to promote high level translational research through the interaction and cooperation of the best Spanish groups. In 2014 it consisted of 51 groups (43 regular groups, 1 associated group and 7 linked clinical groups).

Our mission is:

- Carrying out joint research programmes, development and innovation in digestive and liver diseases, promoting interaction and synergies among the groups.
- Promoting the transfer of research results to society towards both clinical applications and the biotechnological and pharmaceutical industry, and contributing to solving health care issues relating to hepatic and digestive diseases.
- Promoting the active participation in research in priority issues in the national sphere and in projects included in the European Framework R&D&I Programmes.
- 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 responsibility for all CIBEREHD actions with the assistance of the Assistant Scientific Manager and the rest of the Steering Committee comprising the Manager, the Training Coordinator and the Coordinators of Research Programmes and Technological Platforms. The Steering Committee establishes the 4-year action plan, under advisement of the External Scientific Committee and according to the result of the annual evaluations of its activity.

CIBEREHD funding primarily (80%) comes from the ISCIII. The funding is mainly used for covering researcher and support staff salaries, to acquire scientific infrastructure and support research programmes, and to a lesser extent to train research staff and for management expenses. Consortium institutions contribute with their facilities, services and part of their staff (researchers attached to CIBEREHD). CIBEREHD also provides its own funding for a significant percentage of its budget through competitive research projects, contracts with the industry and service contracts with other institutions, and through donations.

RESEARCH PROGRAMMES AND SCIENTIFIC-TECHNOLOGICAL PLATFORMS

CIBEREHD maintains 6 research programmes, each of which is developed through several major lines of research.

- P1. Portal hypertension and mechanisms of transition to cirrhosis
- P2. Viral hepatitis
- P3. Hepatotoxicity, cholestasis and disorders metabolic
- P4. Immunology and liver transplantation
- P5. Hepatic and gastrointestinal oncology
- P6. Gastrointestinal inflammation and motility

CIBEREHD has international opinion leaders in all of these programmes.

Technological Platforms include a Biobank (with two locations, one in Barcelona and one in Valencia), a Transcriptomic, Proteomic, Gene Silencing and Metabolomic Platform (in Vizcaya), a Pyrosequencing Platform, and a Bioinformatic Platform, Platform for Supporting the Diagnosis and Therapeutic Guidance in Liver cancer, Hepatitis B, Hepatitis C and Vascular Hepatic Disease Databases (that depend on Scientific Management).

This year 490 articles were published in first and second quartile journals, 74. 8 % (367) of which belong to the first quartile and 44% (216) to the first decile of their specialty. This indicates a continued increase in the quantity and quality of the scientific results of CIBEREHD. Moreover, in 294 publications the main author or the corresponding author belonged to CIBEREHD and 385 of these publications were the produce of a national cooperation and 193 of an international cooperation. Finally, there were 19 publications in high impact journals. The publication of 15 Clinical Guidelines, 9 Clinical trials, the performance of 6 projects with the industry and the licensing of 3 patents stand out among transfer activities.

LIST OF GROUPS AND INSTITUTIONS

CIBEREHD was founded on 29 November 2006 and is currently comprised of the same 51 groups (43 regular groups, 1 associated group and 7 linked clinical groups) from 30 centres distributed throughout 9 Autonomous Communities.
The CIBEREHD research groups are:

Principal investigator	Programme	Institution
Agustín Albillos	Prog. 1	Universidad de Alcalá de Henares
Rocío Álvarez	Linked Prog. 2	Hospital Virgen de La Arrixaca
Raul Andrade	Prog. 3	Fundacion IMABIS
Fernando Azpiroz	Prog. 6	Hospital Valle Hebrón
Rafael Bañares	Prog. 1	Hospital Gregorio Marañón
Belén Beltrán	Linked Prog. 6	Hospital La Fe
Marina Berenguer	Prog. 4	Hospital La Fe
Jaume Bosch	Prog. 1	Hospital Clínico y Provincial de Barcelona
Jordi Bruix	Prog. 5	Hospital Clínico y Provincial de Barcelona
Luis Bujanda	Prog. 5	Hospital de Donostia
Llorenç Caballeria	Linked Prog. 3	IDIAP Jordi Gol
Eduard Cabré	Prog. 6	Hospital Germans Trias i Pujol
José Luis Calleja	Linked Prog. 2	Hospital Universitario Puerta de Hierro Majadahonda
Xavier Calvet	Prog. 6	Corporación Sanitaria Parc Taulí
José V Castell	Prog. 3	Hospital La Fe
Antoni Castells	Prog. 5	Hospital Clínico y Provincial de Barcelona
Joan Genescà	Prog. 1	Hospital Valle Hebrón
Pere Ginés	Prog. 1	Hospital Clínico y Provincial de Barcelona
Pere Clavé	Prog. 6	Hospital de Mataró
Juan V Esplugues	Prog. 6	Facultad de Medicina Valencia
Juan Ignacio Esteban	Prog. 2	Hospìtal Valle Hebrón
Rafael Esteban	Prog. 2	Hospìtal Valle Hebrón
Maria Esteve	Linked Prog. 6	Fundació Docència i Recerca Mutua de Terrassa
José Carlos Fernández Checa	Prog. 3	Cons. Sup. de Investigaciones Científicas
Xavier Forns	Prog. 2	Hospital Clínico y Provincial de Barcelona
Luisa García Buey	Prog. 2	Hospital de La Princesa
José Juan García Marín	Prog. 5	Universidad de Salamanca
Carmelo García Monzón	Linked Prog. 3	Hospital Sta. Cristina

Principal investigator	Programme	Institution
Javier García Samaniego	Prog. 2	Hospital La Paz
Jordi Gómez	Prog. 2	Instituto de Parasitología y Biomedicina López Neyra
Javier González Gallego	Prog. 3	Inst. de Biomedicina de León
Carlos Guarner	Prog. 1	Hospital Santa Creu i Sant Pau
Francisco Guarner	Prog. 6	Hospital Valle Hebrón
Ángel Lanas	Prog. 6	Instituto Aragonés de Ciencias de la Salud
Paloma Martin	Associated Prog. 3	SCIC-Alberto Sols
Manuel de la Mata	Prog. 4	Hospital Reina Sofía
José María Mato	Prog. 3	CIC BIOGUNE
Juan F Medina	Prog. 3	Fund. Investig. Médica Aplicada
Miquel Navasa	Prog. 4	Hospital Clínico y Provincial de Barcelona
Francisco Javier Padillo	Linked Prog. 5	Hospital Virgen del Rocío
Julià Panés	Prog. 6	Hospital Clínico y Provincial de Barcelona
Albert Parés	Prog. 3	Hospital Clínico y Provincial de Barcelona
Pascual Parrilla	Prog. 5	Hospital Virgen de La Arrixaca
Marçal Pastor	Prog. 5	Universidad de Barcelona
Javier Pérez-Gisbert	Prog. 6	Hospital de La Princesa
Ramón Planas	Prog. 1	Hospital Germans Trias i Pujol
Manuel Romero	Prog. 2	Fundación VALME
Fco Javier Salmerón	Prog. 2	FIBAO
Fermín Sánchez	Prog. 6	Universidad de Granada
Bruno Sangro	Prog. 5	Clínica Univ. Navarra
José Such	Prog. 1	Fund. Investig. Hospital General Universitario Alicante

ORGANIZATIONAL STRUCTURE

The organizational structure is based on the objectives strategic and bylaws governing the Consortium. Management and administration of CIBEREHD consists of the following bodies:

- **Board of Trustees**
- **Permanent Commission**
- **Scientific Director**
- **External Scientific Advisory Committee**
- **Steering Committee**
- **Technical Office**

BOARD OF TRUSTEES

This is the highest body in the Consortium and is formed by three representatives of Instituto de Salud Carlos III (ISCIII), a representative from each of our consortium entities, the Scientific Director and the Manager of the CIBER acting as the Board of Trustees Secretary.
The President of the Board of Trustees is the Director of Instituto de Salud Carlos III.

PERMANENT COMMISSION

This commission consists of a President who represents ISCIII, the Manager of the CIBER acting as Secretary, the eight Scientific Directors of the CIBER and representatives of the Institutions.

SCIENTIFIC DIRECTOR

The Scientific Director of the CIBER is a renowned scientist in the area of research for the CIBER, with experience in conducting and managing research projects. This person is appointed by the Board of Trustees for a period of four years, which can be extended conditional to agreement between the parties.
Members of CIBEREHD Scientific Management:

- Scientific Director: **Jaume Bosch**
- Assistant Scientific Director: **Jordi Bruix**

EXTERNAL SCIENTIFIC ADVISORY COMMITTEE

This committee is formed by relevant figures in the health science area distinguished for the professional or scientific career consistent with the objectives of the Consortium. It is a scientific advisory body that evaluates CIBEREHD activity and the activity of its research groups every year.
Members of the External Scientific Advisory Committee of CIBEREHD:

- President: **Guadalupe García-Tsao** (Yale University)
- Members:

Roger Butterworth (Université de Montréal)

Massimo Pinzani (Royal Free Hospital, London)

Sophie Lotersztajn (Université de Paris)

Jean Pierre Vinel (Université de Toulouse)

Silvio Danese (Università degli Studi di Milano)

Evelien Dekker (Universiteit van Amsterdam)

STEERING COMMITTEE

This committee is formed by the Scientific Director, the Coordinator of each research programme and the Teaching Coordinator. It assumes the responsibility of the actions of the CIBER, establishes the multiannual scientific action plan and the budget.
Members of the Steering Committee:

- Scientific Director and President of the Steering Committee: **Dr. Jaume Bosch**
- Assistant Scientific Director and Programme 5 Coordinator: **Dr. Jordi Bruix**
- Teaching Coordinator: **Dr. Joan Caballería**
- Programme 1 Coordinator: **Dr. Agustín Albillos**
- Programme 2 Coordinator: **Dr. Juan I. Esteban**
- Programme 3 Coordinator: **Dr. Juan F. Medina**
- Programme 4 Coordinator: **Dr. M. Navasa**
- Programme 6 Coordinator: **Dr. Julián Panés**
- Transfer Coordinator: **Dr. JM. Mato**
- Manager: **Manuel Sánchez**
- Steering Committee Secretary: **José Antonio Fernández**

SOLE TECHNICAL OFFICE

This is the administrative coordination and management unit responsible for assuring the proper running of the Consortium. In fiscal year 2013, the CIBEREHD management office was restructured due to Centralization of the Technical Offices of the CIBERS into a single office located in ISCIII (Madrid), which began operating after 1 January 2014.
Its structure is the following:

- **Management: The sole Manager of the 8 CIBERs is Manuel Sánchez**
- **Scientific Management Assistant: Clara Esteva**
- **Financial Department: Laura Ribé**
- **Economic Resources and General Services: Raquel Field**
- **HR and Occupational Hazard Prevention: Liber Montaño, Lourdes Granero** and **Rocío Buendía**
- **Technology Transfer: Luzma García**

The contact persons for the EHD are:

- Projects: **Francesc Martí**
- Administration, orders, purchasing and expenses: **Begoña Saenz de Tejada**
- Human Resources: **Liber Montaño**
- Communication: **Begoña Navarro**

BUDGET

TOTAL EXPENSES	3.835.000
Sicientific Programmes	2.990.000
Group Budget	2.950.000
External income private finalists	40.000
Technology Platforms	170.000
CicBiogune Platform	60.000
BioBanK Support	5.000
Hep. Biotecnology (Bioinformatics)	85.000
New methods image not invasive	0
Cancer Diagnostic Platform	20.000
Strategic actions	100.000
Support to Junior Researchers Programme	0
Incorporation Researcher Programme	0
Strategic actions Programme	100.000
Agreements	85.000
Research collaboration /support agreements	25.000
Agreements with consortium inst. and others	60.000
Trainning	60.000
Internships abroad	35.000
Internships in CIBEREHD groups	5.000
Visiting Professor Program	5.000
Participation in courses and meetings	15.000
Coordination and Management	430.000
Steering and Coordination	110.000
Management Expenses	45.000
Informatic Platform: web, intranet	5.000
Annual report and Communication actions	10.000
Scientific meeting, others meetings and expenses travel	50.000
Expenses of management	320.000
Technical office staff	205.000
Maintenance facilities	2.000
Support to information of management, manag. accounting	7.000
Advisings (legal, tax, risks lab)	45.000
Audit	2.000
Insurances (resp.civil, injure)	39.000
Material office	10.000
Management of projects and patents	10.000

TOTAL INCOMES	3.833.580
Instituto de Salud Carlos III	3.653.580
Nominative subsidy	3.653.580
Other incomes	180.000
2014 Proyects	40.000
2012 Remnants	110.000
Financial incomes	30.000

STAFF CIBEREHD

Number of hires in the year ending December 31 classified by categories and genders.

	MEN			Total MEN
	Indefinite	Works & Services	Postdoctoral	
CIBEREHD	19	8	1	28
PhD	11	4	1	16
Degree Holder	5	3		8
Diploma Holder				
Technician	3	1		4
Total general	19	8	1	28

	WOMEN			Total WOMEN
	Indefinite	Works & Services	Postdoctoral	
CIBEREHD	45	40	1	86
PhD	20	3	1	24
Degree Holder	11	24		35
Diploma Holder	5	4		9
Technician	9	9		18
Total general	45	40	1	86

	Indefinite	Works & Services	Postdoctoral	Total general
CIBEREHD	64	48	2	114
PhD	31	7	2	40
Degree Holder	16	27		43
Diploma Holder	5	4		9
Technician	12	10		22
Total general	**64**	**48**	**2**	**114**

SCIENTIFIC PRODUCTION

CIBEREHD scientific activity in 2014 was top-quality activity, as shown in the following tables.

Number of papers published in 2014 affiliated with our Centre:

Total No. of Publications	641
1 quartile	367
1 decile	216
2 quartile	123
3 quartile	41

The following table shows the name of the journal and the number of papers published in first quartile journals:

Journal name	Nº	Catergory JournalJCR	Impact factor
Alimentary pharmacology & therapeutics	16	PHARMACOLOGY & PHARMACY	5,4780
American Journal of Gastroenterology	1	GASTROENTEROLOGY & HEPATOLOGY	9,2130
American Journal of Pathology	2	PATHOLOGY	4,6020
American Journal of Physiology - Gastrointestinal and Liver Physiology	2	PHYSIOLOGY	3,7370
American Journal of Transplantation	4	SURGERY	6,1900
Analyst	1	CHEMISTRY, ANALYTICAL	3,9060
Analytical and Bioanalytical Chemistry	1	CHEMISTRY, ANALYTICAL	3,5780
Annals of Surgery	2	SURGERY	7,1880
Antimicrobial Agents and Chemotherapy	2	MICROBIOLOGY	4,4510
Antioxidants & redox signaling	2	BIOCHEMISTRY & MOLECULAR BIOLOGY	7,6670
Archives of Toxicology	2	TOXICOLOGY	5,0780
Bioinformatics	1	MATHEMATICAL & COMPUTATIONAL BIOLOGY	4,6210
Biosensors and Bioelectronics	1	BIOTECHNOLOGY & APPLIED MICROBIOLOGY	6,4510
BJU International	2	UROLOGY & NEPHROLOGY	3,1300
BMC bioinformatics	1	MATHEMATICAL & COMPUTATIONAL BIOLOGY	2,6720
BMC Genomics	1	BIOTECHNOLOGY & APPLIED MICROBIOLOGY	4,0410
BMC medicine	1	MEDICINE, GENERAL & INTERNAL	7,2760
British Journal of Cancer	1	ONCOLOGY	4,8170
British journal of pharmacology	3	PHARMACOLOGY & PHARMACY	4,9900
British Journal of Surgery	1	SURGERY	5,2100
Cancer Causes and Control	1	PUBLIC, ENVIRONMENTAL & OCCUPATIONAL HEALTH	2,9610
Cancer Cell	2	CELL BIOLOGY	23,8930

Cancer Epidemiology Biomarkers and Prevention	1	PUBLIC, ENVIRONMENTAL & OCCUPATIONAL HEALTH	4,3240
Cancer Letters	2	ONCOLOGY	5,0160
Cancer Research	1	ONCOLOGY	9,2840
Cell Death and Differentiation	3	BIOCHEMISTRY & MOLECULAR BIOLOGY	8,3850
Cell Reports	1	CELL BIOLOGY	7,2070
Cell Transplantation	1	TRANSPLANTATION	3,5700
Cellular and Molecular Life Sciences	1	BIOCHEMISTRY & MOLECULAR BIOLOGY	5,8560
Circulation	1	CARDIAC & CARDIOVASCULAR SYSTEMS	14,9480
Circulation: Cardiovascular Imaging	1	CARDIAC & CARDIOVASC. SYSTEMS	6,7520
Clinica Chimica Acta	1	MEDICAL LABORATORY TECHNOLOGY	2,7640
Clinical Cancer Research	2	ONCOLOGY	8,1930
Clinical Gastroenterology and Hepatology	5	GASTROENTEROLOGY & HEPATOLOGY	6,5340
Clinical Infectious Diseases	2	IMMUNOLOGY	9,4160
Clinical Nutrition	1	NUTRITION & DIETETICS	3,9400
Clinical Rehabilitation	1	REHABILITATION	2,1800
Clinical reviews in allergy & immunology	1	ALLERGY	4,7280
Clinical Science	3	MEDICINE, RESEARCH & EXPERIMENTAL	5,6290
Critical care (London, England)	1	CRITICAL CARE MEDICINE	5,0350
Critical Care Medicine	1	CRITICAL CARE MEDICINE	6,1470
Current Medicinal Chemistry	2	CHEMISTRY, MEDICINAL	3,7150
Current Opinion in Gastroenterology	1	GASTROENTEROLOGY & HEPATOLOGY	3,6640
Current Opinion in Virology	1	VIROLOGY	6,2980
Current Pharmaceutical Design	3	PHARMACOLOGY & PHARMACY	3,2880
Drug Safety	1	PUBLIC, ENVIRONMENTAL & OCCUPATIONAL HEALTH	2,6200
Emergencias	1	EMERGENCY MEDICINE	2,5830
Endoscopy	1	SURGERY	5,1960
European Journal of Cancer	1	ONCOLOGY	4,8190
European Journal of Clinical Investigation	3	MEDICINE, GENERAL & INTERNAL	2,8340
European Journal of Immunology	2	IMMUNOLOGY	4,5180
European Journal of Nutrition	1	NUTRITION & DIETETICS	3,8400
Expert Opinion on Investigational Drugs	1	PHARMACOLOGY & PHARMACY	5,4320
FASEB Journal	1	BIOLOGY	5,4800
Food and Chemical Toxicology	1	FOOD SCIENCE & TECHNOLOGY	2,6100
Gastroenterology	18	GASTROENTEROLOGY & HEPATOLOGY	13,9260
Gut	22	GASTROENTEROLOGY & HEPATOLOGY	13,3190
Hepatology	18	GASTROENTEROLOGY & HEPATOLOGY	11,1900
Hippocampus	1	NEUROSCIENCES	4,3020
Human Gene Therapy	1	BIOTECHNOLOGY & APPLIED MICROBIOLOGY	3,6230
Human Genetics	1	GENETICS & HEREDITY	4,5220
Human molecular genetics	1	GENETICS & HEREDITY	6,6770
Hypertension	1	PERIPHERAL VASCULAR DISEASE	7,6320
Inflammatory bowel diseases	5	GASTROENTEROLOGY & HEPATOLOGY	5,4750

International Journal of Cancer	1	ONCOLOGY	5,0070
International journal of cancer. Journal international du cancer	1	ONCOLOGY	5,0070
International journal of cardiology	1	CARDIAC & CARDIOVASC. SYSTEMS	6,1750
International journal of nanomedicine	1	PHARMACOLOGY & PHARMACY	4,1950
Journal of Agricultural and Food Chemistry	1	AGRICULTURE, MULTIDISCIPLINARY	3,1070
Journal of Antimicrobial Chemotherapy	1	INFECTIOUS DISEASES	5,4390
Journal of Biological Chemistry	2	BIOCHEMISTRY & MOLECULAR BIOLOGY	4,6000
Journal of Biological Chemistry	1	BIOCHEMISTRY & MOLECULAR BIOLOGY	4,6000
Journal of Bone and Mineral Research	1	ENDOCRINOLOGY & METABOLISM	6,5890
Journal of Cellular Physiology	1	PHYSIOLOGY	3,8740
Journal of Clinical Endocrinology and Metabolism	1	ENDOCRINOLOGY & METABOLISM	6,3100
Journal of Clinical Investigation	1	MEDICINE, RESEARCH & EXPERIMENTAL	13,7650
Journal of Clinical Microbiology	1	MICROBIOLOGY	4,2320
Journal of Controlled Release	1	PHARMACOLOGY & PHARMACY	7,2610
Journal of Dental Research	1	DENTISTRY, ORAL SURGERY & MEDICINE	4,1440
Journal of Gastroenterology	3	GASTROENTEROLOGY & HEPATOLOGY	4,0200
Journal of Hepatology	35	GASTROENTEROLOGY & HEPATOLOGY	10,4010
Journal of Immunology	1	IMMUNOLOGY	5,3620
Journal of Infectious Diseases	1	INFECTIOUS DISEASES	5,7780
Journal of Innate Immunity	1	IMMUNOLOGY	4,5570
Journal of Leukocyte Biology	1	HEMATOLOGY	4,3040
Journal of Molecular Medicine	1	GENETICS & HEREDITY	4,7390
Journal of Nursing Administration	1	NURSING	1,3730
Journal of Pathology	1	ONCOLOGY	7,3300
Journal of Pineal Research	3	ENDOCRINOLOGY & METABOLISM	7,8120
Journal of Proteome Research	2	BIOCHEMICAL RESEARCH METHODS	5,0010
Journal of Proteomics	1	BIOCHEMICAL RESEARCH METHODS	3,9290
Journal of the National Cancer Institute	1	ONCOLOGY	15,1610
Journal of Thrombosis and Haemostasis	1	HEMATOLOGY	5,5500
Journal of Urology	1	UROLOGY & NEPHROLOGY	3,7530
Journal of Virology	2	VIROLOGY	4,6480
Journals of Gerontology - Series A	1	GERONTOLOGY	4,9840
Laboratory Investigation	1	PATHOLOGY	3,8280
Liver International	17	GASTROENTEROLOGY & HEPATOLOGY	4,4120
Liver Transplantation	2	SURGERY	3,7930
Medicinal Research Reviews	1	CHEMISTRY, MEDICINAL	8,1310
Molecular Cancer Research	1	ONCOLOGY	4,5020
Molecular Cancer Therapeutics	1	ONCOLOGY	6,1070
Molecular Nutrition and Food Research	3	FOOD SCIENCE & TECHNOLOGY	4,9090
Molecular Pharmaceutics	2	PHARMACOLOGY & PHARMACY	4,7870
Molecular Therapy	1	BIOTECHNOLOGY & APPLIED MICROBIOLOGY	6,4250
Mucosal immunology	2	IMMUNOLOGY	7,5370
Nature Biotechnology	2	BIOTECHNOLOGY & APPLIED MICROBIOLOGY	39,0800

Nature Cell Biology	2	CELL BIOLOGY	20,0580
Nature communications	2	MULTIDISCIPLINARY SCIENCES	10,7420
Nature Immunology	1	IMMUNOLOGY	24,9730
Nature Medicine	1	BIOCHEMISTRY & MOLECULAR BIOLOGY	28,0540
Nature Reviews Clinical Oncology	4	ONCOLOGY	15,6960
Nature Reviews Gastroenterology and Hepatology	8	GASTROENTEROLOGY & HEPATOLOGY	10,8070
Neurogastroenterology and Motility	5	CLINICAL NEUROLOGY	3,4240
Neuron	1	NEUROSCIENCES	15,9820
New England Journal of Medicine	4	MEDICINE, GENERAL & INTERNAL	54,4200
NMR in Biomedicine	1	SPECTROSCOPY	3,5590
Nucleic Acids Research	1	BIOCHEMISTRY & MOLECULAR BIOLOGY	8,8080
Oncogene	2	BIOCHEMISTRY & MOLECULAR BIOLOGY	8,5590
Pharmacological Research	2	PHARMACOLOGY & PHARMACY	3,9760
PLoS Biology	1	BIOCHEMISTRY & MOLECULAR BIOLOGY	11,7710
PLoS ONE	30	MULTIDISCIPLINARY SCIENCES	3,5340
Proceedings of the National Academy of Sciences of the United States of America	2	MULTIDISCIPLINARY SCIENCES	9,8090
RNA Biology	1	BIOCHEMISTRY & MOLECULAR BIOLOGY	5,3770
RSC Advances	1	CHEMISTRY, MULTIDISCIPLINARY	3,7080
Science Translational Medicine	1	CELL BIOLOGY	14,4140
Scientific Reports	1	MULTIDISCIPLINARY SCIENCES	5,0780
Seminars in Cell and Developmental Biology	1	DEVELOPMENTAL BIOLOGY	5,9710
Seminars in liver disease	6	GASTROENTEROLOGY & HEPATOLOGY	5,1230
Stem Cell Research	1	BIOTECHNOLOGY & APPLIED MICROBIOLOGY	3,9120
Talanta	1	CHEMISTRY, ANALYTICAL	3,5110
The Cochrane database of systematic reviews	1	MEDICINE, GENERAL & INTERNAL	5,9390
The Journal of antimicrobial chemotherapy	1	INFECTIOUS DISEASES	5,4390
The Journal of infectious diseases	2	INFECTIOUS DISEASES	5,7780
The Lancet	2	MED, GENERAL & INTERN	39,2070
Toxicology	1	PHARMACOLOGY & PHARMACY	3,7450
Toxicology and Applied Pharmacology	1	TOXICOLOGY	3,6300
Translational Research	2	MEDICAL LABORATORY TECHNOLOGY	4,0440
Transplant International	2	SURGERY	3,1200
Veterinary Research	1	VETERINARY SCIENCES	3,3830
TOTAL	367		3073,035

SUPERVISION AND PREPARATION OF PHD DISSERTATIONS

Scientific production directly associated with training is the supervision of PhD dissertations by CIBEREHD members, as well as the preparation of PhD dissertations by people working in CIBEREHD (contracted and attached). A total of 67 PhD dissertations were supervised in 2014.

2. SCIENTIFIC PROGRAMMES

P1. PORTAL HYPERTENSION AND MECHANISMS OF TRANSITION TO CIRRHOSIS

Coordinator:
Dr. A. Albillos
Associate Coordinators:
Drs. JC García-Pagán, J Genescà and **P. Ginès**

Program num. 1 focuses on collaborative research on the pathogenesis, diagnosis and treatment of liver cirrhosis, portal hypertension and complications. In particular, the cooperative translational research the Program maintains studies the pathogenic mechanisms of hepatic 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 systematised in five lines 1) hepatic fibrogenesis, 2) portal hypertension, 3) ascites/renal function and liver failure, 4) infection and bacterial translocation, and 5) hepatic encephalopathy.

The Program is formed by eight groups, five located in Barcelona and led by Dr. Ginés (Hospital Clinic), Dr. Bosch (Hospital Clinic), Dr. Genescá (Hospital Valle Hebron), Dr. Guarner (Hospital San Pablo) and Dr. Planas (Hospital Germán Trias Pujol), two in Madrid led by Dr. Albillos (Hospital Ramón y Cajal-Universidad de Alcalá) and Dr. Bañares (Hospital Gregorio Marañón), and one in Alicante led by Dr. Such (Hospital General). In spite of its clinical origin, all the groups included in the Program have incorporated experimental research. The latter fact enables Program 1 to cover the whole spectrum of translational research in its field of expertise, 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, CIBEREHD management has stimulated the development of collaborative projects among groups of Program 1, as well as with groups in other areas. The collaboration has included multicentre 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 growing in coming years.

The following table describes the topics of research for the 8 groups of Program 1:

Group	Centre	PI	Lines of research
CB06/04/0024	Universidad de Alcalá-Hospital Ramón y Cajal, Madrid	Agustín Albillos	Portal hypertension Infection/Translocation
CB06/04/0020	Hospital Clínic Barcelona	Pere Ginés	Fibrogenesis Ascites/renal function/ Liver failure Infection/Translocation Hepatic encephalopathy
CB06/04/0082	Hospital Gregorio Marañón, Madrid	Rafael Bañares	Portal hypertension Ascitis/renal function /Liver failure
CB06/04/0026	Hospital Clínic Barcelona	Jaime Bosch	Portal hypertension Infection/Translocation

CB06/04/0007	Hospital Valle de Hebrón, Barcelona	Juan Genescá	Ascites/renal function /Liver failure Hepatic encephalopathy
CB06/04/0030	Hospital San Pablo, Barcelona	Carlos Guarner	Portal hypertension Ascites/renal function Infection/Translocation
CB06/04/0033	Hospital Germans Trías, Badalona	Ramón Planas	Portal hypertension Ascites/renal function Infection/Translocation Hepatic encephalopathy
CB06/04/0041	Hospital General Universitario, Alicante.	José Such	Ascites/renal function Infection/Translocation

Objectives

- Etiopathogenesis of the renal failure in cirrhosis: therapeutic targets.
- Relevance of the intestine in liver damage and systemic inflammation in cirrhosis and its therapeutic modulation.
- Prevention of decompensation in cirrhosis: research for new treatment options.
- Molecular targets of dysfunction of hepatic microcirculation in cirrhosis.

Ongoing cooperative clinical projects in 2014

- Multicentre, randomised, double-blind, placebo-controlled study on the efficacy of beta-blockers to prevent decompensation of cirrhosis with portal hypertension. Instituto de Salud Carlos III Clinical Research Project EC08/00122. Code: PREDESCI. Year started: 2008. Hospital/participating institutions: H. Santa Cruz y San Pablo, H. Clinic, H. Trias Pujol, H. Valle de Hebron, H. Ramon y Cajal-Universidad de 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, randomised, 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.
- 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. Year started: 2012. Hospital/participating institutions: H. Clinic, H. Sant Pau. Principal Investigator/Coordinator: Pere Ginès, Hospital Clinic, Barcelona.
- Effects of the beta-adrenergic blocking on heart function, systemic and splanchnic hemodynamics and renal function in cirrhosis patients with refractory ascites. Code ALB-BET. Participating institutions: H. Ramón y Cajal, H. GregorioMarañón. Principal Investigator/Coordinator: Agustín Albillos, Hospital Ramón y Cajal, Madrid.

Most relevant publications in 2014

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P2. VIRAL HEPATITIS

Coordinator:
Dr. Juan Ignacio Esteban Mur
Associate Coordinators:
Drs. Xavier Forns and **Manuel Romero Gómez**

Area 2 includes 8 research groups led by Dr. Juan Ignacio Esteban Mur (Hospital Universitari Vall d'Hebron. Barcelona), Dr. Rafael Esteban (Hospital Universitari Vall d'Hebron. Barcelona), Dr. Xavier Forns Bernhardt (Hospital Clínic of Barcelona), Dr. Javier García-Samaniego Rey (Hospital La Paz-Carlos III. Madrid), Dr. Jordi Gómez Castilla (CSIC Instituto Lopez Neyra. Granada), Dr. Manuel Romero Gómez (Hospital Universitario de Valme, Sevilla), Dr. Javier Salmeron Escobar (Hospital Universitario San Cecilio. Granada) and Dr. Marisa García Buey (Hospital de la Princesa. Madrid) in addition to a linked clinical group Dr. José Luis Calleja (H. Puerta del Hierro, Madrid).

- Public HBV database named CIBERHEP, owned by CIBEREHD is open to all National Health professionals willing to participate in the Project and is coordinated by Dr. M. Buti and Dr. R. Esteban (HUVH) http://hepatitis.ciberehd.org / https://www.ciberehd.org/ is completely active and has given rise to papers presented in national and international congresses. As an example, the presentation in the 49th Annual Meeting of the EASL (Poster 1211): "Efficacy of tenofovir in patients who have received prior treatment with nucleoside/nucleotide analogues and comparing them with patients who have not previously been treated (naïve)" in which 370 patients in treatment with tenofovir were included. CIBERHEP has over 1149 patients (September 2014), 25 participating centres from 9 Spanish Regions (718 have received Tenofovir; 384 have received Entecavir).
- A HIGH-PERFORMANCE HVC SUBTYPING system based on ultradeep pyrosequencing and molecular phylogenesis has been developed and patented as the successful result of a project funded by the CDTI (Centro para el Development Tecnológico Industrial) in collaboration with Roche Diagnostics and ABL, subsidised by MINECO IDI-20110115 (Coordinated by Dr. J. I. Esteban). In 2014 and continuing in 2015, this methodology, which has had an impact on all means of communication, is being transferred to clinical diagnostic laboratories in Spanish hospitals, and is opening the doors to Innovative Government Procurement systems on a regional and national level. This system is patented in international patent document WO2015001068 A1, and co-owners of said patent include CIBEREHD, Roche and VHIR.
- A public HCV data base named HepatiC, owned by Ciberehd, has been consolidated. An agreement with the AEEH (Asociación Española para el Study del Liver) has been signed to open Hepatic to all National Health professionals who wish to participate in the Project. The database received approval in the Official State Journal BOE-B-2011-20823, 20 June 2011, and was registered in the Agencia Española de Protección de Datos (AEPD). It is fully operative and more than 600 patients have been entered (September 2014).
- With respect to HBV, studies of the variability and evolution of quasispecies by means of ultradeep pyrosequencing (UDPS) are being conducted in the framework of different health research projects. Progress has been made in developing HBV genotyping and the response to antiviral treatment which can be automated and transferred to a clinical diagnostic laboratory; replication cycle regulating regions and their relationship with the severity of the hepatic disease are being studied. The variants involved in resistance to antiviral treatment and which escape the immune system are being analysed. HBV variants in the preS region of HBsAg and in the HBV and HDV input receptor, and whether or not there is a need to establish a cell culture model to study the ineffectiveness of HBV and HDV replication based on primary hepatocytes (Dr. R. Esteban, Dr. M. Buti, Dr. F. Rodriguez-Frías, Dr. J. Muntané, Dr. J. I. Esteban).

- Epidemiological studies focussed in HBV, HCV, HDV and recently on HVE infection have been reinforced, including nosocomial HCV transmission studies thus supporting the National Health Spanish System. In this sense, an epidemiological study is being carried out in HIV+HCV+ homosexual patients BY ultradeep pyrosequencing (Dr. X. Forns, Dr. S. Pérez del Pulgar, Dr. J. Quer, Dr. J. Gregori, Dr. JI. Esteban, Dr. J. Mallolas, Dr. M. Laguno, Dr. M. Martínez-Rebollar).
- Collaboration in studies on liver transplant in patients with HCV infection has increased, and specifically in a study on HCV superinfection after HCV liver transplant + by UDPS; and in another study of the HCV quasispecies dynamics in liver transplant by UDPS in cholestasis patients (Dr. X. Forns, Dr. S. Pérez del Pulgar, Dr. M. Gambato, Dr. J. Quer, Dr. J. Gregori, Dr. J. I. Esteban), as well as in studies on the variability of quasispecies and progression of liver damage in patients treated with everolimus (Dr. I. Bilbao, Dr. Ll. Castells, Dr. F. Rodríguez-Frías, Dr. I. Fields-Varela, Dr. J. Quer, Dr. J. Gregori, Dr. J. I. Esteban).
- Antiviral protocols based on lethal mutagenesis have been developed: sequential inhibitor-mutagen therapies against HCV infections (Dr. E. Domingo, Dr. C. Perales, Dr. Manolo Leal (HIV), Dr. J. I. Esteban, Dr. J. Quer, Dr. J. Gregori).
- A collaborative paper on the use of Ribavirin in monotherapy has been published (Dr. J. Salmerón, Dr. P. Muñoz-Rueda, Dr. R. Quiles-Pérez, Dr. J. Quer, Dr. J. I. Esteban)
- Detection of the HCV resistance mutation Q80K, which is essential for determining the use of Simeprevir in patients with chronic HCV infection, has been designed and is being validated.
- 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 research for the effect of anti-viral drugs on HCV quasispecies dynamics (Dr. J. Gomez and E. Domingo). In this sense, research is being done on the response of HCV to a direct-acting antiviral such as Sofosbuvir on the genomic clone.
- Non-invasive (ARFI) techniques to characterise hepatic fibrosis, including licensed software to analyse magnetic resonance images, have been evaluated. .
- Improvement of the detection of the viral load of the HDV (Dr. García Samaniego) with the use of internal characteristic controls that have opened up field to collaborations with European groups is underway (Dr. F. Rodriguez-Frías).
- Studies on genomic DNA polymorphisms in interferon-stimulated genes (ISGs) have reported their association as independent predictors of the response to anti-HCV treatment (Peg-IFN and ribavirin) in chronic HCV patients (HCC) (Dr. M. García Buey). The immune response and protein expression levels of the host have been involved in the progression towards fibrosis/cirrhosis and in the development of hepatocarcinoma.
- A multicentre, three-year study including all the cases of hepatocarcinoma occurring in NASH, HCV or cryptogenic cirrhosis, called FLIP (Fatty Liver: Inhibition of the Progression) started in 2010. The FDFT1 gene associated with the progression of the liver fibrosis in a cohort of HCV and NASH patients has been validated (Dr. M. Romero-Gómez and Dr. JA del Campo, leading the work in which 8 different Spanish hospitals have been involved)
- 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.
- Progress has been made in the collaboration for the study of vertical mother-child HCV transmission (Dr. J. Salmeron and Dr. A. Ruíz-Extremera).
- A collaborative line of research including three groups from our Area 2 and led by Dr. J. García-Samaniego has been consolidated, foucsing on the study of epigenetic interactions between genomic host DNA and HBV or HCV geneomes and their involvement in the progression of fibrosis and development of hepatocarcinoma (Dr. J. García-Samaniego, Dr. E. Domingo).

- New anti-HCV inhibitors (quercetin, etc.) and the role of different receptors at the entry of HCV into the hepatocyte, such as clatrin and apolypoproteins b and e in cell-to-cell HCV transmission, have been characterised (Dr. L. C. Garcia-Buey, Dr. P. Majano, Dr. Mª Ángeles Muñoz Fernández (CIBERBBN), Dr. X. Forns, Dr. S. Perez del Pulgar).
- Studies on the effect of compounds of natural extracts on in vitro NS3 inhibition activity, as well as GWAS studies in patients subjected to treatment with NS3 inhibitors have been conducted (Dr. M. Romero-Gómez, Dr. JA del Campo leading a group of 8 hospitals)
- Progress has been made in the development of new HCV treatment techniques, as in the case of the synthesis of specific HCV anti-core aptamers (Dr. C. Briones, Dr. J. García-Samaniego, Dr. A. Madejón)
- Another group of collaborative studies is related to the search for non-invasive biomarkers of the prognosis, progression and response to treatment of Chronic Hepatitis B and C (Dr. L. C. Garcia-Buey, Dr. P. Majano, Dr. J. García-Samaniego, Dr. A. Madejon, Dr. J. Salmeron, Dr. F. Abad-Santos, Dr. A. M. Aransay (CicBioGUNE (Bilbao)).
- An example of the close collaboration between groups in Programme 2 is the publication of the paper in which it is proven that HCV replication capacity or fitness is a determining factor in the response to treatment (Dr. E. Domingo, Dr. C. Perales, Dr. J. I. Esteban, Dr. J. Quer, Dr. J. Gregori).
- Most of the groups have participated and are actively participating in multicentre Clinical Trials with new combinations of anti-HCV direct acting antivirals
- Finally, it should be pointed out that with the use of new technologies, such as GWAS, ultradeep pyrosequencing using the 454/Roche platform and structural RNA biosensors using microarrays, have allowed increasing the number of collaborative publications in peer-review journals and opening up new collaborative lines of research.

In summary, the collaborative activity conducted in 2014 in CIBEREHD Programme 2 has allowed increasing the competitive research capacity of our network and has opened up new doors to funding which will materialise in the coming years.

Coordinator:
Dr. Juan F. Medina
Associate Coordinators:
Drs. Albert Parés and **José Carlos Fernández-Checa**

Description

Program 3 includes ten groups, the research activities of which are mainly related to cholestasis, metabolic disorders and hepatotoxicity. The groups led by Dr. Albert Parés, Dr. Llorenç Caballería, and Dr. Juan F. Medina are focusing on clinical, epidemiological and basic studies of cholestatic diseases, such as primary biliary cirrhosis and other chronic cholestatic conditions. As regards the basic aspects, the study of impairments in the transport of various components of bile, as well as the etiopathogenesis of osteopenia associated with cholestatic syndromes stand out. The other seven groups from the program develop their research on metabolic disorders and more specifically, the study of steatohepatitis and liver toxicity. Therefore, these groups conduct studies related to the mechanisms of oxidative stress and apoptosis in hepatocytes, as well as 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. In this regard, the grant of the INTERCIBER Project Understanding obesity (Ob), metabolic syndrome (MetS), type 2 diabetes (T2DM) and fatty liver disease (FL): a multidisciplinary approach, should be highlighted. This project is led by CIBEREHD (particularly Dr. José M. Mato and Dr. Mª Luz Martínez-Chantar) and three other CIBERs actively participate in it within the subject Areas of Obesity and Nutrition (Ciberobn), Diabetes and Associated Metabolic Diseases (Ciberdem) and Mental Health (Cibersam). Moreover, the groups led by Dr. Javier González Gallego and Dr. Carmelo García Monzón and Dr. 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 working closely with one another and with the preceding groups in researching different molecular mechanisms that cause hepatotoxicity.

Program Projects and Collaborations

The groups that form Program 3 maintain collaborative networks with more than 25 groups with one another (intra-nodal collaborations) and with other external groups (inter-nodal collaborations). Dr. José M. Mato's group, from CIC BioGUNE, continues to significantly potentiate these collaborations through its Genomics, Proteomics, Metabolomics and Gene Silencing Platforms, which are also available to all CIBEREHD groups. Also, collaborations based on these platforms continue to be consolidated through the organisation of classroom sessions and other training activities.

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

Fucho R, Martínez L, Baulies A, Torres S, Tarrats N, Fernandez A, Ribas V, Astudillo AM, Balsinde J, Garcia-Rovés P, Elena M, Bergheim I, Lotersztajn S, Trautwein C, Appelqvist H, Paton AW, Paton JC, Czaja MJ, Kaplowitz N, Fernandez-Checa JC, García-Ruiz C. ASMase regulates autophagy and lysosomal membrane permeabilization and its inhibition prevents early stage non-alcoholic steatohepatitis. J Hepatol 2014;61:1126-1134. (IF 2013: 10.401)

Affò S, Morales-Ibanez O, Rodrigo-Torres D, Altamirano J, Blaya D, Dapito DH, Millán C, Coll M, Caviglia JM, Arroyo V, Caballería J, Schwabe RF, Ginès P, Bataller R, Sancho-Bru P. CCL20 mediates lipopolysaccharide induced liver injury and is a potential driver of inflammation and fibrosis in alcoholic hepatitis. Gut 2014;63:1782-92. (IF 2013: 13.319)

Rodríguez-Ortigosa CM, Celay J, Olivas I, Juanarena N, Arcelus S, Uriarte I, Marín JJ, Ávila MA, Medina JF, Prieto J. A GAPDH-mediated trans-nitrosylation pathway is required for feedback inhibition of bile salt synthesis in rat liver. Gastroenterology 2014;147:1084-1093. (IF 2013: 13.926)

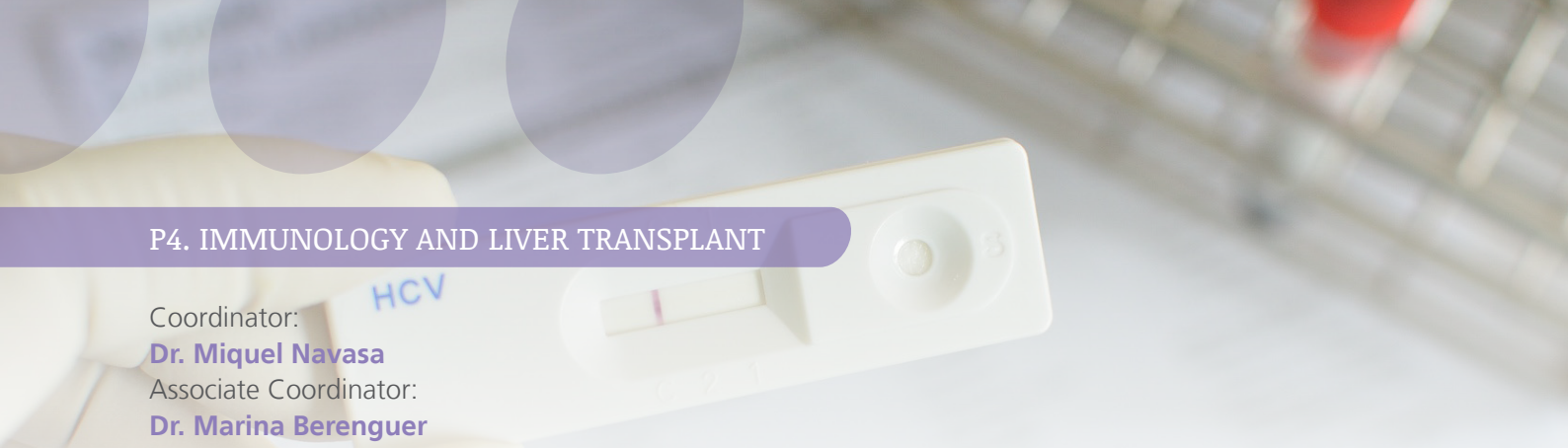
International networks are still important for Program 3. For instance:

Robles-Diaz M, Lucena MI, Kaplowitz N, Stephens C, Medina-Cáliz I, González-Jimenez A, Ulzurrun E, Gonzalez AF, Fernandez MC, Romero-Gómez M, Jimenez-Perez M, Bruguera M, Prieto M, Bessone F, Hernandez N, Arrese M, Andrade RJ; Spanish DILI Registry; SLatinDILI Network; Safer and Faster Evidence-based Translation Consortium. Use of Hy's law and a new composite algorithm to predict acute liver failure in patients with drug-induced liver injury. Gastroenterology 2014;147:109-118. (IF 2013: 13.926)

Altamirano J, Miquel R, Katoonizadeh A, Abraldes JG, Duarte-Rojo A, Louvet A, Augustin S, Mookerjee RP, Michelena J, Smyrk TC, Buob D, Leteurtre E, Rincón D, Ruiz P, García-Pagán JC, Guerrero-Marquez C, Jones PD, Barritt AS 4th, Arroyo V, Bruguera M, Bañares R, Ginès P, Caballería J, Roskams T, Nevens F, Jalan R, Mathurin P, Shah VH, Bataller R. A histologic scoring system for prognosis of patients with alcoholic hepatitis. Gastroenterology. 2014;146:1231-1239. (IF 2013: 13.926)

García-Rodríguez JL, Barbier-Torres L, Fernández-Álvarez S, Gutiérrez-de Juan V, Monte MJ, Halilbasic E, Herranz D, Álvarez L, Aspichueta P, Marín JJ, Trauner M, Mato JM, Serrano M, Beraza N, Martínez-Chantar ML. SIRT1 controls liver regeneration by regulating bile acid metabolism through farnesoid X receptor and mammalian target of rapamycin signalling. Hepatology 2014;59:1972-1983. (IF 2013: 11.190)

Lammers WJ, van Buuren HR, Hirschfield GM, Janssen HL, Invernizzi P, Mason AL, Ponsioen CY, Floreani A, Corpechot C, Mayo MJ, Battezzati PM, Parés A, Nevens F, Burroughs AK, Kowdley KV, Trivedi PJ, Kumagi T, Cheung A, Lleo A, Imam MH, Boonstra K, Cazzagon N, Franceschet I, Poupon R, Caballeria L, Pieri G, Kanwar PS, Lindor KD, Hansen BE; Global PBC Study Group. Levels of alkaline phosphatase and bilirubin are surrogate end points of outcomes of patients with primary biliary cirrhosis: an international follow-up study. Gastroenterology 2014;147:1338-1349. (IF 2013: 13.926)



P4. IMMUNOLOGY AND LIVER TRANSPLANT

Coordinator:
Dr. Miquel Navasa
Associate Coordinator:
Dr. Marina Berenguer

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. Results are satisfactory in terms of transplant recipient survival rates. 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 optimised to adapt to the needs of each patient in order to reduce the risk of rejection and 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, c) suitably detecting and handling complications resulting from immunosuppressants, d) influence of immunosuppression in hepatocarcinoma recurrence, and e) non-invasive markers of rejection. For this reason, some of the objectives of this group focus on the identification and clinical validation of a panel of predictive biomarkers of the risk of rejection, clinical progression of the graft and personal response to immunosuppressant treatment. The implementation of these biomarkers in clinical practice would allow stratifying patients according to risk of rejection and improving the choice of immunosuppressant treatment as well as the identification of patients who are candidates for minimization without it entailing a risk of reactivation of the effector response of the immune system (risk of rejection in the maintenance phase).

Recurrence of the pre-transplant disease, particularly hepatitis C, studies performed by the members of the programme have allowed defining progression of liver fibrosis in transplant patients. After the marketing of new and potent viral agents, the mechanisms of liver damage have lost their interest in these patients. However, the study of the reversibility of fibrosis and the associated mechanisms holds interest both in transplant patients (it would be important to treat before irreversible damage sets in) and in patients on a transplant wait list (if the damage is reversible, the transplant is not necessary). Therefore, Programme 4 also deals with research for this issue.

Complications of the immunosuppressant treatment. Post-liver transplant diabetes mellitus is associated with worse results, a higher rate of infections, rejection and mortality having been reported. Other complications, such as the onset of neoplasias or the increase in cardiovascular risk, are important limiting factors of survival of liver transplant patients. This programme includes the study of these complications in their working projects.

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 by means of investigating strategies that allow increasing the number of liver grafts suitable for transplant were implemented, 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.

The research group has established new targets of therapeutic action based on the modulation of adipocytokines both in liver resections and liver transplant in marginal bodies, which can have a favourable effect on patients who are subjected to liver resections or liver transplant and in a reduction in liver transplant wait lists. The results obtained by the research group have further allowed participation in competitive programmes intended for translation experimental results to clinical practice, which will result in patent application and in the creation of a spin-off.

On the other hand, it is very important to point out the important collaboration established with important groups that are dedicated to studying liver diseases, particularly with the Viral Hepatitis Group (Dr. X. Forns) and with the Portal Hypertension Group (Dr. J. Bosch), as well as with international groups.

Programme 4 consists of the four following groups:

principal Investigator	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
Grupo vinculado: Rocío Álvarez	Hospital Virgen de la Arrixaca	Murcia

The projects of the Programme are described below:

Project 1

Project title:
OPERATIONAL TOLERANCE AND WITHDRAWAL OF IMMUNOSUPPRESSANT IN PATIENTS WITH LIVER TRANSPLANT.
Lead Group: **M. 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** (Lovaina), **Gavin Whitehouse** (London), **Frans Claas** (Leiden).

OBJETIVOS:

- 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 analyse the gene expression profile in liver tissue to even more precisely identify patients that are tolerant to the graft..

Important results have been obtained and have been referenced in successive reports. The work conducted in 2014 explores the relationship between chronic HCV infection and the development of immune tolerance.

Bohne F, Londoño MC, Benítez C, Miquel R, Martínez-Llordella M, Russo C, Ortiz C, Bonaccorsi-Riani E, Brander C, Bauer T, Protzer U, Jaeckel E, Taubert R, Forns X, Navasa M, Berenguer M, Rimola A, Lozano JJ, Sánchez-Fueyo A. HCV-induced immune responses influence the development of operational tolerance after liver transplantation in humans. Sci Transl Med. 2014 Jun 25;6(242).

Project 2

Project title:
LIVER TRANSPLANT AND IMMUNOSUPPRESSION.
Lead Group: **M. de la Mata**
Principal Investigator: **M. de la Mata**,
Co-Researcher: **Manuel Rodríguez Perálvarez**

OBJECTIVES:

The main objective of this line is to improve expectations of survival and quality of life for patients subject to a liver transplant because since livers are a limited and highly valued resource, their performance must be optimised as much as possible.

- **Validation of the REJECT test, a non-invasive method for the diagnosis of acute rejection in liver transplant.**
  Principal Investigator: M. de la Mata,
  Co-Researcher: M. Rodríguez Perálvarez
  Collaborating Groups: M. Berenguer. M. Navasa
- Coordination of a project within CIBEREHD to validate a predictive model of acute cellular rejection called REJECTEST based on routine clinical and analytical data. This model has recently been developed by the group led by the Dr. Manuel de la Mata in collaboration with Royal Free Hospital of United Kingdom and Hospital of Padua (Italy) (Rodríguez-Perálvarez et al. Transplant Int 2015. At press)

COOPERATIVE PROJECTS:

- **Model of donor-recipient assignment in liver transplant.**
  Lead Group: De la Mata M, Briceño J.
  CIBEREHD Groups: Berenguer, Forns, Bañares, Albillos, Navasa
  Other groups: 7 national and international centres.

  This cooperative project has been described in the following paper, which proposes the use of artificial intelligence networks for suitable donor-recipient matching:

Briceño J, Cruz-Ramírez M, Prieto M, Navasa M, Ortiz de Urbina J, Orti R, Gómez-Bravo MÁ, Otero A, Varo E, Tomé S, Clemente G, Bañares R, Bárcena R, Cuervas-Mons V, Solórzano G, Vinaixa C, Rubín A, Colmenero J, Valdivieso A, Ciria R, Hervás-Martínez C, de la Mata M. Use of artificial intelligence as an innovative donor-recipient matching model for liver transplantation: results from a multicenter Spanish study.J Hepatol. 2014 Nov;61(5):1020-8.

COOPERATIVE STUDIES

Liver transplant and HCV.

Different studies led by M. Berenguer and X. Forns (collaboration) have meant important milestones in the definition of hepatitis C recurrence in liver transplant:

Ble, Michel; Aguilera, Victoria; Rubin, Ángel; Garcia-Eliz, Maria; Vinaixa, Carmen; Prieto, Martin; Berenguer, Marina. Liver Transplantation, 2014 Jan;20(1): 25-34. Improved Renal Function in Liver Transplant Recipients Treated for Hepatitis C Virus With a Sustained Virological Response and Mild Chronic Kidney Disease. This study analysed the possible impact of the eradication of HCV in one of the extrahepatic manifestations of HCV, renal dysfunction, in liver transplant patients, verifying that

these complications improve with the elimination of HCV, but only if the liver damage is not too advanced.

Lara J, López-Labrador F, González-Candelas F, Berenguer M, Khudyakov YE. Computational models of liver fibrosis progression for hepatitis C virus chronic infection. BMC Bioinformatics. 2014;15 Suppl 8:S5.

This paper is a collaborative study with the CIBER de Epidemiología y Salud Pública, and with the Center for Disease Control in the United States.

Peña-Moral JM, Pons JA, Tome S, Gude F, Miras M, Bermejo J, Ramirez P, Berenguer M, Varo E, Forteza J, Parrilla P. Acute cellular rejection versus recurrent hepatitis C after liver transplantation: Clinical and pathological features driving a rational diagnostic approach. Hepatol Res. 2015 Apr;45(4):423-31

This is a collaborative study with the group from Virgen la Arrixaca, Murcia, which validated a diagnostic algorithm for the rejection in patients with recurrent hepatitis C based on specific histological findings.

Fernández-Carrillo C, Coto-Llerena M, González P, Crespo G, Mensa L, Caro-Pérez N, Gambato M, Navasa M, Forns X, Pérez-del-Pulgar S. IFNL4 polymorphism predicts response to hepatitis C treatment after liver transplantation. J Clin Virol. 2014 Oct;61(2):282-5.

Mariño Z, Mensa L, Crespo G, Miquel R, Bruguera M, Pérez-Del-Pulgar S, Bosch J, Forns X, Navasa M. Early periportal sinusoidal fibrosis is an accurate marker of accelerated HCV recurrence after liver transplantation. J Hepatol. 2014 Aug;61(2):270-7.

Crespo G, Lens S, Gambato M, Carrión JA, Mariño Z, Londoño MC, Miquel R, Bosch J, Navasa M, Forns X. Liver stiffness 1 year after transplantation predicts clinical outcomes in patients with recurrent hepatitis C. Am J Transplant. 2014 Feb;14(2):375-83

Project 3

Project title:

MULTICENTRE STUDY FOR THE VALIDATION OF BIOMARKERS OF CHOICE THAT REFLECT THE INDIVIDUAL REPONSE OF SOLID ORGAN TRANSPLANT RECIPIENTS TO IMMUNOSUPPRESSIVE TREATMENT.

Lead Group: **Navasa**

Lead Group: **M. Brunet**

COLLABORATING GROUPS:

CIBEREHD Groups: **Álvarez, Parrilla.**

OBJETIVOS:

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). This study has ended. The result of a multicentre study which analyses the predictive value of IFN-γ, IL-17 and IL-2 in the diagnosis of acute liver and kidney rejection was published in 2014.

Millán O, Rafael-Valdivia L, San Segundo D, Boix F, Castro-Panete MJ, López-Hoyos M, Muro M, Valero-Hervás D, Rimola A, Navasa M, Muñoz P, Miras M, Andrés A, Guirado L, Pascual J, Brunet M. Should IFN-γ, IL-17 and IL-2 be considered predictive biomarkers of acute rejection in liver and kidney transplant? Results of a multicentric study. Clin Immunol. 2014 Oct;154(2):141-54.

Project 4

Project Title:
THERAPEUTIC CONTROL OF DIABETES IN LIVER TRANSPLANT PATIENTS
Lead Group: **M. Berenguer**
Principal Investigator: **M. Berenguer**
COLLABORATING GROUPS:
CIBEREHD Groups: **De la Mata.**
National Groups not related to CIBEREHD: **T. Serrano** (Zaragoza), **JI Herrero** (Pamplona)

Post-liver transplant diabetes mellitus is associated with worse results, a higher rate of infections, rejection and mortality having been reported. To date, therapeutic compliance of diabetes in patients of this type has not been analysed in detail.

OBJECTIVES:

To describe the degree of control and care of diabetes in the liver transplant patients.
A prospective, transverse and multicentre study has been conducted. The prevalence and factors associated with DM in 266 liver transplant recipients seen in external Hepatology consults in 4 centres in 2013 are analysed. The remaining parameters analysed are indicative of the degree of how much treatment for diabetes according to international standards is followed.

RESULTS:

The prevalence of diabetes mellitus was 50% (n=134). No differences were observed in the rate of the following complications among diabetic patients and non-diabetic patients (n=132): high blood pressure (63% vs. 56%), renal failure chronic (14% vs. 18%). In contrast, both hyperlipidemia (47% DM vs. 23% no-DM, p<0. 01) and cardiovascular disease (20% vs. 8%, p=0.03) were detected with a higher frequency in the group of patients with diabetes. 69% were overweight/obese (abdominal obesity of 85%). In relation to follow-up and degree of compliance with diabetes, it was observed that in up to one third of all transplant patients (36%), screening was never conducted to rule out diabetes-related complications. In turn, levels of glycosylated haemoglobin showed unsuitable control in 33% of cases. Half the patients (53%) required insulin for treating diabetes. A small percentage of patients practiced moderate exercise (34%), whereas the majority followed a sedentary life or very gentle exercise (20% and 46%, respectively). Although 63% followed a diabetic diet, 37% confessed to not controlling their diet. Less than half had received education on diabetes (37%).

CONCLUSIONS:

- The prevalence of diabetes and of the typical associated co-morbidities are high in liver transplant recipients;
- Diabetes control is insufficient in this context with little control of the risk factors, inadequate screening of diabetes complications and poor glycaemic control;
- Treatment focuses on antidiabetic drugs, leaving aside other aspects with diet or the exercise;
- The role of the transplant team is important in diabetes follow-up but a multidisciplinary approach is necessary for better diabetes follow-up and control.

Project 5

Project Title:
HEPATOCARCINOMA.
Lead Group: **De la Mata M.**
Principal Investigator: **De la Mata M.**

OBJECTIVES:

This line seeks to improve the prognosis of patients with hepatocarcinoma by means of the identification of biomarkers capable of providing an early diagnosis of the disease, as well as rationalizing the use of sorafenib in patients in advanced stages of the disease, such that patients with progression of the disease despite said treatment can access therapies of second line and improve the expectations of survival.

ACTIVE PROJECTS:

- "Importancia de la activación del sistema inmune para eliminar células tumorales circulantes y prevenir la recidiva del hepatocarcinoma tras el trasplante hepático" (FIS PI14/01469). Funded in FIS call for proposals (PI: Dr. Manuel de la Mata; Co-PI: Manuel Rodríguez Perálvarez).
- Inhibition of the mTOR pathway in transplant patients due to hepatocellular carcinoma and its effect on disease recurrence. Funded in FIS call for proposals and extended (PI: Dr. Manuel de la Mata).

ACTIVE STUDY:

"Estudio fase IV, multicéntrico, aleatorizado, doble-ciego, controlado frente a placebo, a evaluar la eficacia y seguridad de Sorafenib en pacientes con hepatocellular carcinoma avanzado con progresión radiológica" (EC11-185). Funded by the Ministry of Health, Equality and Social Services (PI: Dr. JL Montero).

Project 6

Project Title:
BIOMARKERS IN THE DIFFERENTIAL DIAGNOSIS OF ACUTE CELLULAR REJECTION AND THE RECURRENCE OF HEPATITIS C AFTER LIVER TRANSPLANT
Lead Group: **M. Navasa**
Principal Investigator: **M. Navasa**
Collaborating groups: **X. Forns**
CIBEREHD Group: **De la Mata**

OBJECTIVES:

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

The study is in the collected sample processing phase.

P5. GASTROINTESTINAL AND HEPATIC ONCOLOGY

Coordinator:
Dr. Jordi Bruix
Associate Coordinators:
Drs. José Juan García Marín and **Antoni Castells**

Research Groups:

1- **Experimental Hepatology and Drug Vectorization. Antitumor chemotherapy resistance.** (Dr. JJ García Marín. U. Salamanca)
2- **Molecular Pharmacology and Experimental Therapies.** (Dr. M. Pastor. U. Barcelona)
3.- **Gastrointestinal and Pancreatic Oncology** (Dr. A Castells. IDIBAPS)
4.- **Colorectal and Gastroesophageal Cancer. Peptic Acid Disease** (Dr P. Parrilla. U. Murcia)
5.- **Hepatic Oncology** (Dr. J Bruix. IDIBAPS);
6.- **Experimental Hepatology and Gene Therapy** (Dr. B Sangro, CUN)
7.- **Gastrointestinal Oncology** – Hepatobiliary physiopathology (L. Bujanda, Hospital de Donostia)
8.- **Linked Clinical Group** (FJ Padillo, Hospital U. Virgen del Rocío)

The activity of the different lines of activity in this programme in 2014 has resulted in relevant contributions that have increased knowledge about the risk factors and oncogenic mechanisms of both liver and gastrointestinal cancer. The studies have led to diagnostic and therapeutic innovations that have translated into modifications of the clinical management of patients suffering these diseases.

Knowledge about molecular anomalies of hepatocellular carcinoma and cholangiocarcinoma have been expanded in liver cancer, such that in the future, there can be a biological rational base for new treatments. Obviously, better classification of patients must allow a more rational therapeutic assay design.

The most relevant contribution in this field has been describing a genetic anomaly which can determine the hepatocyte or biliary phenotypic pattern of liver cancer.

Mutant IDH inhibits HNF-4α to block hepatocyte differentiation and promote biliary cancer. Saha SK, Parachoniak CA, Ghanta KS, Fitamant J, Ross KN, Najem MS, Gurumurthy S, Akbay EA, Sia D, Cornella H, Miltiadous O, Walesky C, Deshpande V, Zhu AX, Hezel AF, Yen KE, Straley KS, Travins J, Popovici-Muller J, Gliser C, Ferrone CR, Apte U, Llovet JM, Wong KK, Ramaswamy S, Bardeesy N. Nature. 2014 Sep 4;513(7516):110-4.

Simultaneously, further information has been discovered about the role of the mitochondrial genome in the feedback processes regulating the expression of nuclear genes related to the lack of response of liver cancer to pharmacological therapy.

The expression of genes involved in hepatocellular carcinoma chemoresistance is affected by mitochondrial genome depletion. Gonzalez-Sanchez E, Marin JJ, Perez MJ. Molecular Pharmaceutics. 2014; 11(6):1856-68.

Nucleoside transporters and human organic cation transporter 1 determine the cellular handling of DNA-methyltransferase inhibitors. Arimany-Nardi C, Errasti-Murugarren E, Minuesa G, Martinez-Picado J, Gorboulev V, Koepsell H, Pastor-Anglada M. British Journal of Pharmacology (2014) 171(16):3868-80.

As regards the study of new mechanisms regulating biliary function, has been characterised the role of type P1 purinergic receptors in the termination of the ATP-dependent signal regulating bile flow in cholangiocytes and the possible implication in biliary cancer.

Functional crosstalk between the adenosine transporter CNT3 and purinergic receptors in the biliary epithelia. Godoy V, Banales JM, Medina JF, Pastor-Anglada M. Journal of Hepatology (2014) 61(6):1337-43.

As regards the oncogenic processes which are associated with chronic hepatopathy accompanied by cholestasis, the role of biliary acids and their interaction with macrophages in the development of inflammatory processes and the cholangiocarcinoma promoting capacity has been characterised. The role of the chemoresistance protein BCRP as a biliary acid export pump, having an important role in the barrier against these compounds, has been identified.

Important steps have been taken for the development of cancer immunotherapy, conducting the first clinical trial with immunological checkpoint inhibitors in this tumour, demonstrating in animal models the advantages of the combination of these molecules vs. monotherapy, and improving immune response stimulation systems by means of adoptive cell therapy.

Short-term intratumoral interleukin-12 expressed from an alphaviral vector is sufficient to induce an efficient antitumoral response against spontaneous hepatocellular carcinomas. Rodriguez-Madoz JR, Zabala M, Alfaro M, Prieto J, Kramer MG, Smerdou C. Hum Gene Ther. 2014 Feb;25(2):132-43.

Sobrevals L, Mato-Berciano A, Urtasun N, Mazo A, Fillat C. uPAR-controlled oncolytic adenoviruses eliminate cancer stem cells in human pancreatic tumors. Stem Cell Research (2014) 12(1):1-10.

Finally, on a clinical level, research for CIBEREHD has developed and validated non-invasive criteria of hepatocellular carcinoma in the risk population. These criteria have been included in worldwide clinical practice guidelines and have recently been incorporated by the Radiological Society of North America. Trials after curative treatment or coadjuvant to locoregional treatments have been conducted. Unfortunately, the trials have not achieved any positive results. Studies not sponsored by the industry led from CIBEREHD have established clave concepts, such as the association of side effects and better therapeutic efficacy, which makes it necessary to modify the design of clinical trials according to this parameter.

Early dermatologic adverse events predict better outcome in HCC patients treated with sorafenib. Reig M, Torres F, Rodriguez-Lope C, Forner A, LLarch N, Rimola J, Darnell A, Ríos J, Ayuso C, Bruix J. J Hepatol. 2014 Aug;61(2):318-24.

In the field of locoregional therapies, the antineoplastic activity profile of radioembolization has been confirmed with Yttrium 90 microspheres, the dose calculation system has been improved for increasing technique safety and the biological response to treatment, which will allow further studying synergies and prevention of complications, has been studied for the first time.

Radioembolization of hepatocellular carcinoma activates liver regeneration, induces inflammation and endothelial stress and activates coagulation. Fernandez-Ros N, Iñarrairaegui M, Paramo JA, Berasain C, Ávila MA, Chopitea A, Varo N, Sarobe P, Bilbao JI, Dominguez I, D'Avola D, Herrero JI, Quiroga J, Sangro B24836705.. Liver Int. 2014 May 16. doi: 10.1111/liv.12592. [Epub ahead of print] PubMed PMID:

Top-level research aimed at establishing the efficacy of early detection campaigns, supported by the AECC and the Ministry of Health, has been conducted in colorectal cancer. In this context, national studies COLONPREV and EPICOLON, which both seek to establish new strategies for the prevention of colorectal cancer in a population of intermediate and high risk, respectively, should be highlighted. The project COLONPREV is drawn up on the basis of a prospective, controlled and randomised study comparing the immunological detection of fecal occult blood, which is the approach currently recommended in Spain by the Interterritorial Board of Health, and colonoscopy. Round-one results show that both approaches allow

detecting the same number of cancers, with a lower rate of complications and a higher cost-efficiency ratio. The COLONPREV study has given rise to multiple publications that have allowed improving the cost-efficiency ratio of early detection plans and stratifying the population based on the results of examinations and the genetic profile in individuals with hereditary familial cancer.

The impact of this activity is described in publications such as:

Risk stratification for advanced colorectal neoplasia according to fecal hemoglobin concentration in a colorectal cancer screening program. Auge JM1, Pellise M2, Escudero JM3, Hernandez C4, Andreu M5, Grau J6, Buron A4, López-Cerón M2, Bessa X5, Serradesanferm A6, Piracés M4, Macià F4, Guayta R7, Filella X3, Molina R3, Jimenez W3, Castells A2; PROCOLON Group. Gastroenterology. 2014 Sep;147(3):628-636.

Association between CASP8 -652 6N del polymorphism (rs3834129) and colorectal cancer risk: results from a multi-centric study. Pardini B, Verderio P, Pizzamiglio S, Nici C, Maiorana MV, Naccarati A, Vodickova L, Vymetalkova V, Veneroni S, Daidone MG, Ravagnani F, Bianchi T, Bujanda L, Carracedo A, Castells A, Ruiz-Ponte C, Morreau H, Howarth K, Jones A, Castellví-Bel S, Li L, Tomlinson I, Van Wezel T, Vodicka P, Radice P, Peterlongo P; EPICOLON Consortium Collaborators.PLoS One. 2014 Jan 21;9(1):e85538.

Rate of detection of advanced neoplasms in proximal colon by simulated sigmoidoscopy vs fecal immunochemical tests. Castells A, Quintero E, Álvarez C, Bujanda L, Cubiella J, Salas D, Lanas A, Carballo F, Morillas JD, Hernández C, Jover R, Hijona E, Portillo I, Enríquez-Navascués JM, Hernández V, Martínez-Turnes A, Menéndez-Villalva C, González-Mao C, Sala T, Ponce M, Andrés M, Teruel G, Peris A, Sopeña F, González-Rubio F, Seoane-Urgorri A, Grau J, Serradesanferm A, Pozo À, Pellisé M, Balaguer F, Ono A, Cruzado J, Pérez-Riquelme F, Alonso-Abreu I, Carrillo-Palau M, de la Vega-Prieto M, Iglesias R, Amador J, Blanco JM, Sastre R, Ferrándiz J, González-Hernández MJ, Andreu M, Bessa X; COLONPREV Study Investigators. Clin Gastroenterol Hepatol. 2014 Oct;12(10):1708-16.

A genome-wide association study on copy-number variation identifies a 11q11 loss as a candidate susceptibility variant for colorectal cancer. Fernandez-Rozadilla C1, Cazier JB, Tomlinson I, Brea-Fernández A, Lamas MJ, Baiget M, López-Fernández LA, Clofent J, Bujanda L, Gonzalez D, de Castro L; EPICOLON Consortium, Hemminki K, Bessa X, Andreu M, Jover R, Xicola R, Llor X, Moreno V, Castells A, Castellví-Bel S, Carracedo A, Ruiz-Ponte C. Hum Genet. 2014 May;133(5):525-34.

High incidence of large deletions in the PMS2 gene in Spanish Lynch syndrome families. Brea-Fernández AJ1, Cameselle-Teijeiro JM, Alenda C, Fernández-Rozadilla C, Cubiella J, Clofent J, Reñé JM, Anido U, Milá M, Balaguer F, Castells A, Castellvi-Bel S, Jover R, Carracedo A, Ruiz-Ponte C.. Clin Genet. 2014 Jun;85(6):583-8.

Multiple sporadic colorectal cancers display a unique methylation phenotype. Abulí A, Bujanda L, Muñoz J, Buch S, Schafmayer C, Valeria Maiorana M, Veneroni S, van Wezel T, Liu T, Westers H, Esteban-Jurado C, Ocaña T, Piqué JM, Andreu M, Jover R, Carracedo A, Xicola RM, Llor X, Castells A; EPICOLON Consortium, Dunlop M, Hofstra R, Lindblom A, Wijnen J, Peterlongo P, Hampe J, Ruiz-Ponte C, Castellví-Bel S. PLoS One. 2014 Apr 17;9(4):e95022. doi: 10.1371/journal.pone.0095022. eCollection 2014.

P6. GASTROINTESTINAL INFLAMMATION AND MOTILITY

Coordinator:
Dr. J. Panés
Associate Coordinators:
Drs. F. Azpiroz and **A. Lanas.**

The global objective of the Gastrointestinal Inflammation and Motility Programme is to carry out research projects including basic, translational and clinical research aspects, promoting the intra- and inter-group integration of basic and clinical sciences.

In the subprogramme of acid-related diseases, research activities for both environmental and genetic factors linked to increased susceptibility to bleeding in the GI tract in patients taking NSAIDS or antiplatelet agents, as well as research in the treatment and management of H. pylori infection in humans, where substantial contributions have been made possible thanks to the extensive networks of hospitals led by investigators of this area of the CIBEREHD, have been maintained. In addition to these two initiatives, there have been a series of actions aimed at limiting the impact of gastroesophageal reflux disease, to that end actions have commenced to facilitate recognition and apply current therapeutic measures, and on the other hand to limit progression by knowing more about the mechanisms involved and by implementing the diagnostic and therapeutic measures suited to each situation of progression.

The area of Neurogastroenterology and Motility has further developed collaborative studies between the different groups in CIBERehd and with other international teams. On one hand, projects have been developed to characterise the physiopathology of oropharyngeal dysphagia associated with ageing and with neurodegenerative diseases. Three groups of studies have been developed in this area intended to: a) study the expression of TRP family receptors in the human oropharynx and larynx; b) characterise the in vitro pharmacodynamics of different agonists of these receptors, c) evaluation of the in vivo therapeutic effect of different agonists in patients with dysphagia. In this line of work the characterisation of receptors TRPV1, TRPA1 and TRPM8 in samples of human oropharynx and the development of a bioassay with PAC cells expressing these receptors has allowed selecting specific agonists and the development of two clinical studies in patients which have demonstrated that it is possible to improve the oropharyngeal motor response by means of the addition of capsaicin or piperine to the alimentary bolus, opening up the possibility of a completely novel pharmacological treatment of neurogenic and age-related dysphagia. This advancement has also allowed us to conduct studies in which the afferent pathway to the swallowing centre of the brain stem has been stimulated by means of transcutaneous or intrapharyngeal electric stimuli, and we started the study of the mechanisms of cerebral cortex activation by means of multichannel electroencephalography. These studies are performed in the framework of a two-year clinical trial the objective of which is to select the most effective treatment for oropharyngeal dysphagia, having about 50% of patients who have suffered a stroke and thereby preventing serious complications such as malnutrition and aspiration pneumonia.

Research for the development of cell therapies for inflammatory bowel diseases has established the option of an autologous transplant of hematopoietic stem cells as a clinically accepted alternative for the treatment of Crohn's disease not responding to treatment, which has been recognised in the latest guidelines of the European Bone Marrow Transplant Group. Particularly noteworthy has been the completion of the process of developing another form of cell therapy based on the administration of conditioned autologous tolerogenic dendritic cells obtained from peripheral blood monocytes and the process for the production thereof has been granted a European patent in which CIBEREHD has a considerable participation. Furthermore, has been completed in 2014 the phase 1 study in patients with immunosuppressant- and anti-TNF drug-refractory Crohn's disease, these results being presented in congresses held throughout 2015.

Most 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. Particularly

noteworthy has been the completion in 2014 of the analysis, and the study of the phenotypic determinants of the disease has been published in the first quarter of 2015. This is pioneer work that has been possible as a result of the detailed and prospective collection of clinical data from patients with inflammatory bowel disease in the context of the ENEIDA project, funded in part by CIBEREHD, which refers to the biobank associated with this project, functional characterisation of genetic susceptibility variants.

Another one of the projects that has had considerable international repercussion and has ended in 2014 was the establishment of quality standards in inflammatory bowel disease units. This work allows the self-evaluation and planning of structural improvements and processes of the units to improve and homogenise the attendance, teaching and research results.

Studies on intestinal microbiota within the European MetaHIT project have developed novel strategies for detecting unknown commensal species using high-performance sequencing and the concept of metagenomic species (groups of genes that vary among individuals). This strategy has shown several commensal species that are ignored in patients with ulcerative colitis and Crohn's disease.

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 anti-TNF treatment, which allows identifying new therapeutic targets in this hard-to-manage patient subgroup, and optimization of current treatments such as thiopurines and anti-TNF antibodies, to get 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 an appropriate initiative because a biological therapy of a class other than anti-TNF drugs has been approved in 2014 by the EMA: antibody anti a4b7 vedolizumab. In this context, it takes on the meaning of precise prediction of the response in each of the therapeutic options, which will result in the improvement in patient care and a cost reduction.

The members of Programme 6 have shown a high level of participation and international vision concerning the drafting of practice guidelines and consensus documents drafted by national and international medical societies. Several CIBEREHD components have worked as associated editors of first decile journals in the area of hepatic and digestive diseases.

3. TRANSVERSAL PROGRAMMES

TRAINING PROGRAMME

One of the objectives of the CIBEREHD is to promote the training of our researchers, (attached and hired personnel: post-docs, pre-docs, nurses and technicians) to increase the level of research and facilitate interaction between the different groups. These tasks are coordinated through the Training Plan as part of the Annual Action Plan.

The Training Plan of the CIBER for Hepatic and Digestive Diseases is carried out through the following actions:

- Training internships in CIBEREHD centres
- Short training internships in Spain or abroad (maximum of 6 weeks up to 3 months)
- Intramural visiting professor programmes
- Holding training Activities or Courses considered to be of interest for CIBEREHD
- Promoting scientific activities organised by CIBEREHD members (sponsoring and funding seminars, symposiums, post-grad courses), collaboration with training activities of societies scientific and virtual training activities through the web page.

En 2014, a total of 30 aid packages were granted to our researchers for different activities according to the Training Plan programme. Despite budget cutbacks, we were able to handle almost all applications. The beneficiaries of the aid package were 13 attached members and 17 hired members. The funded activities were the researcher internship in another CIBEREHD centre, 4 short internships abroad (USA, UK and Japan), 20 training courses and activities in Spain and 5 international courses.

Among these activities, we would like to highlight the internship of José Antonio del Campo (Dr. Romero's CIBEREHD) who did an internship in the Hospital de la Vall d'Hebró (Dr. JI Esteban's CIBEREHD group), and the internships of Dr. Laia Rofes (Dr. Clavé's group) in the Institute of Inflammation and Repair, Faculty of Medical and Life Sciences, The University of Manchester (UK), and the following internships already approved for 2015:

- Medical Research Council. Laboratory of Molecular Biology (MRC-LMB), en Cambridge (UK)
- Kobe University Hospital (Japón) con el Prof. Toyonaga
- Centro Mayo Clinic, Rochester (USA)

Through the training plan, CIBEREHD also sponsored the Post-graduate Course of the Asociación Española para el Estudio del Hígado (AEEH), which took place when the 40th Annual Congress of the AEEH and of the Asociación Española de Gastroenterología (AEG) was held.

Communication Results

As regards the Communication results for this period, the following was obtained:

PRESS RELEASES:

- "Demuestran que SAMe empeora la neurogénesis y contribuye al deterioro cognitivo". 2/05/14
- "La hepatitis C puede ayudar a algunos pacientes trasplantados a adaptarse a su nuevo hígado" 25/06/14
- "Una combinación de antivirales obtiene una tasa de curación casi total en trasplantados hepáticos con hepatitis C". 9/11/2014.
- "Gisbert y Maté coordinadores de la Cátedra de Docencia e Investigación en Enfermedad Inflamatoria Intestinal impulsada de la UCM". 24/11/2014.

HITS IN THE MEDIA

Total number of hits: 490 (93% internet and 7% print media)
Audience: 83% internet and 17% print media
Hits in most important media outlets:

Date	Headline/subject addressed	Mentioned member	Nº of hits
20/02/2014	Una nueva «penicilina» podrá curar el 90 % de los casos de hepatitis C	Jaume Bosch (CIBEREHD)	101
11/11/2014	Una combinación de antivirales cura la hepatitis C en trasplantados de hígado	Forns (CIBEREHD)	80
26/06/2014	La hepatitis C 'ayuda' contra el rechazo en el trasplante	Alberto Sánchez Fueyo (CIBEREHD)	27
02/05/2014	Demuestran que la coenzima SAMe contribuye al deterioro cognitivo	José María Mato (CIBEREHD)	21
27/06/2014	La Fe acoge 254 proyectos de investigación de dolencias	Jaume Bosch (CIBEREHD)	18

TWITTER STATISTICS

https://twitter.com/ciberehd

	January 2014	December 2014
Updates	46	191
Followers	77	195
Klout (influence level, values between 1 and 100)	34	36

2013 ANNUAL REPORTS (Spanish/English version) (pdf and interactive)

http://www.ciberisciii.es/comunicacion/memorias-anuales;

CIBER NEWSLETTERS EVERY TWO MONTHS

It includes the top 4 news items of the CIBEREHD during that period
http://www.ciberisciii.es/comunicacion/boletines

PARTICIPATION IN SEMANA DE LA CIENCIA.

Activity: TapaConCiencia.
In the TapaConCiencia activity organised during the Semana de la Ciencia, 8 research projects were presented corresponding to the subject areas of the CIBER that served as an inspiration to chef Jorge Cuellar to design 8 elaborate "tapas".
Rafael Bañares (CIBEREHD and Fundación para la Investigación Biomédica of Hospital Gregorio Marañón) presented: ¿Es posible llegar a disponer de un hígado artificial?
The act was covered by over 20 mainstream and specialised media outlets and was presented to 250 people.

NEWS UPDATE ON THE CIBEREHD WEB PAGE

http://www.ciberehd.org

7TH SCIENTIFIC CONFERENCE OF CIBEREHD

Finally, as regards the dissemination activities, it should be highlighted that for yet another year, the 7th Scientific Conference of the CIBER of Hepatic and Digestive Diseases was held in Barcelona. The meetings were held on 27-28 October at Hotel Barceló Sants and were useful to highlight and encourage collaboration between the groups of each Programme. For this reason, the meeting focused particularly on the presentation of the results of the ongoing cooperative projects and on the discussion of the new project proposals.
Documentation and images:
https://www.ciberehd.org/jornadas/vii-jornadas-cientificas-barcelona-2013/

4. PLATFORMS

Platforms

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 OBJECTIVES

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.

BIOINFORMATIC PLATFORM

The primary objective of the Bioinformatic 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 customised solution.

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

Services offered by the platform:

- Development of new bioinformatic 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.

Bioinformatic 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.

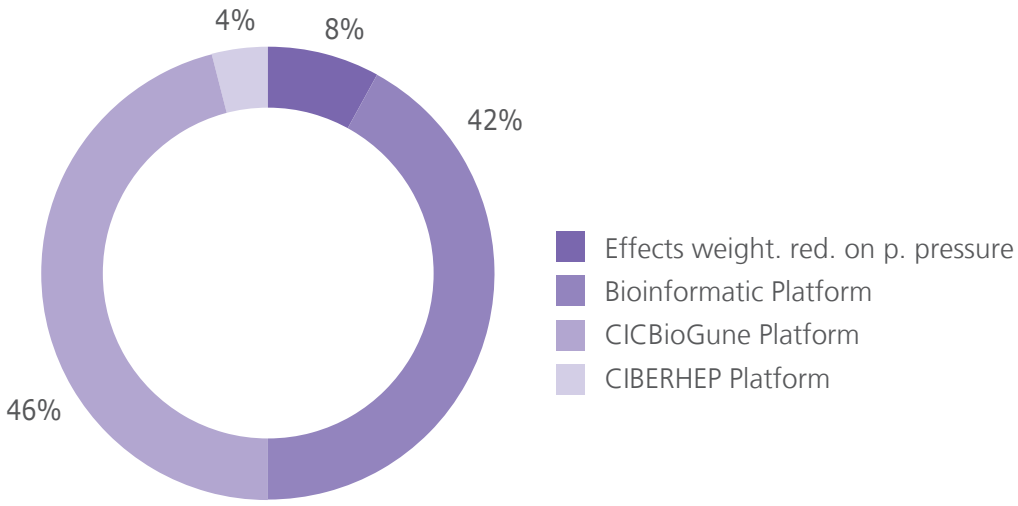
The purpose of this database is to collect the follow-up on patients undergoing treatment with first-line therapy options, i. e. , Entecavir or Tenofovir (in monotherapy or combination with other antiviral agents), for at least the time that they received treatment with these drugs.

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 €
Bioinformatic Platform	57.150 €
CICBIOGUNE Platform	61.983 €
CIBERHEP Platform	4.902 €
TOTAL	135.209 €



5. RESEARCH GROUPS

G0024
Programme: P1. Portal Hypertension and Cirrhosis

Lead Researcher: Albillos Martínez, Agustín

Group members

STAFF MEMBERS: Muñoz Zamarrón, Leticia | Úbeda Cantera, María P.

ASSOCIATED MEMBERS: Álvarez de Mon Soto, Melchor | Calleja Panero, José Luis | Llop Herrera, Elba | Montserrat Sanz, Jorge | Prieto Martín, Alfredo | Reyes Martín, Eduardo.

Main lines of research

The focus group research lines are the following ones:

- 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

- Albillos A., Lario M., Alvarez-Mon M.. Cirrhosis-associated immune dysfunction: Distinctive features and clinical relevance. Journal of Hepatology. 2014;:-.
- Albillos A., Tejedor M.. Secondary prophylaxis for esophageal variceal bleeding. Clinics in Liver Disease. 2014;18(2):359-370.
- Jalan R., Fernandez J., Wiest R., Schnabl B., Moreau R., Angeli P. et al. Bacterial infections in cirrhosis: A position statement based on the EASL Special Conference 2013. Journal of Hepatology. 2014;60(6):1310-1324.
- Romero-Gomez M., Berenguer M., Molina E., Calleja J.-L.. Reply to: Renal impairment and anemia during triple therapy. Journal of Hepatology. 2014;60(5):1100-1101.

Highlights

The most important milestones achieved in 2014 were:

- To systematize the concept and consequences of systemic inflammation in cirrhosis
- Development of the area of clinical research at the service Gastroenterology Ramón y Cajal
- Approval of projects: Institute Health Carlos III and European project partners in preclinical research (Horizon 2020 - Research and Innovation Framework Programme)
- consensus document of bacterial infection in cirrhosis , sponsored by EASL

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G0072

Programme: P4. Immunology and liver transplantation

Lead Researcher: Álvarez López, Mª Rocío

Group members

ASSOCIATED MEMBERS: Campillo Marquina, José A | Fernández Hernández, Juan Ángel | García Alonso, Ana Mª | Minguela Puras, Alfredo | Miras López, Manuel | Moya Quiles, Mª Rosa | Muro Amador, Manuel.

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

- Millan O., Rafael-Valdivia L., San Segundo D., Boix F., Castro-Panete M.J., Lopez-Hoyos M. et al. Should IFN-γ, IL-17 and IL-2 be considered predictive biomarkers of acute rejection in liver and kidney transplant? Results of a multicentric study. Clinical Immunology. 2014;154(2):141-154.
- Tapia-Abellan A., Ruiz-Alcaraz A.J., Anton G., Miras-Lopez M., Frances R., Such J. et al. Regulatory role of PI3K-protein kinase B on the release of interleukin-1β in peritoneal macrophages from the ascites of cirrhotic patients. Clinical and Experimental Immunology. 2014;178(3):525-536.
- Muro M., Lopez-Hernandez R., Mrowiec A.. Immunogenetic biomarkers in inflammatory bowel diseases: Role of the IBD3 region. World Journal of Gastroenterology. 2014;20(41):15037-15048.
- Lopez-Hernandez R., Valdes M., Campillo J.A., Martinez-Garcia P., Salama H., Salgado G. et al. Genetic polymorphisms of tumour necrosis factor alpha (TNF-α) promoter gene and response to TNF-α inhibitors in Spanish patients with inflammatory bowel disease. International Journal of Immunogenetics. 2014;41(1):63-68.
- Boix F., Llorente S., Mrowiec A., Eguia J., Lopez-Hernandez R., Bernardo M.V. et al. Donor specific antibodies median fluorescence intensity levels are the best indicator for monitoring desensitization treatment in kidney transplant. Urology Journal. 2014;11(3):1695-1698.

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G2008

Programme: P3. Cholestasis and Metabolic Disorders

Lead Researcher: Andrade, Raúl

Group members

STAFF MEMBERS: Moreno Herrera, Inmaculada | Stephens, Camilla.

ASSOCIATED MEMBERS: Cabello Porras, María Rosario | Crespo Gil, Esperanza | García Cortes, Mirem | Hidalgo Sánchez, Ramón | Lucena González, María Isabel | Robles Díaz, María Mercedes | Ulzurrun de Asanza Vega, Eugenia.

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

- Robles-Diaz M., Isabel Lucena M., Kaplowitz N., Stephens C., Medina-Caliz I., Gonzalez-Jimenez A. et al. Use of hy's law and a new composite algorithm to predict acute liver failure in patients with drug-induced liver injury. Gastroenterology. 2014;147(1).
- Devarbhavi H., Andrade R.J.. Drug-induced liver injury due to antimicrobials, central nervous system agents, and nonsteroidal anti-inflammatory drugs. Seminars in Liver Disease. 2014;34(2):145-161.
- Ulzurrun E., Stephens C., Ruiz-Cabello F., Robles-Diaz M., Saenz-Lopez P., Hallal H. et al. Selected ABCB1, ABCB4 and ABCC2 polymorphisms do not enhance the risk of drug-induced hepatotoxicity in a Spanish cohort. PLoS ONE. 2014;9(4).
- Stephens C., Andrade R.J., Lucena M.I.. Mechanisms of drug-induced liver injury. Current Opinion in Allergy and Clinical Immunology. 2014;14(4):286-292.
- Avigan M.I., Bjornsson E.S., Pasanen M., Cooper C., Andrade R.J., Watkins P.B. et al. Liver Safety Assessment: Required Data Elements and Best Practices for Data Collection and Standardization in Clinical Trials. Drug Safety. 2014;37(1):19-31.

Highlights

In 2014, we obtained a Grant of the European Association for the Study of the Liver (EASL) for the creation of a European network of hepatic toxicity (with the support of 11 countries), which we are currently implementing (Pro-Euro DILI Registry). In this new project, in addition to clinical and epidemiological data and samples for genetic studies, samples from the acute episode of DILI will be collected for the study of biomarkers of susceptibility, diagnosis and prognosis performance of high powered genetic studies.Moreover, we got a grant for the creation a an Andalusian Hepatotoxicity network (AC-0073-2013), coordinated by the Dr. Andrade. This network is connecting various management units with a high quality technical and scientific level that promote the traslational research. The Dr. Romero-Gómez del H. de Valme de Sevilla (grupo CIBERehd, programa 2), H. Costa del Sol, H. Regional de Málaga, H.Torrecárdenas and H. Virgen de las Nieves are also participating.

Currently, there are more than 1000 well-vetted DILI cases included in our Registry, and we have over 350 DNA patient samples of serum and plasma, and 200 control samples matched with age, sex and drug exposition.

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GO021

Programme: P6. Gastrointestinal Inflammation and Motility

Lead Researcher: Azpiroz Vidaur, Fernando

Group members

STAFF MEMBERS: Méndez Soriano, Sara | Santaliestra Vivaracho, Gloria.

ASSOCIATED MEMBERS: Accarino Garaventa, Anna María | Alonso Cotoner, Carmen | Malagelada Benapres, Juan Ramón | Malagelada Prats, Carolina | Santos Vicente, Javier | Vicario Pérez, María.

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

- Barba E, Burri E, Accarino A, Cisternas D, Quiroga S, Monclus E et al. Abdominothoracic Mechanisms of Functional Abdominal Distension and Correction by Biofeedback.Gastroenterology. 2014.
- Burri E., Barba E., Huaman J.W., Cisternas D., Accarino A., Soldevilla A. et al. Mechanisms of postprandial abdominal bloating and distension in functional dyspepsia. Gut. 2014;63(3):395-400.
- Manichanh C., Eck A., Varela E., Roca J., Clemente J.C., Gonzalez A. et al. Anal gas evacuation and colonic microbiota in patients with flatulence: Effect of diet. Gut. 2014;63(3):401-408.
- Vicario M, González-Castro AM, Martínez C, Lobo B, Pigrau M, Guilarte M et al. Increased humoral immunity in the jejunum of diarrhoea-predominant irritable bowel syndrome associated with clinical manifestations.Gut. 2014.
- Azpiroz F., Hernandez C., Guyonnet D., Accarino A., Santos J., Malagelada J.-R. et al. Effect of a low-flatulogenic diet in patients with flatulence and functional digestive symptoms. Neurogastroenterology and Motility. 2014;26(6):779-785.

Highlights

COLLABORATIONS

- Department of Mathematics UB: development of program for evaluation of intestinal motility using the endoscopy capsule in the process of commercialization (Given Imaging).
- Group Dr Clavé (Marcel Jimenez) joint publication on intestinal motility (Gallego, 2014).
- Program for Systematic investigation of the responses to meal and diet on: a) intestinal microbiota (collaboration with the group CIBEREHD Dr. Guarner) (Manichanh 2014), b) intestinal content collaboration (collaboration with the Grupo de Robótica, Universidad Politécnica de Catalunya), c) cognitive/emotive perception (collaboration with industry and support CENIT program) and d) metabolomic pattern (collaboration with CIBERDEM and Center for Omics Sciences (COS) Universitat Rovira i Virgili, Reus, Barcelona.
- Publications on biofeedback techniques for the treatment of abdominal distension and rumination has attracted much interest of the media.

SCIENTIFIC ACTIVITIES

The Spanish Society of Pre and Probiotics (IP board member) has published a guide on prebiotics. The Join meeting UEG/microbiota and health section (IP Chair) and AGA has been decided to take place in Barcelona every other year. UEGW 2015 (IP UEG councillor) has been decided to take place in Barcelona. The revision of Functional Gut Criteria RomeIV (IP Board of directors) has been implemented. IP has been awarded with the Professional Excellence Award "Biomedical Research", Medical College of Barcelona (COMB).

TRAINING

It has established a European network for investigation training on Neurogastroenterology funding by the Marie Curie program.

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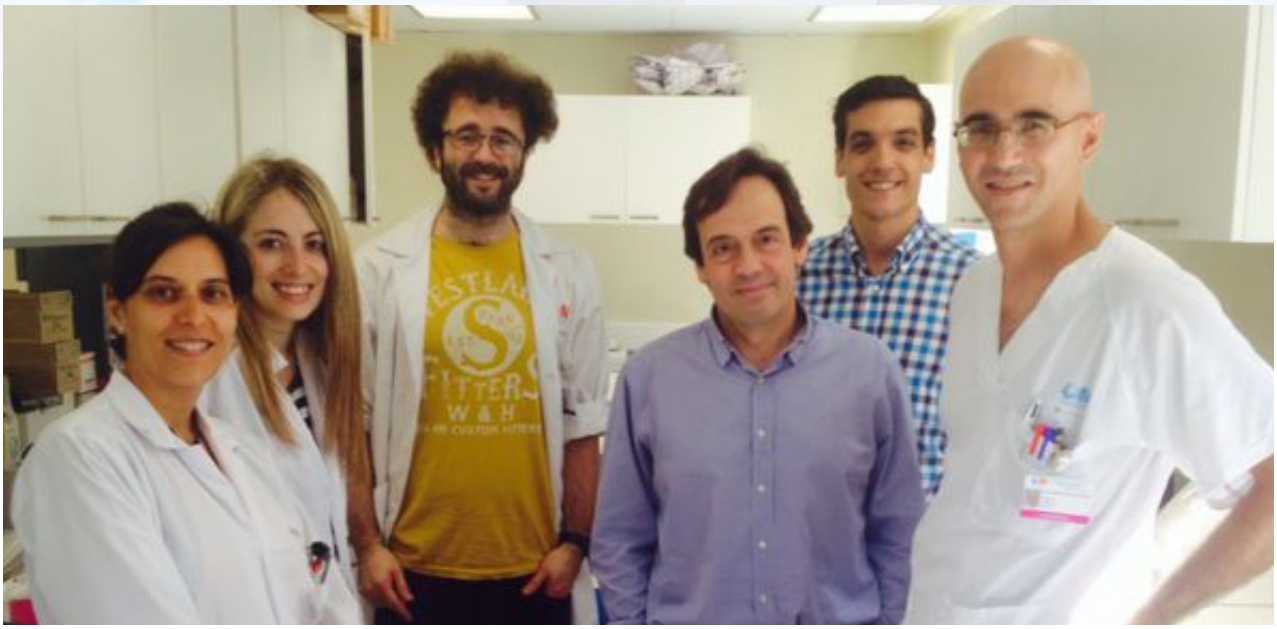
G0082
Programme: P1. Portal Hypertension and Cirrhosis



Lead Researcher: Bañares Cañizares, Rafael

Group members

STAFF MEMBERS: Puerto Cantero, Marta.

ASSOCIATED MEMBERS: Catalina Rodríguez, María de la Vega | Clemente Ricote, Gerardo | Matilla Peña, Ana María | Menchén Viso, Luis Alberto | Rincón Rodríguez, Diego | Ripoll Noiseux, Cristina Alberta | Salcedo Plaza, Magdalena | Vaquero Martín, Javier.

Main lines of research

The research lines developed in 2014 by our group are:

- 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

- Perez-Latorre L., Sanchez-Conde M., Rincon D., Miralles P., Aldamiz-Echevarria T., Carrero A. et al. Prediction of liver complications in patients with hepatitis C virus-related cirrhosis with and without HIV coinfection: Comparison of hepatic venous pressure gradient and transient elastography. Clinical Infectious Diseases. 2014;58(5):713-718.
- Yotti R., Bermejo J., Benito Y., Sanz-Ruiz R., Ripoll C., Martinez-Legazpi P. et al. Validation of noninvasive indices of global systolic function in patients with normal and abnormal loading conditions a simultaneous echocardiography pressure-volume catheterization study. Circulation: Cardiovascular Imaging. 2014;7(1):164-172.
- Altamirano J., Miquel R., Katoonizadeh A., Abraldes J.G., Duarte-Rojo A., Louvet A. et al. A histologic scoring system for prognosis of patients with alcoholic hepatitis. Gastroenterology. 2014;146(5).
- Banares R., Catalina M.-V., Vaquero J.. Molecular Adsorbent Recirculating System and Bioartificial Devices for Liver Failure. Clinics in Liver Disease. 2014.
- Rincon D., Vaquero J., Hernando A., Galindo E., Ripoll C., Puerto M. et al. Oral probiotic VSL#3 attenuates the circulatory disturbances of patients with cirrhosis and ascites. Liver International. 2014;34(10):1504-1512.

Highlights

In 2014, the group has actively maintained ongoing clinical and experimental studies, with the production of relevant results in the field of the present research program.

It is particularly remarkable the group's contribution to the incorporation of non-invasive monitoring techniques in the evaluation of the natural history of cirrhosis in patients coinfected with HIV and hepatitis viruses. Furthermore, the group has also validated non-invasive echographic techniques for evaluating the cardiac systolic function in patients with cirrhosis more precisely than using the conventional tools.

Likewise, the group has participated in the generation of the first score for grading the histological severity of acute alcoholic hepatitis.

Finally, it should be noted that the group has generated results from experimental studies (currently in publication phase) that links the research lines of inflammatory bowel disease and cirrhosis, by focusing in the mechanisms responsible for the alteration of permeability of the intestinal epithelial barrier.

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G0065

Programme: P4. Immunology and liver transplantation

Lead Researcher: Berenguer Haym, Marina

Group members

STAFF MEMBERS: Carvalho Gomes, Ángela Sofía

ASSOCIATED MEMBERS: Aguilera Tello, Victoria | Benlloch Pérez, Salvador | Carmona Iglesias, Elena | Ortiz Canto, Cecilia | Palau Canos, Antonio | Pérez Rojas, Judith | Prieto Castillo, Martín | Rubín Suárez, Ángel.

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

- Bohne F., Londono M.-C., Benitez C., Miquel R., Martinez-Llordella M., Russo C. et al. HCV-induced immune responses influence the development of operational tolerance after liver transplantation in humans. Science Translational Medicine. 2014;6(242).
- Robles-Diaz M., Isabel Lucena M., Kaplowitz N., Stephens C., Medina-Caliz I., Gonzalez-Jimenez A. et al. Use of hy's law and a new composite algorithm to predict acute liver failure in patients with drug-induced liver injury. Gastroenterology. 2014;147(1).
- Forns X, Charlton M, Denning J, McHutchison JG, Symonds WT, Brainard D et al. Sofosbuvir compassionate use program for patients with severe recurrent hepatitis C following liver transplantation.Hepatology (Baltimore, Md.). 2014.
- Sarkar M, Watt KD, Terrault N, Berenguer M. Outcomes in liver transplantation: Does sex matter?. Journal of hepatology. 2014.
- Castells L., Rimola A., Manzardo C., Valdivieso A., Montero J.L., Barcena R. et al. Pegylated interferon plus ribavirin in HIV-infected patients with recurrent hepatitis C after liver transplantation: A prospective cohort study. Journal of Hepatology. 2014;62(1):92-100.

Highlights

PROJECTS

Implementation, coordination and promotion of a support unit for clinical research activity in Hepatology – PI Martin Prieto • Role of the cytomegalovirus-specific Cellular Immune Response in the severity of hepatitis C virus After Liver Transplantation – PI Victoria Aguilera • Diabetes control in liver transplant patients – PI Marina Berenguer • Platform for data collection from Chronic Hepatitis B patients (CIBERHEP) – PI Maria ButiFerrer • Platform for data collection from Chronic Hepatitis C patients (Hepatic) • Inflammation, fat, iron and fibrosis quantification by MRI biomarkers in liver transplant patients with recurrent HCV infection – PI Luis MartiBonmati (Co-investigator: A. Rubín).

CLINICAL TRIALS

Use of Tenofovir as prophylaxis of hematologic anti - HBc positive and negative HBsAg patients receiving therapy with Rituximab. • Safety and anti-cytomegalovirus activity of Maribavir versus Valganciclovir for treatment of CMV infection in transplant recipients without organic CMV disease. • Impact on renal function of an immunosuppressive regimen based on the minimization of tacrolimus in combination with everolimus in liver transplant patients.

SAFETY AND EFFICACY

Telaprevir, peg-Interferon-alpha-2A and Ribavirin in genotype1 HCV-infected stable liver transplant patients. • Simultaneous administration of ABT-450, Ritonavir and ABT-267 in adults with chronic HCV Infection. • Combination of ABT-450/ritonavir/ABT-267 and ABT-333 with or without Ribavirin in Adult Transplant Recipient with Genotype 1 HCV Infection. • Human immunoglobulin versus B Hepatitis Zutectra in liver transplant patients • Asunaprevir and Daclatasvir in patients with chronic C Hepatitis – genotype1b – with partial or no response to peginterferon - alfa and ribavirin, intolerant or ineligible for P/R and naive– Phase 3 • Simeprevir/Daclatasvir/ribavirin combination in liver transplant patients with chronic genotype 1b infection.

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G0026
Programme: P1. Portal Hypertension and Cirrhosis

Lead Researcher: Bosch Genover, Jaume

Group members

STAFF MEMBERS: Berzigotti, Annalisa | Esteva Espinosa, Clara | Gallego Pinos, Javier | García Caldero, Hector | García Pras, Ester | López Sanjurjo, Cristina Isabel | Mejias Hernández, Marc | Sáez Carceller, Rosa María | Vidal García, Nuria | Vila Bellmunt, Sergi | Vilaseca Barceló, Marina.

ASSOCIATED MEMBERS: Deulofeu Piguet, Ramon | Escorsell Mañosa, Ángeles | Fernández Lobato, Mercedes | García Pagan, Juan Carlos | Gracia Sancho, Jordi | Hernández Gea, Virginia

Main lines of research

- Factors regulating hepatic microcirculation in normal and in cirrhosis, studies of liver perfusion and isolated liver sinusoidal endothelial cells.
- Regulation of transcription of protective genes hepatic sinusoidal endothelium:relevance to the pathophysiology of portal hypertension in liver ex vivo preservation, and prevention of the complications of cirrhosis.
- Angiogenesis and portal hypertension: importance in the regulation of development of collateral circulation, hyperdynamic circulation and hepatic fibrogenesis.
- New non invasive methods of evaluation of cirrhosis.
- Randomized clinical trials of new treatments for portal hypertension.
- Hepatic vascular diseases.
- Prevention of decompensated cirrhosis.
- Role of sinusoidal endothelium in ischemia-reperfusion injury liver.

Most relevant scientific articles

- Tsochatzis E.A., Bosch J., Burroughs A.K.. Liver cirrhosis. The Lancet. 2014;383(9930):1749-1761.
- Siramolpiwat S., Seijo S., Miquel R., Berzigotti A., Garcia-Criado A., Darnell A. et al. Idiopathic portal hypertension: Natural history and long-term outcome. Hepatology. 2014;59(6):2276-2285.
- Reverter E., Tandon P., Augustin S., Turon F., Casu S., Bastiampillai R. et al. A MELD-based model to determine risk of mortality among patients with acute variceal bleeding. Gastroenterology. 2014;146(2):-.
- Coch L., Mejias M., Berzigotti A., Garcia-Pras E., Gallego J., Bosch J. et al. Disruption of negative feedback loop between vasohibin-1 and vascular endothelial growth factor decreases portal pressure, angiogenesis, and fibrosis in cirrhotic rats. Hepatology. 2014;60(2):633-647.
- La Mura V., Pasarin M., Rodriguez-Vilarrupla A., Garcia-Pagan J.C., Bosch J., Abraldes J.G.. Liver sinusoidal endothelial dysfunction after LPS administration: A role for inducible-nitric oxide synthase. Journal of Hepatology. 2014.

Highlights

PUBLICATIONS

Our group published a total of 40 publications (19 Originals, 11 Reviews, 7 Editorials, 2 Letters and 1 Clinical Trial), 14 among them are in collaboration with other CIBERehd's groups.

RESEARCH PROJECTS:

Besides the 10 projects in progress during 2014 (1 Regional, 3 SAF, 4 FIS, 1 European and 1 Subprogram INNPACTO) we have been granted with the following new projects:

- BOSCH J. Reconocimiento GRUP DE RECERCA CONSOLIDAT-AGAUR (2014SGR209): "HEMODINAMICA HEPATICA I HIPERTENSIO PORTAL". (2014-2016). Regional Project • JC GARCIA-PAGAN ICI14/00133. Estudio prospectivo multicéntrico, aleatorizado del efecto de Rivaroxaban sobre la supervivencia y el desarrollo de complicaciones de la hipertensión portal en pacientes con cirrosis. • JORDI GRACIA-SANCHO FIS PI14/00029. El sinusoide hepático en la vejez: caracterización de los mecanismos celulares fisiopatológicos para el desarrollo de nuevas estrategias terapéuticas. • VIRGINIA HERNANDEZ-GEA FIS PI14/00182: Papel de la autofagia en la modulación de la disfunción endotelial y la fibrosis: caracterización de una nueva diana terapéutica para el desarrollo de nuevos tratamientos antifibróticos. • ANGELS ESCORSELL FIS PI14/00392: Eficacia de la derivación portosistémica intrahepática (TIPS) en el tratamiento de la hemorragia aguda por varices gástricas: estudio aleatorizado y controlado vs tratamiento convencional.

DOCTORAL THESES:

- PhD-fellow: GIUSI MARRONE. University of Barcelona (20/06/2014). Title: "Cellular and molecular mechanisms of novel therapies to ameliorate liver sinusoidal dysfunction in cirrhotic portal hypertension". Supervised by: Jaime Bosch and Jordi Gracia Sancho.
- PhD-fellow: LAURA COCH. University of Barcelona (27/06/2014). Title: Implicació de factors antiangiogènics en la hipertensió portal i la cirrosi hepática. Supervised by: Jaume Bosch and Mercedes Fernández.

PATENTS

- Contract of Exploiting with the company YMAGING of the granted Patent *A computer implemented method for assessing vascular networks from medical images and uses thereof.*
- New Patent granted: *Bioreactor for cell co-culture.*

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G0005

Programme: P5. Hepatic and gastrointestinal oncology

Lead Researcher: Bruix Tudó, Jordi

Group members

STAFF MEMBERS: Boix Ferrero, Loreto | Martínez Quetglas, Iris | Peix Gallofre, Judit | Pérez Pons, Nuria | Reig Monzon, Mª Elisa | Rengel Gelada, Ingrid.

ASSOCIATED MEMBERS: Ayuso Colella, María Carmen | Bianchi Cardona, Luis | Bru Saumell, Concepción | Forner González, Alejandro | Fuster Obregón, Josep | Llovet Bayer, Josep Maria | Real Martí, María Isabel | Sole Arques, Manuel | Vilana Puig, Ramón.

Main lines of research

This group known as the BCLC group is devoted to clinical and translational research in liver cancer, especially to two major fields: 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.

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

- Bruix J., Gores G.J., Mazzaferro V.. Hepatocellular carcinoma: Clinical frontiers and perspectives. Gut. 2014;63(5):844-855.
- Sapisochin G., Rodriguez De Lope C., Gastaca M., Ortiz De Urbina J., Suárez M.A., Santoyo J. et al. "very early" intrahepatic cholangiocarcinoma in cirrhotic patients: Should liver transplantation be reconsidered in these patients?. American Journal of Transplantation. 2014;14(3):660-667.
- Reig M., Torres F., Rodriguez-Lope C., Forner A., Llarch N., Rimola J. et al. Early dermatologic adverse events predict better outcome in HCC patients treated with sorafenib. Journal of Hepatology. 2014;61(2):318-324.
- Mudbhary R., Hoshida Y., Chernyavskaya Y., Jacob V., Villanueva A., Fiel M. et al. UHRF1 Overexpression Drives DNA Hypomethylation and Hepatocellular Carcinoma. Cancer Cell. 2014;25(2):196-209.
- Cornella H, Alsinet C, Sayols S, Zhang Z, Hao K, Cabellos L et al. Unique Genomic Profile of Fibrolamellar Hepatocellular Carcinoma.Gastroenterology. 2014.

Highlights

PROJECTS

The Liver Cancer group has mantained the international leadership through papers in first level publications. At the same time, the group has leaded and initiated several projects in order to expand the knowledge of the génesis and treatment of different liver cáncer types, such as cholangiocarcinoma, hepatoblastoma and hemangioendotelioma. International phase 3 studies have been leaded for the adjuvant treatment posttreatment with surgical resection / ablation, as well as phase 3 studies in advanced stage to evalute the efficacy of regorafenib and tivatinib in second line postsorafenib.

Studies made by the group have allowed to refine the diagnostic criteria for liver cáncer, and a consense document with the American Society of Radiology has been leaded in order to develop the LIRADS system at an international level.

Studies have been made to evaluate the potential indication of liver transplantation in patients with cholangiocarcinoma, and a study has been initiated in this sense, including centers in Europe and the United States.

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.

At a translational level we have widen the knowledge in hepatic oncogénesis with the final goal of getting molecular classifications of hepatocellular carcinoma and cholangiocarcinoma, in order to refine the prognostic evaluation and, in this way, to be able to prescribe a personalized treatment according to the biological profile.

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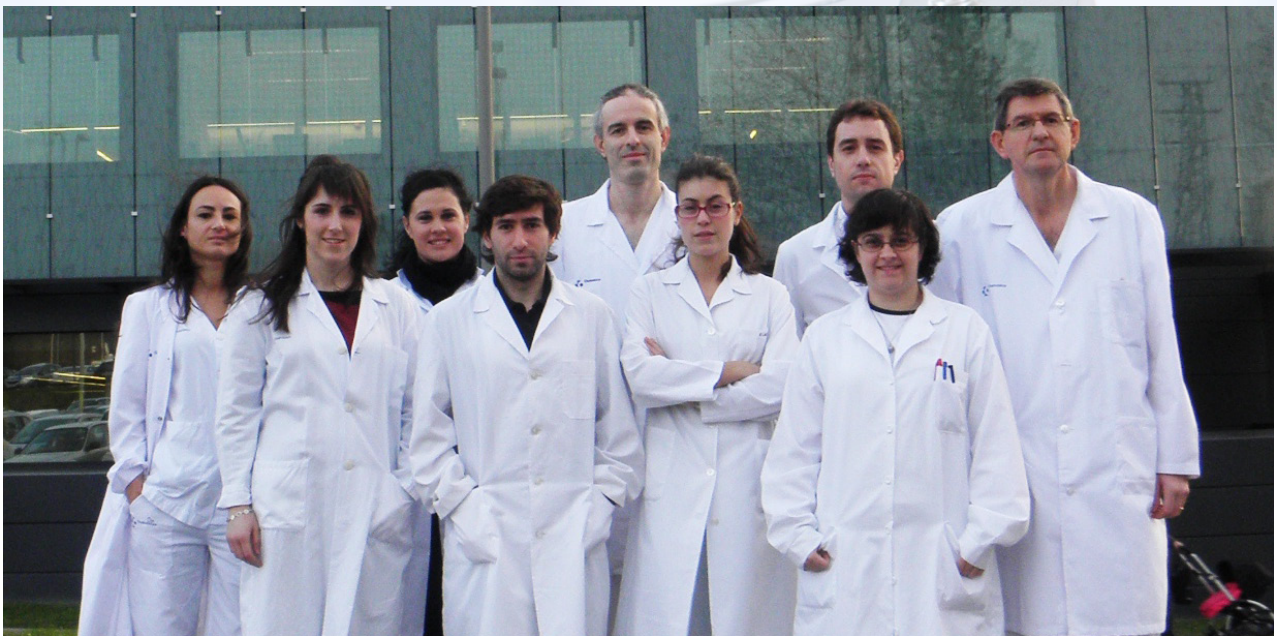
G1081

Programme: P5. Hepatic and gastrointestinal oncology



Lead Researcher: Bujanda Fdez. de Pierola, Luis

Group members

STAFF MEMBERS: Goitia Viaña, Ana Isabel | Muñoz Garrido, Patricia.

ASSOCIATED MEMBERS: Banales Asurmendi, Jesús María | Herreros Villanueva, Marta | Hijona Muruamendiaraz, Elizabeth | Perugorria Montiel, María Jesús.

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

- Jiménez-Agüero R, Emparanza JI, Beguiristain A, Bujanda L, Alustiza JM, García E et al. Novel equation to determine the hepatic triglyceride concentration in humans by MRI: diagnosis and monitoring of NAFLD in obese patients before and after bariatric surgery.BMC medicine. 2014;12:137.
- Sánchez Y, Segura V, Marín-Béjar O, Athie A, Marchese FP, González J et al. Genome-wide analysis of the human p53 transcriptional network unveils a lncRNA tumour suppressor signature.Nature communications. 2014;5:5812.
- Urribarri A.D., Munoz-Garrido P., Perugorria M.J., Erice O., Merino-Azpitarte M., Arbelaiz A. et al. Inhibition of metalloprotease hyperactivity in cystic cholangiocytes halts the development of polycystic liver diseases. Gut. 2014.
- Castro-Lopez V., Elizalde J., Pacek M., Hijona E., Bujanda L.. A simple and portable device for the quantification of TNF-α in human plasma by means of on-chip magnetic bead-based proximity ligation assay. Biosensors and Bioelectronics. 2014;54:499-505.
- Perugorria M.J., Masyuk T.V., Marin J.J., Marzioni M., Bujanda L., Larusso N.F. et al. Polycystic liver diseases: advanced insights into the molecular mechanisms. Nature Reviews Gastroenterology and Hepatology. 2014.

Highlights

The group has achieved significant milestones in 2014, such as obtaining a contract Miguel Servet I (PI Dr. Jesus Bañales: € 304,000) with an associated research project on "the role of extracellular microvesicles in the pathogenesis of primary sclerosing cholangitis and cholangiocarcinoma "; part of this project has also received funding from the "Diputación of Guipúzcoa" (PI Dr. Luis Bujanda: € 68,000). On the other hand, Dr. Maria J. Perugorria has obtained a FIS project as PI (PI14 / 00399: € 109,626) for studying the role of the membrane receptor TREM-2 in the pathogenesis of liver fibrosis and hepatocellular carcinoma; in addition, Drs. Perugorría and Bujanda have obtained a 4 years predoctoral grant from the University of the Basque Country (UPV) for carrying out a doctoral thesis on this topic. Another important point of the group in 2014 is the initiation of an International Multicenter Phase II Clinical Trial (CURSOR: https://clinicaltrials.gov/ct2/show/NCT02021110) to evaluate the role of ursodeoxycholic acid (UDCA) for the treatment of polycystic liver diseases. During 2014, there was a consolidation of the collaborative CIBERehd projects on colon cancer: COLONPREV, EPICOLON III or EPIPOLIP projects. We have also initiated other collaborative projects (SEGUICOL and EPOS projects) to establish practice guidelines for monitoring patients with polyps. This EPOS project is a prospective randomized European level that aims to determine the best strategy for patients with colon polyps. Moreover, we are carrying out genetic studies associated to the development of gastric cancer. Thus, genetic variations in preneoplastic lesions can help to establish future guidelines for monitoring individuals at high risk of developing cancer.

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G0034

Programme: P6. Gastrointestinal Inflammation and Motility

Lead Researcher: Cabré Gelada, Eduard

Group members

STAFF MEMBERS: Loren Moreno, Violeta | Mañe Almero, Josep | Marín Sánchez, Laura.

ASSOCIATED MEMBERS: Domenech Morral, Eugeni | Lorenzo-Zuñiga García, Vicente María | Mañosa Ciria, Miriam | Pedrosa Tapias, Elisabet | Serra Pueyo, Jordi | Zabane Abdo, Yamile.

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

- Alonso A, Domènech E, Julià A, Panés J, García-Sánchez V, Mateu PN et al. Identification of Risk Loci for Crohn's Disease Phenotypes Using a Genome-Wide Association Study.Gastroenterology. 2014.
- Julià A, Domènech E, Chaparro M, García-Sánchez V, Gomollón F, Panés J et al. A genome-wide association study identifies a novel locus at 6q22.1 associated with ulcerative colitis.Human molecular genetics. 2014;23(25):6927-34.
- Naves J.E., Llao J., Ruiz-Cerulla A., Romero C., Manosa M., Lobaton T. et al. Long-term comparative efficacy of cyclosporine- or infliximab-based strategies for the management of steroid-refractory ulcerative colitis attacks. Inflammatory Bowel Diseases. 2014;20(8):1375-1381.
- Cabre E., Manosa M., Garcia-Sanchez V., Gutierrez A., Ricart E., Esteve M. et al. Phenotypic concordance in familial inflammatory bowel disease (IBD). Results of a nationwide IBD Spanish database. Journal of Crohn's and Colitis. 2014;8(7):654-661.
- Llao J., Naves J.E., Ruiz-Cerulla A., Marin L., Manosa M., Rodriguez-Alonso L. et al. Intravenous corticosteroids in moderately active ulcerative colitis refractory to oral corticosteroids. Journal of Crohn's and Colitis. 2014.

Highlights

In 2014, three FIS-funded scientific projects were ongoing. They were related to the main research line of our group (the study of steroid resistance in IBD, and postoperative recurrence in Crohn's disease). These projects have obtained additional funding from the Societat Catalana de Digestologia and GETTECU-Otsuka. Preliminary results of these studies have been presented as oral communications in international (n=6) and national (n=15) congresses, and got the award to the best poster in the CIBEREHD annual scientific meeting.

On the other hand, a total of 18 scientific articles have been published – three in 1st quartile (two of them in 1st decile), and 12 in 2nd quartile journals. Ten of these publications resulted from collaborative studies among CIBER groups.

Regarding transfer of results, we are next to reach collaboration agreements with the company Vitae Natural Nutrition (Barcelona) for the development of a novel therapy for ulcerative colitis (450.000€ funding from CDTI have been obtained). Also, a study promoted by AB-Biotics (Barcelona) on probiotic therapy in SBI has been performed. Also, our group has been involved in 16 multicentre RCTs, and members of the group have participated in the elaboration of two clinical guidelines.

The most relevant educational activity of the groups has been the organisation of XXI Miquel Ángel Gassull International Course on IBD. Also, three predoc students made stages in our Laboratory, which also participated in the programme of the Fundación BCN Formació Professional of the Catalan Government.

Dr. Domènech has been elected as president of GETECCU and Dr. Serra is member of the national committees of the UEG and the European Society of Neurogastroenterology and Motility.

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G0036

Programme: P6. Gastrointestinal Inflammation and Motility

Lead Researcher: Calvet Calvo, Xavier

Group members

STAFF MEMBERS: Figuerola Ferrer, Ariadna | Ramírez Lazaro, María José.

ASSOCIATED MEMBERS: Brullet Benedi, Enrique | Campo Fernández de los Ríos, Rafael | Gene Tous, Emili | Junqueras Flórez, Felix | Lario Garca, Sergio | Miquel Planas, Mireia | Montserrat Torres, Antonia | Sánchez Delgado, Jorge | Vergara Gómez, Mercedes | Villoria Ferrer, Albert

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

- McNicholl A.G., Marin A.C., Molina-Infante J., Castro M., Barrio J., Ducons J. et al. Randomised clinical trial comparing sequential and concomitant therapies for Helicobacter pylori eradication in routine clinical practice. Gut. 2014;63(2):244-249.
- Vergara M., Bennett C., Calvet X., Gisbert J.P.. Epinephrine injection versus epinephrine injection and a second endoscopic method in high-risk bleeding ulcers. The Cochrane database of systematic reviews. 2014;10.
- Lanas Á, Carrera-Lasfuentes P, Arguedas Y, García S, Bujanda L, Calvet X et al. Risk of Upper and Lower Gastrointestinal Bleeding in Patients Taking Nonsteroidal Anti-inflammatory Drugs, Antiplatelet Agents, or Anticoagulants.Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2014.
- Algaba A., Linares P.M., Fernandez-Contreras M.E., Figuerola A., Calvet X., Guerra I. et al. The effects of infliximab or adalimumab on vascular endothelial growth factor and angiopoietin 1 angiogenic factor levels in inflammatory bowel disease: Serial observations in 37 patients. Inflammatory Bowel Diseases. 2014;20(4):695-702.
- Puig I., Calvet X., Baylina M., Isava A., Sort P., Llao J. et al. How and when should NSAIDs be used for preventing post-ERCP pancreatitis? A systematic review and meta-analysis. PLoS ONE. 2014;9(3).

Highlights

PROYECTOS

Developed and presented projects to calls for official grants are classified into three lines:

• Clinical Helicobacter: Application of new high sensitivity technologies for the diagnosis of *Helicobacter pylori* in patients with low levels of infection.

• Basic and translational Helicobacter: Identification of metabolomic biomarkers for a non-invasive diagnosis of digestive diseases related to Helicobacter pylori infection.

Evaluation of non-coding RNAs as non-invasive biomarkers of precancerous gastric lesions in patients infected with H. pylori. Identification of biomarkers to determine the carcinogenic potential of strains of *H. pylori*.

Crohn's disease: Development and validation of a target rate of disability in Crohn . Subclinical inflammation disease and fatigue in patients with Inflammatory Bowel Disease.

CLINICAL GUIDELINES

Regarding the clinical guides, the grup has coordinated or participated in the development of a Cochrane review: "Epinephrine injection versus epinephrine injection and a second endoscopic method in high risk bleeding ulcers and several clinical guidelines on the use of NSAIDs, and management of upper gastrointestinal bleeding and low 'and ulcerative colitis: Recommendations for safe prescribing NSAIDs: consensus document prepared by experts nominated by three scientific societies (SER-SEC-AEG).

• Management of acute lower gastrointestinal bleeding: position paper of the Catalan Society of Digestology.

• Practice Guidelines for the management of non-variceal upper gastrointestinal bleeding.

• Clinical Guide GETECCU treatment of ulcerative colitis made with GRADE methodology.

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G0081
Programme: P3. Cholestasis and Metabolic Disorders

Lead Researcher: Castell Ripoll, José Vicente

Group members

ASSOCIATED MEMBERS: Bort Martí, Bernardo Roque | Donato Martín, María Teresa | Gómez-Lechón Moliner, María José | Jover Atienza, Ramiro

Main lines of research

- **Drug hepatotoxicity and metabolism:** this line is devoted to the design and validation of new strategies for a more effective and safe drug development by studying the molecular mechanisms of hepatotoxicity (cholestasis, steatosis, metabolic idiosyncrasy, bioactivation ...) and new biomarkers (metabonomics, microRNAs, toxicogenomics ...) in advanced predictive liver cell models. Another objective is its clinical translation (diagnostic, monitoring, prevention, prognosis, treatment and influence of drugs on the progression of highly prevalent liver disease such as NAFLD ...).
- **Advanced liver therapies:** the group seeks to explore and strengthen the liver cell therapy with adult hepatocytes as well as with hepatic progenitors for the treatment of different liver diseases. Another objective is to explore the clinical utility of other cell types such as reprogrammed cells (iPSC: direct and indirect conversion of fibroblasts to iHEP) or embryonic stem cells (hESC). Finally, we are proposing the use of iPSC technology along with genomic editing (personalized medicine) as a realistic treatment for certain congenital metabolic disorders.
- **Etiology of NAFLD:** transcriptional mechanisms involved: the main hypothesis of this project proposes that in the pathogenesis of nonalcoholic fatty liver disease (NAFLD) multiple transcriptional regulatory pathways are involved. The general objective is, therefore, to discover new transcriptional mechanisms involved in the development and progression of NAFLD, and in particular to investigate the toxicogenomic effects caused by steatotic drugs and their mechanisms. It also aims to discover specific biomarkers (eg microRNAs, metabolites, etc) for discriminating between metabolic and drug-induced steatosis.

- **Advanced strategies in surgery and liver transplantation.** Liver metabonomics and chemometrics: Improved preservation of deceased donor liver and search of metabolomic based biomarkers as indicators of the quality of donor liver before implantation. Development of test to evaluate liver functional capacity in patients undergoing major hepatic resection. Study of liver function and regeneration after portal embolization and surgical resections. Improved planning of surgical resection and percutaneous treatment of liver tumors with the support of computer software.

Most relevant scientific articles

- Cortes M., Pareja E., Garcia-Canaveras J.C., Donato M.T., Montero S., Mir J. et al. Metabolomics discloses donor liver biomarkers associated with early allograft dysfunction. Journal of Hepatology. 2014;61(3):564-574.
- Benet M., Moya M., Donato M.T., Lahoz A., Hervas D., Guzman C. et al. A simple transcriptomic signature able to predict drug-induced hepatic steatosis. Archives of Toxicology. 2014;88(4):967-982.
- Marfil V., Blazquez M., Serrano F., Castell J.V., Bort R.. Growth-promoting and tumourigenic activity of c-Myc is suppressed by Hhex. Oncogene. 2014.
- Tolosa L., Carmona A., Castell J.V., Gomez-Lechon M.J., Donato M.T.. High-content screening of drug-induced mitochondrial impairment in hepatic cells: effects of statins. Archives of Toxicology. 2014.
- Pareja E., Cortes M., Hervas D., Mir J., Valdivieso A., Castell J.V. et al. A score model for the continuous grading of early allograft dysfunction severity. Liver Transplantation. 2014;21(1):38-46.

Highlights

Among the research projects during 2014 it is important to remark three international grants: one funded by The Roche Organ Transplantation Research Foundation: "Fast Metabolomic Assessment of Donor Liver Transplant Prior to Quality" (ROTRF); and two projects of the European Union: One ended in 2014 "INNOVALIV: Innovative Strategies to Generate Human hepatocytes for Treatment of Metabolic Liver Diseases: Tools for Personalized Cell Therapy" and another that will run until 2018 "Hecatos. Cardiac and Hepatic Toxicity Systems Modelling". For this last project, and as a result of the synergy between our Unit and the Hepatology Unit (UH), we have recently created a hepatotoxicity medical office in the Hospital La Fe. Patients with suspected drug-induced hepatotoxicity are referred to this office for detailed and personalized study.

Regarding competitive projects of national calls it is worth to mention four of them: "Metabonomic approaches to study idiosyncratic hepatotoxicity with a metabolic base and identification of the causative agent" (PI13 / 00986, ISCIII-FIS); "Drug induced fatty liver: new mechanisms and biomarkers applicable to pharmaceutical development and a more rational therapy in patients with metabolic syndrome" (PI13 / 01470, ISCIII-FIS); "Finding metabonomic patterns for rapid assessment of the quality of the donor liver, pre-implantation and subsequent monitoring of its evolution after transplant" (PI11 / 02942, ISCIII-FIS); and "Induction of myc activity by HHEX homeoprotein: basic aspects and application to oncology issues and reprogramming " (SAF2011-29718).

Regarding the translation of our results to the clinical practice is noteworthy our participation in three Clinical Trials: "Efficacy of N-acetylcysteine in the preservation solution during liver transplantation" (IISLAFE, NAC400, Phase III); "pilot study for the assessment of the hepatotest in the preoperative valuation of liver function " (IISLAFE, HEPATOTEST, Phase IV); "Pilot clinical trial Phase I / IIA to determine conditions, low dose and effectiveness of a liver function tests" (IISLAFE, HEPATOTEST, Phase I / IIA).

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G0016

Programme: P5. Hepatic and gastrointestinal oncology

Lead Researcher: Castells Garangou, Antoni

Group members

STAFF MEMBERS: Durán Sanchón, Saray | Esteban Jurado, Clara | Gironella Cos, Meritxell | Muñoz Sancho, Jenifer | Samper Lirola, Esther | Vila Navarro, Elena

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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

- Whissell G., Montagni E., Martinelli P., Hernando-Momblona X., Sevillano M., Jung P. et al. The transcription factor GATA6 enables self-renewal of colon adenoma stem cells by repressing BMP gene expression. Nature Cell Biology. 2014;16(7):695-707.
- Auge J.M., Pellise M., Escudero J.M., Hernandez C., Andreu M., Grau J. et al. Risk stratification for advanced colorectal neoplasia according to fecal hemoglobin concentration in a colorectal cancer screening program. Gastroenterology. 2014;147(3).
- Balaguer F., Pellise M.. Colorectal cancer: Serrated polyposis - Should we screen first-degree relatives?. Nature Reviews Gastroenterology and Hepatology. 2014;11(6):333-334.
- Fernandez-Hevia M., Delgado S., Castells A., Tasende M., Momblan D., Diaz del Gobbo G. et al. Transanal total mesorectal excision in rectal cancer: Short-term outcomes in comparison with laparoscopic surgery. Annals of Surgery. 2014.
- Castells A., Quintero E., Alvarez C., Bujanda L., Cubiella J., Salas D. et al. Rate of Detection of Advanced Neoplasms in Proximal Colon by Simulated Sigmoidoscopy vs Fecal Immunochemical Tests. Clinical Gastroenterology and Hepatology. 2014;12(10):1708-1716.

Highlights

Our research lines are aimed at understanding the molecular 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 2014 are framed in the context of cooperative projects, coordinated by our group, in the fields of colorectal cancer (CRC) screening and the development of biomarkers for early detection.

With respect to CRC screening, it is important to point out the ColonPrev study, a prospective, randomized controlled trial comparing the fecal occult blood testing and colonoscopy. After presenting the results of the first round *(N Engl J Med 2012;366:697-706)*, we have recently published results of nested projects, including the comparison of sigmoidoscopy with fecal occult blood testing *(Clin Gastroenterol Hepatol 2014; 12:1708-1716)*, as well as the usefulness of this test in prioritizing colonoscopy *(Gastroenterology 2014; 147:628-636)*.

On the other hand, the development and validation of biomarkers for early diagnosis of CRC is framed in the EPICOLON project, a transversal strategic action of various groups of the CIBEREHD. In this field, it is important to mention our recent publications *(PLoS ONE 2014; 9:e91033; PLoS ONE 2014; 9:e104285; Nat Cell Biol 2014; 16:695-707)*, patents *(PCT / US2013 / 028401, US61 / 391,585 and US61 / 550 148)*, and a grant of the Spanish Association against Cancer achieved by our group.

Finally, we would like to point out the social commitment of our group, as evidenced by supporting the creation of the Association of Families Affected by Lynch syndrome (www.afalynch.org) and the Alliance for Cancer Prevention Colon (www.alianzaprevencioncolon.es).

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G1087

Programme: P6. Gastrointestinal Inflammation and Motility

Lead Researcher: Clavé Civit, Pere

Group members

STAFF MEMBERS: Arenas Bailón, Claudia | Gallego Pérez, Diana | Rofes Salsench, Laia | Rychter, Jakub.

ASSOCIATED MEMBERS: Farré Martí, Ricard Lluis | Jiménez Farrerons, Marcelo | Martín Ibáñez, María Teresa | Martínez Perea, Vicente | Serra Prat, Mateu | Vergara Esteras, Patrocinio

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., Mukherjee R., Swanson J., Clave P.. The effects of a xanthan gum-based thickener on the swallowing function of patients with dysphagia. Alimentary Pharmacology and Therapeutics. 2014;39(10):1169-1179.
- Cabre M., Serra-Prat M., Force L., Almirall J., Palomera E., Clave P. Oropharyngeal dysphagia is a risk factor for readmission for pneumonia in the very elderly persons: Observational prospective study. Journals of Gerontology - Series A Biological Sciences and Medical Sciences. 2014;69 A(3):330-337.
- Jimenez M., Clave P., Accarino A., Gallego D.. Purinergic neuromuscular transmission in the gastrointestinal tract; functional basis for future clinical and pharmacological studies. British Journal of Pharmacology. 2014.
- Teran-Ventura E., Aguilera M., Vergara P., Martinez V.. Specific changes of gut commensal microbiota and TLRs during indomethacin-induced acute intestinal inflammation in rats. Journal of Crohn's and Colitis. 2014;8(9):1043-1054.
- Vanheel H., Vicario M., Vanuytsel T., Van Oudenhove L., Martinez C., Keita A.V. et al. Impaired duodenal mucosal integrity and low-grade inflammation in functional dyspepsia. Gut. 2014;63(2):262-271.

Highlights

We have adopted several techniques of neurophysiology (pharyngeal evoked potentials and Transcranial Magnetic Stimulation to improve the study of pathophysiology and treatment of post stroke oropharyngeal dysphagia with the aim to promote brain plasticity. This will allow to develop studies to improve clinical practice from compensation to recovery of swallow function. We have also completed a group of studies exploring the clinical and health-economic impact of the complications associated to oropharyngeal dysphagia. Translational studies show the impact of the changes in mucosal permeability on the pathophysiology of functional dyspepsia. Our basic studies further characterized the mechanisms of neuromuscular communication in the human enteric nervous system and the specific role of several families of inhibitory neurotransmitters. Using animal models we have also studies the relationship between the enteric microbiota and intestinal inflammation.

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G0071

Programme: P6. Gastrointestinal Inflammation and Motility

Lead Researcher: Esplugues Mota, Juan Vicente

Group members

STAFF MEMBERS: Normanly, Brian James

ASSOCIATED MEMBERS: Álvarez Ribelles, Ángeles | Apostolova Atanasovska, Nadezda | Barrachina Sancho, María Dolores | Blas García, Ana | Calatayud Romero, Sara | Hernández Sáez, Carlos | Martí Cabrera, Miguel | Martínez Cuesta, María Ángeles | Rocha Barajas, Milagros | Víctor González, Víctor Manuel

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.
- Mechanisms of toxicity, metabolic alterations, mitochondrial dysfunction and inflammation produced by antiretroviral drugs.

Most relevant scientific articles

- Ortiz-Masia D., Cosin-Roger J., Calatayud S., Hernandez C., Alos R., Hinojosa J. et al. Hypoxic macrophages impair autophagy in epithelial cells through Wnt1: Relevance in IBD. Mucosal Immunology. 2014;7(4):929-938.
- Apostolova N, Funes HA, Blas-Garcia A, Alegre F, Polo M, Esplugues JV. Involvement of Nitric Oxide in the Mitochondrial Action of Efavirenz: A Differential Effect on Neurons and Glial Cells.The Journal of infectious diseases. 2014.
- Blas-García A, Polo M, Alegre F, Funes HA, Martínez E, Apostolova N et al. Lack of mitochondrial toxicity of darunavir, raltegravir and rilpivirine in neurons and hepatocytes: a comparison with efavirenz.The Journal of antimicrobial chemotherapy. 2014;69(11):2995-3000.
- Polo M, Alegre F, Funes HA, Blas-Garcia A, Victor VM, Esplugues JV et al. Mitochondrial (dys)function - a factor underlying the variability of efavirenz-induced hepatotoxicity?. British journal of pharmacology. 2014.
- Hernandez C., Barrachina M.D., Cosin-Roger J., Ortiz-Masia D., Alvarez A., Terradez L. et al. Progastrin represses the alternative activation of human macrophages and modulates their influence on colon cancer epithelial cells. PLoS ONE. 2014;9(6).

Highlights

In 2014 our group was granted a project from the Acción Estratégica en Salud 2014 call of the Instituto de Salud Carlos III, y has received another 4 years of funding in Phase II of the Valencian Regional Government´s PROMETEO programme for research groups of excellence. While continuing with our usual research lines, we have initiated two important studies in collaboration with international pharmaceutical industry about the toxicity produced by antiretroviral drugs.

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G0028
Programme: P2. Viral hepatitis

Lead Researcher: Esteban Mur, Juan Ignacio

Group members

STAFF MEMBERS: García Cehic, Damir | Quer Sivila, Josep | Rico Blázquez, Ángeles.

ASSOCIATED MEMBERS: Bes Maijo, Marta | Bilbao Aguirre, Itxarone Izaskun | Campos Varela, Isabel | Castells Fuste, Lluis | Dopazo Taboada, Cristina | Gregori Font, Josep | Guardia Masso, Jaime | Pirón Pirón, Maria | Puig Rovira, Lluis | Sauleda Oliveras, Silvia.

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 Nossocomial 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

- Castells L., Rimola A., Manzardo C., Valdivieso A., Montero J.L., Barcena R. et al. Pegylated interferon plus ribavirin in HIV-infected patients with recurrent hepatitis C after liver transplantation: A prospective cohort study. Journal of Hepatology. 2014;62(1):92-100.
- Gregori J., Salicru M., Domingo E., Sanchez A., Esteban J.I., Rodriguez-Frías F. et al. Inference with viral quasispecies diversity indices: Clonal and NGS approaches. Bioinformatics. 2014;30(8):1104-1111.
- Cubero M., Gregori J., Esteban J.I., Garcia-Cehic D., Bes M., Perales C. et al. Identification of host and viral factors involved in a dissimilar resolution of a hepatitis C virus infection. Liver International. 2014;34(6):896-906.
- Sheldon J., Beach N.M., Moreno E., Gallego I., Pineiro D., Martinez-Salas E. et al. Increased replicative fitness can lead to decreased drug sensitivity of hepatitis C virus. Journal of Virology. 2014;88(20):12098-12111.
- Campos-Varela I., Esteban J.I., Bes M., Caralt M., Allende H., Rodriguez-Frías F. et al. Early predictors of antiviral treatment response in liver transplant recipients with recurrent hepatitis C genotype 1. Journal of Viral Hepatitis. 2014;21(10):e118-e128.

Highlights

During 2014, our group has consolidated its leadership in the implementation of massive sequencing to study viral hepatitis A, B, C, D and E. The result has been the publication of several manuscripts (in virus B, C and E) and some that are under writing for A and D viruses. This leadership has enabled us to establish new collaborations with groups of Ciber and beyond.

The development of the methodology of high resolution HCV subtyping has led to a patent issued in January 2015 and a publication also published in January 2015 that has had a huge mass media impact. This methodology is being transferred to a Molecular Diagnostics laboratory from the University Hospital Vall d'Hebron, to other hospitals where Ciberehd members are developing their activity and other hospital centers together with Spanish molecular diagnosis centers. Our interest is to expand such methodology to other countries. The methodology has been offered as an innovative public procurement system in Spain.

The massive sequencing is being applied to study liver transplants, especially in the case of HCV infected patients. This has allowed us to maintain and expand collaborations. Studies on acute HCV infections in HIV+ men that have sex with other men, are conducted, and also studies of HCV nosocomial transmission.

Currently, massive sequencing methodology is being adapted to study the presence of resistance mutations in virus from patients who have failed treatment with novel direct active antivirals. We are applying for Public National and Private funds. This work will enable more efficient design protocols to rescue these patients using personalized treatments.

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G0025
Programme: P2. Viral Hepatitis

Lead Researcher: Esteban Mur, Rafael

Group members

STAFF MEMBERS: Blasi Fornaguera, María | Homs Riba, Maria | Tabernero Caellas, David.

ASSOCIATED MEMBERS: Buti Ferrer, María Asunción | Rodríguez Frías, Francisco.

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

- Afdhal N., Zeuzem S., Kwo P., Chojkier M., Gitlin N., Puoti M. et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. New England Journal of Medicine. 2014;370(20):1889-1898.
- Manns M., Marcellin P., Poordad F., De Araujo E.S.A., Buti M., Horsmans Y. et al. Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): A randomised, double-blind, placebo-controlled phase 3 trial. The Lancet. 2014;384(9941):414-426.
- Riveiro-Barciela M., Buti M., Homs M., Campos-Varela I., Cantarell C., Crespo M. et al. Cirrhosis, liver transplantation and HIV infection are risk factors associated with hepatitis E virus infection. PLoS ONE. 2014;9(7).
- Homs M., Giersch K., Blasi M., Lutgehetmann M., Buti M., Esteban R. et al. Relevance of a full-length genomic RNA standard and a thermal-shock step for optimal hepatitis delta virus quantification. Journal of Clinical Microbiology. 2014;52(9):3334-3338.
- Homs M., Caballero A., Gregori J., Tabernero D., Quer J., Nieto L. et al. Clinical application of estimating hepatitis b virus quasispecies complexity by massive sequencing: Correlation between natural evolution and on-treatment evolution. PLoS ONE. 2014;9(11).

Highlights

In 2014 we have continued working on the research related to the study of variability and evolution of the hepatitis B virus (HBV) quasispecies using massive sequencing by ultra-deep pyrosequencing (UDPS), as part of research projects PI11/01973 and PI12/01893 of the Health Institute Carlos III. In addition, we have also begun to study the variability of the hepatitis delta virus (HDV) quasispecies of using these technologies.The continuity of these lines of research is guaranteed in the coming years for a new health research project from the Institute of Health Carlos III (PI14/01416) and a grant from the Fellowship program of Gilead Sciences (GLD14-00296), through which we will analyze the interaction of HBV and HDV with their common receptor for entry into the hepatocyte and prospectively study the complexity of their viral quasispecies. Among our lines of collaborative research stands out the platform for the collection of data from patients with chronic hepatitis B (CIBERHEP), which in 2014 has reached the 1149 patients under antiviral treatment, with analyzable data recorded. We have also collaborated with the group from Dr. Maura Dandri (Germany) in optimizing the quantification of HDV-RNA in serum by validation of a HDV-RNA standard, and also we have participated in an international quality control study to evaluate the methods employed to quantify this viral RNA, coordinated by the group of Dr. Frederic Le Gal (France). In addition we have also participated in an international validation of a scoring system for predicting the development of liver complications in patients with chronic hepatitis delta (BEA-Score), coordinated by Dr. Heiner Wedemeyer (Germany). Finally, in relation to the hepatitis E virus (HEV) we also have been conducted phylogenetic and variability studies by UDPS, and also epidemiological studies.

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G0035
Programme: P3. Cholestasis and Metabolic Disorders

Lead Researcher: Fernández-Checa Torres, José Carlos

Group members

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ASSOCIATED MEMBERS: Caballería Rovira, Juan | Colell Riera, Ana | García Ruiz, María del Carmen | Lluis Dúquez, José María | Mari García, Montserrat | Morales Muñoz, Albert

Main lines of research

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

Most relevant scientific articles

- Garcia-Ruiz C., Mato J.M., Vance D., Kaplowitz N., Fernandez-Checa J.C.. Acid sphingomyelinase-ceramide system in steatohepatitis: A novel target regulating multiple pathways. Journal of Hepatology. 2014;62(1):219-233.
- Fucho R., Martinez L., Baulies A., Torres S., Tarrats N., Fernandez A. et al. ASMase regulates autophagy and lysosomal membrane permeabilization and its inhibition prevents early stage non-alcoholic steatohepatitis. Journal of Hepatology. 2014.
- Altamirano J., Miquel R., Katoonizadeh A., Abraldes J.G., Duarte-Rojo A., Louvet A. et al. A histologic scoring system for prognosis of patients with alcoholic hepatitis. Gastroenterology. 2014;146(5).
- Win S., Than T.A., Fernandez-Checa J.C., Kaplowitz N.. JNK interaction with Sab mediates ER stress induced inhibition of mitochondrial respiration and cell death. Cell Death and Disease. 2014;5(1).
- Ribas V., Garcia-Ruiz C., Fernandez-Checa J.C.. Glutathione and mitochondria. Frontiers in Pharmacology. 2014;5 JUL.

Highlights

In 2014, our group has published 10 peer-review articles in international journals, of which 75% belong to the first quartile and more than 50% are inside the first decile. Of relevance is the novel role of the enzyme acid sphingomyelinase in the resolution of steatosis and stetaohepatitis and a new approach to identify histologic features associated with the severity of alcoholic steatohepatitis and to develop a patient classification system that might be used in clinical decision making.

During this year, financial resources have been provided by various national and international agencies that include six competitive national grants and three private foundation projects. The group has a consolidated collaborative project with the European Union (META CALL) with research partners from Germany and France. Of note is the continuous funding from the National Institute of Health granted to Dr. Fernández-Checa since 1995, which implies a close collaboration with basic and clinical researchers from the University of Southern California among others.

The group also applied and granted a national collaborative project (RETOS-COLABORACION, 2014) that was initiated in 2014. Furthermore, in 2014 has begun a project awarded in the last *Fundacio La Marató de TV3* call.

We have stablished a new collaboration with CIBEREHD partners from the Leon University, related to the role of sphingolipids in liver diseases.

We keep working in collaboration with Dr. Mato's group also at CIBEREHD and with new partners from CIBERDEM and CIBERER.

Collaborations have been established and continued at the national environment (Hospital Vall d'Hebró, IQAC-CSIC, Universitat Autònoma de Barcelona, Universitat de Barcelona, Universidad Complutense, Universidad del Pais Vasco UPV/EHU-CSIC) and international levels (Chile, Germany, Portugal, France. Italy, USA, UK).

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G0004
Programme: P2. Viral Hepatitis

Lead Researcher: Forns Bernhardt, Xavier

Group members

STAFF MEMBERS: González Ferndández de Córdoba, Patricia | Mingorance Pérez, Lidia | Pérez del Pulgar Gallart, Sofía.

ASSOCIATED MEMBERS: Costa Camps, Josep | Londoño Hurtado, María Carlota | Sánchez Tapias, José María

Main lines of research

- Genetic evolution of hepatitis C virus in the liver transplant 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.
- Evaluation of new hepatitis C treatments and impact of antiviral treatment in the natural history of chronic hepatitis C.
- Study of host factors in relation to the natural history and treatment response among patients with chronic hepatitis C.
- Evaluation of early histological markers of fibrosis progession in liver transplant recipients with hepatitis C recurrence and validation of non-invasive diagnostic methods of liver fibrosis.

Most relevant scientific articles

- Poordad F., Hezode C., Trinh R., Kowdley K.V., Zeuzem S., Agarwal K. et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. New England Journal of Medicine. 2014;370(21):1973-1982.
- Kwo P.Y., Mantry P.S., Coakley E., Te H.S., Vargas H.E., Brown R. et al. An interferon-free antiviral regimen for HCV after liver transplantation. New England Journal of Medicine. 2014;371(25):2375-2382.
- Forns X., Lawitz E., Zeuzem S., Gane E., Bronowicki J.P., Andreone P. et al. Simeprevir with peginterferon and ribavirin leads to high rates of SVR in patients with HCV genotype 1 who relapsed after previous therapy: A phase 3 trial. Gastroenterology. 2014;146(7).
- Mingorance L., Friesland M., Coto-Llerena M., Perez-del-Pulgar S., Boix L., Lopez-Oliva J.M. et al. Selective inhibition of hepatitis c virus infection by hydroxyzine and benztropine. Antimicrobial Agents and Chemotherapy. 2014;58(6):3451-3460.
- Fernandez-Carrillo C., Coto-Llerena M., Gonzalez P., Crespo G., Mensa L., Caro-Perez N. et al. IFNL4 polymorphism predicts response to hepatitis C treatment after liver transplantation. Journal of Clinical Virology. 2014.

Highlights

- Participation and leadership of international clinical trials for the evaluation of the efficacy and safety of new direct acting antivirals against hepatitis C virus in special populations: decompensated cirrhotics, cirrhotics awaiting liver transplantation and liver transplant recipients.
- Participation of group members in the development of EASL and AEEH clinical guidelines for the management of chronic hepatitis C, as well as in the AEMPS expert reports for the new antivirals.
- The completion of hepatitis C virus imaging studies in liver biopsies has allowed us to implement in the clinical practice a reliable method to assess the presence of HCV antigens in liver tissue.
- We are currently participating in 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 realization of a proof of concept clinical trial for the prevention of graft infection after liver transplantation. This consortium is composed of 7 European partners from different areas: industry, academia, research institutes and hospitals.
- Dr. Xavier Forns has directed the postgraduate course of AEEH-CIBEREHD "Management of patients with rare liver disease" within the XXXIX AEEH's Annual Congress, held in February 2014 in Madrid.

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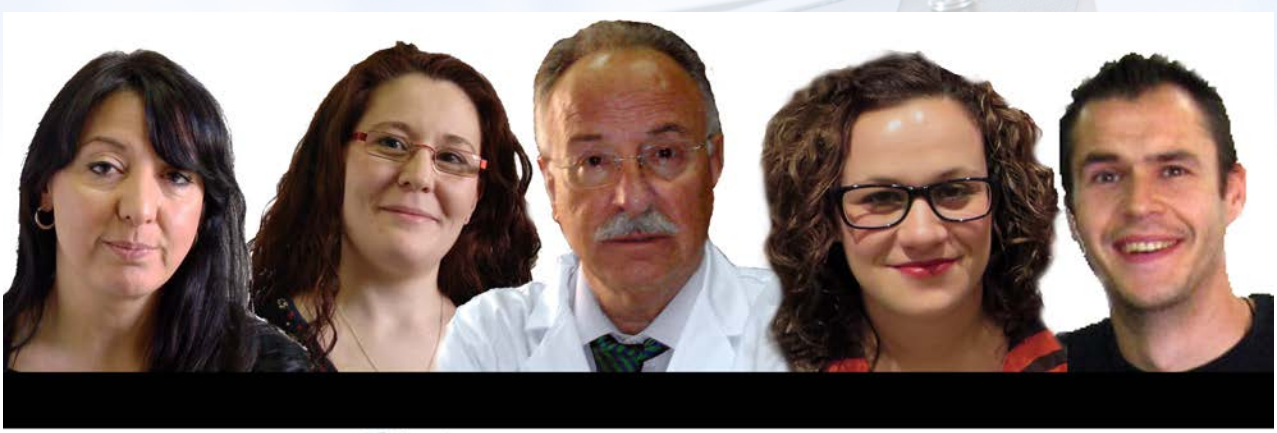
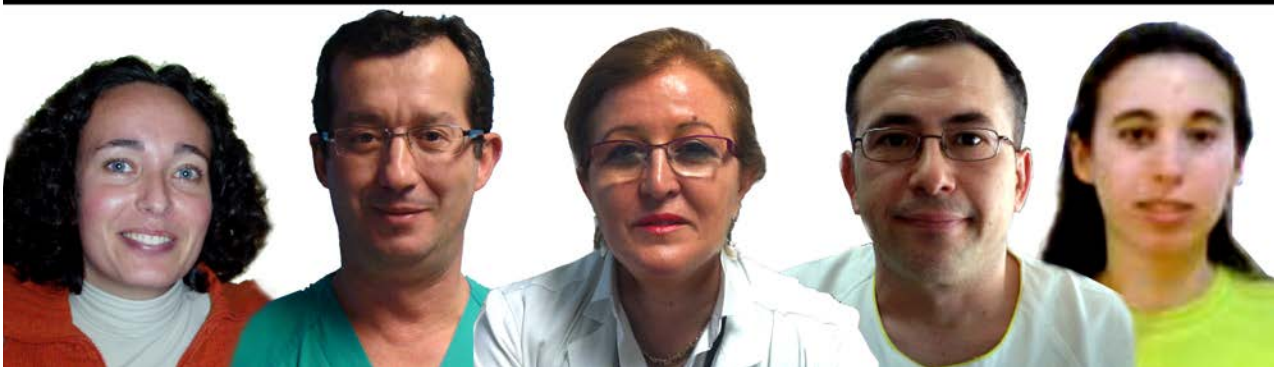
G0048
Programme: P2. Viral Hepatitis





Lead Researcher: García Buey, Luisa Consuelo

Group members

STAFF MEMBERS: Alonso Martín, M Jesús | Sanz Cameno, Paloma.

ASSOCIATED MEMBERS: Gondar Sousa, Virginia | López Rodríguez, Rosario | Majano Rodríguez, Pedro Lorenzo | Moreno Monteagudo, José Andrés | Moreno Otero, Ricardo | Muñoz Calleja, Cecilia | Trapero Marugan, María |

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

- Pisonero-Vaquero S., Garcia-Mediavilla M.V., Jorquera F., Majano P.L., Benet M., Jover R. et al. Modulation of PI3K-LXRα-dependent lipogenesis mediated by oxidative/nitrosative stress contributes to inhibition of HCV replication by quercetin. Laboratory Investigation. 2014;94(3):262-274.
- Cabaleiro T., Ochoa D., Lopez-Rodriguez R., Roman M., Novalbos J., Ayuso C. et al. Effect of polymorphisms on the pharmacokinetics, pharmacodynamics, and safety of risperidone in healthy volunteers. Human Psychopharmacology. 2014.
- Reglero-Real N., Alvarez-Varela A., Cernuda-Morollon E., Feito J., Marcos-Ramiro B., Fernandez-Martin L. et al. Apicobasal polarity controls lymphocyte adhesion to hepatic epithelial cells. Cell Reports. 2014;8(6):1879-1893.
- Martin-Vilchez S., Rodriguez-Munoz Y., Lopez-Rodriguez R., Hernandez-Bartolome A., Borque-Inurrita M.J., Molina-Jimenez F. et al. Inhibition of Tyrosine Kinase Receptor Tie2 Reverts HCV-Induced Hepatic Stellate Cell Activation. PLoS ONE. 2014;9(10).
- Sanmamed M.F., Carranza-Rua O., Alfaro C., Onate C., Martin-Algarra S., Perez G. et al. Serum interleukin-8 reflects tumor burden and treatment response across malignancies of multiple tissue origins. Clinical Cancer Research. 2014;20(22):5697-5707.

Highlights

Our research group is particularly focused on identifying non-invasive prognostic biomarkers of chronic liver diseases (CLD) progression to cirrhosis and hepatocellular carcinoma (HCC). We are also interested in understanding how 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 including entry, assembly, egress and spread.

We found that peripheral levels of angiopoietins significantly correlated with hepatic fibrosis in patients with chronic hepatitis C (CHC) and characterized the significance of certain genetic variants in relation to fibrosis progression (Patents ES2422874 and ES2423154).

Our group also reported the expansion of proangiogenic and immunosuppressive Tie2-expressing monocytes (TEMs) in the peripheral blood of CHC patients, which might prevent proper immune response and promote liver damage. Tie2 expression on the surface of this subtype of monocytes might serve as useful "tag" for the non-invasive monitoring of CLD progression. Moreover, we believe that a more in depth understanding of TEMs regulation can lead to important therapeutic advances. Based on such evidences, our research group is focused on addressing the role of all above humoral, cellular and genetic angiogenic factors together as liquid biopsy for diagnosis, prognosis and monitoring of CLD progression to HCC.

We also determined that HCV egress is a clathrin-dependent process. We are studying 1) cellular factors implicated in HCV entry in highly polarized cultures; 2) the role of apolipoproteins in HCV spread; 3) changes in hepatocyte proteome after HCV infection. Also, we are exploring whether dendrimer-based therapies could be used to inhibit HCV infection.

Therefore, these studies may provide new insights for our understanding of virus-host interactions and the molecular mechanisms underlying pathogenesis of progressive liver disease. We believe that these projects could identify molecular targets involved in CLD, improving their clinical management.

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GO023

Programme: P5. Hepatic and gastrointestinal oncology

Lead Researcher: García Marín, José Juan

Group members

STAFF MEMBERS: Briz Sánchez, Oscar

ASSOCIATED MEMBERS: González San Martín, Francisco | Herráez Aguilar, Elisa | Jiménez Vicente, Felipe Alfonso | Monte Río, María Jesús | Pérez García, María José | Rodríguez Macías, Rocío Isabel | Rodríguez Romero, Marta | Serrano García, María Ángeles

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

- Gonzalez-Sanchez E., Marin J.J.G., Perez M.J.. The expression of genes involved in hepatocellular carcinoma chemoresistance is affected by mitochondrial genome depletion. Molecular Pharmaceutics. 2014;11(6):1856-1868.
- Lozano E., Sanchez-Vicente L., Monte M.J., Herraez E., Briz O., Banales J.M. et al. Cocarcinogenic effects of intrahepatic bile acid accumulation in cholangiocarcinoma development. Molecular Cancer Research. 2014;12(1):91-100.
- Garcia-Rodriguez J.L., Barbier-Torres L., Fernandez-Alvarez S., Gutierrez-de Juan V., Monte M.J., Halilbasic E. et al. SIRT1 controls liver regeneration by regulating bile acid metabolism through farnesoid X receptor and mammalian target of rapamycin signaling. Hepatology. 2014;59(5):1972-1983.
- Urribarri A.D., Munoz-Garrido P., Perugorria M.J., Erice O., Merino-Azpitarte M., Arbelaiz A. et al. Inhibition of metalloprotease hyperactivity in cystic cholangiocytes halts the development of polycystic liver diseases. Gut. 2014.
- Andress E.J., Nicolaou M., Romero M.R., Naik S., Dixon P.H., Williamson C. et al. Molecular mechanistic explanation for the spectrum of cholestatic disease caused by the S320F variant of ABCB4. Hepatology. 2014;59(5):1921-1931.

Highlights

During 2014, the Laboratory of Experimental Hepatology and Drug Targeting (HEVEFARM) has actively developed several lines of research in collaboration with other groups of the CIBERehd, especially theses involving doctors Bujanda and Bañales in Biodonostia (San Sebastián), Prieto and Ávila in CIMA (Pamplona) and Mato and Martinez-Chantal in CICbioGUNE (Bilbao). In addition, we have established several collaborations with groups in Würzburg (Germany), Ancona (Italy) and Groningen (Netherlands), which have allowed the participation of the HEVEFARM in two applications for funding of research projects to international agencies. The research efforts have been focused on characterizing the role of drug transporters in the lack of response of hepatocellular carcinoma and cholangiocarcinoma to chemotherapy and the development of biotechnological strategies to overcome such chemoresistance. The later was the subject of the PhD Thesis defended by Laura Sanchez Vicente in June 2014. In September 2014, Cecilia Estiú, coordinator in Argentina of the program for prevention and management of gestational cholestasis, also presented her Doctoral Thesis. With her participation and the collaboration of the Department of Obstetrics, Gynecology and Pediatrics, University of Salamanca, a Clinical Practice Guidelines for Intrahepatic Cholestasis of Pregnancy was elaborated (http://campus.usal.es/~ogyp). A significant effort has been devoted to studying another subject in hepatology research related to the control of the expression of plasma membrane transporters. More precisely, the signalling pathway mediated by the nuclear receptor FXR and their participation in both chemoprotection of healthy liver cells and refractoriness to chemotherapy of liver tumors. Regarding education, the HEVEFARM has coordinated a PhD program and Master's Degree on Cellular and Molecular Pathophysiology and Pharmacology.

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G0009
Programme: P3. Cholestasis and Metabolic Disorders

Lead Researcher: García Monzón, Carmelo

Group members

ASSOCIATED MEMBERS: Lozano Trotonda, Carlos | Pita Fernández, Luís | Sáez Sáez, Alicia | Vargas Castrillón, Rodolfo Javier

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

- Sheedfar F., Sung M.M.Y., Aparicio-Vergara M., Kloosterhuis N.J., Miquilena-Colina M.E., Vargas-Castrillon J. et al. Increased hepatic CD36 expression with age is associated with enhanced susceptibility to nonalcoholic fatty liver disease. Aging. 2014;6(4):281-295.
- Gonzalez-Rodriguez A., Mayoral R., Agra N., Valdecantos M.P., Pardo V., Miquilena-Colina M.E. et al. Impaired autophagic flux is associated with increased endoplasmic reticulum stress during the development of NAFLD. Cell Death and Disease. 2014;5(4).
- Martínez-Una M., Varela-Rey M., Mestre D., Fernandez-Ares L., Fresnedo O., Fernandez-Ramos D. et al. S-Adenosylmethionine increases circulating very-low density lipoprotein clearance in non-alcoholic fatty liver disease. Journal of Hepatology. 2014.
- García-Monzón C., Lo Iacono O., Crespo J., Romero-Gómez M., García-Samaniego J., Fernández-Bermejo M. et al. Increased soluble CD36 is linked to advanced steatosis in nonalcoholic fatty liver disease. European Journal of Clinical Investigation. 2014;44(1):65-73.

Highlights

During the past 2014, my group largely focused on 2 main research lines. 1) To unravel the molecular mechanisms involved in the pathogenesis of NAFLD/NASH and extrahepatic comorbidities searching for potential therapeutic targets. In that regard, we demonstrated, such in distinct NAFLD animal models as in liver biopsies from NAFLD patients, that aging increased hepatic lipid content by inducing CD36 expression on the plasmatic membrane of hepatocytes (1). Moreover, we found that autophagic flux is impaired in hepatocytes from NASH patients and murine models of NASH (2) and we are, therefore, proposing to investigate in the next future whether therapies aimed to restore the autophagic flux might prevent or attenuate the progression of NAFLD. On the other hand, we shown that excess hepatic S-adenosylmethionine levels disrupt VLDL assembly and features and increase circulating VLDL clearance which will cause increased VLDL-lipid supply to tissues and might contribute to the extrahepatic complications of NAFLD (3). 2) Identification of biomarkers able to be used for noninvasive diagnosis of NASH. A recent study on non-diabetic healthy subjects found that circulating levels of soluble CD36 (sCD36) were associated with the degree of fatty liver estimated by ultrasound and analytical algorithms, suggesting that sCD36 might be a biomarker of liver fat. Therefore, we aimed to determine serum sCD36 levels in a population of 399 individuals including patients with biopsy-proven NAFLD, with chronic hepatitis C and with histologically normal liver, searching for potential correlations between circulating sCD36 and hepatic CD36 expression as well as clinical, metabolic and histological features of each liver disease. The main conclusion of this study was that serum level of sCD36 correlated with the histological grade of steatosis and is an independent factor associated with advanced steatosis in NAFLD but not in chronic hepatitis C patients (4).

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GO083
Programme: P2. Viral Hepatitis

Lead Researcher: García-Samaniego Rey, Javier

Group members

STAFF MEMBERS: Madejón Seiz, Antonio.

ASSOCIATED MEMBERS: Martín Carbonero, Luz | Romero Portales, Miriam | Sheldon, Julie Ann

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

- Razavi H., Waked I., Sarrazin C., Myers R.P., Idilman R., Calinas F. et al. The present and future disease burden of hepatitis C virus (HCV) infection with today's treatment paradigm. Journal of viral hepatitis. 2014;21:34-59.
- Wedemeyer H., Duberg A.S., Buti M., Rosenberg W.M., Frankova S., Esmat G. et al. Strategies to manage hepatitis C virus (HCV) disease burden. Journal of viral hepatitis. 2014;21:60-89.
- Garcia-Monzon C., Lo Iacono O., Crespo J., Romero-Gomez M., Garcia-Samaniego J., Fernandez-Bermejo M. et al. Increased soluble CD36 is linked to advanced steatosis in nonalcoholic fatty liver disease. European Journal of Clinical Investigation. 2014;44(1):65-73.
- Bruggmann P., Berg T., Ovrehus A.L., Moreno C., Brandao Mello C.E., Roudot-Thoraval F. et al. Historical epidemiology of hepatitis C virus (HCV) in selected countries. Journal of viral hepatitis. 2014;21:5-33.
- Ampuero J., Del Campo J.A., Rojas L., Garcia-Lozano J.R., Sola R., Andrade R. et al. PNPLA3 rs738409 causes steatosis according to viral & IL28B genotypes in hepatitis C. Annals of Hepatology. 2014;13(4):356-363.

Highlights

PUBLIC AND PRIVATE FUNDING

- Active and competitive public projects:

  Identification in plasma and PBMCs of telaprevir or boceprevir treatment resistant HCV variants using the Cold-PCR technique. Usefulness for monitorization of the treatment response (FIS PI12/02146).
- Active and competitive private projects:

  Genetic and epigenetic analysis of HBV in inactive carriers. Implications for the therapeutic decision. I Convocatoria del Programa de Ayudas a Proyectos de Investigacion en VIH y VHC. (GLD13/00046).
- Collaboration with private companies and foundations:

  Performance evaluation of a qPCR based point-of-care test (POCT) for blood-borne viral infections: HCV, HIV and HTLV. Granted by Epistem, Inc., and Bill & Melinda Gates Foundation.
- Participation in translation activities:

  The members of the working group participated in 12 international clinical trials.
- Participation in training and teaching activities:

The group has received during the year 2014 two pre-doctoral students in training.

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G0007
Programme: P1. Portal Hypertension and Cirrhosis

Lead Researcher: Genesca Ferrer, Joan

Group members

STAFF MEMBERS: Chavarría Vilarasau, Laia | García Lezana, Teresa.

ASSOCIATED MEMBERS: Augustín Recio, Salvador | Jacas Escarcelle, Carlos | Martell Pérez Alcalde, María | Mínguez Rosique, Beatriz | Vargas Blasco, Víctor

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

- Cordoba J., Ventura-Cots M., Simon-Talero M., Amoros A., Pavesi M., Vilstrup H. et al. Characteristics, risk factors, and mortality of cirrhotic patients hospitalized for hepatic encephalopathy with and without acute-on-chronic liver failure (ACLF). Journal of Hepatology. 2014;60(2):275-281.
- Reverter E., Tandon P., Augustin S., Turon F., Casu S., Bastiampillai R. et al. A MELD-based model to determine risk of mortality among patients with acute variceal bleeding. Gastroenterology. 2014;146(2):
- Augustin S., Millan L., Gonzalez A., Martell M., Gelabert A., Segarra A. et al. Detection of early portal hypertension with routine data and liver stiffness in patients with asymptomatic liver disease: A prospective study. Journal of Hepatology. 2014;60(3):561-569.
- Cordoba J., Ventura-Cots M.. Drug-induced removal of nitrogen derivatives in urine: A new concept whose time has come. Hepatology. 2014;59(3):764-766.
- Ezkurdia N., Raurell I., Rodriguez S., Gonzalez A., Esteban R., Genesca J. et al. Inhibition of neuronal apoptosis and axonal regression ameliorates sympathetic atrophy and hemodynamic alterations in portal hypertensive rats. PLoS ONE. 2014;9(1).

Highlights

During 2014, we have continued with a high number of collaborative research projects with other CIBER groups and international groups, which have led to high impact publications. It is worth to mention that the group has been awarded with a grant by the ISCIIII for a national multicenter clinical trial in the specific calll for independent clinical research.

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G0020
Programme: P1. Portal Hypertension and Cirrhosis

Lead Researcher: Ginés Gibert, Pere

Group members

STAFF MEMBERS: Castro Villa, Miriam | Fernández Varo, Guillermo | Pavesi, Marco | Ribera Sabaté, Jordi | Titos Rodríguez, Esther

ASSOCIATED MEMBERS: Bataller Arberola, Ramón | Casals Mercadal, Gregori | Claria Enrich, Joan | Coll Loperena, Mar | Fernández Gómez, Javier | Graupera García Mila, Isabel | Guevara Montserrat, Monica | Jiménez Povedano, Wladimiro | Marfa Bruix, Santiago | Morales Ruiz, Manuel | Poblet, Roser | Rodrigo Torres, Daniel | Sancho Bru, Pau | Sola Verges, Elsa | Van Berckel, Nicola

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

- Lee M.Y., Luciano A.K., Ackah E., Rodriguez-Vitad J., Bancroft T.A., Eichmann A. et al. Endothelial Akt1 mediates angiogenesis by phosphorylating multiple angiogenic substrates. Proceedings of the National Academy of Sciences of the United States of America. 2014;111(35):12865-12870.
- Rodriguez E., Elia C., Sola E., Barreto R., Graupera I., Andrealli A. et al. Terlipressin and albumin for type-1 hepatorenal syndrome associated with sepsis. Journal of Hepatology. 2014;60(5):955-961.
- Rius B., Titos E., Moran-Salvador E., Lopez-Vicario C., Garcia-Alonso V., Gonzalez-Periz A. et al. Resolvin D1 primes the resolution process initiated by calorie restriction in obesity-induced steatohepatitis. FASEB Journal. 2014;28(2):836-848.
- Lopez-Vicario C., Gonzalez-Periz A., Rius B., Moran-Salvador E., Garcia-Alonso V., Lozano J.J. et al. Molecular interplay between Δ5/Δ6 desaturases and long-chain fatty acids in the pathogenesis of non-alcoholic steatohepatitis. Gut. 2014;63(2):344-355.
- Barreto R., Elia C., Sola E., Moreira R., Ariza X., Rodriguez E. et al. Urinary neutrophil gelatinase-associated lipocalin predicts kidney outcome and death in patients with cirrhosis and bacterial infections. Journal of Hepatology. 2014;61(1):35-42.

Highlights

Studies on 'Acute-on-Chronic Liver Failure (ACLF) in the setting of the EASL-CLIF CONSORTIUM have created 2 new scores useful to predict the prognosis of patients with ACLF.

Another field of research has been based on the study of AKI (Acute Injury Kideny) in patients with cirrhosis. One study has demonstrated the efficacy of terlipressin and albumin in the treatment of type 1 HRS associated with bacterial infections, a new indication that had not been previously established. Pere Ginès as a member of the International Ascites Club (IAC), is the author of a consensus document for the diagnosis and management AKI in cirrhosis.

Restoration of the hepatic omega-6 to omega-3 fatty acid balance is a potential strategy for the prevention of metabolic liver disease.

Administration of pro-resolving lipid mediators derived from omega-3 fatty acids potentiates the beneficial effects of a calorie restriction diet in obesity–induced steatohepatitis.

A phosphoproteomics study in vascular endothelium has allowed us to characterize the phosphoproteome of the Akt1 and Akt2 isoforms. Specifically, targets involved in vascular maintenance and development are preferably phosphorylated by Akt1. We identified novel targets of Akt that may have therapeutic potential.

The lack of a 5.9 kDa peptide of fibrinogen a chain is an early serum biomarker of fibrosis progression in patients. In addition, we evaluated the therapeutic potential of novel agents that combine the safety and biospecificity of nanoparticles with the antioxidant properties of cerium oxide and the efficacy of selective vasopressin V1 receptor agonists.

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G0086
Programme: P2. Viral Hepatitis

Lead Researcher: Gómez Castilla, Jordi

Group members

STAFF MEMBERS: Ariza Mateos, M Ascensión | Perales Viejo, C. Belén

ASSOCIATED MEMBERS: Briones Llorente, Carlos | Domingo Solans, Esteban | García Sacristán, Ana |

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-delJesus, 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'. Article in revision.

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

- Romero-Lopez C., Barroso-DelJesus A., Garcia-Sacristan A., Briones C., Berzal-Herranz A.. End-to-end crosstalk within the hepatitis C virus genome mediates the conformational switch of the 30X-tail region. Nucleic Acids Research. 2014;42(1):567-582.
- Moreno E., Ojosnegros S., Garcia-Arriaza J., Escarmis C., Domingo E., Perales C.. Exploration of sequence space as the basis of viral RNA genome segmentation. Proceedings of the National Academy of Sciences of the United States of America. 2014;111(18):6678-6683.
- Perales C., Beach N.M., Sheldon J., Domingo E.. Molecular basis of interferon resistance in hepatitis C virus. Current Opinion in Virology. 2014;8:38-44.
- Sheldon J., Beach N.M., Moreno E., Gallego I., Pineiro D., Martinez-Salas E. et al. Increased replicative fitness can lead to decreased drug sensitivity of hepatitis C virus. Journal of Virology. 2014;88(20):12098-12111.
- Cubero M., Gregori J., Esteban J.I., Garcia-Cehic D., Bes M., Perales C. et al. Identification of host and viral factors involved in a dissimilar resolution of a hepatitis C virus infection. Liver International. 2014;34(6):896-906.

Highlights

The replicative and strucutral properties of RNA in the infection of by hepatitis C virus and resistance to interferon treatment.

Institution: Agencia Estatal Consejo Superior de Investigaciones Científicas

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G0013
Programme: P3. Cholestasis and Metabolic Disorders

Lead Researcher: González Gallego, Javier

Group members

STAFF MEMBERS: Crespo Gómez, Irene | García Mediavilla, M Victoria.

ASSOCIATED MEMBERS: Jorquera Plaza, Francisco | Mauriz Gutiérrez, José Luis | Olcoz Goñi, José Luis | Sánchez Campos, Sonia | Tuñón González, María Jesús

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

- Ordonez R., Carbajo-Pescador S., Prieto-Dominguez N., Garcia-Palomo A., Gonzalez-Gallego J., Mauriz J.L.. Inhibition of matrix metalloproteinase-9 and nuclear factor kappa B contribute to melatonin prevention of motility and invasiveness in HepG2 liver cancer cells. Journal of Pineal Research. 2014;56(1):20-30.
- San-Miguel B., Crespo I., Vallejo D., Alvarez M., Prieto J., Gonzalez-Gallego J. et al. Melatonin modulates the autophagic response in acute liver failure induced by the rabbit hemorrhagic disease virus. Journal of Pineal Research. 2014;56(3):313-321.

- Vallejo D., Crespo I., San-Miguel B., Alvarez M., Prieto J., Tunon M.J. et al. Autophagic response in the Rabbit Hemorrhagic Disease, an animal model of virally-induced fulminant hepatic failure. Veterinary Research. 2014;45(1).
- Pisonero-Vaquero S., Garcia-Mediavilla M.V., Jorquera F., Majano P.L., Benet M., Jover R. et al. Modulation of PI3K-LXRα-dependent lipogenesis mediated by oxidative/nitrosative stress contributes to inhibition of HCV replication by quercetin. Laboratory Investigation. 2014;94(3):262-274.
- Mauriz E., Carbajo-Pescador S., Ordonez R., Garcia-Fernandez M.C., Mauriz J.L., Lechuga L.M. et al. On-line surface plasmon resonance biosensing of vascular endothelial growth factor signaling in intact-human hepatoma cell lines. Analyst. 2014;139(6):1426-1435.

Highlights

- Publications 1stdecil: 4 • Publications 1stquartile: 6 • IF total: 30.456
- Nº projects/contract: 8
- Public funding: €64.913
- Private funding: €30.304
- Multicentric clinical trials: 5
- Collaborations CIBERehd: José V Castell (Valencia); Ricardo Moreno (Madrid); Jesús Mª Prieto (Navarra).
- Collaborations other CIBER: Laura M Lechuga (CIBERbbn, Barcelona).

RELEVANT PROJECTS:

"Estudio del efecto del tratamiento con quercetina y del trasplante de microbiota intestinal en modelos experimentales de hígado graso no alcohólico". Ministerio de Economía y Competitividad. 2014-2016. • "Efecto de flavonoides sobre el desarrollo de esteatosis, esteatohepatitis y hepatocarcinoma en modelos in vivo e in vitro de NAFLD". Programa de apoyo a proyectos de investigación, Consejería de Educación JCyL. 2014-2016. • "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 I+D+i 2013-2015. • "Eficacia de la glutamina en la prevención de enteritis rádica aguda y su efecto sobre el estrés oxidativo". Gerencia Regional de Salud JCyL. 2011-2014. • "Efecto de moléculas antioxidantes sobre la progresión de NAFLD a hepatocarcinoma". Fundación Investigación Sanitaria. 2013-2014. • "Nuevas opciones terapéuticas en la fibrosis hepática: estudios in vivo e in vitro". Fundación Investigación Sanitaria. 2014. • "Estudios de nuevas estrategias para el tratamiento del hepatocarcinoma: Papel de la autofagia". Sandoz. 2014. • "Estudio de nuevas estrategias para el tratamiento de la fibrogénesis en patologías hepáticas: Papel de la autofagia". CombinoPharm. 2014.

THESES

- "Efecto de la melatonina sobre la autofagia, el estrés del retículo endoplasmático y la apoptosis en el fallo hepático agudo inducido por el virus de la enfermedad hemorrágico del conejo". Daniela Vallejo. Directores: Mª Jesús Tuñón/Marcelino Álvarez Sobresaliente "Cum Laude" (Mención Internacional).
- "Estudio de los mecanismos patogénicos de la hepatitis C y su relación con el desarrollo de esteatosis. Efecto de un tratamiento antioxidante con flavonoides". Sandra Pisonero. Directores: Sonia Sánchez-Campos/Mª Victoria García-Mediavilla. Sobresaliente "Cum Laude".

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GO030

Programme: P1. Portal Hypertension and Cirrhosis

Lead Researcher: Guarner Aguilar, Carlos

Group members

STAFF MEMBERS: Pavel, Oana | Sánchez Ardid, Elisabet.

ASSOCIATED MEMBERS: Román Abal, Eva Mª | Soriano Pastor, Germán | Torras Colell, Javier | Villanueva Sánchez, Candido

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

- Cuenca S., Sanchez E., Santiago A., El Khader I., Panda S., Vidal S. et al. Microbiome composition by pyrosequencing in mesenteric lymph nodes of rats with CCl4-induced cirrhosis. Journal of Innate Immunity. 2014;6(3):263-271.
- Rodriguez E., Elia C., Sola E., Barreto R., Graupera I., Andrealli A. et al. Terlipressin and albumin for type-1 hepatorenal syndrome associated with sepsis. Journal of Hepatology. 2014;60(5):955-961.
- Puente A., Hernandez-Gea V., Graupera I., Roque M., Colomo A., Poca M. et al. Drugs plus ligation to prevent rebleeding in cirrhosis: An updated systematic review. Liver International. 2014;34(6):823-833.
- Roman E., Torrades Ma.T., Nadal Ma.J., Cardenas G., Nieto J.C., Vidal S. et al. Randomized pilot study: Effects of an exercise programme and leucine supplementation in patients with cirrhosis. Digestive Diseases and Sciences. 2014;59(8):1966-1975.
- Concepcion-Martin M., Gomez-Oliva C., Juanes A., Diez X., Prieto-Alhambra D., Torras X. et al. Somatostatin for prevention of post-ERCP pancreatitis: A randomized, double-blind trial. Endoscopy. 2014.

Highlights

The Group CIBEREHD IP Dr. Carlos Guarner has had great scientific activity in clinical and basic lines. Emphasize collaboration with groups of CIBEREHD (Drs. Arroyo, Bosch, Córdoba, Genescá, Albillos, Such, Andrade, F. Guarner) of CIBERNED (Dr. Kulisevsky) and CIBERER (Dr. Diaz-Way).

Among the published results highlight the clinical hepatic encephalopathy field show that an exercise program in patients with cirrhosis without ascites is safe, functional capacity increases and improves quality of life.

In clinical field of portal hypertension we completed the analysis of PRAKO study, which shows that a guided hemodynamic monitoring treatment improves the effectiveness of the current first-line therapy (with ß-blockers and endoscopic ligation) for the prevention of variceal rebleeding.

Has been extended PREDESCI study to assess the prevention of decompensation in cirrhosis by treating portal hypertension, with new FIS. Has completed the corresponding manuscript to study development of hyperdynamic circulation and response to ß-bloquenates at different stages of compensated cirrhosis with subclínical and clinically significant portal hypertension.

In the experimental field, we have published the probiotic VSL # 3 improves the intestinal barrier, reduces bacterial translocation and modulates the proinflammatory state in rats with cirrhosis. This study has allowed to initiate a randomized double-blind trial to evaluate the effect of VSL # 3 on the inflammatory response and cognitive status in cirrhotic patients.

In an experimental study on bacterial translocation determined by pyrosequencing technique we found that in cirrhotic and normal rats bacterial load present in the mesenteric lymph nodes was similar, but less diversity was observed in cirrhotic. The study is ongoing.

We have organized two continuing education courses, led by IP: XCVII Course of the School of Digestive Pathology and XXXI Course of deep sedation with propofol for endoscopists.

We have participated in 14 projeects and clinical assays in 2014.

The Dra. A. Puente presented his Doctoral Thesis being the co-director Dr. C. Villanueva of our group.

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G0062

Programme: P6. Gastrointestinal Inflammation and Motility

Lead Researcher: Guarner Aguilar, Francisco

Group members

STAFF MEMBERS: Varela Castro, Encarnación.

ASSOCIATED MEMBERS: Antolin Mate, María | Borruel Sáinz, Natalia | Casellas Jorda, Francisco | Manichanh, Chaysavanh | Molero Richard, Francesc Xavier | Vilaseca Momplet, Jaime

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

- Manichanh C., Eck A., Varela E., Roca J., Clemente J.C., Gonzalez A. et al. Anal gas evacuation and colonic microbiota in patients with flatulence: Effect of diet. Gut. 2014;63(3):401-408.
- Hill C., Guarner F., Reid G., Gibson G.R., Merenstein D.J., Pot B. et al. Expert consensus document: The international scientific association for probiotics and prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nature Reviews Gastroenterology and Hepatology. 2014;11(8):506-514.
- Li J., Wang J., Jia H., Cai X., Zhong H., Feng Q. et al. An integrated catalog of reference genes in the human gut microbiome. Nature Biotechnology. 2014;32(8):834-841.
- Nielsen H.B., Almeida M., Juncker A.S., Rasmussen S., Li J., Sunagawa S. et al. Identification and assembly of genomes and genetic elements in complex metagenomic samples without using reference genomes. Nature Biotechnology. 2014;32(8):822-828.
- Cendrowski J., Sanchez-Arevalo Lobo V.J., Sendler M., Salas A., Kuhn J.-P., Molero X. et al. Mnk1 is a novel acinar cell-specific kinase required for exocrine pancreatic secretion and response to pancreatitis in mice. Gut. 2014.

Highlights

In 2014, we completed a catalog of 10 million non-human genes that coexist with humans as part of the living entities that colonize the gastrointestinal tract, in a symbiotic relationship with the human body. The catalog includes genes from bacteria, archaea, yeasts, viruses and protists, and was achieved by metagenomic sequencing of samples from 1300 individuals from Spain, Denmark, France, Italy, China and the United States. It is one of the achievements resulting from our participation in the International Human Microbiome Consortium, and will become a highly valuable tool for fully understanding metabolic and trophic functions provided by the human gut microbiota.

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G0066

Programme: P6. Gastrointestinal Inflammation and Motility

Lead Researcher: Lanas Arbeola, Ángel

Group members

STAFF MEMBERS: Arechavaleta Tabuenca, Samanta P. | Jiménez Molinos, Pilar.

ASSOCIATED MEMBERS: Arroyo Villarino, María Teresa | Baptista, Pedro Miguel | Benito Ruesca, Rafael | Casado Arroyo, Rubén | Ferrández Arenas, Ángel | García González, María Asunción | Gomollón García, Fernando | Ortego Fernández de Retana, Francisco Javier | Piazuelo Ortega, Elena | Roncales Casado, Pilar | Sáinz Samitier, Ricardo | Sopeña Biarge, Federico | Sostres Homedes, Carlos | Strunk Groot, Mark

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 Á, Carrera-Lasfuentes P, Arguedas Y, García S, Bujanda L, Calvet X et al. Risk of Upper and Lower Gastrointestinal Bleeding in Patients Taking Nonsteroidal Anti-inflammatory Drugs, Antiplatelet Agents, or Anticoagulants.Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2014.
- Lanas A., Sostres C.. PPI therapy: The small bowel, low-dose aspirin and PPIs-Should we be concerned?. Nature Reviews Gastroenterology and Hepatology. 2014;11(8):458-460.
- Patrignani P., Tacconelli S., Piazuelo E., Di Francesco L., Dovizio M., Sostres C. et al. Reappraisal of the clinical pharmacology of low-dose aspirin by comparing novel direct and traditional indirect biomarkers of drug action. Journal of Thrombosis and Haemostasis. 2014;12(8):1320-1330.
- Castells A., Quintero E., Alvarez C., Bujanda L., Cubiella J., Salas D. et al. Rate of Detection of Advanced Neoplasms in Proximal Colon by Simulated Sigmoidoscopy vs Fecal Immunochemical Tests. Clinical Gastroenterology and Hepatology. 2014;12(10):1708-1716.
- Alonso A, Domènech E, Julià A, Panés J, García-Sánchez V, Mateu PN et al. Identification of Risk Loci for Crohn's Disease Phenotypes Using a Genome-Wide Association Study.Gastroenterology. 2014.

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. • Fernando Gomollón. Eurpean project. Inflammatory Bowel Disease CHARACTERization by a multi-modal integrated biomarker study. Project acronym: IBD-CHARACTER, Grant agreement no: 305676. • Angel Lanas. European Project. CANCER12-014-PREDICT. Personalized prevention of colorectal neoplasia by use of genetic variability for the prediction of efficacy and toxicity of treatment with COX-2 inhibitors and aspirin. Coordinador del proyecto Dr. Aber NADIR. • Angel Lanas. Acetil salicilic acid and platelets in colon cancer. PI14/01218 • Elena Piazuelo. Proton transport inhibition for chemoprevention and treatment of esophageal adenocarcinoma. PI14/01931 • Angel Lanas. Acetylsalicylic acid and colorectal cancer prevention: Exploring the platelet function of its mechanism of action. Bayer International. 2014 • Elena Piazuelo. Epigenetic changes in the progression of Barrett's esophagus to esophageal adenocarcinoma: application to the identification of high risk patients. PI11/02089

EECC

• Fernando Gomollon. An Open-Label, Multicenter, Efficacy and Safety Study to Evaluate Two Treatment Algorithms in Subjects with Moderate to Severe Crohn's Disease.(CALM). Phase III. • Fernando Gomollon. A multicenter, randomized, double-blind study to evaluate the efficacy and safety of two Adalimumab induction regimens in subjetcts with moderately to severely active Crohn's disease and evidence of mucosal ulceration. Phase III. • Fernando Gomollon. A Double-Blind, Randomized, Multicenter Study of Higher Versus Standard Adalimumab Dosing Regimens for Induction and Maintenance Therapy in Subjects with Moderately to Severely. Phase III. • Fernando Gomollon. A Long-Term Non-Interventional Registry to Assess Safety and Effectiveness of HUMIRA® (Adalimumab) in Patients with Moderately to Severely Active Ulcerative Colitis (UC).

AWARDS

• II Prize "II Contest to Innovation" HCU Lozano Blesa. Innovative project: "Adequacy of waiting lists by management of agendas". Mª Teresa Arroyo Villarino.

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G1069
Programme: P3. Cholestasis and Metabolic Disorders

Lead Researcher: Martín Sanz, Paloma

Group members

ASSOCIATED MEMBERS: Bosca Gomar, Lisardo | Casado Pinna, Marta | Mayoral Moñibas, Rafael

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.

Most relevant scientific articles

- Traves P.G., Pardo V., Pimentel-Santillana M., Gonzalez-Rodriguez A., Mojena M., Rico D. et al. Pivotal role of protein tyrosine phosphatase 1B (PTP1B) in the macrophage response to pro-inflammatory and anti-inflammatory challenge. Cell Death and Disease. 2014;5(3).
- Gonzalez-Rodriguez A., Mayoral R., Agra N., Valdecantos M.P., Pardo V., Miquilena-Colina M.E. et al. Impaired autophagic flux is associated with increased endoplasmic reticulum stress during the development of NAFLD. Cell Death and Disease. 2014;5(4).
- Moreno-Caceres J., Caja L., Mainez J., Mayoral R., Martin-Sanz P., Moreno-Vicente R. et al. Caveolin-1 is required for TGF-ß-induced transactivation of the EGF receptor pathway in hepatocytes through the activation of the metalloprotease TACE/ADAM17. Cell Death and Disease. 2014;5(7).
- Pimentel-Santillana M., Traves P.G., Perez-Sen R., Delicado E.G., Martin-Sanz P., Miras-Portugal M.T. et al. Sustained release of prostaglandin e2in fibroblasts expressing ectopically cyclooxygenase 2 impairs p2y-dependent ca2+-mobilization. Mediators of Inflammation. 2014;2014.

Highlights

During 2014, we have focused on studying the autophagic flux and endoplasmic reticulum stress during the development of NAFLD in collaboration with Carmelo García Monzón del Ciberehd and Ángela Valverde from Ciberdem. Our study demonstrated that autophagic flux is impaired in livers from both patients and murine models of NAFLD, as well as in long-term palmitate-loaded hepatocytes, providing evidences that disruption of autophagy could be due to elevated endoplasmic reticulum stress leading to apoptosis. Our results strongly suggest that therapies aimed to restore the autophagic flux might prevent or attenuate the progression of NAFLD.

A collaborative study with Isabel Fabregat from IDIBELL has examined the role of Cav-1 in the antiapoptotic signals induced by TGF-ß in hepatocytes. Cav-1 is required for TGF-ß-mediated activation of the metalloprotease TACE/ADAM17 that is responsible for shedding of EGFR ligands and activation of the EGFR pathway, which counteracts the TGF-ß pro-apoptotic effects. Therefore, Cav-1 contributes to the pro-tumorigenic effects of TGF-ß in liver cancer cells.

Our group has also focused its work on studying the role of macrophages in the pathophysiology of major organs. Again with Ángela Valverde, we have studied the role of protein tyrosine phosphatase 1B (PTP1B) in the macrophage response to pro-inflammatory and anti-inflammatory challenge indicating that the broad use of PTP1B inhibitors, although with potential benefits for the treatment of diabetes, it accentuates pro-inflammatiry responses compromising at least macrophage viability and pro-resolution balance.

Finally, our results showed that the sustained release of prostaglandin E2 in fibroblasts impairs purinergic receptor P2Y-dependent Ca2+ mobilization. The inhibition of P2Y responses by PGE2 involves the activation of PKCs and PKD. Our data extend previous work in macrophages and suggest that this communication between PGs and P2 signaling in macrophage and fibroblasts contribute to the regulation of inflammatory response and repair of tissue damage.

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G0077

Programme: P4. Immunology and liver transplantation

Lead Researcher: De la Mata García, Manuel

Group members

STAFF MEMBERS: Ferrín Sánchez, Gustavo.

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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

- Rodriguez-Peralvarez M., Manousou P., Lerut J., De la Mata M., Burroughs A.K.. How much immunosuppression is needed after liver transplantation?. Clinical Transplantation. 2014;28(1):6-7.
- Rodriguez-Peralvarez M., De La Mata M., Burroughs A.K.. Liver transplantation: Immunosuppression and oncology. Current Opinion in Organ Transplantation. 2014;19(3):253-260.
- Ferrin G., Ranchal I., Llamoza C., Rodriguez-Peralvarez M.L., Romero-Ruiz A., Aguilar-Melero P. et al. Identification of candidate biomarkers for hepatocellular carcinoma in plasma of HCV-infected cirrhotic patients by 2-D DIGE. Liver International. 2014;34(3):438-446.
- Herencia C., Almaden Y., Ferrin G., Martinez-Romero R., de la Mata M., Ciria R. et al. Cardiotrophin-1 decreases liver apoptosis through calpastatin induction. Journal of Surgical Research. 2014.

Highlights

One of our main research lines is the influence of the immunosuppressor regime in the recurrence of hepatocarcinoma after liver transplant. Our results have shown that higher levels of calcineurin inhibitors during the first month after liver transplant were associated with a higher risk of tumor recurrence. These results have been published in several articles in journals of high impact factors. It should be pointed out the paper entitled "Reduced exposure to calcineurin inhibitors early after liver transplantation prevents recurrence of hepatocellular carcinoma", published in Journal of Hepatology, that has been awarded by IMIBIC as the most outstanding article in 2014 and with the XII "premio nacional de investigación del Ilustre Colegio Oficial de Médicos de Córdoba". Beside, our group has obtained funding from ISCIII to follow the research in this field, carrying out the project entitled "Relevance of the immune system activation to eliminate circulating tumor cells and preventing recurrence of hepatocellular carcinoma after liver transplantation".

As a result of the FIS project entitled "Proteomics approach to identification and validation of new molecular markers of diagnosis and progression of hepatocellular carcinoma", our group has identified 4 plasma biomarkers for the diagnosis of hepatocarcinoma in patients with cirrhosis related to HCV. Our results have been published in the first quartile journal, Liver International, and they have produced as a result the patent of a diagnosis blood method for detecting the hepatocarcinoma in patients with HCV.

Finally, it should be pointed out our contribution to the clnical guide entitled "Libro Blanco de la Hepatología en España".

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G0017
Programme: P3. Cholestasis and Metabolic Disorders

Lead Researcher: Mato De la Paz, José Mª

Group members

STAFF MEMBERS: Fernández Ramos, David | González Lahera, Aintzane | Royo López, Felix Miguel | Varela Rey, Marta.

ASSOCIATED MEMBERS: Abrescia, Nicola Gerardo | Aransay Bañares, Ana María | Beraza Aguilar, Naiara | Elortza Basterrika, Felix | Falcón Pérez, Juan Manuel | Martínez Chantar, María Luz

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 noninvasive 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

- Varela-Rey M., Iruarrizaga-Lejarreta M., Lozano J.J., Aransay A.M., Fernandez A.F., Lavin J.L. et al. S-adenosylmethionine levels regulate the schwann cell DNA methylome. Neuron. 2014;81(5):1024-1039.
- Garcia-Rodriguez J.L., Barbier-Torres L., Fernandez-Alvarez S., Gutierrez-de Juan V., Monte M.J., Halilbasic E. et al. SIRT1 controls liver regeneration by regulating bile acid metabolism through farnesoid X receptor and mammalian target of rapamycin signaling. Hepatology. 2014;59(5):1972-1983.
- Salazar M., Lorente M., Garcia-Taboada E., Perez Gomez E., Davila D., Zuniga-Garcia P. et al. Loss of Tribbles pseudokinase-3 promotes Akt-driven tumorigenesis via FOXO inactivation. Cell Death and Differentiation. 2014.
- Gradilla AC, González E, Seijo I, Andrés G, Bischoff M, González-Mendez L et al. Exosomes as Hedgehog carriers in cytoneme-mediated transport and secretion.Nature communications. 2014;5:5649.
- Azkargorta M., Wojtas M.N., Abrescia N.G.A., Elortza F.. Lysine methylation mapping of crenarchaeal DNA-directed RNA polymerases by collision-induced and electron-transfer dissociation mass spectrometry. Journal of Proteome Research. 2014;13(5):2637-2648.

Highlights

- Our group coordinates the project titled "Understanding obesity, metabolic syndrome, type 2 diabetes and fatty liver disease: a multidisciplinary approach" (JM Mato y ML Martínez-Chantar). This is one of the three projects funded by the ISCIII (Proyectos Integrados de Excelencia) with the participation of 12 groups belonging to CIBERSAM, CIBERDEM, CIBEROBN and CIBEREHD.
- The project titled "A study of the biogenesis and tissue distribution of exosomes to develop new therapeutic agents" by Dr. Juan Manuel Falcón is funded by Fundación Ramón Areces.
- Dr. Félix Elortza and Dr. Juan Manuel Falcón participate in the project MICROXOM (Development of a new technology for the collection of different subpopulations of exosomes from body fluids) founded by the Basque Government.
- The genome analysis platform, headed by Dr. Ana M Aransay, achieves a total of 63 services (more than 2300 samples) to 31 different users, which considered whole genome and customized genotyping by arrays, gene expression studies by arrays and massive-sequencing, as well as metilome and exome sequencing from different species.
- The project titled "Prohibitin 1 in liver injury and cancer" by Dr. José M Mato and Dr. M Luz Martínez-Chantar is funded by the NIH, USA.

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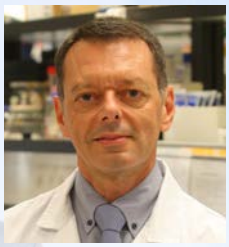
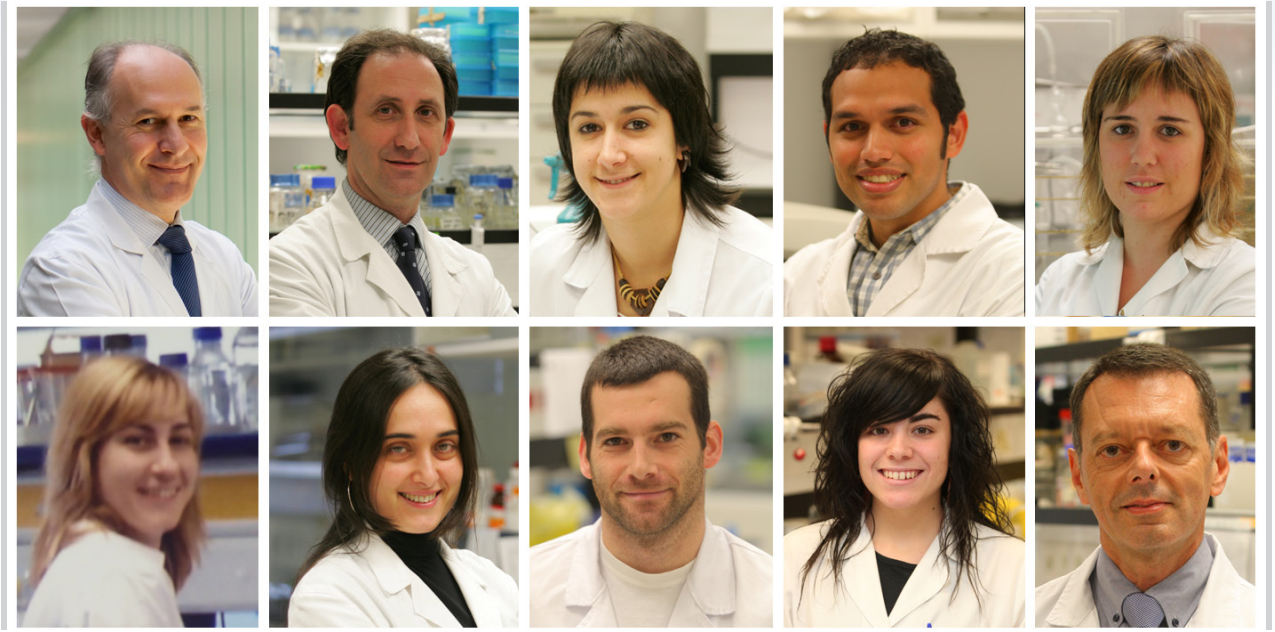


G0067
Programme: P3. Cholestasis and Metabolic Disorders



Lead Researcher: Medina Cabrera, Juan Francisco

Group members

STAFF MEMBERS: Arcelus Echavarri, Sara | Portu Garcia, Ainhoa

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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 (PBC); effects of ursodeoxycholic acid in PBC 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; role of protein nitrosylation for the regulation of the synthesis of bile acids.
- 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

- Rodriguez-Ortigosa C.M., Celay J., Olivas I., Juanarena N., Arcelus S., Uriarte I. et al. A GAPDH-mediated trans-nitrosylation pathway is required for feedback inhibition of bile salt synthesis in rat liver. Gastroenterology. 2014;147(5):1084-1093.
- Concepcion A.R., Salas J.T., Sarvide S., Saez E., Ferrer A., Lopez M. et al. Anion exchanger 2 is critical for CD8+ T cells to maintain pHi homeostasis and modulate immune responses. European Journal of Immunology. 2014;44(5):1341-1351.
- Godoy V., Banales J.M., Medina J.F., Pastor-Anglada M.. Functional crosstalk between the adenosine transporter CNT3 and purinergic receptors in the biliary epithelia. Journal of Hepatology. 2014;61(6):1337-1343.
- Concepcion A.R., Lopez M., Ardura-Fabregat A., Medina J.F.. Role of AE2 for pHi regulation in biliary epithelial cells. Frontiers in Physiology. 2014;4 JAN.

Highlights

Our data related to the role of protein nitrosylation for the regulation of the synthesis of bile acids may open a new area of research thus far unexplored. We may therefore envision that the impact of our publication in Gastroenterology by Rodríguez-Ortigosa et al. will increase steadily.

Something equivalent may be said regarding our publications in Eur J.Immunol y J. Hepatol (Concepcion et al. and Godoy et al., respectively).The first one uncovers the mechanism by which the Ae2 deficiency leads to lymphocyte immunoreactivity (an aspect putatively relevant for PBC). The second publication (by Godoy et al.) describes the purinome and its function in the bile-duct epithelial cells.

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G0011

Programme: P4. Immunology and liver transplantation

Lead Researcher: Navasa Anadon, Miquel Àngel

Group members

STAFF MEMBERS: Martínez Picola, Marta | Massip Salcedo, Marta | Millán López, Olga | Muñoz Luque, Javier

ASSOCIATED MEMBERS: Brunet Serra, Mercedes | Fondevila Campo, Constantino | García-Valdecasas Salgado, Juan Carlos | Peralta Uroz, Carmen | Rosello Catafau, Joan | Sánchez Fueyo, Alberto

Main lines of research

- Aloimmune response and immunosuppression. A new project will start aimed at evaluating the effect of alloreactivity on the evolution of the graft FISS: PI14/01055.
- Ischemic reperfussion injury. evaluation of new ways of graft preservation. Brain death and its role in the ischemic preservation injury.
- Hepatitis C recurrence. Study of fibrosis regression after antiviral treatment. FISS: PI14/01055.
- Complications of immunosuppression. Evaluation of a new protocol of immunosuppression: the effect on graft rejection and kidney failure.

Most relevant scientific articles

- Bohne F., Londono M.-C., Benitez C., Miquel R., Martinez-Llordella M., Russo C. et al. HCV-induced immune responses influence the development of operational tolerance after liver transplantation in humans. Science Translational Medicine. 2014;6(242).
- Elias-Miro M., Mendes-Braz M., Cereijo R., Villarroya F., Jimenez-Castro M.B., Gracia-Sancho J. et al. Resistin and visfatin in steatotic and non-steatotic livers in the setting of partial hepatectomy under ischemia-reperfusion. Journal of Hepatology. 2014;60(1):87-95.
- Marino Z., Mensa L., Crespo G., Miquel R., Bruguera M., Perez-Del-Pulgar S. et al. Early periportal sinusoidal fibrosis is an accurate marker of accelerated HCV recurrence after liver transplantation. Journal of Hepatology. 2014;61(2):270-277.
- Jimenez-Castro M.B., Merono N., Mendes-Braz M., Gracia-Sancho J., Martinez-Carreres L., Cornide-Petronio M.E. et al. The effect of brain death in rat steatotic and non-steatotic liver transplantation with previous ischemic preconditioning. Journal of Hepatology. 2014;62(1):83-91.
- Hessheimer A.J., Escobar B., Munoz J., Flores E., Gracia-Sancho J., Taura P. et al. Somatostatin therapy protects porcine livers in small-for-size liver transplantation. American Journal of Transplantation. 2014;14(8):1806-1816.

Highlights

The more relevant results in 2014 are the following:

- Sirtuir 1 has an important role in ischemic reperfusion injury in liver transplantation in rat. Sirtuir 1 activation ameliorates the ischemic reperfusion injury and its regulation opens a new way to improve graft preservation.
- Characterization of the inflammatory response associated with brain death in steatosic and non-steatosic livers in rats. Surgical and pharmacologic regulation of the cholinergic pathway.
- Evaluation of a bioreactor in the characterization of paracrine interaction between different types of cells in liver transplantation. New Patent: Bioreactor for cell co-culture.
- Characterization of sinusoidal fibrosis in the recurrence of HCV in liver transplant patients. The new project will be Study of fibrosis regression after antiviral treatment. FISS: PI14/01055

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G0018

Programme: P6. Gastrointestinal Inflammation and Motility

Lead Researcher: Panés Díaz, Julià

Group members

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ASSOCIATED MEMBERS: Bordas Alsina, José María | Cabezón Cabello, Raquel | Delgado Rivilla, Salvadora | Feu Caballe, Faust | Lacima Vidal, Gloria | Llach Vila, Josep | Mora Buch, Rut | Ordas Jiménez, Ingrid | Pique Badia, Josep Maria | Ricart Gómez, Elena | Salas Martínez, Azucena

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

- Ordas I., Rimola J., Rodriguez S., Paredes J.M., Martinez-Perez M.J., Blanc E. et al. Accuracy of magnetic resonance enterography in assessing response to therapy and mucosal healing in patients with Crohn's disease. Gastroenterology. 2014;146(2).
- Leal R.F., Planell N., Kajekar R., Lozano J.J., Ordas I., Dotti I. et al. Identification of inflammatory mediators in patients with Crohn's disease unresponsive to anti-TNFα therapy. Gut. 2014.
- Jauregui-Amezaga A., Lopez-Ceron M., Aceituno M., Jimeno M., De Miguel C.R., Pino-Donnay S. et al. Accuracy of advanced endoscopy and fecal calprotectin for prediction of relapse in ulcerative colitis: A prospective study. Inflammatory Bowel Diseases. 2014;20(7):1187-1193.
- Danese S., Panes J.. Development of drugs to target interactions between leukocytes and endothelial cells and treatment algorithms for inflammatory bowel diseases. Gastroenterology. 2014;147(5):981-989.
- Pontes C, Vives R, Torres F, Panés J. Safety and activity of dersalazine sodium in patients with mild-to-moderate active colitis: double-blind randomized proof of concept study.Inflammatory bowel diseases. 2014;20(11):2004-12.

Highlights

In the area of assessment of Crohn's Disease using imaging, in particular MRI, we have shown that the Magnetic resonance index of activity (MaRIA) is a reliable index to measure disease activity and severity in Crohn's disease, responsive to treatment, and with changes highly correlated with those of endoscopy, setting the basis for the use of this index in clinical trials.

Based on the characterization of the molecular mechanisms of the inflammatory response in patients with Crohn's disease not responding to anti-TNF therapy, we established the key mediators of inflammation in this difficult to treat condition of the disease, and identified promising drugable targets, mostly related to IL-1 and IL-17 signaling pathways. This is highly informative for selection of drug candidates among pipeline products, and also in selecting subpopulations of patients that may particularly benefit from these therapeutic interventions.

The group has an active program of hematopoietic stem cell transplantation in patients with refractory Crohn's disease, being the leading center of Europe in the number of patients transplanted so far (26) and in innovations that increase safety of the procedure. The group has obtained a generous grant from Leona and Harry Helmsley Trust to characterize the cellular molecular, immune, and microbiome components involved in achieving long lasting remission after transplant with the aim at developing more specific and safe intervencions based on cell therapies.

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G0015
Programme: P3. Cholestasis and Metabolic Disorders

Lead Researcher: Parés Darnaculleta, Albert

Group members

STAFF MEMBERS: Ruiz Gaspa, Silvia

ASSOCIATED MEMBERS: Álvarez Domínguez, Luisa | De Osaba Madariaga, María Jesús | Guañabens Gay, Nuria | Mas Ordeig, Antonio | Peris Bernal, Pilar

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

- Lens S., Leoz M., Nazal L., Bruguera M., Pares A.. Bezafibrate normalizes alkaline phosphatase in primary biliary cirrhosis patients with incomplete response to ursodeoxycholic acid. Liver International. 2014;34(2):197-203.
- Pares A.. Old and novel therapies for primary biliary cirrhosis. Seminars in Liver Disease. 2014;34(3):341-351.
- Ruiz-Gaspa S., Dubreuil M., Guanabens N., Combalia A., Peris P., Monegal A. et al. Ursodeoxycholic acid decreases bilirubin-induced osteoblast apoptosis. European Journal of Clinical Investigation. 2014;44(12):1206-1214.
- Floreani A, Spinazzè A, Caballeria L, Reig A, Cazzagon N, Franceschet I et al. Extrahepatic Malignancies in Primary Biliary Cirrhosis: A Comparative Study at Two European Centers.Clinical reviews in allergy & immunology. 2014.
- Lammers W.J., Van Buuren H.R., Hirschfield G.M., Janssen H.L.A., Invernizzi P., Mason A.L. et al. Levels of alkaline phosphatase and bilirubin are surrogate end points of outcomes of patients with primary biliary cirrhosis: An international follow-up study. Gastroenterology. 2014;147(6):1338-1349.e5.

Highlights

During 2014 the group has described the beneficial effects of the combined treatment with bezafibrate and ursodeoxycholic acid in patients with primary biliary cirrhosis with insufficient biochemical response to monotherapy with ursodeoxycholic acid. This effect is characterized by a decrease in the markers of cytolysis and cholestasis, which is constant in all the patients, and the response is apparently more favorable in patients in early stage of the disease. This study also noted a favorable effect on itching that requires further investigation. If this beneficial effect is established, the administration of fibrates could represent a new form of theraoy for cholestatic pruritus. Another remarkable aspect was to determine the incidence of extrahepatic malignancies in primary biliary cirrhosis, a fact very similar to that observed in the area of Padua (Italy) in a joint comparative study with series from these two countries. Furthermore, the group has also provided information on new prognostic indicators of primary biliary cirrhosis.

In relation to the pathogenesis of osteoporosis in cholestatic diseases, it has demonstrated apoptotic effects of bilirubin and bile acids on osteoblasts in culture, effect which is neutralized by ursodeoxycholic acid. Other studies were performed regarding the potential involvement of sclerostin, a protein synthesized by osteocytes, in the development of osteoporosis in cholestatic diseases.

The research group has co-organized the Monothematic Conference on Primary Biliary Cirrhosis of the European Association for the Study of the Lliver (EASL) which was held in Milan in May of this year, with significant contributions from the research group on the pathogenesis of metabolic disease bone and management of cholestatic pruritus.

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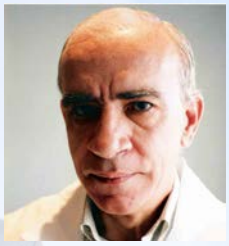

G1092

Programme: P5. Hepatic and gastrointestinal oncology

Lead Researcher: Parrilla Paricio, Pascual

Group members

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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

- Baroja-Mazo A., Martin-Sanchez F., Gomez A.I., Martinez C.M., Amores-Iniesta J., Compan V. et al. The NLRP3 inflammasome is released as a particulate danger signal that amplifies the inflammatory response. Nature Immunology. 2014;15(8):738-748.
- Martinez-Bosch N., Iglesias M., Munne-Collado J., Martinez-Caceres C., Moreno M., Guerra C. et al. Parp-1 genetic ablation in Ela-myc mice unveils novel roles for Parp-1 in pancreatic cancer. Journal of Pathology. 2014;234(2):214-227.
- Parrilla P., Robles R., Varo E., Jimenez C., Sanchez-Cabus S., Pareja E.. Liver transplantation for bile duct injury after open and laparoscopic cholecystectomy. British Journal of Surgery. 2014;101(2):63-68.
- Sapisochin G., De Lope C.R., Gastaca M., De Urbina J.O., Lopez-Andujar R., Palacios F. et al. Intrahepatic cholangiocarcinoma or mixed hepatocellular-cholangiocarcinoma in patients undergoing liver transplantation: A spanish matched cohort multicenter study. Annals of Surgery. 2014;259(5):944-952.
- Sapisochin G., Rodriguez De Lope C., Gastaca M., Ortiz De Urbina J., Suárez M.A., Santoyo J. et al. "very early" intrahepatic cholangiocarcinoma in cirrhotic patients: Should liver transplantation be reconsidered in these patients?. American Journal of Transplantation. 2014;14(3):660-667.

Highlights

Our group is focus in five closely related research areas: Barrett oesophagus and the development of oesophagus adenocarcinoma, Inflammation and cancer, Poly(ADP-ribose) polymerases and cancer, Liver regeneration and liver tumour, and Liver transplantation. During 2014, we have continue to study the Barrett oesophagus stability after radiofrequency treatment and the identification of genetic alterations induced by this treatment (project funding by FIS). In relation with inflammation and cancer, we have received funding from FIS and ERC to study the regulation of inflammatory response to extracellular ATP and P2X7 receptor signalling: through and beyond the inflammasome. As a main achieve in this area, we have demonstrated that the NLRP3 inflammasome is released as a particulate danger signal, acting as an extracellular oligomeric complex, that amplifies the inflammatory response. In relation to the study play by Poly(ADP-ribose) polymerase enzymes in cancer, se have received funding from the Marató de TV3 Foundation to explore the lethal interactions between PARP proteins and the DNA damage response in cancer treatment. Among the data obtained, we have demonstrated that PARP-1 plays a key role in pancreatic cancer. Other achievements of our group are related to liver tumour and tumoral progression after portal occlusion in patients with liver resection in two times. Finally, we continue working in liver tolerance after liver transplant, funding by a project from FIS, aim to analysis immunological factors and gene expression profiles involved in liver tolerance.

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G0063

Programme: P5. Hepatic and gastrointestinal oncology

Lead Researcher: Pastor Anglada, Marçal

Group members

STAFF MEMBERS: Iglesias Garanto, Ingrid | Pérez Torras, Sandra

ASSOCIATED MEMBERS: Casado Merediz, Francisco Javier | Mazo Sánchez, Adela

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.
- Purinergic singaling in liver and gastrointestinal diseases. The purinome and purinergic signaling are being studied in the context of liver and intestinal physiology, as well as under inflammatory and oncologic conditions.
- 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.

Most relevant scientific articles

- Arimany-Nardi C., Errasti-Murugarren E., Minuesa G., Martinez-Picado J., Gorboulev V., Koepsell H. et al. Nucleoside transporters and human organic cation transporter 1 determine the cellular handling of DNA-methyltransferase inhibitors. British Journal of Pharmacology. 2014;171(16):3868-3880.
- Pinilla-Macua I., Fernandez-Calotti P., Perez-Del-Pulgar S., Pastor-Anglada M.. Ribavirin uptake into human hepatocyte HHL5 cells is enhanced by interferon-α via up-regulation of the human concentrative nucleoside transporter (hCNT2). Molecular Pharmaceutics. 2014;11(9):3223-3230.
- Godoy V., Banales J.M., Medina J.F., Pastor-Anglada M.. Functional crosstalk between the adenosine transporter CNT3 and purinergic receptors in the biliary epithelia. Journal of Hepatology. 2014;61(6):1337-1343.
- Sobrevals L., Mato-Berciano A., Urtasun N., Mazo A., Fillat C.. UPAR-controlled oncolytic adenoviruses eliminate cancer stem cells in human pancreatic tumors. Stem Cell Research. 2014;12(1):1-10.
- Wojtal K.A., Cee A., Lang S., Gotze O., Fruhauf H., Geier A. et al. Downregulation of duodenal SLC transporters and activation of proinflammatory signaling constitute the early response to high altitude in humans. American Journal of Physiology - Gastrointestinal and Liver Physiology. 2014;307(7):G673-G688.

Highlights

Two of the most relevant contributions of the MPET laboratory during 2014 deal with the physiology of the cholangiocyte and the role the plasma membrane protein hCNT2 plays in the hepatic bioavailability of ribavirin. Both projects were developed under the framework of joint collaborations within the CIBEREHD. In the former, purinergic regulation of adenosine removers was stuied in cholangiocytes, thereby completing the biliary purinome map. This novel model of physiological regulation will have to be further addressed in the context of biliary pathology. hCNT2 has also been identified as a suitable ribavirin transporter which regulated by IFN-a in hepatocytes. This mechanism of regulation anticipates one of the cellular basis responsible for the potentiation of certain drugs action by this cytokine. Using our orthotopic platform of human pancreatic adenocarcinoma the efficacy of novel oncolytic viruses has been studied within a joint inter-CIBER (CIBEREHD and CIBERER) collaboration. The cellular models generated in the lab aimed at predicting drug-transporter interactions have been used in a research contract with the british pharma company Mundipharma, managed within the CIBEREHD.

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G1088

Programme: P6. Gastr. inflammation and motility

Lead Researcher: Pérez Gisbert, Javier

Group members

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ASSOCIATED MEMBERS: Abad Santos, Francisco | Chaparro Sánchez, María | González Guijarro, Luis Alberto | Parra Cid, Trinidad | Santander Vaquero, Cecilio | Torrado Durán, Santiago

Main lines of research

The Gastrointestinal Inflammatory Disease Group, under the direction of Dr. J.P. Gisbert, 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. Different projects have been developed in collaboration with the Pathology service, the Immunology service and the Clinical Pharmacology service of La Princesa Hospital, the Research Unit of Guadalajara's Hospital, the Pharmaceutical Technology Department and the Organic Chemistry department of the Complutense University of Madrid, the Biochemistry and Molecular Biology Department of Alcalá de Henares University, the Oncology Institute of Catalunya and the Galician Genomics Foundation and numerous digestive services throughout Spain.

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 (PSGL-1, MT1-MMP, IFG-1, ERß, CB1 and CB2)

Most relevant scientific articles

- McNicholl A.G., Marin A.C., Molina-Infante J., Castro M., Barrio J., Ducons J. et al. Randomised clinical trial comparing sequential and concomitant therapies for Helicobacter pylori eradication in routine clinical practice. Gut. 2014;63(2):244-249.
- Vergara M., Bennett C., Calvet X., Gisbert J.P.. Epinephrine injection versus epinephrine injection and a second endoscopic method in high-risk bleeding ulcers. The Cochrane database of systematic reviews. 2014;10.
- Gisbert J.P., Chaparro M.. Systematic review with meta-analysis: Inflammatory bowel disease in the elderly. Alimentary Pharmacology and Therapeutics. 2014;39(5):459-477.
- Linares P.M., Chaparro M., Gisbert J.P.. Angiopoietins in inflammation and their implication in the development of inflammatory bowel disease. A review. Journal of Crohn's and Colitis. 2014;8(3):183-190.
- Algaba A., Linares P.M., Fernandez-Contreras M.E., Figuerola A., Calvet X., Guerra I. et al. The effects of infliximab or adalimumab on vascular endothelial growth factor and angiopoietin 1 angiogenic factor levels in inflammatory bowel disease: Serial observations in 37 patients. Inflammatory Bowel Diseases. 2014;20(4):695-702.

Highlights

In 2014 the group has focused on strengthening its activity in European and international contexts:

• Coordinates the 'Pan-European Registry on Helicobacter pylori infection management' (300 gastroenterologists from 31 European countries). Preliminary results from this project have been awarded with three international recognitions, including the National Scholar Award by the United European Gastroenterology.

• The group has continued working on the 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. This project is funded by a UEG competitive Grant.

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.

The group has also signed an agreement for a Sponsorship Chair at the Autonomous University of Madrid on Inflammatory Bowel Disease.

Finally, the group has promoted and coordinated agreements to create stable collaboration tools for research on the field of gastroenterology:

AEG-REDCap. This group has promoted, and is coordinating, the Spanish Association of Gastroenterology Research Electronic Database Capture platform which provides a versatile and free tool for the management of multicenter studies.

GETECCU-CIBER. This group has promoted, and is coordinating, the Inflammatory Bowel Disease Strategic Line and Clinical Research Unit at CIBER. A unit created in collaboration with the Spanish Work Group on IBD (GETECCU) and the Spanish Network of Clinical Research Units (SCReN)

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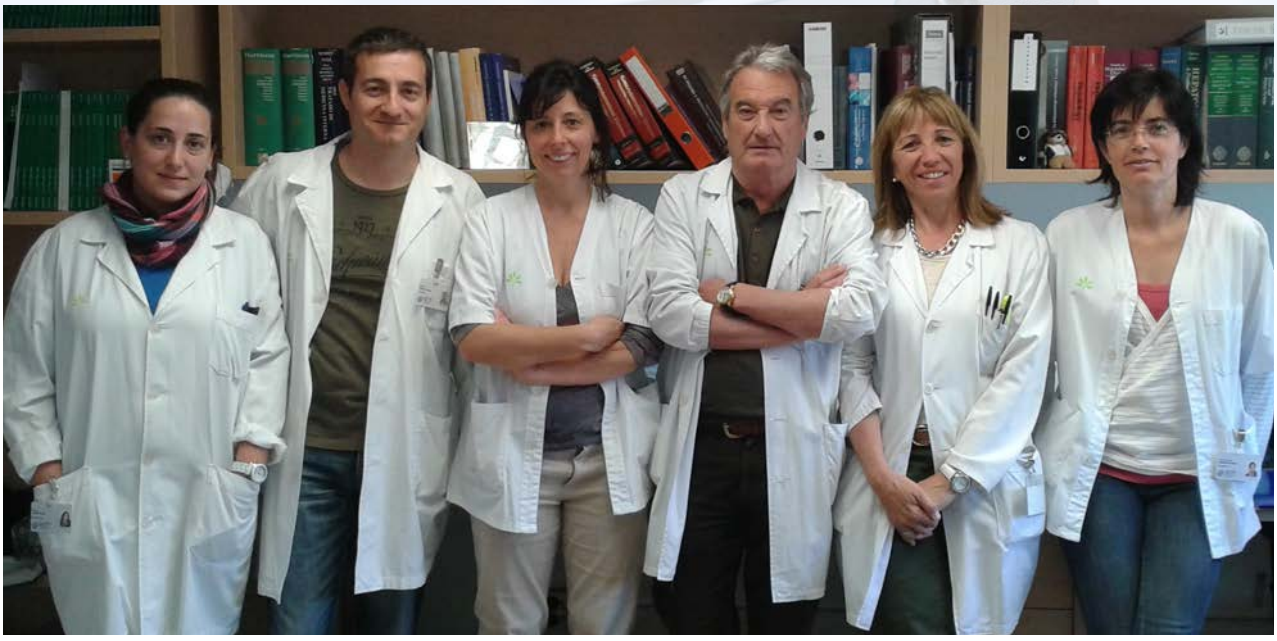
GO033

Programme: P1. Portal Hypertension and Cirrhosis



Lead Researcher: Planas Vila, Ramon

Group members

STAFF MEMBERS: Bartoli Solé, Ramon | Simón Coma, Marina

ASSOCIATED MEMBERS: Armengol Niell, Carolina | Morillas Cunill, Rosa | Odena García, Gemma | Sala Llinas, Margarita | Sarrias Fornes, María Rosa

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.
- Three. 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

- Amezaga N., Sanjurjo L., Julve J., Aran G., Perez-Cabezas B., Bastos-Amador P. et al. Human scavenger protein AIM increases foam cell formation and CD36-mediated oxLDL uptake. Journal of Leukocyte Biology. 2014;95(3):509-520.
- Ferenci P., Bernstein D., Lalezari J., Cohen D., Luo Y., Cooper C. et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. New England Journal of Medicine. 2014;370(21):1983-1992.
- Sanmartin R., Tor J., Sanvisens A., Lopez J., Jou A., Muga R. et al. Progression of liver fibrosis in HIV/hepatitis C virus-coinfected individuals on antiretroviral therapy with early stages of liver fibrosis at baseline. HIV Medicine. 2014;15(4):203-212.
- Saludes V., Gonzalez V., Planas R., Matas L., Ausina V., Martro E.. Tools for the diagnosis of hepatitis C virus infection and hepatic fibrosis staging. World Journal of Gastroenterology. 2014;20(13):3431-3442.
- Bargallo A., Abad L., Odena G., Planas R., Bartoli R.. New method for isolation of rat lamina propria macrophages in colonic tissue. Journal of Immunological Methods. 2014;408:132-136.

Highlights

During 2014 the group has consolidated several lines of basic and translational research such as the study of innate immunity in cirrhosis, developing several studies and publications on the role of spa protein in cirrhosis and liver cancer. Also, the group has signed a collaboration agreement with an international company to develop several studies.

Moreover, the line for the study of liver cancer and hepatoblastoma has consolidated its activity during 2014 participating and leading various national and international collaborative studies in addition to various competitive projects, besides being our coordinator in Spain of the international group for the study of childhood liver tumors (SIOPEL).

The group has also maintained a very active participation in several collaborative studies both in portal hypertension and encephalopathy as in clinical studies of hepatitis C in mono and co-infected patients, with 14 active trials during 2014. This has allowed the group to participate in international multicenter studies of great relevance as evidenced by the publication in a magazine this year with a high impact as the New England Journal of Medicine.

During this period, the group leading 5 competitive projects, most of them health research projects (FIS).

The training activity has been important, since during this period the group have organized two training courses for physicians of our area, one thesis has been read during this period and the group has participated in a position paper on NAFLD. In total 10 articles have been published with an impact factor close to 90.

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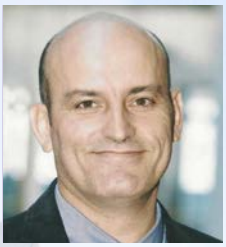

GO047
Programme: P2. Viral Hepatitis

Lead Researcher: Romero Gómez, Manuel

Group members

STAFF MEMBERS: Del Campo Castillo, José A. | Gallego Durán, Rocío

ASSOCIATED MEMBERS: Ampuero Herrojo, Javier | Bautista Palomas, Juan | Camacho Benítez, Inés | Castro Fernández, Manuel | Díaz Gómez, Daniel | Fernández López, Manuel | Grande Santamaría, Lourdes | Irles Rocamora, José Antonio | Jover Cobos, María | Ranchal Illescas, Isidora | Robles Frías, Antonio | Sánchez Muñoz, Diego | Suárez García, Emilio | Vargas Romero, Julio | Vázquez Cerezuela, Teresa

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

- Diaz-Herrero M.M., Del Campo J.A., Carbonero-Aguilar P., Vega-Perez J.M., Iglesias-Guerra F., Perina N I. et al. THDP17 decreases ammonia production through glutaminase inhibition. A new drug for hepatic encephalopathy therapy. PLoS ONE. 2014;9(10).
- Eslam M., Leung R., Romero-Gomez M., Mangia A., Irving W.L., Sheridan D. et al. IFNL3 polymorphisms predict response to therapy in chronic hepatitis C genotype 2/3 infection. Journal of Hepatology. 2014;61(2):235-241.
- Afdhal N., Zeuzem S., Kwo P., Chojkier M., Gitlin N., Puoti M. et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. New England Journal of Medicine. 2014;370(20):1889-1898.
- Romero-Gomez M., Ampuero J.. Deciphering the spectrum of low-grade hepatic encephalopathy in clinical practice. Gastroenterology. 2014;146(4):887-890.
- Jover-Cobos M., Noiret L., Lee K., Sharma V., Habtesion A., Romero-Gomez M. et al. Ornithine phenylacetate targets alterations in the expression and activity of glutamine synthase and glutaminase to reduce ammonia levels in bile duct ligated rats. Journal of Hepatology. 2014;60(3):545-553.

Highlights

- Diaz-Herrero et al. analyze a new inhibitor (THDP17) for glutaminase activity that plays a key role in hepatic encephalopathy. This work has also led to the publication of a patent protecting this compound for the mentioned purpose.
- The work by Mohammed Eslam and collaborators is an international collaborative study demonstrating the impact of the polymorphisms in the interleukin 28B (IL28B) gene in patients with HCV genotypes 2-3. These results belong to an extensive international collaboration network. Our group has been heavily involved with the inclusion of 1500 patients.
- The work performed by Afdhal et al has been published in The New England Journal of Medicine. This work is especially relevant because it shows the usefulness of the Ledipasvir- sofosfubir combination in infected patients with HCV genotype 1. This combination is one of the top therapies against hepatitis C. Our participation in this publication is derived from the broad involvement in the clinical trial-ONE.
- "Deciphering the spectrum of low-grade hepatic encephalopathy in clinical practice" is an editorial from several papers reviewed by us for the prestigious magazine "Gastroentology" as well as the contributions of our group.
- Dr. Maria Jover-Cobos is a researcher in our group who received a Marie Curie fellowship. She published in J Hepatol the effect of Ornithinephenylacetate on glutaminase activity and glutamine synthetase activity in rats with bile duct ligation reducing levels of ammonium. These data reflect the importance of collaboration between groups -Valme University Hospital and Royal Free Hospital in London- directed by Rajiv Jalan.

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G0044
Programme: P2. Viral Hepatitis

Lead Researcher: Salmerón Escobar, Francisco Javier

Group members

STAFF MEMBERS: Quiles Pérez, Rosa.

ASSOCIATED MEMBERS: Caballero Morales, Trinidad | Gila Medina, Ana | León López, Josefa | Muñoz Rueda, Paloma | Ocete Hita, Esther | Palacios Pérez, Ángel | Quintero Fuentes, Dolores | Ruiz Extremera, Ángeles

Main lines of research

- 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

- Leon J., Casado J., Jimenez Ruiz S.M., Zurita M.S., Gonzalez-Puga C., Rejon J.D. et al. Melatonin reduces endothelin-1 expression and secretion in colon cancer cells through the inactivation of FoxO-1 and NF-κβ. Journal of Pineal Research. 2014;56(4):415-426.
- Munoz-Gamez J.A., Lopez Viota J., Barrientos A., Carazo A., Sanjuan-Nunez L., Quiles-Perez R. et al. Synergistic cytotoxicity of the poly (ADP-ribose) polymerase inhibitor ABT-888 and temozolomide in dual-drug targeted magnetic nanoparticles. Liver International. 2014.
- Quiles-Perez R., Munoz-de-Rueda P., Martin-Lagos Maldonado A., Martin-Alvarez A., Quer J., Salmeron J.. Effects of ribavirin monotherapy on the viral population in patients with chronic hepatitis C genotype 1: Direct sequencing and pyrosequencing of the HCV regions. Journal of Medical Virology. 2014;86(11):1886-1897.
- Quiles-Perez R., Pavon-Castillero E.J., Munoz-de-Rueda P., Carmona I., Salmeron J.. The Value Of Genetics In The Era Of Hepatitis C Triple Therapy. Gastroenterologia y Hepatologia. 2014;37(7):427-437.
- Blanco-Reina E., Medina-Claros A.F., Vega-Jimenez M.A., Ocana-Riola R., Marquez-Romero E.I., Ruiz-Extremera A.. Drug utilization pattern in children and off-label use of medicines in a pediatric intensive care unit. Medicina Intensiva. 2014.

Highlights

In the year 2014, our research group has worked the most time in the active projects granted in previous calls, with results that will be published in the present year 2015. In addition, 5 doctoral theses have been presented, all of them qualified with distinction "cum laude", reflection of the results obtained in the different lines of research carried out by our group, each with its corresponding scientific publication. On the other hand, have granted us the project entitled "Follow-up study of the vertical transmission (VT) of HCV and HBV: analysis of the risk factors involved", of the II Projects of Research on HIV and hepatitis (GILEAD), within the Fellowship Program has carried out the "Subdirección General de Evaluación y Fomento de la Investigación del Instituto de Salud Carlos III". It has obtained the national patent entitled "Polimorfismos para predecir o pronosticar la respuesta al tratamiento antiviral", with P-06781 reference number; currently in transmit to be international, and other two national patents in concession phase related to the vertical transmission of hepatitis C virus. By the Department of Medicine of the University of Granada, we have been a research award to the communication entitled "Study of the influence of HLA factor on the vertical transmission of hepatitis C virus". The Official College of Medical of Granada has awarded us the prize "Arsacio Peña" to the work entitled "La obesidad como proceso adaptativo. Estudio de la grasa y lesiones hepatobiliares en la obesidad mórbida".

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G0042

Programme: P6. Gastrointestinal Inflammation and Motility

Lead Researcher: Sánchez de Medina López Huertas, Fermín

Group members

STAFF MEMBERS: González Pérez, Raquel | Rodríguez Cabezas, María Elena

ASSOCIATED MEMBERS: Concha López, Ángel | Gálvez Peralta, Julio | Martínez Agustín, Olga | Olivares Martín, Mónica | Suárez Ortega, María Dolores | Utrilla Navarro, Pilar | Xaus Pey, Jordi

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

- Mascaraque C., Aranda C., Ocon B., Monte M.J., Suárez M.D., Zarzuelo A. et al. Rutin has intestinal antiinflammatory effects in the CD4+ CD62L+ T cell transfer model of colitis. Pharmacological Research. 2014;90:48-57.
- Mascaraque C., Suárez M.D., Zarzuelo A., de Medina F.S., Martinez-Augustin O.. Active hexose correlated compound exerts therapeutic effects in lymphocyte driven colitis. Molecular Nutrition and Food Research. 2014;58(12):2379-2382.
- Toral M., Gomez-Guzman M., Jimenez R., Romero M., Sanchez M., Utrilla M.P. et al. The probiotic Lactobacillus coryniformis CECT5711 reduces the vascular pro-oxidant and pro-inflammatory status in obese mice. Clinical Science. 2014;127(1):33-45.
- Lozano-Pérez AA, Rodriguez-Nogales A, Ortiz-Cullera V, Algieri F, Garrido-Mesa J, Zorrilla P et al. Silk fibroin nanoparticles constitute a vector for controlled release of resveratrol in an experimental model of inflammatory bowel disease in rats.International journal of nanomedicine. 2014;9:4507-20.
- Ortega-Gonzalez M., Ocon B., Romero-Calvo I., Anzola A., Guadix E., Zarzuelo A. et al. Nondigestible oligosaccharides exert nonprebiotic effects on intestinal epithelial cells enhancing the immune response via activation of TLR4-NFκB. Molecular Nutrition and Food Research. 2014;58(2):384-393.

Highlights

First and foremost, we would like to dedicate our heartfelt memory to our dear colleague, friend, and principal investigator of the group, Antonio Zarzuelo. We hope to honor him by continuing the work he led for years.

The research activity of the group has resulted in 16 articles, some of them stemming from partnerships with other CIBER groups, as well as with other research groups of the Heracles network, which have enabled us to achieve considerable progress in the investigations. It is noteworthy that most publications are framed in the first quartile, including 5 in the first decile.

We have published studies focusing on new intestinal anti-inflammatory effects of natural products , including pre- and probiotics , natural extracts, resveratrol and flavonoids, as well as other unrelated studies. We have identified mechanisms independent of the microbiota of nondigestible oligosaccharides such as fructooligosaccharides or galactooligosaccharides. And for the first time we have applied the lymphocyte transfer colitis model to investigate the therapeutic properties of natural products such as the flavonoid rutin or bovine glycomacropeptide.

Our research work has been funded by several research projects, both public (MINECO, Junta de Andalucía) and private.

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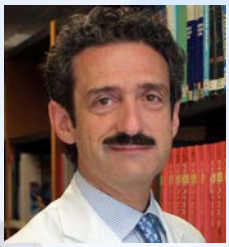
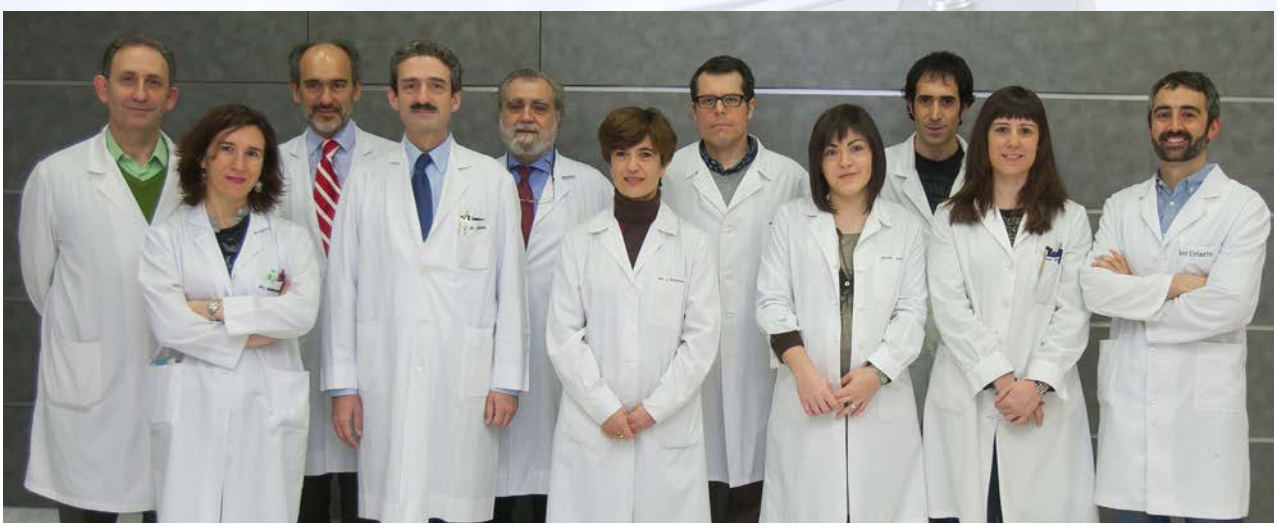


G0006

Programme: P5. Hepatic and gastrointestinal oncology



Lead Researcher: Sangro Gómez-Acebo, Bruno Carlos

Group members

STAFF MEMBERS: Barbero López, Roberto | D'avola, Delia | Larequi Ardanaz, Eduardo | Santa María Monasterio, Eva | Uriarte Díaz Varela, Iker

ASSOCIATED MEMBERS: Ávila Zaragoza, Matías Antonio | Civeira Murillo, María Pilar | Fontanellas Romas, Antonio | Herrero Santos, José Ignacio | Iñarrairaegui Bastarrica, Mercedes | Quiroga Vila, Jorge

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 antitumor 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.

Most relevant scientific articles

- Fernandez-Ros N., Inarrairaegui M., Paramo J.A., Berasain C., Ávila M.A., Chopitea A. et al. Radioembolization of hepatocellular carcinoma activates liver regeneration, induces inflammation and endothelial stress and activates coagulation. Liver International. 2014.
- Elizalde M., Urtasun R., Azkona M., Latasa M.U., Goni S., Garcia-Irigoyen O. et al. Splicing regulator SLU7 is essential for maintaining liver homeostasis. Journal of Clinical Investigation. 2014;124(7):2909-2920.
- Rodriguez-Ortigosa C.M., Celay J., Olivas I., Juanarena N., Arcelus S., Uriarte I. et al. A GAPDH-mediated trans-nitrosylation pathway is required for feedback inhibition of bile salt synthesis in rat liver. Gastroenterology. 2014;147(5):1084-1093.
- Uriarte I, Latasa MU, Carotti S, Fernandez-Barrena MG, Garcia-Irigoyen O, Elizalde M et al. Ileal FGF15 contributes to fibrosis-associated hepatocellular carcinoma development.International journal of cancer. Journal international du cancer. 2014.
- Sangro B, Salem R. Transarterial chemoembolization and radioembolization.Seminars in liver disease. 2014;34(4):435-43.

Highlights

2014 has been a year of significant activity in our group. From the clinical perspective, we completed the design of the clinical trial that is the main aim of the European project HEPAVAC for developing a multipeptide vaccine for patients with hepatocellular carcinoma, we also completed several clinical trials of first-use-in-disease (gene therapy of acute intermittent porphyria, cell therapy of cirrhosis with endothelial progenitor cells) whose results will be released this year, we participated in the creation of a European Register of Radioembolization, and have worked on the implementation of collaborative projects with other groups CIBEREHD, for instance in the treatment of cholangiocarcinoma. From a translational view we have completed the creation of a three-dimensional model and the optimization of the boundary conditions that are the basis of the project aiming at fluid-mechanical improvement of liver radioembolization procedures and have successfully worked to develop the first animal model of atrophy-hypertrophy induced by lobar radioembolization. In the field of basic research we have identified a key role for Slu7 gene, a regulatory factor of "splicing" in the maintenance of the differentiated phenotype and quiescent hepatocytes. Slu7 expression is decreased in cirrhosis and hepatocellular carcinoma, and maintaining levels is essential to preserve liver function, including responding to key hormones like insulin. Moreover we have described a novel mechanism of regulation of bile salt synthesis mediated by nitric oxide and GAPDH protein, acting at the level of the promoter of CYP7A1 gene. And finally we have shown that FGF15/19 growth factor produced by ileum enterocytes participates in liver carcinogenesis in an experimental model associated with fibrosis.

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G0041
Programme: P1. Portal Hypertension and Cirrhosis

Lead Researcher: Such Ronda, José

Group members

STAFF MEMBERS: Giménez Martínez, Paula | Gómez-Hurtado Cubillana, Isabel Ner

ASSOCIATED MEMBERS: Bellot García, Pablo | Francés Guarinos, Rubén | González Navajas, José Manuel | Palazón Azorín, José María | Pascual Bartolome, Sonia | Zapater Hernández, Pedro

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

- Lozano-Ruiz B., Bachiller V., Garcia-Martinez I., Zapater P., Gomez-Hurtado I., Moratalla A. et al. Absent in melanoma 2 triggers a heightened inflammasome response in ascitic fluid macrophages of patients with cirrhosis. Journal of Hepatology. 2014;62(1):64-71.
- Moratalla A., Gomez-Hurtado I., Santacruz A., Moya A., Peiro G., Zapater P. et al. Protective effect of Bifidobacterium pseudocatenulatum CECT7765 against induced bacterial antigen translocation in experimental cirrhosis. Liver International. 2014;34(6):850-858.
- Ortiz S., Zapater P., Estrada J.L., Enriquez P., Rey M., Abad A. et al. Bacterial DNA translocation holds increased insulin resistance and systemic inflammatory levels in morbid obese patients. Journal of Clinical Endocrinology and Metabolism. 2014;99(7):2575-2583.
- Bertin S, Lozano-Ruiz B, Bachiller V, García-Martínez I, Herdman S, Zapater P et al. Dual-specificity phosphatase 6 regulates CD4+ T-cell functions and restrains spontaneous colitis in IL-10-deficient mice.Mucosal immunology. 2014.
- Gutierrez A., Scharl M., Sempere L., Holler E., Zapater P., Almenta I. et al. Genetic susceptibility to increased bacterial translocation influences the response to biological therapy in patients with Crohn's disease. Gut. 2014;63(2):272-280.

Highlights

During 2014, the Group has been working on 4 projects and 1 clinical trial funded by the National Strategic Action in Health, ISCIII. The main results of the Group refer to the identification of mechanisms of inflammation and bacterial translocation in cirrhosis, which extend to the pathogenesis of other chronic inflammatory diseases. The Group has also studied the gut microbiota interaction with these mechanisms as well as new therapeutic strategies at a preclinical levels to control the complications of bacterial translocation episodes in liver diseases.

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GOOV1

Programme: P3. Cholestasis and Metabolic Disorders

Lead Researcher: Caballeria Rovira, Llorenç

Group members

ASSOCIATED MEMBERS: Aizpurua Pérez, Miren Maite | Alcaraz Ferrer, Enriqueta | Aluma Trullas, Alba | Auba Llambrich, Josep | Auladell Llorens, Mª Antonia | Bernad Suárez, Jesús | Canut Cavero, Santiago | Casas Curto, José Dario | Miranda Badia, Mª Dolores | Nieto Márquez, Laura | Pera Blanco, Guillem | Rodríguez González, Lluis | Sánchez García, Mª Carmen | Tibau Catalan, Albert.

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

- Caballeria L., Pera G., Bernad J., Canut S., Navarro E., Bruguera M.. Strategies for the detection of hepatitis C viral infection in the general population. Revista Clinica Espanola. 2014;214(5):242-246.
- Caballeria L., Salo J., Berzigotti A., Planas R., Vila C., Huertas C. et al. Non-alcoholic fatty liver: Position document of the Catalan Society of Gastroenterology. Gastroenterologia y Hepatologia. 2014;37(6):372-383.
- Arteaga I., Buezo I., Exposito C., Pera G., Rodriguez L., Aluma A. et al. Non-invasive markers of fibrosis in the diagnosis of non-alcoholic fatty liver disease. Gastroenterologia y Hepatologia. 2014;37(9):503-510.
- Lammers W.J., Van Buuren H.R., Hirschfield G.M., Janssen H.L.A., Invernizzi P., Mason A.L. et al. Levels of alkaline phosphatase and bilirubin are surrogate end points of outcomes of patients with primary biliary cirrhosis: An international follow-up study. Gastroenterology. 2014;147(6):1338-1349.e5.

Highlights

During this year we have continued to recruit patients from the FIS project on detection of chronic liver disease in the general population through the practice of liver elastography. At year-end 2300 we recruited subjects. In order to complete the number of subjects proposed FIS has given us a one year extension.

We have presented a new project to the 2014 FIS called "Predictive value of the transient hepatic elastography in the early diagnosis of hepatic and cardiovascular diseases" on the subjects included in the above mentioned project which has been given to us. This will allow us to follow up the cohort of these subjects and help us examine the presence of cardiovascular disease in the cohort and its relation to liver and especially in patients with nonalcoholic fatty liver disease. For this, all subjects, addition to monitoring through analytics and elastography practice them an abdominal ultrasound and carotid ultrasound.

We have initiated the study of liver fibrosis in patients with moderately impaired liver function in general population through the study of serological markers both direct and indirect, as well as its correlation with liver elastography.

For indication of the of the Catalan Society of Gastroenterology we have conducted with other members of CIBERehd a position document of non-alcoholic fatty liver disease. This has been the first document published in our country.

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GOOV2

Programme: P6. Gastrointestinal Inflammation and Motility

Lead Researcher: Esteve Comas, Maria

Group members

ASSOCIATED MEMBERS: Andújar Murcia, Xavier | Carrasco García, Anna | Fernández Bañares, Fernando | Forne Bardera, Montserrat | Loras Alastruey, Carme | Mariné Guillem, Meritxell | Rosinach Ribera, Mercè | Salas Caudevila, Antonio | Santaolalla Saula, Rebeca | Viver Pi-Sunyer, Josep Mª

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, particularly leads the research on microscopic colitis in Spain. The group leads in Spain the registry of microscopic colitis through the ENEIDA project (see below in Inflammatory Bowel Disease) 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. In 2013 he finished the project (BFU - BFI 2010-19888) The group is leading f 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

- Fernandez-Banares F., Carrasco A., Garcia-Puig R., Rosinach M., Gonzalez C., Alsina M. et al. Intestinal intraepithelial lymphocyte cytometric pattern is more accurate than subepithelial deposits of anti-tissue transglutaminase IgA for the diagnosis of celiac disease in lymphocytic enteritis. PLoS ONE. 2014;9(7).
- Loras C., Gisbert J.P., Saro M.C., Piqueras M., Sanchez-Montes C., Barrio J. et al. Impact of surveillance of hepatitis b and hepatitis c in patients with inflammatory bowel disease under anti-TNF therapies: Multicenter prospective observational study (REPENTINA 3). Journal of Crohn's and Colitis. 2014.
- Rahier J.F., Magro F., Abreu C., Armuzzi A., Ben-Horin S., Chowers Y. et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. Journal of Crohn's and Colitis. 2014;8(6):443-468.
- Calvet X., Panes J., Alfaro N., Hinojosa J., Sicilia B., Gallego M. et al. Delphi consensus statement: Quality indicators for inflammatory bowel disease comprehensive care units. Journal of Crohn's and Colitis. 2014;8(3):240-251.
- Andreu M., Marquez L., Domenech E., Gisbert J.P., Garcia V., Marin-Jimenez I. et al. Disease severity in familial cases of IBD. Journal of Crohn's and Colitis. 2014;8(3):234-239.

Highlights

Development of the group lines

- Coeliac disease: Multicenter projects leaded by the group: Project on the natural history (FIS PI13 / 00413), assessments of factors that determine the persistence of atrophy (CADER Project), search and analysis of biomarkers by means of integrated "OMIC" technology applied to lymphocytic enteritis secondary to gluten-sensitive enteropathy (FISPI13/02499).
- Microscopic colitis and chronic diarrhea: National registry of microscopic colitis and preparation of a guide, based on GRADE methodology, regarding the diagnosis and treatment.
- Inflammatory Bowel Disease (IBD): Development of projects on pathophysiology, clinical aspects and therapeutics. Development of studies in the seting of ENEIDA project (National Study on Inflammatory Bowel Disease on Genetic and Environmental Determinants) about opportunistic infections (Project INFEII) and endoscopic treatments of Crohn's disease strictures (Project TEDEII). Development and leadership of the study "Baloon dilation versus stent placement in the treatment of stenosis in Crohn's disease with 22 participant Spanish centers (Project PROTDILAT PI13 / 01226). Collaboration in the European guides on opportunistic infections in IBD.
- Leathership of the project of the TV3 Marathon 2012 foccused on the achievement of predictive parameters of advanced colonic neoplasia.

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GOOV4

Programme: P5. Hepatic and gastrointestinal oncology

Lead Researcher: Padillo Ruiz, Francisco Javier

Group members

ASSOCIATED MEMBERS: Álamo Martínez, José Mª | De la Portilla de Juan, Fernando | Gómez Bravo, Miguel Ángel | Limón Mirón, Mª Luisa | Márquez Galán, José Luis | Muntane Relat, Jordi | Pascasio Acevedo, Juan Manuel

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 induction 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

- Castano D., Larequi E., Belza I., Astudillo A.M., Martinez-Anso E., Balsinde J. et al. Cardiotrophin-1 eliminates hepatic steatosis in obese mice by mechanisms involving AMPK activation. Journal of Hepatology. 2014;60(5):1017-1025.
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