# ANNUAL REPORT 2015

ciberehd

Centro de Investigación Biomédica en Red
Enfermedades Hepáticas y Digestivas

ciber

Centro de Investigación Biomédica en Red

# Index


# Scientific Director's Presentation

Our scientific work kept a high profile in 2015, with a large number of publications in top-level journals. This vouches for the CIBEREHD's consolidation as a powerful research structure which has been capable of overcoming budget hardships and limitations to taking on new staff.

The annual report sets forth the most relevant results in the different programmes around which the CIBEREHD is structured and enables verifying the gradual increase in collaborative studies with international impact. This trait can be seen in all the programmes in which nationwide network research and successful internationalisation in multiple projects can be found. International cooperation is frequently led by CIBEREHD researchers, which is a result of the recognition that has been attained.

Research has been relevant in basic aspects but particularly in patients affected by hepatic and digestive diseases. It should be noted in this respect that clinical practice guides have been generated in different fields based on scientific evidence and on consensus documents in which the criteria and methods that should be applied in both basic and clinical research are defined.

The CIBEREHD is supported by shared platforms of services that have played a relevant role in different research work at the same time as carrying out teaching activity so that trainee researchers can acquire the knowledge needed for their work.

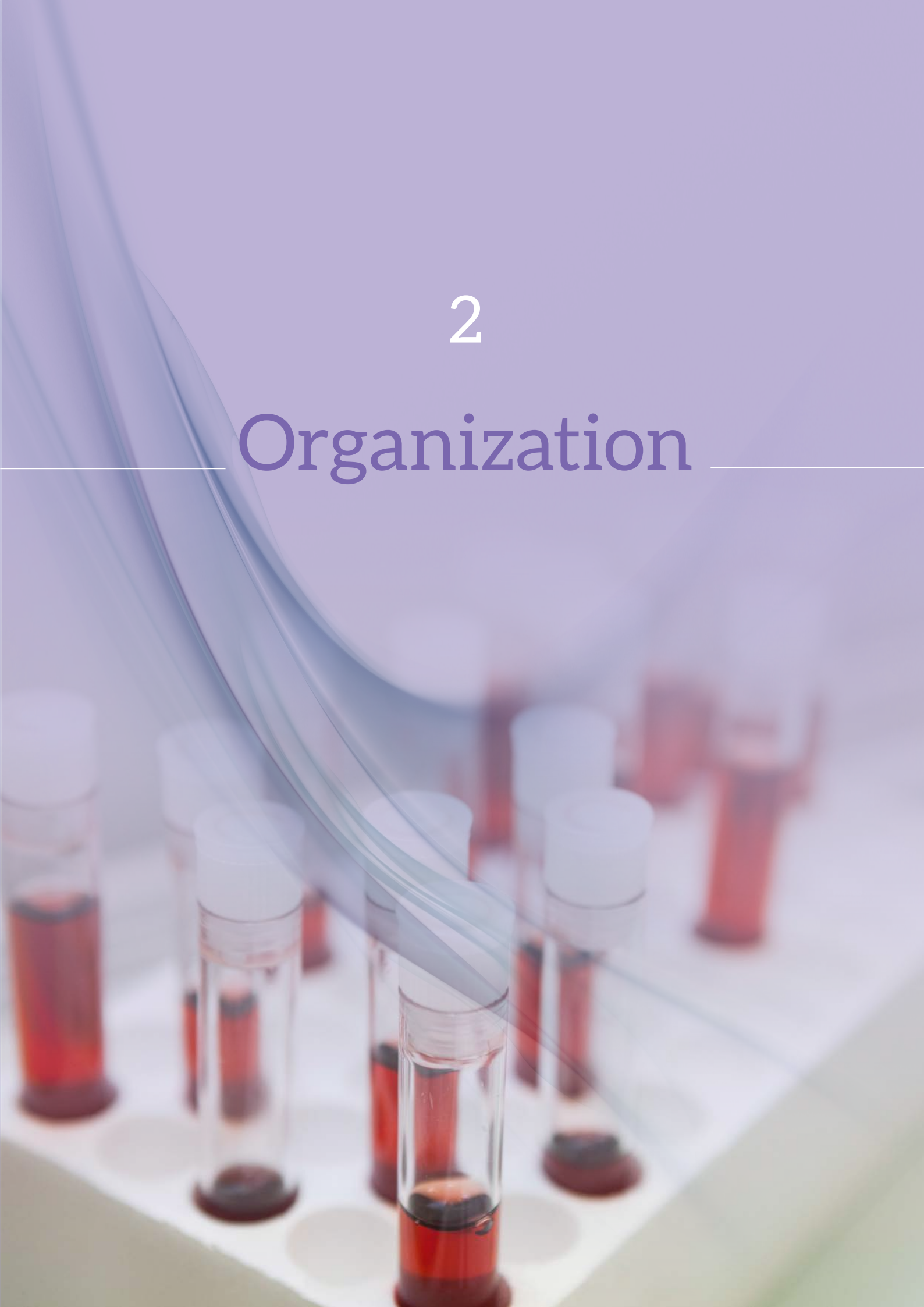
In 2015 the Scientific Management and Management Committee were renewed. This coincides with the completion of the present four-year action plan and requires redefining the objectives in the new period. CIBEREHD groups have been structured in four programmes which cover the need to adapt to new requirements and in 2016 the new Four-Year action plan will be drawn up. It should be emphasised that one of the challenges to be faced is generational renewal and the critical analysis of the current teams. In some cases, continuity will not be feasible and they will have to be replaced by emerging groups which at present lie outside the CIBEREHD but which can provide complementary aspects required to maintain the CIBEREHD's scientific excellence.

Jordi Bruix

Scientific Director of the CIBEREHD

# 2

# Organization



# Organizational Structure

The CIBEREHD is one of the eight thematic areas forming the Centro de Investigación Biomédica en Red (CIBER), a Spanish research consortium in the field of biomedical research with great scientific potential, under the Instituto de Salud Carlos III (ISCIII) – Ministry of the Economy and Competitiveness.

The Hepatic and Digestive Diseases area is made up of 43 research groups, keeping its independence as regards scientific management. Its organisational structure is based on the research groups belonging to this and its activity revolves around the Research Programmes and Transversal Programmes, with a coordinator for each Programme belonging to the Steering Committee. Scientific decisions are made by the Scientific Director, advised by said Steering Committee and the External Scientific Committee.

The Steering Committee is presided over by the Scientific Director and made up of the coordinators of the programmes and Managing Director of the CIBER.

The External Scientific Committee is a body for scientific support and advice, made up of relevant personalities in the field of health sciences standing out for their professional or scientific careers in line with the objectives of the of the thematic area.

The senior administrative bodies of the CIBEREHD are the Governing Body and the Permanent Commission, common for all the CIBER research areas.

The Governing Body is made up of three representatives of the ISCIII and of an institutional representative of each of the centres in the consortium. It is presided over by the Director of the ISCIII and meets every six months.

The Permanent Commission is an executive committee made up by the ISCIII and 8 members of the Governing Body, who can be renewed on an annual basis.

Both the operation and the purposes of the governing, support and advisory bodies are established in the statutes of the CIBER.

## Members of the Steering Committee of CIBEREHD

| NAME | POST HELD |
|---|---|
| Jordi Bruix | Scientific Director |
| Rafael Bañares | Programme 1 Coordinator |
| Pere Clavé | Programme 2 Coordinator |
| Xavier Forns | Programme 3 Coordinator |
| Bruno Sangro | Programme 4 Coordinator |
| Joan Caballería | Teaching Coordinator |
| Mª Luz Martínez-Chantar | Transfer Coordinator |
| Manuel Sánchez | Managing Director |

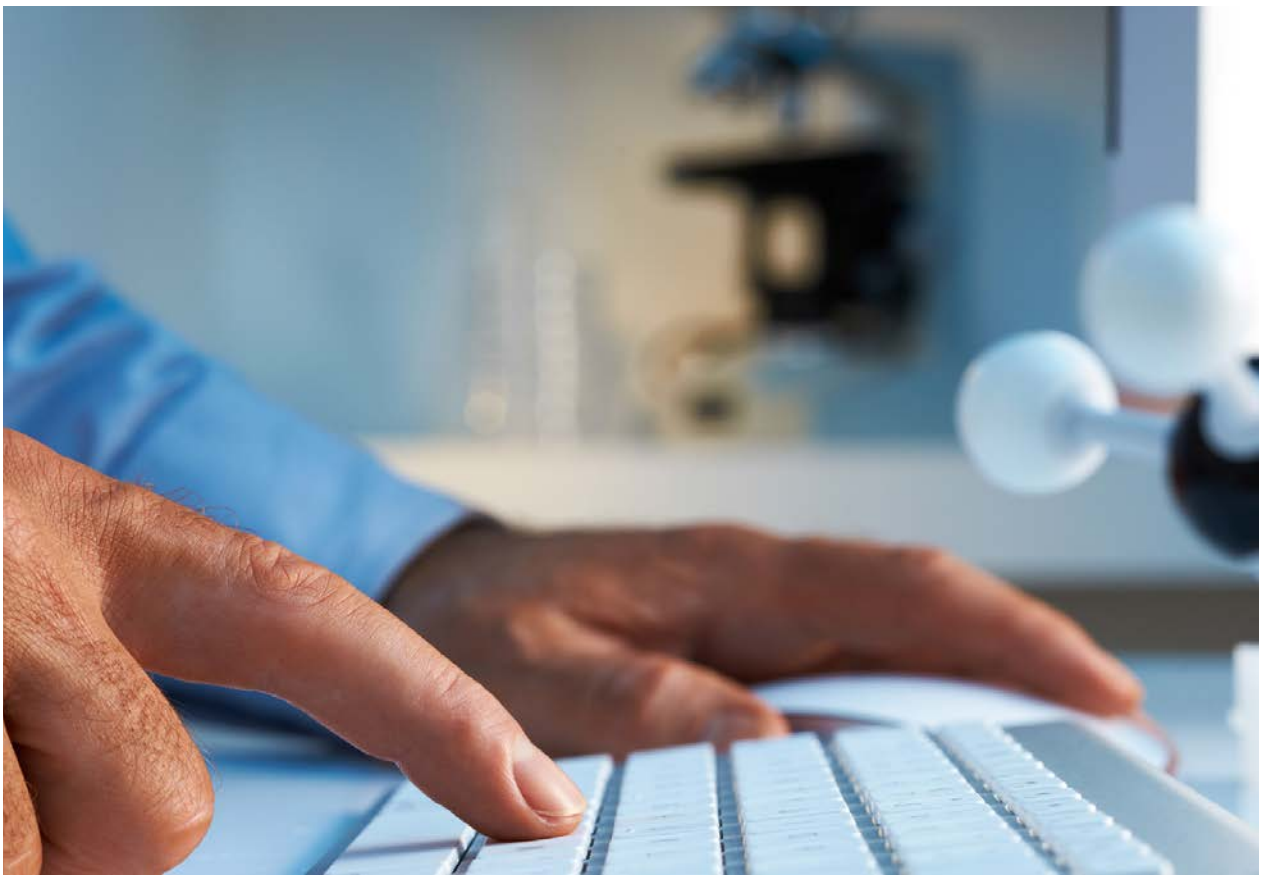
Scientific Management Assistant: Clara Esteva

## External Scientific Advisory Committee of CIBEREHD

| | |
|---|---|
| Guadalupe García-Tsao (Yale University) | President |
| Roger Butterworth (Montreal University) | Member |
| Massimo Pinzani (Royal Free Hospital, London) | Member |
| Sophie Lotersztajn (Paris University) | Member |
| Jean Pierre Vinel (Toulouse University) | Member |
| Silvio Danese (Milan University) | Member |
| Evelien Dekker (Amsterdam University) | Member |

## Technical Unit

See personnel list: http://www.ciberisciii.es/en/about-us/head-office



# Directory of groups and institutions

| Group leader | Institution | Centre | Prov. Centre |
|---|---|---|---|
| Albillos Martínez, Agustín | Universidad de Alcalá | Facultad de Medicina | Madrid |
| Andrade, Raúl | Fundación Pública Andaluza para la Investigación de Málaga en Biomedicina y Salud | Hospital Virgen de la Victoria | Malaga |
| Azpiroz Vidaur, Fernando | Fundación Hospital Universitario Vall d´Hebron - Ins.de Recerca | Hospital Vall d'Hebron | Barcelona |
| Bañares Cañizares, Rafael | Servicio Madrileño de Salud | Hosp. Gregorio Marañón | Madrid |
| Berenguer Haym, Marina | Fundación para la Investigación del Hospital la Fe | Hospital Universitario de la Fe | Valencia |
| Bosch Genover, Jaume | Hosp. Clínico y Provincial de Barcelona | Hospital Clínic de Barcelona | Barcelona |
| Bruix Tudó, Jordi | Hosp. Clínico y Provincial de Barcelona | Hospital Clínic de Barcelona | Barcelona |
| Bujanda Fernández de Pierola, Luis | Asociación Instituto Biodonostia | Hospital Donostia | Guipuzcoa |
| Cabré Gelada, Eduard | Fundación Instituto de Investigación Germans Trias I Pujol | Hospital Germans Trias i Pujol | Barcelona |
| Calvet Calvo, Xavier | Corporación Sanitaria Parc Taulí | Corp. Sanitaria Parc Tauli | Barcelona |
| Castell Ripoll, José Vicente | Fundación para la Investigación del Hospital la Fe | Hospital Universitario de la Fe | Valencia |
| Castells Garangou, Antoni | Hosp. Clínico y Provincial de Barcelona | Hospital Clínic de Barcelona | Barcelona |
| Clave Civit, Pere | Fundación Privada Salud del Consorcio Sanitario del Maresme | Fund. Privada Salud del Consorcio Sanitario del Maresme | Barcelona |
| Esplugues Mota, Juan Vicente | Universitat de València | Facultad de Medicina | Valencia |
| Esteban Mur, Juan Ignacio | Fundación Hospital Universitario Vall D´Hebron - Institut de Recerca | Hospital Vall d'Hebron | Barcelona |
| Esteban Mur, Rafael | Fundación Hospital Universitario Vall d´Hebron - Institut de Recerca | Hospital Vall d'Hebron | Barcelona |
| Fernández-Checa Torres, José Carlos | Agencia Estatal Consejo Superior de Investigaciones Científicas | Instituto de Investigaciones Biomedicas | Barcelona |
| Forns Bernhardt, Xavier | Hosp. Clínico y Provincial de Barcelona | Hospital Clínic de Barcelona | Barcelona |
| Francés Guarinos, Rubén | Fund. Investigación Sanitaria y Biomédica de la Com. Valenciana. | Hospital General Universitario de Alicante | Alicante |
| García Buey, Luisa | Servicio Madrileño de Salud | Hospital Universitario la Princesa | Madrid |
| García Marín, José Juan | Universidad de Salamanca | Univ. de Salamanca | Salamanca |
| García-Samaniego Rey, Javier | Servicio Madrileño de Salud | Hospital la Paz | Madrid |
| Genesca Ferrer, Joan | Fundación Hospital Universitario Vall D´Hebron - Institut de Recerca | Hospital Vall d'Hebron | Barcelona |
| Gines Gibert, Pere | Hosp. Clínico y Provincial de Barcelona | Hospital Clínic de Barcelona | Barcelona |

| Group leader | Institution | Centre | Prov. Centre |
|---|---|---|---|
| Gómez Castilla, Jordi | Agencia Estatal Consejo Superior de Investigaciones Científicas | Instituto de Parasitología y Biomedicina López Neyra | Granada |
| González Gallego, Javier | Universidad de León | Instituto Biomedicina de León | León |
| Guarner Aguilar, Carlos | Instituto de Investigación del Hospital de la Santa Creu i Sant Pau | Instituto de Investigación Del Hospital de la Santa Cruz Y San Pablo | Barcelona |
| Guarner Aguilar, Francisco | Fundación Hospital Universitario Vall D´Hebron - Institut de Recerca | Hospital Vall d'Hebron | Barcelona |
| Lanas Arbeloa, Angel | Instituto Aragonés de Ciencias de la Salud | Hospital Clínico Universitario Lozano Blesa | Zaragoza |
| Martín Sanz, Paloma | Agencia Estatal Consejo Superior de Investigaciones Científicas | Inst. de Investigaciones Biomedicas Alberto Sols | Madrid |
| Mata García, Manuel de la | Fundación para la Investigación Biomédica de Córdoba | Hospital Universitario Reina Sofia | Cordoba |
| Mato de la Paz, José María | CIC BioGUNE | CIC BioGUNE | Vizcaya |
| Navasa Anadón, Miquel Angel | Hosp. Clínico y Provincial de Barcelona | Hospital Clínic de Barcelona | Barcelona |
| Padillo Ruiz, Francisco Javier | Hospital Universitario Virgen del Rocío de Sevilla | Hospital Universitario Virgen del Rocío | Sevilla |
| Panes Díaz, Julián | Hosp. Clínico y Provincial de Barcelona | Hospital Clínic de Barcelona | Barcelona |
| Pares Darnaculleta, Albert | Hosp.Clínico y Provincial de Barcelona | Hospital Clínic de Barcelona | Barcelona |
| Parrilla Paricio, Pascual | Fund. para la Formación e Investigación Sanitarias de la Región de Murcia | Hospital Universitario Virgen de la Arrixaca | Murcia |
| Pastor Anglada, Marçal | Universitat de Barcelona | Facultad de Biología. Universitat de Barcelona | Barcelona |
| Pérez Gisbert, Javier | Servicio Madrileño de Salud | Hospital Universitario la Princesa | Madrid |
| Planas Vilà, Ramon | Fundación Instituto de Investigación Germans Trias i Pujol | Hospital Germans Trias i Pujol | Barcelona |
| Romero Gómez, Manuel | Fund. Pública Andaluza para pa Gestion de la Investigación en Salud de Sevilla | Hospital Virgen del Rocío | Sevilla |
| Salmerón Escobar, Francisco Javier | Fundación para la Investigación Biosanitaria en Andalucía Oriental | Hospital Clínico San Cecilio | Granada |
| Sánchez de Medina López Huertas, Fermín | Universidad de Granada | Facultad de Farmacia | Granada |
| Sangro Gómez-Acebo, Bruno Carlos | Clínica Universitaria de Navarra | Clínica Universitaria de Navarra | Navarra |

# Budget

| INCOME | 5.493.393,55 |
|---|---|
| NOMINAL ISCIII GRANT | 3.653.580,00 |
| COMPETITIVE INCOME | 588.599,35 |
| OWN FUNDS | 1.251.214,20 |

| EXPENDITURE | 4.136.430,51 |
|---|---|
| GROUP | 3.391.944,07 |
| TRAINING | 26.445,48 |
| TECHNICAL OFFICE | 150.000,00 |
| SCIENTIFIC MANAGEMENT, CONFERENCE. SECRETARIAT | 80.128,41 |
| PLATFORMS | 146.473,60 |
| DRAFT AGREEMENT FEES | 61.311,92 |
| STRATEGIC ACTIONS | 16.297,41 |
| COMPETITIVE PROJECTS | 263.829,62 |

# Personnel

Personnel contracted during the year as of 31st December, separated by categories:

| Category | Permanent | Works and service | Post-doctoral | Main Total |
|---|---|---|---|---|
| Diploma holder | 5 | 3 | - | 8 |
| Doctor | 30 | 4 | 3 | 37 |
| Graduate | 16 | 30 | - | 46 |
| Technical | 12 | 8 | - | 20 |
| **Total** | 63 | 45 | 3 | 111 |

# Significant activities

## Projects

The projects active in 2015 were as follows:

### NATIONAL PROJECTS

**Financing agency: Instituto de Salud Carlos III**

- Financing agency: Instituto de Salud Carlos III
- Characterisation of microRNAs in pancreatic cancer: from new biomarkers to therapeutic targets.
- Clinical effectiveness and safety in the intralesional administration of tolerogenic dendritic cells in patients with refractory Crohn's disease.
- Virological and immunological factors connected with antiviral treatment and the recurrence of hepatitis C after a liver transplant.
- Implementation of a tool based on ultra-sequencing to determine sub-genotypes of the hepatitis C virus: optimisation of the treatment.
- Implication of the extra-cell matrix in the appearance of progressive complications in Crohn's disease and in the development of new therapeutic proposals.
- Understanding obesity (OB), metabolic syndrome (METS), type 2 diabetes (T2DM) and fatty liver disease (FL): a multidisciplinary approach.
- Impact in treatment of new antivirals on the natural history of cirrhosis through the hepatitis C virus. Identification of factors predicting no response. Part A: Impact of treatment with new direct-acting antivirals on the natural history of chronic advanced hepatopathy (cirrhosis) and pathogenic mechanisms.
- Impact in treatment of new antivirals on the natural history of cirrhosis through the hepatitis C virus. Identification of factors predicting no response. Separation B optimisation of direct antiviral treatment of chronic Hepatitis C in clinical practice and identification of the factors associated with the lack of response.
- Rio Hortega Contract.

**Financing agency: Ministry of the Economy and Competitiveness:**

- Development of a Kit for early diagnosis of colorectal cancer – Detection in plasma (miRNAs).

**Other financing agencies:**

- Fundació la Marató de TV3: "Anàlisi per biología de sistemes de la tolerància immunitària en trasplantament d'òrgans."
- Proyecto AECC.

We should stress the participation of the CIBEREHD in two of the interdisciplinary CIBER excellence projects financed by the AES. The project led by Dr José María Mato (CIBEREHD) will attempt to identify biomarkers for the early diagnosis of the metabolic syndrome (MS) and to find new therapeutic approaches. The CIBEREHD also takes part in another of the projects led by CIBERDEM which investigates inflammation in diverse diseases to obtain therapies.

## Technology transfer

One of the CIBER's main aims is the transfer of research results to clinical practice, and one of the best tools existing for this purpose is technology transfer. The Unit managing this at the CIBER sets out to act as a bridge between our researchers and other agents in the Science and Technology System (companies, business associations, other research organisations, etc.) to make cooperation with these bodies more effective. This means that research results will be efficiently developed and can succeed in being applied. Work is done in several lines to this end:

- **Training in innovation management and continuous contact with our researchers to monitor their results.**

  In this respect, last year the first general event of the CIBER in training on technology transfer and innovation was held, on 26th February 2015, where national experts took part sharing their knowledge in matters such as industrial property, business creation or open access publication, etc.

- **Protection of their research results and management of cooperation with other agents, as vouched for by applications for patents and signing licensing contracts, amongst other agreements.**

  Hence, over 20 new patent applications were made and seven licensing agreements were signed at the CIBER in 2015.

- **The presentation of research results and technological capacities of our groups.**

  Among many other measures and only as an example, in 2015, several projects were presented at the II Foro de Innovación en Diagnóstico in Vitro – FENIN in Barcelona (December 2015).

- **Support for technology-based business creation stemming from CIBER groups.**

  The CIBER has since 2014 taken part in Epidisease (http://www.epidisease.com/es/) which it continued to support in 2015.

- **Other activities connected with innovation, public-private cooperation and industrial and intellectual property.**

  For example, the registration of the "community trademark" of the CIBER has been processed, or steps have been taken for registering intellectual property rights for audio-visual projects, amongst many others.

- **In this period CIBEREHD applied for seven priority patents and signed two licences.**

## Dissemination activities

In 2015 CIBER's Communication Department carried out different measures for dissemination and disclosure in order to improve the Centre's visibility, as well as publicising the research work done by the groups in its eight thematic areas. We now detail the 2015 milestones in CIBEREHD Communication.

### THE CIBEREHD IN THE MEDIA:

During the 2015 period 50 CIBER press releases were issued, two of these from the CIBEREHD and four in cooperation between several CIBER areas.

| Date | Thematic Area | Title |
|---|---|---|
| January | SEVERAL CIBER | El CIBER pone en marcha tres proyectos de excelencia interdisciplinares financiados con casi 2 millones de euros por la AES |
| February | SEVERAL CIBER | Investigadores del CIBER identifican diversos factores de riesgo de sufrir cáncer |
| January | SEVERAL CIBER | El CIBER acerca su investigación al público de la mano de la improvisación teatral en #ImproCiencia |
| February | SEVERAL CIBER | Investigadores del CIBER identifican diversos factores de riesgo de sufrir cáncer |
| September | CIBEREHD | Jordi Bruix, nuevo director científico del CIBER de Enfermedades Hepáticas y Digestivas |
| November | CIBEREHD | Investigadores del CIBEREHD exponen estudios para mejorar el diagnóstico precoz del cáncer colorrectal |

There were 270 appearances in the media in this period:

| CIBEREHD | NEWS | AUDIENCE |
|---|---|---|
| Internet | 238 | 44.861.500 |
| Press | 32 | 3.240.000 |
| **Total** | **270** | **48.101.500** |

## NEW WEB PAGE OF THE CIBEREHD:

In September 2015 the new web page of the CIBEREHD was launched in order to have a common structure, image and contents manager for all the CIBER areas.

http://www.CIBEREHD.org/en

## CIBER NEWSLETTER

Five CIBER newsletters were drawn up and distributed over this period, including relevant content about both the CIBEREHD and about the other thematic areas. Digital newsletters were sent to around 4000 subscribers.

http://www.ciberisciii.es/comunicacion/boletines

## SOCIAL NETWORKS

Main indicators of the presence of CIBEREHD on Twitter:

| UPDATES | | FOLLOWERS | | FOLLOWING | | KLOUT (influence, values from 1 to 100) | |
|---|---|---|---|---|---|---|---|
| JANUARY | DECEMBER | JANUARY | DECEMBER | JANUARY | DECEMBER | JANUARY | DECEMBER |
| 202 | 319 | 253 | 382 | 203 | 212 | 38 | 37 |

## CIBEREHD ANNUAL REPORT

The Communication area of the CIBER in cooperation with the CIBEREHD coordinated the content of the CIBEREHD report 2014 in Spanish/English, drawing up and disseminating 2 reports in interactive format (Flipbook) and PDF. These were distributed over the web page and Twitter account: http://www.ciberisciii.es/en/press/annual-report

## CIBER #IMPROCIENCIA SCIENCE WEEK

The #ImproCiencia dissemination event, arranged by the CIBER in the framework of the Madrid Science Week 2015, took place on 3rd November at the Nave 73 rooms in Madrid. The event combined science and theatre improvisation to give a light-hearted explanation of the biomedical research done by the CIBER in its eight thematic areas.

Games and improvisations were alternated with live connections with CIBER researchers during the event. . As far as CIBEREHD was concerned, the connection was with Jordi Bruix, its scientific director, who as part of the Scientific Conferences of the CIBEREHD given from Barcelona, informed the public of the importance of network research and of pooling investigation at these events.

# Scientific Production

The evolution of CIBEREHD publications can be appreciated from the following graphs in which the data from 2011 to 2015 is analysed.

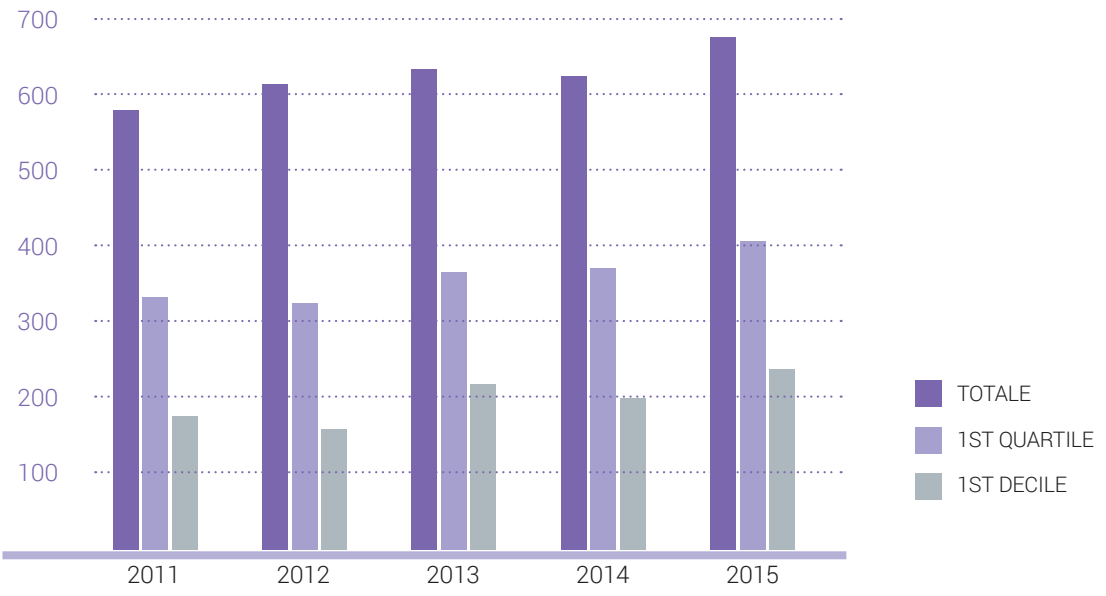
Details are also given of the publications per group for the current year, as well as of interCIBER and intraCIBER cooperation.

## Publications:

**No. of affiliated publications 2015**

| CIBEREHD | 2011 | 2012 | 2013 | 2014 | 2015 |
|---|---|---|---|---|---|
| **Total publications** | **581** | **615** | **636** | **626** | **678** |
| First quartile | 334 | 326 | 367 | 372 | 408 |
| First Decile | 177 | 160 | 219 | 200 | 239 |

### EVOLUTION OF CIBEREHD PUBLICATIONS 2011-2015




### MOST RELEVANT CIBEREHD PUBLICATIONS IN 2015 BY IMPACT FACTOR

| Publication | Impact Factor |
|---|---|
| BRUIX J., TAKAYAMA T., MAZZAFERRO V., CHAU G.-Y., YANG J., KUDO M. ET AL. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): A phase 3, randomised, double-blind, placebo-controlled trial. The Lancet Oncology. 2015;16(13):1344-1354 | 24.690 |
| CHARLTON M, GANE E, MANNS MP, BROWN RS JR, CURRY MP, KWO PY, FONTANA RJ, GILROY R, TEPERMAN L, MUIR AJ, MCHUTCHISON JG, SYMONDS WT, ET AL. Sofosbuvir and ribavirin for treatment of compensated recurrent hepatitis C virus infection after liver transplantation. Gastroenterology. 2015 Jan;148(1):108-17 | 16.716 |
| AMPUERO J., SIMON M., MONTOLIU C., JOVER R., SERRA M.A., CORDOBA J., ROMERO-GOMEZ M. Minimal Hepatic Encephalopathy and Critical Flicker Frequency Are Associated with Survival of Patients with Cirrhosis. Gastroenterology. 2015;149(6):1483-1489. | 16.716 |

| Publication | Impact Factor |
|---|---|
| ALONSO A., DOMENECH E., JULIA A., PANES J., GARCIA-SANCHEZ V., MATEU P.N., GUTIERREZ A., GOMOLLON F., MENDOZA J.L., GARCIA-PLANELLA E., BARREIRO-DE ACOSTA M., MUNOZ F., VERA M., SARO C., ESTEVE M., ANDREU M., CHAPARRO M., MANYE J., CABRE E., LOPEZ-LASANTA M., TORTOSA R., GELPI J.L., GARCIA-MONTERO A.C., BERTRANPETIT J., ABSHER D., MYERS R.M., MARSAL S., GISBERT J.P. Identification of risk loci for crohn's disease phenotypes using a genome-wide association study. Gastroenterology. 2015;148(4):794-805. | 16.716 |
| LEAL R.F., PLANELL N., KAJEKAR R., LOZANO J.J., ORDAS I., DOTTI I., ESTELLER M., MASAMUNT M.C., PARMAR H., RICART E., PANES J., SALAS A. Identification of inflammatory mediators in patients with Crohn's disease unresponsive to anti-TNFα therapy. Gut. 2015;64(2):233-242. | 14.660 |
| BERZIGOTTI A., REIG M., ABRALDES J.G., BOSCH J., BRUIX J. Portal hypertension and the outcome of surgery for hepatocellular carcinoma in compensated cirrhosis: A systematic review and meta-analysis. Hepatology. 2015;61(2):526-536. | 11.055 |
| MICHELENA J., ALTAMIRANO J., ABRALDES J.G., AFFO S., MORALES-IBANEZ O., SANCHO-BRU P., DOMINGUEZ M., GARCIA-PAGAN J.C., FERNANDEZ J., ARROYO V., GINES P., LOUVET A., MATHURIN P., MEHAL W.Z., CABALLERIA J., BATALLER R.. Systemic inflammatory response and serum lipopolysaccharide levels predict multiple organ failure and death in alcoholic hepatitis. Hepatology. 2015;62(3):762-772. | 11.055 |
| LOPEZ-VICARIO C., ALCARAZ-QUILES J., GARCIA-ALONSO V., RIUS B., HWANG S.H., TITOS E., LOPATEGI A., HAMMOCK B.D., ARROYO V., CLARIA J. Inhibition of soluble epoxide hydrolase modulates inflammation and autophagy in obese adipose tissue and liver: Role for omega-3 epoxides. Proceedings of the National Academy of Sciences of the United States of America. 2015;112(2):536-541 | 9.674 |
| MARFIL V., BLAZQUEZ M., SERRANO F., CASTELL J.V., BORT R. Growth-promoting and tumourigenic activity of c-Myc is suppressed by Hhex. Oncogene. 2015;34(23):3011-3022. | 8.459 |
| SÁNCHEZ-TILLÓ E, DE BARRIOS O, VALLS E, DARLING D, CASTELLS A, POSTIGO A. ZEB1 and TCF4 reciprocally modulate their transcriptional activities to regulate Wnt target gene expression. Oncogene. 2015 Nov 12;34(46):5760-70. doi: 10.1038/onc.2015.352. | 8.459 |

**CIBEREHD Publications per group**

| PI | Total No. pub. | Q1 | D1 |
|---|---|---|---|
| Albillos Martínez, Agustín | 8 | 8 | 7 |
| Ginés Gibert, Pere | 29 | 21 | 16 |
| Bañares Cañizares, Rafael | 16 | 10 | 7 |
| Bosch Genover, Jaume | 31 | 24 | 21 |
| Genesca Ferrer, Joan | 13 | 10 | 6 |
| Guarner Aguilar, Carlos | 12 | 7 | 3 |
| Planas Vilà, Ramon | 10 | 6 | 3 |
| Francés Guarinos, Rubén | 8 | 5 | 3 |
| Esteban Mur, Juan Ignacio | 11 | 3 | 2 |
| Esteban Mur, Rafael | 23 | 13 | 4 |
| Forns Bernhardt, Xavier | 30 | 17 | 10 |
| Gómez Castilla, Jordi | 11 | 7 | 4 |
| García-Samaniego Rey, Javier | 9 | 5 | 1 |
| García Buey, Luisa | 10 | 4 | 1 |
| Romero Gómez, Manuel | 24 | 12 | 7 |
| Salmerón Escobar, Francisco Javier | 6 | 2 | 0 |
| Andrade, Raúl | 12 | 7 | 5 |
| Castell Ripoll, José Vicente | 12 | 9 | 6 |

CIBEREHD Publications per group

| PI | Total No. pub. | Q1 | D1 |
|---|---|---|---|
| Fernández-Checa Torres, José Carlos | 14 | 12 | 11 |
| González Gallego, Javier | 15 | 10 | 6 |
| Mato de la Paz, José María | 34 | 23 | 12 |
| Medina, J | 4 | 2 | 2 |
| Parés Darnaculleta, Albert | 20 | 13 | 10 |
| Minguela Puras, Alfredo | 5 | 2 | 1 |
| Berenguer Haym, Marina | 14 | 9 | 6 |
| Mata García, Manuel de la | 15 | 3 | 1 |
| Parrilla Paricio, Pascual | 7 | 6 | 3 |
| Navasa Anadón, Miquel Angel | 17 | 10 | 8 |
| Bruix Tudó, Jordi | 29 | 28 | 27 |
| Bujanda Fernández de Pierola, Luis | 18 | 12 | 6 |
| Castells Garangou, Antoni | 29 | 21 | 15 |
| García Marín, José Juan | 8 | 7 | 5 |
| Pastor Anglada, Marçal | 6 | 4 | 0 |
| Sangro Gómez-Acebo, Bruno Carlos | 28 | 22 | 12 |
| Azpiroz Vidaur, Fernando | 16 | 14 | 3 |
| Calvet Calvo, Xavier | 15 | 2 | 2 |
| Cabré Gelada, Eduard | 10 | 6 | 3 |
| Clave Civit, Pere | 22 | 16 | 3 |
| Closa, D | 3 | 1 | 0 |
| Esplugues Mota, Juan Vicente | 11 | 8 | 5 |
| Guarner Aguilar, Francisco | 9 | 4 | 2 |
| Lanas Arbeloa, Angel | 23 | 15 | 6 |
| Panes Díaz, Julián | 20 | 16 | 13 |
| Pérez Gisbert, Javier | 41 | 17 | 15 |
| Sánchez de Medina López Huertas, Fermín | 11 | 8 | 4 |
| Caballería Rovira, Llorenç | 2 | 2 | 1 |
| Esteve Comas, María | 7 | 4 | 4 |
| García Monzón, Carmelo | 4 | 4 | 2 |
| Beltrán Niclós, Ana Belén | 4 | 3 | 0 |
| Padillo Ruiz, Francisco Javier | 14 | 6 | 1 |
| Martín Sanz, Paloma | 7 | 4 | 3 |

## COLLABORATION WORK:

No. of intraCIBER publications 2015: **150**

No. of interCIBER publications 2015: **61**

3

# Scientific Programmes

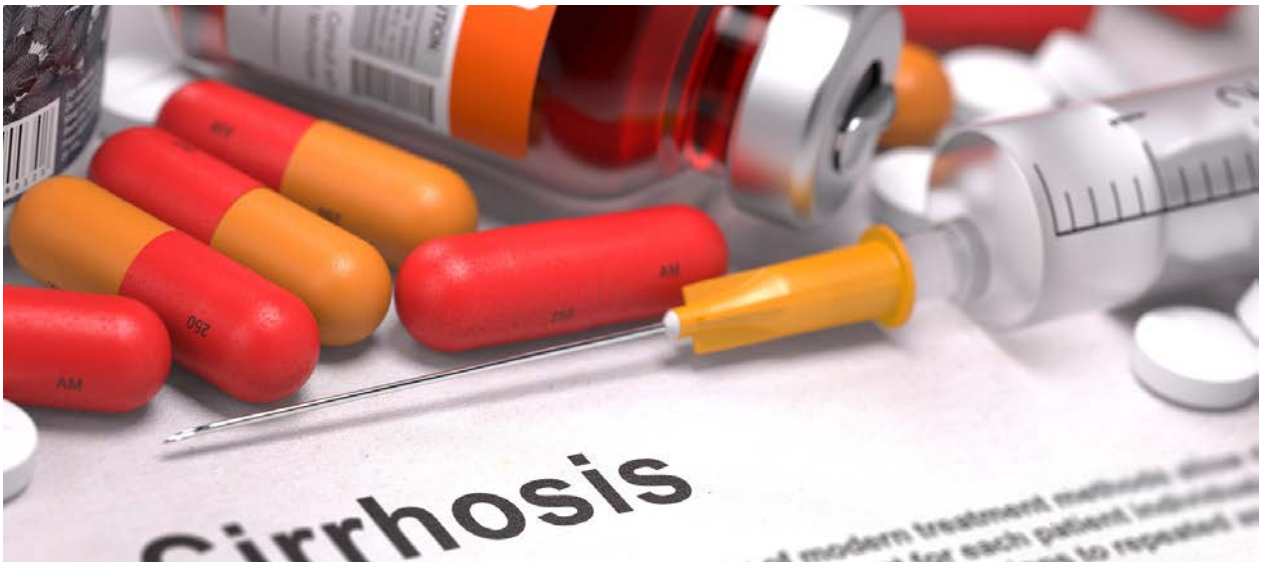
# Portal Hypertension and Mechanisms producing Transition to Cirrhosis

COORDINATOR: DR. AGUSTÍN ALBILLOS

Programme 1 focusses on cooperative research into the pathogeny, diagnosis and treatment of hepatic cirrhosis, portal hypertension and its complications. The cooperative translational research done in the Programme specifically studies the pathogenic mechanisms of hepatic fibrogenesis and portal hypertension. It seeks to develop drugs and therapeutic strategies to improve portal hypertension and its associated complications (bleeding gastroesophageal varices, kidney failure and ascites, bacterial infection, hepatic encephalopathy). The research is structured into five lines: 1) hepatic fibrogenesis, 2) portal hypertension, 3) ascites/renal function and liver failure, 4) bacterial infection and translocation and 5) hepatic encephalopathy. In spite of their clinical origin, all the groups in the programme have incorporated experimental research, which covers the entire translational spectrum, including cellular and molecular biology studies, concept tests in cirrhosis and clinical trials to assess different therapies.

The achievements attained in 2015 were:

- Identifying the protective role of hepatic KLF2 in fibrosis, endothelial dysfunction and portal hypertension in cirrhosis.
- Establishing the role of Danis oesophageal stents in handling refractory variceal haemorrhages.
- Characterising the haemodynamic response to beta-blockers in the different stages of compensated advanced chronic liver disease.
- Describing the effect of enoxaparin reducing portal pressure through the modification of the structural component of hepatic vascular resistance.
- Establishing the prognostic relevance of the systemic inflammatory response syndrome in severe alcoholic hepatitis.
- Describing the clinical characteristics, the prognosis and evolution of the syndrome of acute-on-chronic liver failure.
- Contributing to the consensuses of the VI Conferencia de Consenso de Baveno en Hipertensión Portal and of the International Club of Ascites on acute liver damage.
- Establishing the effect of obeticholic acid by reducing intestinal bacterial translocation on reducing intestinal inflammation in cirrhosis.



# Viral Hepatitis

COORDINATOR: **DR. JUAN IGNACIO ESTEBAN MUR**

- The public HBV database known as CIBERHEP has gone on expanding and now has 1245 patients, 25 participating centres in nine Spanish administrative regions (822 have received Tenofovir; 408 have received Entecavir).
- The HIGH-RESOLUTION HCV SUBTYPING system based on mass sequencing and Molecular Phylogeny has been incorporated as a centralised diagnostic test at HUVH Hospital with an access code which gives service to the whole Catalan health service. This system has international patent WO2015001068 A1 and CIBEREHD has a partial interest in said patent.
- A procedure for detecting Resistances to Inhibitors with direct action against HCV based on massively parallel sequencing has been developed.
- Financing has been obtained for a Proposal as part of the Strategic Plan in Health for Hepatitis C 2015 in which all the groups in programme 2 are taking part (2015-2017).
- "Hepa-C", a public HCV database owned by CIBEREHD has been consolidated. This is completely operative, over 1100 patients have been entered and it has produced presentations at congresses.
- Methodologies for genotyping and detecting mutations of resistance of HBV and HDV based on mass sequencing have been developed. Software enabling the detection of Insertions and Deletions has been installed.
- Epidemiological studies have been reinforced on HBV, HCV, HDV and HEV. Studies on nosocomial transmission of HCV have been carried out with the Health Agencies of Spanish administrative regions. In this respect a cooperative study has been completed on new HCV (acute) infections in men who have sex with male HIV+ patients by mass sequencing.
- A work on HCV+ patients receiving the transplant of a C+ virus liver has been published. Work is being done on massively parallel sequencing studies on Cholestatic patients as well as on studies on Variability of Quasispecies and progression of liver damage in patients treated with everolimus.
- Research with genomic HCV replicons has enabled investigating the effect of direct-acting antivirals on the quasispecies dynamic of HCV, proving for the first time that viral fitness can condition resistance to a treatment (even against sofosbuvir) in the absence of resistance mutations.
- We proceeded to the diagnosis of Q80K resistance mutation of HCV by means of Lightcycler with FRET probes.
- Non-invasive techniques (ARFI) for characterising hepatic fibrosis have been appraised, including approved software for analysing magnetic resonance images.
- We have continued with the "FLIP project" research on hepatocarcinoma through NASH, HCV or cryptogenic cirrhosis. European cooperation goes on in the subject of "Prevention and treatment of non-alcoholic fatty liver disease (NAFLD)".
- Cooperation for studying vertical mother-child transmission of HCV has been reinforced.
- A line of research into epigenetic signatures between the host's genomic DNA and HBV or HCV genomes has been consolidated, as well as studies on lncRNAs and miRNAs in biopsies of chronic hepatitis C and their implication in the progression of fibrosis and the development of hepatocarcinoma.
- New anti-HCV inhibitors (quercetin, etc.) have been characterised and the role of different receptors such as clatrine in the entry of HCV to the hepatocyte, and apolipoproteins b and e in the cell to cell transmission of HCV.
- Studies have been carried out on the effect of compounds of natural extracts on the inhibition of NS3 activity in vitro, as well as GWAS studies in patients subject to treatment with NS3 inhibitors.
- Progress has been made in the development of new techniques for HCV treatment such as the case of Synthesis of specific polyanionic carbosilane dendrimers against HCV.
- Another group of cooperative studies concerns the search for non-invasive angiogenic prognostic

biomarkers, progression of chronic hepatitis C to cirrhosis and hepatocellular carcinoma of Hepatitis B and C.

- Most of the groups have taken part and still actively participate in multicentre clinical trials with new combinations of direct-acting antivirals against HCV.

# Hepatotoxicity, Cholestasis and Metabolic Disorders

COORDINATOR: **DR. JUAN F. MEDINA**

Research work connected with cholestasis and metabolic and hepatotoxity disorders in Programme 3 is done by 10 groups. The groups directed by Doctors Albert Parés, Llorenç Caballería and Juan F. Medina concentrate on clinical, epidemiological and basic studies of cholestatic diseases such as cirrhosis/primary biliary cholangitis and other chronic cholestasis. As regards basic aspects, one should also stress the research done into alterations in the transport of different components of bile, as well as in the etiopathogeny of osteopaenia associated with cholestatic syndromes. The other seven groups in the Programme cover research into metabolic disorders and work more specifically on the study of steatohepatitis and hepatic toxicity. These groups thus carry out studies connected with mechanisms of oxidative stress and apoptosis in hepatocytes as well as with the role of cytokines and adipocytokines in infectious, toxicological and metabolic disorders. Some very significant work is done in this respect by the groups of Dr José M. Mato and Dr José C. Femández-Checa, which have been granted a large number of competitive projects and which carry out several cooperation schemes with other groups. We should thus point out the INTERCIBER Project Understanding obesity (Ob), metabolic syndrome (MetS), type 2 diabetes (T2DM) and fatty liver disease (FL): a multi-disciplinary approach, which, led by the CIBEREHD (specifically, Dr José M. Mato and Dr Mª Luz Martínez-Chantar) is also actively worked on by a further three Thematic areas of the CIBER: Obesidad y Nutrición (CIBEROBN), Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM) and Salud Mental (CIBERSAM). The groups run by Doctors Javier González Gallego, Carmelo García Monzón and Paloma Martín Sanz also work in close cooperation for studying antioxidant therapies in models of hepatitis C. Finally, the groups directed by Dr José V. Castell and Dr Raúl Andrade cooperate closely with each other and with the previously mentioned groups in the investigation of different molecular mechanisms producing hepatotoxicity.

## Projects in the Programme and Cooperation

### CHOLESTASIS, METABOLIC DISORDERS AND HEPATOTOXICITY

The groups forming Programme 3 have over 25 cooperation networks, both between each other (intranodal cooperation) and with other external groups (internodal cooperation). The group led by Dr José M. Mato, from CIC BioGUNE, continues to significantly bolster these cooperation schemes through its platforms for genomics, proteomics, metabolomics and gene silencing, which are also available in all the CIBEREHD groups. The cooperation based on these platforms include arranging different teaching sessions and training activities.

The cooperation activities of Programme 3 are substantiated in their publications in journals of great impact such as Hepatology (IF 2014: 11.055), the official journal of the American Association for the Study of Liver Diseases (AASLD), as is the case of:

- Barbier-Torres L, Beraza N, Fernández-Tussy P, Lopitz-Otsoa F, Fernández-Ramos D, Zubiete-Franco I, Varela-Rey M, Delgado TC, Gutiérrez V, Anguita J, Pares A, Banales JM, Villa E, Caballería J, Alvarez L, Lu SC, Mato JM, Martínez-Chantar ML. Histone deacetylase 4 promotes cholestatic liver injury in the absence of prohibitin-1. Hepatology 2015;62:1237-48.

# Immunology, Cell Therapy and Liver Transplantation

COORDINADOR: DR. MIQUEL NAVASA

Liver transplantation is the treatment for chronic liver diseases in the terminal stage and for acute liver diseases which go along with severe acute liver failure. It is also the final treatment for liver tumours such as hepatocellular carcinoma. This treatment has several traits: the first is that it is associated with an allogenic immune response which attempts to reject the implant so that the treatment becomes an immunological disease requiring the use of immunosuppressors to control this. The use of immunosuppressors in turn causes different diseases such as diabetes, high blood pressure, kidney failure, endothelial disorders, which very significantly increase these patients' cardiovascular risk. Similarly, the reduction of immune vigilance causes the appearance of neoplasias which are the main cause of death of these patients in the long term. Lastly, another of the problems involved in transplants is ischaemia reperfusion injury, both static (liver in the freezer with different conservation liquids), and dynamic (ex vivo perfusion of the implant). It is thus difficult to define the transplant as simply a treatment and it would seem more proper to define this as the only treatment which prolongs the survival of the patients with terminal chronic hepatopathy or acute hepatopathy with severe liver failure but which generates new diseases whose study and control is highly important to increase patients' survival.

## Most important achievements:

Prior studies of our group showed that before withdrawing the immunosuppressor medication, patients with operational tolerance and non-tolerant patients were differentiated in the expression of genes related with the homeostasis of Fe. The group has recently shown that small changes in the homeostasis of iron can have a significant effect on the regulation of the intrahepatocytary lymphocytic response, meaning that iron deprivation deteriorates the activation and proliferation of intrahepatic lymphocytes, which is associated with a beneficial effect in autoimmune hepatitis.

New targets for therapeutic action have been established, based on modulating adipocytokines in liver transplant in marginal organs. The results obtained have also enabled taking part in competitive programmes intended for translation of experimental results to clinical practice, so that the use of steatotic livers can be increased. The role of polyethylene glycol in preservation solutions for grafts has been established, indicating that better and longer conservation of organs can be guaranteed.

From the clinical standpoint we should stress a study which evaluates the hepatorenal syndrome in patients in the waiting list for a transplant and a study which shows the relevance of tuberculosis in transplanted patients. Two studies have evaluated alterations of the metabolism of carbohydrates and the impact of cardiovascular risk in patients with a liver transplant. The use of everolimus de novo and the effect on the renal function has also been evaluated. Researchers from the Programme have taken part in the preparation of the consensus document: V Consensus Meeting of the Spanish Society for Liver Transplant on high-risk recipients, immunosuppression scenarios and management of hepatocarcinoma on the transplant waiting list of the Sociedad Española de Trasplante Hepático. Gastroenterol Hepatol. 2015 Dec;38(10):600-18.

# Hepatic and Gastrointestinal Oncology

COORDINATOR: DR. JORDI BRUIX

The activity in the different lines of work in this programme in 2015 has resulted in some relevant contributions which have increased knowledge of risk factors and oncogenic mechanisms of both liver and gastrointestinal cancer. The studies have produced diagnostic and therapeutic innovations which have led to modifications in the clinical management of patients affected by these diseases.

Knowledge of the molecular anomalies of hepatocellular carcinoma and cholangiocarcinoma in liver cancer has been extended, in such a way that a rational biological basis for new treatments will be available in the future. Better classification of patients must obviously enable a more rational design of therapeutic tests.

Greater knowledge has been obtained about the role of the mitochondrial genome and P1 type purinergic receptors in the retrocontrol processes which regulate the expression of nuclear genes connected with the failure of liver cancer to respond to pharmacological therapy. The role of biliary acids and their interaction with macrophages in the oncogenic transformation of cholangiocytes has also been displayed.

On the clinical level, the first clinical trials with immune checkpoint inhibitors on patients with hepatocellular carcinoma have been started with some promising preliminary results. Leadership has been maintained in phase 3 tests evaluating agents such as tivantinib and regorafenib so that the results can be made known in 2016.

In the field of locoregional therapies the evaluation in phase 2 and in phase 3 tests has been maintained with a leading role in the design of an international multi-centre clinical trial for evaluating the effectiveness of radioembolisation in patients with intrahepatic cholangiocarcinoma.

In colorectal cancer top level research intended to establish the effectiveness of early detection campaigns has continued. This was backed by the AECC and the Ministry of Health. In this context we should stress the nationwide COLONPREV and EPICOLON studies, intended to establish new strategies for preventing colorectal cancer in intermediate and high risk-populations, respectively. The COLONPREV project is structured on the basis of a prospective, controlled and randomised study which compares the immunological detection of faecal occult blood, which constitutes the approach currently recommended in Spain by the Consejo Interterritorial de Sanidad, and colonoscopy. The results of the first round show that both approaches enable detecting the same number of cancers, with a lower rate of complications and better cost-effectiveness ratio. The COLONPREV study has led to several publications which have enabled improving the cost-effectiveness ratio of early detection plans and stratifying the population based on the results of examinations and their genetic profile in individuals affected by family hereditary cancer.

# Inflammation and Gastrointestinal Motility

COORDINATOR: DR. JULIÀ PANÉS

In the sphere of understanding the mechanisms of inflammatory bowel diseases, molecular bases of cortical refractoriness in ulcerative colitis have been established, as well as post-surgical recurrence in Crohn's disease, leading to therapeutic targets based on modulating the activity of the extracellular matrix. In a basic project, the presence of macrophages expressing surface receptors of phenotype M2 and their accumulation with chronicity has been observed in the mucus of patients with inflammatory bowel disease. These macrophages persistently express Wnt ligands and activate Wnt signalling in the epithelial cells, which is associated with defects in autophagy, in enterocyte differentiation and in the process of mucus regeneration.

As regards aspects of the clinical management of patients with inflamed bowel disease, we have provided evidence showing that the valuation of activity and complications of Crohn's disease by magnetic resonance is of greater value than endoscopy in identifying patients with a bad prognosis. The following two projects were completed this year: "Evaluation of the effectiveness of two vaccines against the hepatitis b virus in patients with inflammatory bowel disease and their impact on the immune system", and "Prediction of short and long-term response to treatment with anti-TNFα drugs in patients with Crohn's disease".

In the area of therapeutic progress, new studies on the anti-inflammatory effects of natural products including prebiotics and probiotics, natural extracts and flavonoids have been completed and published. In the clinical field it should be stressed that a study in phase I has been completed evaluating the safety and effectiveness of treatment with tolerogenic dendritic cells in patients with active refractory Crohn's disease.

In cooperation with the digestive oncology programme studies have been carried out on the role of acetylsalicylic acid and platelets in colon cancer, and the value of inhibiting the transport of protons in chemoprevention and treatment of adenocarcinoma of the oesophagus. In the diagnostic field a new fast and non-invasive method for early detection of pancreatic cancer has been validated.

In the neurogastroenterology area, studies have been performed on mechanisms for control of the swallowing motor response with potential therapeutic application in clinical practice on patients with post-ictus oropharyngeal dysphagia. The relationship between the digestive motor function and the nutritional condition of fragile elderly people and the morbidly obese has also been characterised, as well as the effect of diverse gastrointestinal peptides on the mechanisms for control of the appetite and satiety.

As regards organisational aspects we should stress the large number of cooperative projects among the groups in programme 6 and the cooperation with nationwide research networks. The financing of research work stems from both official national projects and from the European H2020 programme, the Marie Curie programme and from cooperation schemes with industry. Members of several research groups have taken part in drawing up clinical guides on a nationwide and international scale.

# 4

# Transversal Programmes

# Training Programme

One of the aims of the CIBEREHD is to promote the training of our researchers (attached and contracted staff: post-doctoral, pre-doctoral, nurses and technical personnel) to raise 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 de Enfermedades Hepáticas y Digestivas is materialised in the following measures:

- Training stays at CIBEREHD centres.
- Short training stays in Spain or abroad (at most 8 weeks and exceptionally up to 3 months).
- Programmes for visiting intermural teachers.
- Holding Courses or Training activities considered of interest for the CIBEREHD.
- Promoting scientific activities arranged by members of the CIBEREHD (sponsoring and financing seminars, symposia, courses for postgraduates), cooperation with training activities of scientific associations and virtual training activities over the web.

In 2015, a total number of 23 Grants were awarded to our researchers for different activities according to the Training Plan programme. In spite of the cutbacks in the budget, we have been able to meet almost all the applications. The beneficiaries of the aid were 8 attached members and 12 hired staff. The activities financed were 2 short stays abroad (France and Austria), 13 training courses and activities in Spain and 5 courses abroad.

Some of these activities which we would like to stress are the stays of Dr Sofía Pérez del Pulgar (Dr Forns' group) at the Cancer Research Center of Lyon (CRCL) - Lyon, (France) with Dr Fabien Zoulim and that of Dr Mª Jesús Perugorria (Dr Luis Bujanda's group) at the Research Center for Molecular Medicine of the Austrian Academy of Sciences (CeMM), Vienna, (Austria), with the Investigator in Charge Sylvia Knapp.

We have also co-financed the following courses organised by members of our Centre:

- XIV Conference on Progress in Hepatology, 22-23 in May 2015 in Malaga, organised by Dr Raúl J. Andrade.
- XIII National Virology Congress, Madrid from 07th to 10th June 2015, organised by Dr Josep Quer Silva.
- Basic Training Course on the Design and Management of Projects on the On-line Platform AEG-REDcap, 19th June 2015 in Madrid, organised by Adrian G. McNicholl.

Through its training plan, the CIBEREHD sponsored the Post-Graduate Course of the Asociación Española para el Estudio del Hígado (AEEH) which took place during the 41 Congreso Anual de la AEEH y de la Asociación Española de Gastroenterología (AEG).

# 5

# Platforms

# BIOBANK

## Hospital Clinic de Barcelona Biobank (Biobanc Clinic)

The CIBEREHD has set up a platform which collects, stores and distributes biological samples connected with digestive diseases, supported by the infrastructure of the IDIBAPS Biobank. This work includes two types of collections: gastrointestinal and pancreatic oncology (OGP) and intestinal diseases (EII).

**GASTROINTESTINAL AND PANCREATIC ONCOLOGY (OGP).** The Biobank has samples of plasma, serum, DNA and lymphocytes of donors with the following characteristics:

- Patient with colorectal cancer: 283 donors.
- Patient with intermediate risk of colorectal cancer: 5720 donors.
- Patient or relative with high risk of colorectal cancer (polyposic or non-polyposic syndrome): 671 donors.
- Patient or relative with moderate risk of colorectal cancer (familial colorectal cancer): 48 donors.
- Patient with pancreatic cancer: 6 donors.
- Patient with intraductal papillary mucinous tumour or mucinous cystic tumour; 16 donors
- Patient with chronic pancreatitis: 19 donors.
- Patient with gastric cancer: 1 donor.

The samples are deposited at the IDIBAPS Biobank. In 2015 1291 new donors were received exclusively from the Hospital Clínico de Barcelona. 1023 of these donors are patients with intermediate risk of colorectal cancer (79.2% new donations) and 142 patients or relatives with a high risk of colorectal cancer (11% new donations).

In 2015 a total number of 5358 different aliquots were assigned. The projects involved are as follows:

- Serum miR-21 as blood tests for early colorectal neoplasia. Francesc Balaguer, assignment of 800 serums and 800 plasmas.
- Metabolomics-based detection of early stage cancers. Kristi Kruusma, assignment of 523 serums.
- Design and preparation of kits for diagnosing colon cancer in the blood based on multiplex platforms (COLONTEST Project). Antoni Castells, assignment of 1075 serums.
- Identification of new biomarkers for prevention of colorectal cancer. Antoni Castells, assignment of 762 serums and 1398 DNA.

**INTESTINAL INFLAMMATORY DISEASES (EII).** The Biobank mainly has samples of DNA (in some cases also of plasma and lymphocytes) of donors with the following characteristics:

- Crohn's disease: 1575 donors.
- Ulcerative colitis: 769 donors.
- Indeterminate colitis: 15 donors.
- Lymphocytic colitis: 34 donors.
- Collagenous colitis: 39 donors.
- Intestinal diseases to be determined: 672.

The samples are deposited at the IDIBAPS Biobank. In 2015, 217 new donors were received, 197 of which (90.8% of the new donations) are from health centres in Catalonia other than the Hospital Clínic de Barcelona. Furthermore, 108 of the donors are patients with Crohn's disease (49.8% new donations) and 89 patients with ulcerative colitis (41% new donations).

In 2015 a total number of 43 aliquots of DNA were assigned to the project entitled Microbial-specific humoral response and HLA typing of Crohn's disease. Azucena Salas.

## La Fe Hospital Biobank in Valencia (Collection of Steatotic Livers)

La Fe Biobank is an authorised and consolidated service in the Hospital and the Healthcare Research Institute. It was authorised in 2013 by Royal Decree 1716/2011, of 18th November, by means of which the basic requisites for operation of biobanks for purposes of biomedical research were established.

In 2015, La Fe Biobank received 3253 donations from the collections that it has running until now, specifically 36 in the biobank system. More specifically, two livers from the "Steatotic Liver" collection not valid for transplanting were donated for use in biomedical research. At the present time the collection has 173 livers characterised and managed according to normative and quality criteria.

The samples deposited at the Biobank have been requested, during its six years' operation, by sound and competitive research groups. In 2015, more specifically, 1253 samples were assigned, 41 of which were steatotic livers (41 patients).

The Biobanco La Fe forms part of the "Biobanks Platform (PT13/0010/0026. AES-2013)" cooperating in four currently active programmes/work lines: "Programme for collections with strategic value", "Network Services Management", "R+D+i Programmes (Management Technologies and Quality Control Programmes)" and "Training". La Fe Biobank has taken part in the ("ISBER Proficiency Test") international quality control programme in 2012 and 2015 and has been certified according to UNE-EN ISO 9001:2008 Standard on Quality Management.

# Bioinformatics

The Bioinformatics platform has taken an active part in the operation of this CIBER, as is vouched for by the 13 publications reflecting their support in 2015. Special attention should go to the contribution made in the areas of colon cancer, specifically the group directed by Dr Toni Castells (G0016) whose bioinformatic work was directed and performed by our group. Two important publications are:

- Whole-exome sequencing identifies rare pathogenic variants in new predisposition genes for familial colorectal cancer. Esteban-Jurado C, Vila-Casadesús M, Garre P, Lozano JJ, Pristoupilova A, Beltran S, Muñoz J,Ocaña T, Balaguer F, López-Cerón M, Cuatrecasas M, Franch-Expósito S, Piqué JM, Castells A, Carracedo A, Ruiz-Ponte C, Abulí A, Bessa X, Andreu M, Bujanda L, Caldés T, Castellví-Bel S.Genet Med. 2015 Feb;17(2):131-42. doi: 10.1038/gim.2014.89. Epub 2014 Jul 24.(IF: 7.329).
- Patterns of somatic uniparental disomy identify novel tumor suppressor genes in colorectal cancer. Torabi K, Miró R, Fernández-Jiménez N, Quintanilla I, Ramos L, Prat E, del Rey J, Pujol N, Killian JK, Meltzer PS, Fernández PL, Ried T, Lozano JJ, Camps J, Ponsa I.Carcinogenesis. 2015 Oct;36(10):1103-10. doi: 10.1093/carcin/bgv115. Epub 2015 Aug 4.(IF:5,33).

In the liver transplantation area our group has performed and directed bioinformatic work to propose a signature predicting rejection in HCV-negative patients, cooperating with other groups from the CIBER and Dr Sánchez-Fueyo (King's College of London).

- Molecular Characterization of Acute Cellular Rejection Occurring During Intentional Immunosuppression Withdrawal in Liver Transplantation. Bonaccorsi-Riani E, Pennycuick A, Londoño MC, Lozano JJ, Benítez C, Sawitzki B, Martínez-Picola M, Bohne F, Martínez-Llordella M, Miquel R, Rimola A, Sánchez-Fueyo.Am J Transplant. 2016 Feb;16(2):484-96.(IF:5.683).

Our group has led the bioinformatic work of different projects cooperating with CIBER groups: Dr Pere Ginés (G0020) and Vrije Universiteit Brussel, to integrate gene expression data on mRNA and microRNA and learning of mechanisms of activation of hepatic stellate cells.

- Integrative miRNA and Gene Expression Profiling Analysis of Human Quiescent Hepatic Stellate Cells.Coll M, El Taghdouini A, Perea L, Mannaerts I, Vila-Casadesús M, Blaya D, Rodrigo-Torres D, Affò S, Morales-Ibanez O, Graupera I, Lozano JJ, Najimi M, Sokal E, Lambrecht J, Ginès P, van Grunsven LA, Sancho-Bru P.Sci Rep. 2015 Jun 22;5:11549. doi: 10.1038/srep11549.(IF:5,578).

Our group took part in the achievement of financed projects and/or projects with R+d+i companies such as for example:

- Title: Kit easy-CCR: Development of a diagnosis kit for early detection of colorectal cancer by a non-invasive method in plasma based on the expression of miRNAs. Organisation: Ministry of the Economy and Competitiveness. Call: Challenges-Cooperation 2015 (Case file: RTC- 2015-3850-1). Duration: 2015-2018.
- Coordinated project. Coordinating entity: Amadix. PI for CIBER: Meritxell Gironella.

  Amount: 1,549,174€ (CIBER part: 171,800€).

# CIBERHEP. Platform for Chronic Hepatitis B

The CIBERHEP platform for chronic hepatitis B is a cooperation scheme run by the CIBER and the Asociación Española para el Estudio del Hígado (AEEH). At the present time this is the main database of patients being treated for chronic hepatitis B in Spain: in 2015 data was registered on around 1300 patients monitored at 25 centres in 9 different administrative regions.

This data has meant that different studies could be carried out, such as the analysis of the effectiveness of entecavir and tenofovir in patients previously treated at the clinical practice, presented as a poster at the 40th annual congress of AEEH (Madrid, 24-27th February 2015). A study has also been made on the impact of nucleoside/nucleotide analogue antivirals in the incidence of hepatocellular carcinoma in Caucasian patients, the results of which were recently presented as an oral communication at the 41st Annual Congress of the AEEH (Madrid, 17-19th February 2016) and will be presented as a poster at the annual congress of the European Association for the study of liver diseases [EASL (Barcelona, 13-17th April 2016)]. This study is currently being written in the format of an article to be sent to a clinical journal indexed in international databases.

Finally, in 2015 an updating/remodelling process was started with the aim of extending the data collected in the database of this platform, at the same time as simplifying the registration of this data through its web page. This update/remodelling is currently still under way.

# CIC BioGUNE. Platform for Genomics, Proteomics, Metabolomics and Gene Silencing

## Genomics Platform

Over 2015 the CIC BioGUNE platform for analysis of genomes carried out a total number of 40 services for characterisation of DNA or RNA from a total of 600 samples and a further 18 services or cooperation measures in projects for analysis of genotyping, transcriptomic, epigenomic and metagenomic data.

In this period the members of the group published 6 articles in journals of international impact on research done in cooperation projects, 2 chapters of a book and published a book entitled “Field Guidelines for Experi- mental Genetic Designs in High-Throughput Sequen- cing” which we consider will be a great help for any researcher wishing to include mass sequencing technologies in their projects.

In mid-2015, the platform managed to join a special programme provided by the company Oxford Nanopore Technologies (The MinION Access Programme) to test its new mass sequencing system thanks to which we hope to be able to offer services connected with said technologies in the near future.

## Metabolomics Platform

Over 2015, the metabolomics platform implemented the methodology of analysis by UPLC-MS of the metabolism of polyamines and glutathione, being incorporated to the already existing method for analysing the metabolism of the methionine cycle. In 2015 these methods were used in the study of the disorders undergone by these metabolites during hepatic damage, and to evaluate the effectiveness of different treatments. Furthermore in 2015 new methods were developed to evaluate methionine adenosyl-transferase (MAT) activity as well as catechol-O-methyl transferase (COMT) activity in hepatic microsomes and samples of liver. Lastly, the preparation for carrying out fluoxomic studies was got under way. In 2015, the platform carried out 25 services and took part in three articles published in Frontier in Immunology, Journal of Hepatology and Cell Metabolism.

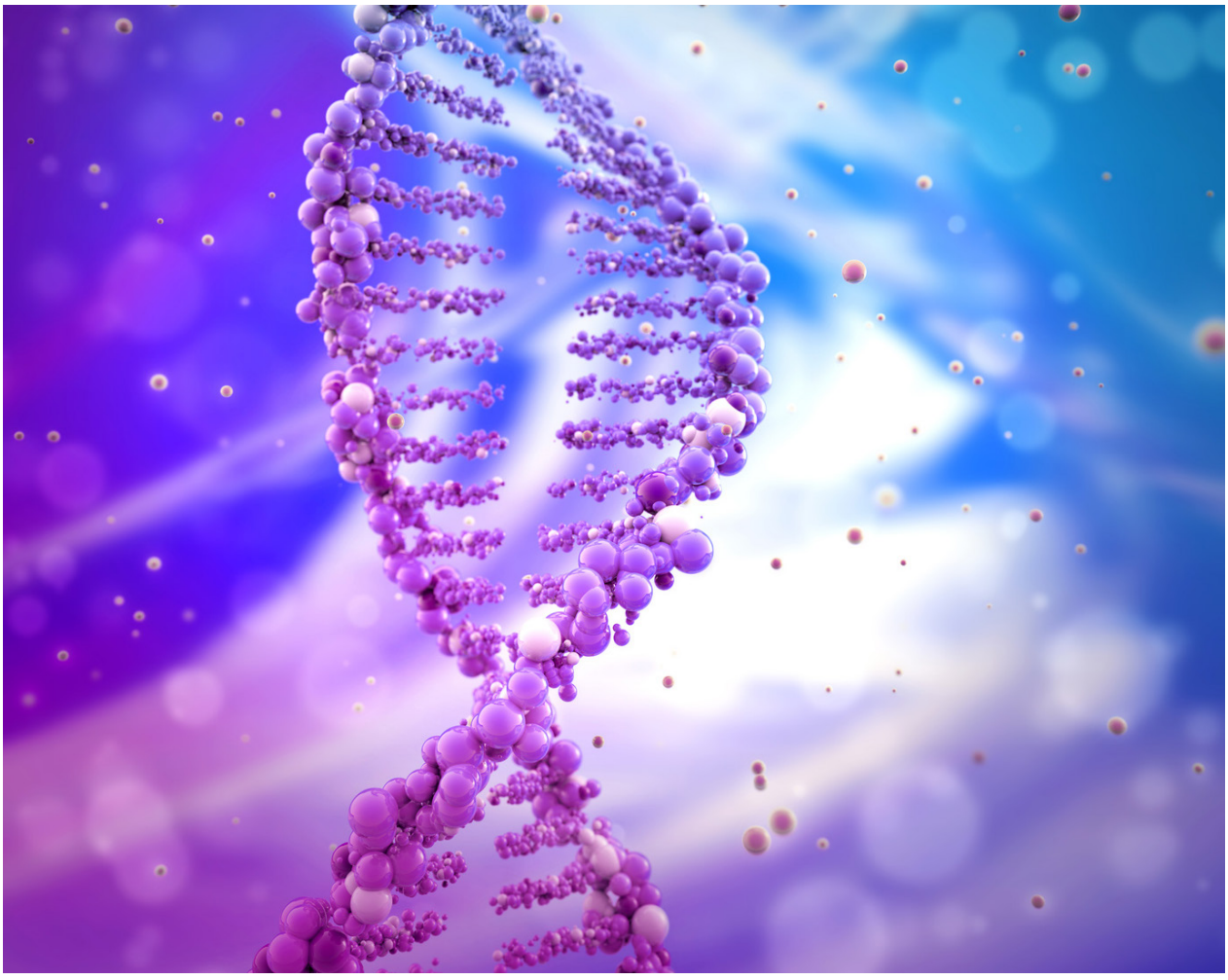
## Proteomics Platform

In 2015 the proteomics platform provided service for, and cooperated with, different groups in the CIBEREHD (bioGUNE, H. Clinic, ITGP and BioDonostia). Six articles were published in scientific journals with international impact. Methods for preparing the sample and acquisition for what is known as peptidomics were also made ready. Lastly, the work done in preparing the differential quantification of proteomes by the nanoscale liquid chromatography method coupled on line to tandem mass spectrometers by the label-free approach (Label-Free nLC MS/MS Quantification), was reflected in the publication of the cooperation performed with Dr Woddhoo (Gómez-Sánchez et al. J Cell Biol).

## Metabolomics Platform (RMN)

In 2015, the NMR metabolomics platform consolidated and validated the standardised work procedures for metabolomic analysis of urine and serum. More specifically, the protocols for preparing samples and acquisition of spectra were adapted to the ones established by the company Bruker and the international consortium led by the Imperial College and the I.T. solutions required for univariate and multivariate analysis of the sets of data were implemented.

In the field of applications, a set of samples of serum from patients with hepatic fibrosis was analysed. Metabolomic analysis by NMR has enabled establishing a protocol for separation of stages 1 and 4 of hepatic fibrosis and has identified metabolites able to act as fibrotic progression markers. Said results are shown in a scientific publication (currently being revised).



# E-CATCH. Diagnosis and Treatment of Liver Cancer

The e-CATCH platform aims to provide diagnostic and therapeutic guidance services by electronic consultation for patients with liver cancer. The possibility of evaluating both reports and imaging techniques enables consulting doctors to reliably review the information available and provides guidance based on scientific evidence. In 2015 a contract was established with pharmaceutical company Bayer which financed the telemedicine work.

In 2015 over 50 consultations were made over the platform and its review has been started in order to offer consultation services internationally and thus ensure the sustainability of the platform.

As well as the consultancy services the platform has enabled transferring tomography or resonance images in order to validate the results of multi-centre studies and thus guarantee the validity of the readings of images by independent radiologists.

# HEPA-C. National Database for Patients with chronic Hepatitis C

Hepa-C is a cooperation project which in 2015 enabled storing the data of 3000 patients infected with hepatitis C undergoing treatment in real clinical practice with direct-acting antivirals, most of which were interferon-free. Its design has enabled a compilation of all the variables needed to carry out high quality research projects. The information has been monitored and is thus much more reliable than other well-known collaborative registers, in turn providing technical assistance for the participants. In 2015 60 attached centres had joined the scheme, most of them taking an active part. The information contained in Hepa-C has enabled the presentation of several works at the XL congress of the AEEH and at the International Liver Congress of the EASL:

- Poster Nº 92: The season of the year in which triple therapy starts predicts fast viral response in patients with the hepatitis C virus (VHC) genotype 1: Analysis of the Hepa-C register.
- Oral communication: First data on real clinical practice in Spain with Sofosbuvir, Simeprevir and Daclatasvir in patients with HCV infection: experience of the Hepa-C registry.
- Oral communication: first data on clinical practice in Spain through compassionate use of Sofosbuvir, Simeprevir and Daclatasvir in transplanted patients with recurrent HCV: experience of the Hepa-C register.
- Poster Nº 0785: First real clinical practice data in Spain on Sofosbuvir, Simeprevir and Daclatasvir in post-transplant HCV recurrence: the Hepa-C Registry Experience.
- Poster Nº 0862: First real clinical practice data on Sofosbuvir, Simeprevir and Daclatasvir with HCV-Chronically infected patients in Spain: the Hepa-C Registry Experience.

Two manuscripts were also approved for sending to high-impact journals (pending acceptance) and a large number of communications were sent for the coming congresses of the AEEH/ EASL in 2016, with many posters and oral communications already having been accepted to be given in the coming year.

# REHEVASC. Registry of Vascular Liver Diseases

The REHEVASC platform, active since 2011, has the purpose of registering a group of rare vascular liver diseases (Budd-Chiari syndrome, non-neoplastic non-cirrhotic portal thrombosis, idiopathic portal hypertension) whose common characteristics include the high risk of being able to go on to portal hypertension in the absence of cirrhosis. Over these years the dissemination of REHEVASC and its associated documents which establish consensus recommendations for the diagnosis and treatment of these diseases has enabled increasing the interest and recognition of these diseases (often under-diagnosed).

Hence, there are at the present time 17 Spanish care centres which are actively registering patients. In the last export of data in the register (February 2016) over 450 patients were registered. In spite of their infrequency, 7 of these centres registered over 20 patients. The exploitation of the register has enabled presenting a work this year at the congress of the AEEH on the incidence of rethrombosis in patients with non-neoplastic non-cirrhotic portal thrombosis which is at the present time in the stage of drafting for publication.

# 6

# Research Groups

# G0024

**Programme:** Portal Hypertension & Mechanisms of Transition to Cirrhosis
**Lead Researcher:** Albillos Martínez, Agustín

## Group members

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

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

## Main lines of research

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

# Most relevant scientific articles

REVERTER E., MESONERO F., SEIJO S., MARTÍNEZ J., ABRALDES J.G., PENAS B. ET AL. Effects of sapropterin on portal and systemic hemodynamics in patients with cirrhosis and portal hypertension: A bicentric double-blind placebo-controlled study. American Journal of Gastroenterology. 2015;110(7):985-992.

ALBILLOS A, MARTÍNEZ J, TÉLLEZ L. Continued controversy over the safety of beta-blockers in decompensated cirrhosis.Hepatology (Baltimore, Md.). 2015.

LENS S., RINCON D., GARCÍA-RETORTILLO M., ALBILLOS A., CALLEJA J.L., BANARES R. ET AL. Association Between Severe Portal Hypertension and Risk of Liver Decompensation in Patients With Hepatitis C, Regardless of Response to Antiviral Therapy. Clinical Gastroenterology and Hepatology. 2015;13(10):1846-1853.

CERINI F., GONZÁLEZ J.M., TORRES F., PUENTE A., CASAS M., VINAIXA C. ET AL. Impact of anticoagulation on upper-gastrointestinal bleeding in cirrhosis. A retrospective multicenter study. Hepatology. 2015;62(2):575-583.

THIELE M., ALBILLOS A., ABAZI R., WIEST R., GLUUD L.L., KRAG A.. Non-selective beta-blockers may reduce risk of hepatocellular carcinoma: A meta-analysis of randomized trials. Liver International. 2015;35(8):2009-2016.

# Highlights

Involvement of the group in the following projects:

1) The European Commission “Carbalive project” to study the use of carbons for the treatment of cirrhosis and NASH,
2) VI Baveno Consensus Conference on Portal Hypertension, and
3) the Scientific Board of the Spanish Hepatitis C Action Plan.

**Institution:** Universidad de Alcalá · **Contact:** Facultad de Medicina. Campus Universitario Ctra. Madrid-Barcelona, km. 33,600. 28871 Alcalá de Henares · E.mail: agustin.albillos@uah.es

# G2008

Programme: **Hepatotoxicity, Cholestasis & 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., GONZÁLEZ-JIMÉNEZ A., MEDINA-CALIZ I., STEPHENS C., GARCÍA-CORTES M., GARCÍA-MUNOZ B. ET AL. Distinct phenotype of hepatotoxicity associated with illicit use of anabolic androgenic steroids. Alimentary Pharmacology and Therapeutics. 2015;41(1):116-125.

TESCHKE R., ANDRADE R.J.. Drug-induced liver injury: Expanding our knowledge by enlarging population analysis with prospective and scoring causality assessment. Gastroenterology. 2015;148(7):1271-1273.

ANDRADE R.J.. Reducing Risk of Severe Liver Injury in Patients Treated With Isoniazid. Clinical Gastroenterology and Hepatology. 2015;13(9):1683-1685.

CHEN M., SUZUKI A., BORLAK J., ANDRADE R.J., LUCENA M.I.. Drug-induced liver injury: Interactions between drug properties and host factors. Journal of Hepatology. 2015;63(2):503-514.

ROBLES-DIAZ M., GARCÍA-CORTES M., MEDINA-CALIZ I., GONZÁLEZ-JIMÉNEZ A., GONZÁLEZ-GRANDE R., NAVARRO J.M. ET AL. The value of serum aspartate aminotransferase and gamma-glutamyl transpetidase as biomarkers in hepatotoxicity. Liver International. 2015;35(11):2474-2482.

# Highlights

## GRANTS:

- FIS PI15/01440: Analysis of physico-chemical drug properties, host factors and their interaction in hepatotoxicity phenotype presentation and outcome.
- Grant "Stabilisation programme of researchers & Intensification of the research activity in the National Health System. Carlos III Health Institute.
- COST proposal OC-2015-2-20045 "Pro Euro DILI Net
- PLAN PROPIO UMA FOR THE CREATION OF THEMATICS NETWORKS, denominada "Pro-Euro-DILI Registry – Creation of a multicentre and multidisciplinary European registry of prospective drug-induced liver injury cases".
- Contract with the Spanish Medicines Agency.

TRANSFER OF SCIENTIFIC KNOWLEDGE/INNOVATION: Design of an Hepatotoxicity APP for iOS and androids: eDILI gives information about hepatotoxicity and calculates the indeces used in this pathology.

## DEVELOPING OUR HEPATOTOXICITY NETWORKS:

- Spanish and Latin-American DILI Registry (www.spanishdili.uma.es; www.slatindili.uma.es).
- Prospective European Drug-Induced Liver Injury Registry (Pro-EuroDILI Registry).

## OTHERS:

- Chair of the Commision for Evaluating progress of Clinical independent Research projects ICI 2015. Member of the Executive Committee IUPHAR.
- Application for "MEP-SCIENTIST PAIRING SCHEME 2015" to interact with the deputies (members of the European Parliament).
- Prize of the Spanish Society of Pharmacology for the best Comunicación (poster). Valencia 2015.
- Director and Coordinator of the XV Course on Advances in Hepatology 2015.
- Establishing Collaboration with the National Center for Toxicological Research (FDA, USA), Central Arkansas Veterans Healthcare System (USA) & Center of Pharmacology and Toxicology (Germany).
- Invited Speaker at International Conferences HEPATOLOGIA DO MILÊNIO 2015, BRAZIL; EASL/AASLD MONOTHEMATIC CONFERENCE AUTOIMMUNE HEPATITIS, LONDON 2015; JAPAN DIGESTIVE DISEASE WEEK 2015; 5TH SYMPOSIUM HEPATOLOGY 2015, SWITZERLAND; NIH- ASSLD Workshop, Bethesda 2015.

**Institution:** Fundación Pública Andaluza para la Investigación de Málaga en Biomedicina y Salud (FIMABIS)
**Contact:** Hospital Virgen de La Victoria. Campus Universitarios Teatinos s/n. 29010 Málaga
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# G0021

Programme: **Inflammation & Gastrointestinal Motility**

Lead Researcher: **Azpiroz Vidaur, Fernando**

## Group members

STAFF MEMBERS: Nieto Ruiz, Adoración | 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., MALAGELADA C., RODRÍGUEZ-URRUTIA A., SOLDEVILLA A. ET AL. Biofeedback-guided control of abdominothoracic muscular activity reduces regurgitation episodes in patients with rumination. Clinical Gastroenterology and Hepatology. 2015;13(1):100-106.

WOUTERS M.M., VICARIO M., SANTOS J.. The role of mast cells in functional GI disorders. Gut. 2015.

BENDEZU R.A., BARBA E., BURRI E., CISTERNAS D., MALAGELADA C., SEGUI S. ET AL. Intestinal gas content and distribution in health and in patients with functional gut symptoms. Neurogastroenterology and Motility. 2015;27(9):1249-1257.

MALAGELADA C., DROZDZA M., SEGUI S., MENDEZ S., VITRIA J., RADEVA P. ET AL. Classification of functional bowel disorders by objective physiological criteria based on endoluminal image analysis. American Journal of Physiology - Gastrointestinal and Liver Physiology. 2015;309(6):G413-G419.

AZPIROZ F., MALAGELADA C.. Diabetic neuropathy in the gut: pathogenesis and diagnosis. Diabetología. 2015;:1-5.

# 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 , Center for Omics Sciences (COS) Universitat Rovira i Virgili, Reus, Tarragona.

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 (Corzo N, Alonso, JL, Azpiroz F, et al. Prebióticos; concepto, propiedades y efectos beneficiosos. Nutrición Hospitalaria 31(1): 99-118, 2015). The Join meeting UEG/microbiota and health section (IP Chair) and AGA has been decided to take place in Barcelona every other year. The book of Functional Gut Criteria RomeIV ( IP Board of directors ) is in the process of publication.

TRAINING. The European network for investigation training on Neurogastroenterology funded by the Marie Curie program has been established a net work of European Center related to Neurogastroenterology and Motility.

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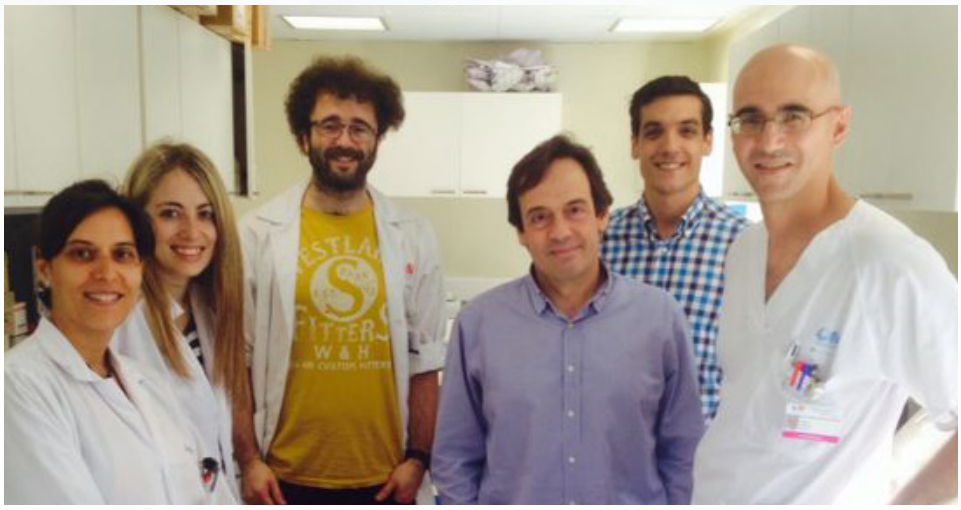
**Contact:** Hospital Vall d'Hebron. Passeig Vall d'Hebron, 119-129 08035 Barcelona · Tel.: 93 489 44 02
E.mail: azpiroz.fernando@gmail.com

# G0082

Programme: **Portal Hypertension & Mechanisms of Transition to Cirrhosis / Inflammation & Gastrointestinal Motility**

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 | Menchen Viso, Luis Alberto | Rincón Rodríguez, Diego | Ripoll Noiseux, Cristina Alberta | Salcedo Plaza, Magdalena | Vaquero Martín, Javier.

## Main lines of research

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

# Most relevant scientific articles

CHIVA T., RIPOLL C., SARNAGO F., RINCON D., GÓMEZ-CAMARERO J., GALINDO E. ET AL. Characteristic haemodynamic changes of cirrhosis may influence the diagnosis of portopulmonary hypertension. Liver International. 2015;35(2):353-361.

RODRÍGUEZ-FEO J.A., PUERTO M., FERNÁNDEZ-MENA C., VERDEJO C., LARA J.M., DIAZ-SÁNCHEZ M. ET AL. A new role for reticulon-4B/NOGO-B in the intestinal epithelial barrier function and inflammatory bowel disease. American Journal of Physiology - Gastrointestinal and Liver Physiology. 2015;308(12):981-993.

LATORRE R., VAQUERO J., RINCON D., PUERTO M., PONCE M.D., SARNAGO F. ET AL. Determinants of platelet count are different in patients with compensated and decompensated cirrhosis. Liver International. 2015.

OLMEDILLA L., LISBONA C.J., PÉREZ-PENA J.M., LÓPEZ-BAENA J.A., GARUTTI I., SALCEDO M. ET AL. Early Measurement of Indocyanine Green Clearance Accurately Predicts Short-Term Outcomes After Liver Transplantation. Transplantation. 2015.

CERINI F., GONZÁLEZ J.M., TORRES F., PUENTE A., CASAS M., VINAIXA C. ET AL. Impact of anticoagulation on upper-gastrointestinal bleeding in cirrhosis. A retrospective multicenter study. Hepatology. 2015;62(2):575-583.

# Highlights

The group has continued to consolidate the research structure of its double-edge clinical and experimental lines. In the last year, the group has incorporated two researchers from competitive calls of Instituto de Salud Carlos III (Río Hortega and Juan Rodes), and has obtained funding for research projects in public (FIS PI15 PI: Rafael Bañares, and PI15/01083 PI: Javier Vaquero) and private (Gilead Fellowship PI: Rita García) calls.

The most relevant results from our group proceed from the clinical as well as the experimental research lines. Among the first ones, the group has provided insight into the non-hepatic manifestations of cirrhosis finely characterizing the pulmonary circulation in patients with cirrhosis with and without portopulmonary hypertension, as well as defining the determinants of platelet count in cirrhosis as a function of the stage of the disease. In the context of a multi-center study, the group has participated in the characterization of the impact of anticoagulation on the evolution of gastrointestinal bleeding in patients with cirrhosis.

Another relevant result is provided by an ample study aiming to determine the predictive ability of Indocyanine green clearance evaluated non-invasively in liver trasnplantation recipients. Based on this study, we were able to elaborate a prognostic index highly discriminant for diagnosing primary dysfunction of the graft.

The group has also identified NOGO-B as a new protein with a relevant role on the intestinal barrier permeability in humans as well as in diverse experimental animal models. This study clearly shows the link between our group's research lines: Gastroenterology and Hepatology.

Lastly, the group has been able to elaborate, present and defend (in the first weeks of 2016) several doctoral Thesis (6) derived from some of the previously mentioned projects.

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# G0065

Programme: **Immunology & Liver Transplantation**
Lead Researcher: **Berenguer Haym, Marina**

## Group members

STAFF MEMBERS: Carvalho Gomes, Ángela Sofía.

ASSOCIATED MEMBERS: Aguilera Tello, Victoria | Benlloch Pérez, Salvador | Pérez Rojas, Judith | Prieto Castillo, Martín | Rubín Suárez, Ángel.

## Main lines of research

**Hepatitis B, C, D and E** (clinical, virological and immunological studies): Focus on assessing the effectiveness and risk-benefit of new direct-acting antivirals for the treatment of HCV (and to a lesser extent HBV/HDV) both in immunocompetent and liver transplant patients (pre and posttransplant). Studies performed usually within clinical trials sponsored by industry We also collaborate in national and international real life cohorts. These studies/collaborations have resulted in several publications in first decile journals (some in preparation). We are leading a multicenter study ( FIS project ) assessing interactions between HCV and other viruses, such as CMV. Finally, we have obtained private and public funding for epidemiological studies on the prevalence of HCV infection and selection of cost-effective screening strategies.

**Post-liver transplantation (LT) long-term complications:** research to study several post-TH complications such as sexual and renal function, diabetes, cardiovascular disease and de novo tumors. These studies have resulted in publications in first decile journals. Likewise, we collaborate with other centers to determine prognostic factors for cellular rejection and operational mechanisms involved in tolerance.

**Hepatocellular carcinoma (HCC) and LT:** Collaboration with the National HCC Registry. We are also collaborating with UCSF and the Radiodiagnostic Department to identify LT failure associated factors.

**Wilson's disease:** Collaboration with several national centers(IPPC and the "Mixed Rare Diseases Research Unit")to perform cellular and genetic studies and generate a database to better understand this disease.

**Non-cirrhotic portal hypertension:** The group belongs to the Spanish multicenter REHEVASC which aims to study this disease by creating a Spanish database and a bank of blood samples for possible future studies.

**Cirrhotic portal hypertension:** Collaborations with national groups to improve the management of cirrhotic patients with portal hypertension and portal vein thrombosis.

# Most relevant scientific articles

HEZODE C., ASSELAH T., REDDY K.R., HASSANEIN T., BERENGUER M., FLEISCHER-STEPNIEWSKA K. ET AL. Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naive and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-I): A randomised, open-label trial. The Lancet. 2015;385(9986):2502-2509.

CERINI F., GONZÁLEZ J.M., TORRES F., PUENTE A., CASAS M., VINAIXA C. ET AL. Impact of anticoagulation on upper-gastrointestinal bleeding in cirrhosis. A retrospective multicenter study. Hepatology. 2015;62(2):575-583.

BERENGUER M., GARCÍA-ELIZ M., BAIGUERA C., PUOTI M.. Beyond cure: Preventing and managing the complications of end-stage liver disease. Current Opinion in HIV and AIDS. 2015;10(5):355-360.

FORNS X., POORDAD F., PEDROSA M., BERENGUER M., WEDEMEYER H., FERENCI P. ET AL. Ombitasvir/paritaprevir/r, dasabuvir and ribavirin for cirrhotic HCV patients with thrombocytopaenia and hypoalbuminaemia. Liver International. 2015;35(11):2358-2362.

BILBAO I., SALCEDO M., GÓMEZ M.A., JIMÉNEZ C., CASTROAGUDIN J., FABREGAT J. ET AL. Renal function improvement in liver transplant recipients after early everolimus conversion: A clinical practice cohort study in Spain. Liver Transplantation. 2015;21(8):1056-1065.

# Highlights

In 2015 the group has obtained and/or continued 13 research projects with public and private funding: PI15/02010-M.Berenguer (78045,00€), 2013/0049,Exp.2013_004)-M.Berenguer (11689,82€), 2014/0430,P.I. Exp. 2014_0430_GILEAD_BERENGUER-M.Berenguer (49800,00€), PI13/01770–V.Aguilera (64130,00€), 2014/0055,P.I. Exp.2014_0055. V.Aguilera (29821,60€), 2014/0234,P.I.Exp.2014_0234_SAC_TOYA-V.Aguilera(9234,60€), Defining High Risk Variceal Bleeding: A Rational For The Use Of Early Tips In Acute Bleeding And Preventing Rebleeding-C.Vinaixa (Colab.M.Berenguer), 2012/0154,P.I.Exp.PI12/01262–Luis MartiBonmati (Colab.A.Rubín) (19965,00€), 2011/0421, P.I. Exp.2011_0421_PP_BERENGUER.-M. Berenguer, EHD14PLAT004–MariaButiFerrer (Colab. M.Berenguer) (68208,34€), ICI14/00367-R.Esteban-Mur(Colab.M.Berenguer)(231360,00€), 2013/0424, P.I. Exp. 2013_0424_PP_PRIETO-M.Prieto(58885,03€) y 2014/0671, P.I. Exp. 2014_0671_FOR_OMNIPREX_PRIETO-M.Prieto(9861,50€).

In addition, the group has won a RIO HORTEGA contract(Ref:2015/0137)(53,762.00€)and an award from the SETH that sponsored a stay of three months in a foreign center of excellence-Group UCSF Viral Hepatitis(Norah Terrault), University of California, San Francisco(9,000.00€)

During that year a total of 34 clinical trials were ongoing and/ or approved. We enclose the protocol number, PI and financing obtained to date: M11-665 (M. Berenguer) (2.322,00€), MK-5172-059 (M. Berenguer), M13-393 (M. Berenguer), IMI-TRI-2013-01 (M. Berenguer), M12-999 (M. Berenguer) (29.976,00€), M13-102 (M. Berenguer), TMC435HPC3016 (M. Berenguer) (28.644,25€), VX950-HPC3006 (M. Berenguer) (70.553,90€), JAN-HEP-2011-01 (M. Berenguer) (4.800,00€), WEUKSTV1115 (M. Berenguer) (2.200,00€), MSD-BOC-2012-01 (M. Berenguer) (7.125,00€), M13-099 (M. Berenguer) (26.833,28€), GSK-ELT-2011-01 (M. Berenguer) (260,62€), M13-393 (M. Berenguer) (11.455,84€), VX-950-C211 (M. Berenguer) (4.480,20€), CIRROXABAN (M. Berenguer), 747-302(M. Berenguer), M14-726 (M. Berenguer), OCR002-HE209 (M. Berenguer), ISTH2015 (M. Berenguer), REG-HEPE-2014-01 (M. Prieto), BIO-ZUT-2014-01 (M. Prieto), TMC435HPC2019 (M. Prieto), 1423M0634 (M. Prieto), VTI-210(M. Prieto),MRG-TEN-2011-01(M. Prieto), REM-TEN-2011-01 (M. Prieto), AI444-026 (M. Prieto), AI447-028 (M. Prieto), CRAD001HES01 (M. Prieto), GS-US-320-0110 (M. Prieto), GS-US-337-0124 (M. Prieto), E5501-G000-310 (M. Prieto), E5501-G000-310 (M. Prieto).

These studies have resulted in the publication of 26 scientific papers in international journals (2015), an award for the best comunication at a conference (1500€) and the publication of two book chapters.

The principal investigator is a member of the Board of ESOT and ILTS well as Deputy Editor of the journal Transplantation and has been a guest speaker on 20 occasions at international conferences besides participating in 3 national masters. Three researchers have submitted in 2015 their doctoral thesis.

**Institution:** Fundación para la Investigación del Hospital la Fe · **Contact:** Hospital Universitario de La Fe Avda. Fernando Abril Martorell, 106. 46009 Valencia.

# G0026

Programme: **Portal Hypertension & Mechanisms of Transition to Cirrhosis**
Lead Researcher: **Bosch Genover, Jaume**

## Group members

STAFF MEMBERS: Gallego Pinos, Javier | García Caldero, Héctor | García Pras, Ester | Guixe Muntet, Sergi | López Sanjurjo, Cristina Isabel | Mejías Hernández, Marc | Orts Salvador, Lara | Sáez Carceller, Rosa María | Vila Bellmunt, Sergi.

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

## Main lines of research

- Factors regulating hepatic microcirculation in normal conditions and in cirrhosis: studies in hepatic perfusion and in isolated sinusoidal endothelial cells. <?xml:namespace prefix = "o" ns = "urn:schemas-microsoft-com:office:office" />
- Regulation of the transcription of protective genes of liver sinusoidal endothelium: relevance in the pathophysiology of portal hypertension, prevention of complications of cirrhosis, in ex vivo liver preservation, and liver aging.
- Interaction between different hepatic cell lines. Importance in maintaining the homeostasis of the liver and on the progression / regression of cirrhosis.
- Angiogenesis and portal hypertension: mechanisms of regulation / alteration in chronic liver disease and relevance in hepatic fibrosis and oncogenesis.
- New methods for noninvasive assessment in patients with cirrhosis.
- Prevention of decompensation of cirrhosis.
- Randomized clinical trials of new treatments for portal hypertension and bleeding esophageal and gastric varices.
- Hepatic vascular diseases.

# Most relevant scientific articles

PROCOPET B., BERZIGOTTI A., ABRALDES J.G., TURON F., HERNÁNDEZ-GEA V., GARCÍA-PAGAN J.C. ET AL. Real-time shear-wave elastography: Applicability, reliability and accuracy for clinically significant portal hypertension. Journal of Hepatology. 2015;62(5):1068-1075.

BOSCH J., FORNS X.. Therapy: Statins and liver disease: From concern to 'wonder' drugs?. Nature Reviews Gastroenterology and Hepatology. 2015;12(6):320-321.

BOSCH J., GROSZMANN R.J., SHAH V.H.. Evolution in the understanding of the pathophysiological basis of portal hypertension: How changes in paradigm are leading to successful new treatments. Journal of Hepatology. 2015;62(S1):S121-S130.

Antiangiogenic and antifibrogenic activity of pigment epithelium-derived factor (PEDF) in bile duct-ligated portal hypertensive rats. Gut. 2015 Apr;64(4):657-66. doi: 10.1136/gutjnl-2014-307138. Epub 2014 May 21.

SILVA-JUNIOR G., BAIGES A., TURON F., TORRES F., HERNÁNDEZ-GEA V., BOSCH J. ET AL. The prognostic value of hepatic venous pressure gradient in patients with cirrhosis is highly dependent on the accuracy of the technique. Hepatology. 2015;62(5):1584-1592.

# Highlights

PUBLICATIONS: Our group published a total of 30 publications (19 Originals, 8 Reviews, 1 Editorial and 2 Clinical Trials).

GRANTS FOR RESEARCH IN PROGRESS. The group has 12 grants:

- **Bosch J:**
  a. Contrast-enhanced uLtrasound for livEr-disease eValuation: development and validation of a novel E-Health-software for Risk-stratification (CLEVER). European Commission.
  b. Hemodinamica hepatica i hipertensió portal. AGAUR 2014_SGR_209.
  c. Hemodinámica hepática e hipertensión portal en la cirrosis. Avances en la fisiopatología y tratamiento (Estudios clínicos y experimentales). ISCIII. PI13/00341.
  d. PIE14/00031 - Understanding obesity (Ob), metabolic syndrome (MetS), type 2 diabetes (T2DM) and fatty liver disease (FL): a multidisciplinary approach. Participan 4 CIBERS.
- **García-Pagán J.C:**
  a. Mecanismos moleculares y implicados en las alteraciones estructurales y funcionales en el hígado en la progresión a cirrosis con hipertensión portal. MINECO. SAF2013-44723-R.
  b. 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.
- **Gracia-Sancho J:**
  a. FIS PI14/00029: El sinusoide hepático en la vejez: caracterización de los mecanismos celulares fisiopatológicos para el desarrollo de nuevas estrategias terapéuticas.
  b. Explora BIO2014-61377-EXP: BioLiver: La Deconstrucción aplicada a la Hepatología. MINECO.
- **Fernández M:**
  a. SAF2014-55473-R/BES2015-071399: Mecanismos moleculares y celulares implicados en la interacción entre obesidad y enfermedad hepática crónica: papel y potencial terapéutico de la angiogénesis y proteínas CPEB. MINECO.
  b. Molecular regulation of the progression from hepatic steatosis to cirrhosis and hepatocellular carcinoma: Role and therapeutic potential of CPEB proteins. AECC.
- **Hernández-Gea V:** 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.
- **Escorsell A:** 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.

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# G0005

Programme: **Hepatic & Gastrointestinal Oncology**
Lead Researcher: **Bruix Tudó, Jordi**

## Group members

STAFF MEMBERS: Boix Ferrero, Loreto | Esteva Espinosa, Clara | Martínez Quetglas, Iris | Peix Gallofre, Judit | Pérez Pons, Nuria | Reig Monzón, Mª Elisa | Ribeiro de Souza, Andrea.

ASSOCIATED MEMBERS: Ayuso Colella, Mª Carmen | Bianchi Cardona, Luis | Bru Saumell, Concepción | Forner González, Alejandro | Fuster Obregón, Josep | Llovet Bayer, Josep Mª | Solé Arques, Manuel | Vilana Puig, Ramon.

## 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. In-

deed, 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., TAKAYAMA T., MAZZAFERRO V., CHAU G.-Y., YANG J., KUDO M. ET AL. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): A phase 3, randomised, double-blind, placebo-controlled trial. The Lancet Oncology. 2015;16(13):1344-1354.

SIA D, LOSIC B, MOEINI A, CABELLOS L, HAO K, REVILL K ET AL. Massive parallel sequencing uncovers actionable FGFR2-PPHLN1 fusion and ARAF mutations in intrahepatic cholangiocarcinoma.Nature communications. 2015;6:6087.

BERZIGOTTI A., REIG M., ABRALDES J.G., BOSCH J., BRUIX J.. Portal hypertension and the outcome of surgery for hepatocellular carcinoma in compensated cirrhosis: A systematic review and meta-analysis. Hepatology. 2015;61(2):526-536.

SCHULZE K., IMBEAUD S., LETOUZE E., ALEXANDROV L.B., CALDERARO J., REBOUISSOU S. ET AL. Exome sequencing of hepatocellular carcinomas identifies new mutational signatures and potential therapeutic targets. Nature Genetics. 2015;47(5):505-511.

BRUIX J., HAN K.-H., GORES G., LLOVET J.M., MAZZAFERRO V.. Liver cancer: Approaching a personalized care. Journal of Hepatology. 2015;62(S1):S144-S156.


## Highlights

The research activity of the groups has continued in all the topics that are the main components of our field of interest. The group has gained several competitive grants from official agencies and from the EU that will allow to support this task.

As expected, we further assess the molecular abnormalities in tumor tissue and have started to explore that challenges posed by tumor heterogeneity. Studies are underway to evaluate the value of the so-called liquid biopsy based in the analysis of cell material circulating in peripheral blood.

At the clinical level the major tasks are related to investigations around diagnosis, prognosis and new treatment options. We have assessed new methodology and reporting systems for the diagnostic approach in patients with suspected liver cancer and found that the new LIRADS system may not be optimal for clinical use. We have also refined the conventional criteria and are opening studies to study image fractality. In prognosis prediction the major results have been the confirmation of adverse events development to treatment and pattern of progression under treatment as a major predictor of outcome. In addition, we have produced a model that combines clinical profile with biomarkers of angionenesis and hypoxia to predict the evolution of sorafenib treated patients with hepatocellular carcinoma. This allows a stratified approach. At the same time, international multicentric phase 3 trials testing regorafenib and tivantinib where J Bruix is international principal investigator have finished recruitment and will deliver results in 2016.

During 2015 we have written the Spanish Guidelines for the Treatment of Hepatocellular Carcinoma that will ultimately be published in 2016 to also be part of Clinical Practice Guidelines portfolio of the Ministry of Health.


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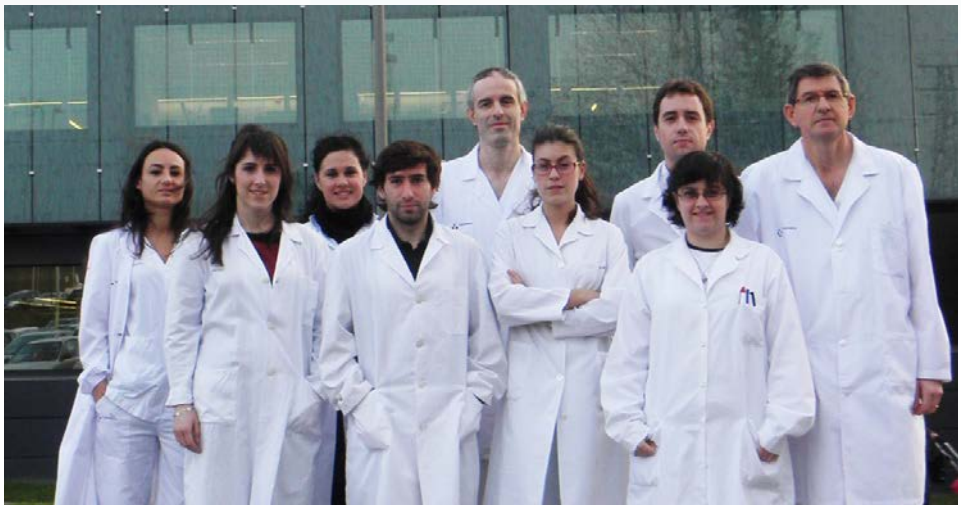
# G1081

Programme: **Hepatic & Gastrointestinal Oncology**
Lead Researcher: **Bujanda Fernández de Pierola, Luis**

## Group members



STAFF MEMBERS: Goitia Viaña, Ana Isabel | Labiano Ciriza, Ibone.

ASSOCIATED MEMBERS: Banales Asurmendi, Jesús María | Herreros Villanueva, Marta | Hijona Muruamendiaraz, Elizabeth | Perugorría 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

MUNOZ-GARRIDO P., MARIN J.J.G., PERUGORRIA M.J., URRIBARRI A.D., ERICE O., SAEZ E. ET AL. Ursodeoxycholic acid inhibits hepatic cystogenesis in experimental models of polycystic liver disease. Journal of Hepatology. 2015;63(4):952-961.

BARBIER-TORRES L, BERAZA N, FERNÁNDEZ-TUSSY P, LOPITZ-OTSOA F, FERNÁNDEZ-RAMOS D, ZUBIETE-FRANCO I ET AL. Histone Deacetylase 4 promotes cholestatic liver injury in the absence of Prohibitin-1.Hepatology (Baltimore, Md.). 2015.

CARBALLAL S., RODRÍGUEZ-ALCALDE D., MOREIRA L., HERNÁNDEZ L., RODRÍGUEZ L., RODRÍGUEZ-MORANTA F. ET AL. Colorectal cancer risk factors in patients with serrated polyposis syndrome: A large multicentre study. Gut. 2015.

CASTILLEJO A., HERNÁNDEZ-ILLAN E., RODRÍGUEZ-SOLER M., PÉREZ-CARBONELL L., EGOAVIL C., BARBERA V.M. ET AL. Prevalence of MLH1 constitutional epimutations as a cause of Lynch syndrome in unselected versus selected consecutive series of patients with colorectal cancer. Journal of Medical Genetics. 2015;52(7):498-502.

CALVETE O., REYES J., ZUNIGA S., PAUMARD-HERNÁNDEZ B., FERNÁNDEZ V., BUJANDA L. ET AL. Exome sequencing identifies ATP4A gene as responsible of an atypical familial type I gastricneuroendocrine tumour. Human Molecular Genetics. 2015;24(10):2914-2922.

# Highlights

During the year 2015 have started new projects related to colon cancer (EPOs-Qualyscopia) attempting to assess the most appropriate follow-up in patients who have polyps and the quality of colonoscopy. We have also been getting results from other started in previous years as the study of biomarkers in colon cancer in different biological fluids. On this year we have created along with 15 research groups from 10 European countries "European Network for the Study of Cholangiocarcinoma" (ENS-CCA: www.enscca.org ; www.cholangiocarcinoma.eu) to promote international collaborative research this disease; Dr. Jesus Bañales is the International Network Coordinator. In addition, we got the competitive public financing of a project FIS cholangiocarcinoma (CCA), a collaborative project of excellence (CIBEREHD), two projects of the Basque Government (Polycystic Liver Disease) and a project of the Council of Gipuzkoa on Polycystic Liver disease.

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# G0034

Programme: **Inflammation & Gastrointestinal Motility**

Lead Researcher: **Cabré Gelada, Eduard**

## Group members

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

ASSOCIATED MEMBERS: Domènech Morral, Eugeni | Lorenzo-Zuñiga García, Vicente María | Mañosa Ciria, Miriam | Serra Pueyo, Jordi.

## 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. 2015.

GORDILLO J, CABRÉ E, GARCÍA-PLANELLA E, RICART E, BER-NIETO Y, MÁRQUEZ L ET AL. Thiopurine Therapy Reduces the Incidence of Colorectal Neoplasia in Patients with Ulcerative Colitis. Data from the ENEIDA Registry.Journal of Crohn's & colitis. 2015;9(12):1063-70.

LOREN V., CABRE E., OJANGUREN I., DOMENECH E., PEDROSA E., GARCÍA-JARAQUEMADA A. ET AL. Interleukin-10 enhances the intestinal epithelial barrier in the presence of corticosteroids through p38 MAPK activity in Caco-2 monolayers: A possible mechanism for steroid responsiveness in ulcerative colitis. PLoS ONE. 2015;10(6).

CALAFAT M, CABRÉ E, MAÑOSA M, LOBATÓN T, MARÍN L, DOMÈNECH E. High within-day variability of fecal calprotectin levels in patients with active ulcerative colitis: what is the best timing for stool sampling?. Inflammatory bowel diseases. 2015;21(5):1072-6.

LORENZO-ZUNIGA V., MORENO DE VEGA V., MARIN I., BARBERA M., BOIX J.. Improving the quality of colonoscopy bowel preparation using a smart phone application: A randomized trial. Digestive Endoscopy. 2015;27(5):590-595.

# Highlights

During 2015 the FIS projects studying the molecular basis of steroid refractoriness in ulcerative colitis (UC) (PI11 / PI11 / 011,691), the postoperative recurrence in Crohn's disease (PI13 / 02198), therapeutic innovation based on modulating the activity of extracellular matrix (PI12 / 00621 and PI13 / 02217) have continued active. Bioinformatic approach of experimental omic data identified the influence of O2 in the molecular processes related to the complications studied. We have identified signaling pathways in involved tissue of Crohn's resected patients related with postoperative recurrence, which have been reproduced in pre-clinical models. We also studied the translation of intestinal changes related to steroid refractoriness in UC in, which allowed us to indentify plasma microRNAs capable of predicting response to steroids. In this sense, and sponsored by transfer offices and CIBER asd IGTP, we have taken steps to obtain a patent for a predictive biomarker of steroid response in UC. Similarly, the results of studies on the treatment of lesions after endoscopic intervention follow the same protection process (collaboration intraCIBER). Clinical studies have succeeded in linking thiopurine with decreasing de risk o colorectal cancern UC, and assessed the predictive ability of calprotectin. In addition, we have participated in a clinical guideline on the use of methotrexate in inflammatory bowel disease, in organizing an international course, and we heve participated in organizing national and international conferences. Finally, despite the limits on the dissemination of results by the ongoing patent procedures, some of these have concluded a doctoral thesis, and in some cases, be accepted in national and international conferences.

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# G0036

Programme: **Inflammation & Gastrointestinal Motility**

Lead Researcher: **Calvet Calvo, Xavier**

## Group members

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

ASSOCIATED MEMBERS: Brullet Benedi, Enrique | Campo Fernández de los Ríos, Rafael | Gené Tous, Emili | Junqueras Flórez, Felix | Lario García, 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

LÓPEZ-GONGORA S., PUIG I., CALVET X., VILLORIA A., BAYLINA M., MUNOZ N. ET AL. Systematic review and meta-analysis: Susceptibility-guided versus empirical antibiotic treatment for Helicobacter pylori infection. Journal of Antimicrobial Chemotherapy. 2015;70(9):2447-2455.

CALVET X.. Diagnosis of Helicobacter pylori Infection in the Proton Pump Inhibitor Era. Gastroenterology Clinics of North America. 2015;44(3):507-518.

CASTAÑO-MILLA C, CHAPARRO M, SARO C, BARREIRO-DE ACOSTA M, GARCÍA-ALBERT AM, BUJANDA L ET AL. Effectiveness of adalimumab in perianal fistulas in crohn's disease patients naive to anti-TNF therapy.Journal of clinical gastroenterology. 2015;49(1):34-40.

BRUNET-VEGA A., PERICAY C., QUILEZ M.E., RAMIREZ-LAZARO M.J., CALVET X., LARIO S.. Variability in microRNA recovery from plasma: Comparison of five commercial kits. Analytical Biochemistry. 2015;488:28-35.

RAMÍREZ-LÁZARO MJ, LARIO S, CALVET X, SÁNCHEZ-DELGADO J, MONTSERRAT A, QUÍLEZ EM ET AL. Occult H. pylori infection partially explains 'false-positive' results of (13) C-urea breath test.United European gastroenterology journal. 2015;3(5):437-42.

# Highlights

## BASIC RESEARCH:

Project 1: FIS (PI14/00464) "Novel high-sensitivity technologies for an accurate diagnosis of low-level H.pylori infection". The aim is to detect Helicobacter, using molecular techniques (digital PCR) in patients where it is not detected by conventional techniques.

Project 2: TV3 (1007/C/2013) "Novel technologies as non invasive tools for prognosis/diagnosis of gastric cancer". The aim is to find molecular markers (miRNAs) in the blood, for early detection of precursor lesions of gastric cancer.

Project 3: FIS (PI12/01802). In this project the aim is to determine the expression profile of miRNA in H. pylori infected patients and precursor lesions of gastric cancer (atrophy, metaplasia, dysplasia).

Due to the increase of the resources and the consolidation of the basic and translational group, during 2015 it has increased productivity and impact factor of the studies.

## CLINICAL RESEARCH:

European patent. 14731610.3-1707The patent entitled: "Container and method for the storage and externporaneus reconstitution of a mixture of compounds in fixed proportions". This is a device for the preparation of combination therapies in a single syrup, designed for the treatment of H. pylori infection in children.

Clincial research structure: The consolidation of the clinical research structure has allowed the collaboration in multiple collaborative clinical studies either of our group or comoing for other CIBERehd groups.

Publications: The number and the impact of published studies continues on increasing with few random oscilations, despite the difficult economical situation.

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# G0081

Programme: **Hepatotoxicity, Cholestasis & Metabolic Disorders**
Lead Researcher: **Castell Ripoll, José Vicente**

## Group members

ADSCRITOS: 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


MARFIL V., BLAZQUEZ M., SERRANO F., CASTELL J.V., BORT R.. Growth-promoting and tumourigenic activity of c-Myc is suppressed by Hhex. Oncogene. 2015;34(23):3011-3022.

TOLOSA L., GÓMEZ-LECHON M.J., DONATO M.T.. High-content screening technology for studying drug-induced hepatotoxicity in cell models. Archives of Toxicology. 2015;89(7):1007-1022.

TOLOSA L., CARMONA A., CASTELL J.V., GÓMEZ-LECHON M.J., DONATO M.T.. High-content screening of drug-induced mitochondrial impairment in hepatic cells: effects of statins. Archives of Toxicology. 2015;89(10):1847-1860.

BENET M., GUZMAN C., PISONERO-VAQUERO S., GARCÍA-MEDIAVILLA M.V., SÁNCHEZ-CAMPOS S., MARTÍNEZ-CHANTAR M.L. ET AL. Repression of the nuclear receptor small heterodimer partner by steatotic drugs and in advanced nonalcoholic fatty liver disease. Molecular Pharmacology. 2015;87(4):582-594.

TOLOSA L., LÓPEZ S., PAREJA E., DONATO M.T., MYARA A., NGUYEN T.H. ET AL. Human neonatal hepatocyte transplantation induces long-term rescue of unconjugated hyperbilirubinemia in the Gunn rat. Liver Transplantation. 2015;21(6):801-811.


## Highlights

In 2015 the group has had 7 research projects funded by public bodies. Among them we would like to highlight two European projects: EUTOXRISK. *An integrated European "flagship" program driving mechanism-based toxicity testing and risk assessment for the 21st century*, recently granted; and HECATOS. *Hepatic and cardiac toxicity modeling systems*. For the latter, we have a hepatotoxicity care office in the Hospital La Fe as a result of the synergy between our Unit and the Hepatology Unit, where patients with suspected drug hepatotoxicity are sent for a detailed and personalized study. We can also highlight two ISCIII-FIS projects "*Metabonomic approaches for studying idiosyncratic hepatotoxicity with metabolic basis and identification of the causative agent*" and "*Drug-induced fatty liver disease, new mechanisms and biomarkers applicable to the pharmaceutical development and to a more rational therapy in patients with metabolic syndrome*"; and two from the Ministry of Education and Science: "*Induction of myc activity by HHEX homeoprotein: basics aspects and applications in cancer and reprogramming*" and "*New Strategy for the derivation of functional hepatocytes from women affected by ornithine transcarbamylase deficiency*".

Finally, regarding the transfer of results to the clinical practice we should emphasized our participation in three clinical trials: "*Efficacy of N-acetylcysteine in the preservation solution for liver transplantation*" (IISLAFE, NAC400, FASEIII); "*Pilot study for assessment of hepatotest in the preoperative assessment of liver function* "(IISLAFE, HEPATOTEST, FASEIV); and "*Pilot clinical trial Phase I / IIA to determine conditions, minimum dose and effectiveness of a liver function test*" (IISLAFE, HEPATOTEST, Phase I / IIA).


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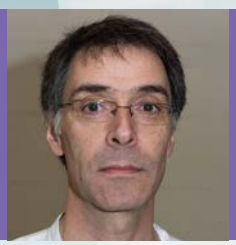
# G0016

Programme: **Hepatic & Gastrointestinal Oncology**
Lead Researcher: **Castells Garangou, Antoni**



## Group members

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ASSOCIATED MEMBERS: Balaguer Prunes, Francesc | Camps Polo, Jordi | Castellví Bel, Sergi | Cuatrecasas, Miriam | Elizalde Fernández, José Ignacio | Fernández Esparrach, Gloria | Fernández-Cruz Pérez, Laureano | Ginés Gibert, Àngels | Lacy Fortuny, Antonio María | Maurel Santasusana, Joan | Moreira, Leticia | Nadal SanMartín, Cristina | Navarro Colás, Salvador | Pellise Urquiza, María | Postigo Angón, Antonio Andrés | Quintanilla Leo, Isabel | Sendino, Oriol | Vaquero Raya, Eva | Vila Casadesús, María.

## 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 population-based screening strategies.
- Diagnostic and therapeutic endoscopy and minimally invasive surgery in gastrointestinal and pancreatic oncology.

# Most relevant scientific articles

CARBALLAL S., RODRÍGUEZ-ALCALDE D., MOREIRA L., HERNÁNDEZ L., RODRÍGUEZ L., RODRÍGUEZ-MORANTA F. ET AL. Colorectal cancer risk factors in patients with serrated polyposis syndrome: A large multicentre study. Gut. 2015.

SÁNCHEZ-TILLO E., DE BARRIOS O., VALLS E., DARLING D.S., CASTELLS A., POSTIGO A.. ZEB1 and TCF4 reciprocally modulate their transcriptional activities to regulate Wnt target gene expression. Oncogene. 2015;34(46):5760-5770.

FERNÁNDEZ-HEVIA M., DELGADO S., CASTELLS A., TASENDE M., MOMBLAN D., DEL GOBBO G.D. ET AL. Transanal total mesorectal excision in rectal cancer short-term outcomes in comparison with laparoscopic surgery. Annals of Surgery. 2015;261(2):221-227.

MADISON B.B., JEGANATHAN A.N., MIZUNO R., WINSLOW M.M., CASTELLS A., CUATRECASAS M. ET AL. Let-7 Represses Carcinogenesis and a Stem Cell Phenotype in the Intestine via Regulation of Hmga2. PLoS Genetics. 2015;11(8).

CASTELLS A.. Postoperative surveillance in nonmetastatic colorectal cancer patients: Yes, but...Annals of Oncology. 2015;26(4):615-617.

# Highlights

With respect to the study of hereditary and familial colorectal cancer (CRC) forms, it has established the prevalence of epimutations and somatic methylation of the MHL1 gene in patients with Lynch syndrome, and the risk of developing CRC in patients with serrated polyposis syndrome. Both achievements may have a high impact in clinical practice. Moreover, within the international COGENT consortium, new susceptibility factors for the development of this neoplasm have been identified.

Regarding the characterization of molecular mechanisms involved in the development, progression and resistance to therapy, the most notable contributions are the demonstration that Let-7 represses carcinogenesis and a stem cell phenotype in the intestine via regulation of HMGA2, a study performed in collaboration with the University of Pennsylvania, and that ZEB1 and TCF4 reciprocally modulate their transcriptional activities to regulate Wnt target gene expression. However, from a translational point of view, the most significant contributions are the pharmacogenomic analyses focused on the prediction of tumor response and toxicity from capecitabine- and 5-fluorouracil-based treatments in patients with CRC.

With respect to the evaluation of CRC screening strategies, it is important to point out the international recognition to the contributions of ColonPrev project in a recent issue of Digestive Diseases and Science, and the consolidation of our group in the field of biomarkers development, in terms of both publications and funding (Retos-Colaboración 2015, RTC-2015-3850-1; Strategic Action CIBER 2015), the latter resulting from a patent recently licensed to Amadix group.

Finally, in the field of advanced endoscopy and minimally invasive surgery, it is important to note the active participation in international consensus documents for the classification of colorectal polyps and polyposis, and the validation by our group of the transanal excision approach to rectal cancer.

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# G1087

Programme: **Inflammation & Gastrointestinal Motility**
Lead Researcher: **Clavé Cívit, Pere**

## Group members

STAFF MEMBERS: Álvarez Berdugo, Daniel | Arenas Bailón, Claudia | Ortega Fernández, Omar | Rofes Salsench, Laia.

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

CLAVE P., SHAKER R.. Dysphagia: Current reality and scope of the problem. Nature Reviews Gastroenterology and Hepatology. 2015;12(5):259-270.

MANE N., GIL V., MARTÍNEZ-CUTILLAS M., CLAVE P., GALLEGO D., JIMÉNEZ M.. Differential functional role of purinergic and nitrergic inhibitory cotransmitters in human colonic relaxation. Acta Physiologica. 2015;212(4):293-305.

MANS E., SERRA-PRAT M., PALOMERA E., SUNOL X., CLAVE P.. Sleeve gastrectomy effects on hunger, satiation, and gastrointestinal hormone and motility responses after a liquid meal test1. American Journal of Clinical Nutrition. 2015;102(3):540-547.

RYCHTER J., ORTEGA O., BERDUN S., ARENAS C., LÓPEZ I., ESPIN F. ET AL. Mast cell degranulation inhibits motor patterns of human ileum and sigmoid colon in vitro: Relevance for postoperative ileus. Neurogastroenterology and Motility. 2015;27(8):1098-1109.

CARRION S., CABRE M., MONTEIS R., ROCA M., PALOMERA E., SERRA-PRAT M. ET AL. Oropharyngeal dysphagia is a prevalent risk factor for malnutrition in a cohort of older patients admitted with an acute disease to a general hospital. Clinical Nutrition. 2015;34(3):436-442.

# Highlights

- The development of neurorehabilitation protocols for post-stroke dysphagia to be implemented in clinical practice. To do this, we will assess the effect of different brain neurostimulation techniques (rTMS) in terms of cortical excitability and swallow biomechanics. Our aim is to change clinical practice from compensatory strategies to the recovery of the swallowing function. Our hypothesis, based on our previous studies, states that sensory function impairment is critical in the pathophysiology of OD, and that neuromodulation strategies should target the afferent sensory pathway to achieve changes in the swallow response and promote brain plasticity.
- The Organization of the 5th annual Congress of the European Society for Swallowing Disorders (ESSD www.essd2015.org), 1-3 October 2015 in Barcelona, "Swallowing Disorders, from compensation to recovery" endorsed by Ciberehd which have emerged two clinical guidelines related to rheological adaptation of foods and the clinical management of OD as a major geriatric syndrome, both endorsed by various European scientific societies (EUGMS, ERS).
- Clinical studies linking the oropharyngeal and gastrointestinal motility impairments of morbidly obese and frail elderly people with their nutritional status, as well as the characterization of the effect of several gastrointestinal peptides (Ghrelin, CCK, GLP-1) in the mechanisms of control of hunger and satiety in these patients. The identification of sarcopenia, frailty, and changes in the oral microbiota as complications of these gastrointestinal motility disorders and the development of specific therapeutic strategies.
- Basic in vitro motility studies in animal models, but mainly in human gastrointestinal tissue that have allowed us to characterize the oropharyngeal receptors (TRPV1, TRPA1, and two new receptors) involved in the swallow response; and the physiological myenteric mechanisms of control of gastric, intestinal and colonic human motility (pacemakers, gradients NO-purines, and H2S), the role of mast cell activation (stabilizers, tryptases and NGF) in the intestinal dysmotility associated with postoperative ileus and the characteristics of the motor alteration of the human sigmoid colon in diverticular disease.

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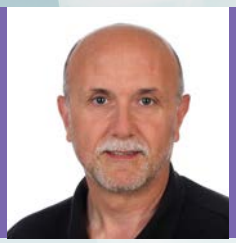
# G0071

Programme: **Inflammation & Gastrointestinal Motility**

Lead Researcher: **Esplugues Mota, Juan Vicente**



## Group members

STAFF MEMBERS: Normanly, Brian James.

ASSOCIATED MEMBERS: Álvarez Ribelles, Angeles | 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 and adaptive responses induced by antiretroviral drugs: role of mitochondrial dysfunction, autophagy, reticular stress and inflammation.

# Most relevant scientific articles

COSÍN-ROGER J, ORTIZ-MASIÁ D, CALATAYUD S, HERNÁNDEZ C, ESPLUGUES JV, BARRACHINA MD. The activation of Wnt signaling by a STAT6-dependent macrophage phenotype promotes mucosal repair in murine IBD.Mucosal immunology. 2015.

APOSTOLOVA N, VÍCTOR VM. Molecular strategies for targeting antioxidants to mitochondria: therapeutic implications.Antioxidants & redox signaling. 2015;22(8):686-729.

HERNÁNDEZ C., BARRACHINA M.D., VALLECILLO-HERNÁNDEZ J., ALVAREZ A., ORTIZ-MASIA D., COSIN-ROGER J. ET AL. Aspirin-induced gastrointestinal damage is associated with an inhibition of epithelial cell autophagy. Journal of Gastroenterology. 2015.

ROVIRA-LLOPIS S., DIAZ-MORALES N., BANULS C., BLAS-GARCÍA A., POLO M., LÓPEZ-DOMENECH S. ET AL. Is Autophagy Altered in the Leukocytes of Type 2 Diabetic Patients?. Antioxidants and Redox Signaling. 2015;23(13):1050-1056.

MIOVA B., DINEVSKA-KJOVKAROVSKA S., ESPLUGUES J.V., APOSTOLOVA N.. Heat Stress Induces Extended Plateau of Hsp70 Accumulation - A Possible Cytoprotection Mechanism in Hepatic Cells. Journal of Cellular Biochemistry. 2015;116(10):2365-2374.

# Highlights

In 2015 our research has been supported by 3 state-funded projects and 1 grant from the regional government. In addition, the group has received 3 grants from different public health organisms and we have formed part of a European project (COST Action TRANSAUTOPHAGY: European Network of Multidisciplinary Research and Translation of Autophagy Knowledge). Among the results obtained in 2015 we should highlight the following: 1) we have observed the presence of M2 phenotype macrophages in the mucosa of patients with ulcerative colitis or Crohn's disease and their accumulation as the condition becomes chronic. These macrophages persistently express Wnt ligands and activate Wnt signalling in epithelial cells, which is associated with defects in autophagy, in the differentation of enterocytes and, finally, in mucosal regeneration; 2) obese patients present a proinflammatory state associated with mitochondrial dysfunction, expressed as an increase in the levels of superoxide and mitochondrial membrane potential, while the mitochondrial consumption of oxygen is not altered; there is also an increase of polymorphonuclear neutrophil (PMN) "rolling" associated with a slowing down and an increased adhesion of PMNs to the endothelium; 3) we have confirmed the hypothesis that autophagy is activated in the leukocytes of patients with type 2 diabetes and that both oxidative stress and reticular stress signalling are implicated in the induction of autophagy; 4) some, but not all, anti-HIV drugs induce autophagy and reticular stress in in vitro cell models; and 5) the purine analogues abacavir and didanosine increase the hepatotoxicity induced by acetaminophen (paracetamol), thus exacerbating the mitochondrial dysfunction produced by this drug.

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# G0028

Programme: **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 Fusté, Lluis | Dopazo Taboada, Cristina | Gregori Font, Josep | Guardia Massó, Jaime | Pirón Pirón, María | 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., SÁNCHEZ A., ESTEBAN J.I., RODRÍGUEZ-FRIAS 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., GARCÍA-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., MARTÍNEZ-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., RODRÍGUEZ-FRIAS 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.

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# G0025

Programme: **Viral Hepatitis**

Lead Researcher: **Esteban Mur, Rafael**

## Group members

STAFF MEMBERS: Godoy Cruz, Cristina | Homs Riba, María | 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).

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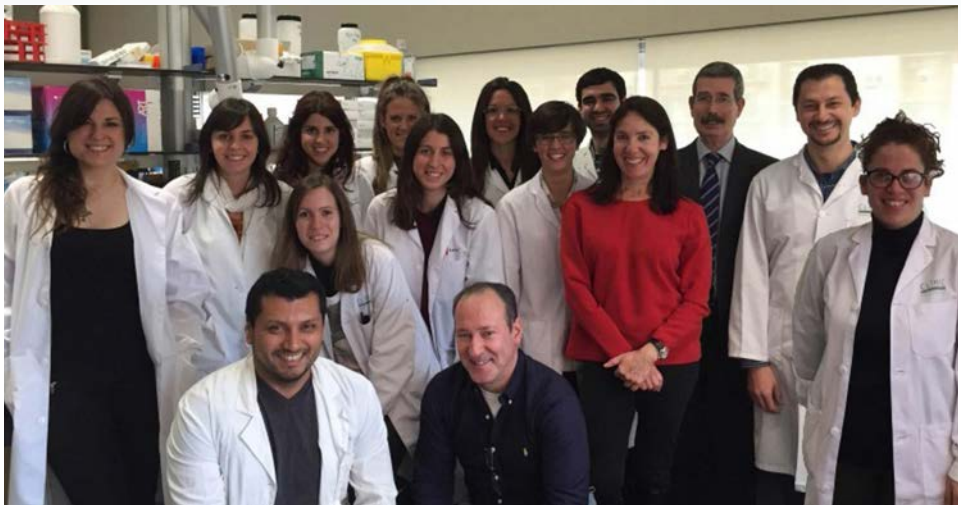
# G0035

Programme: **Hepatotoxicity, Cholestasis & Metabolic Disorders**
Lead Researcher: **Fernández-Checa Torres, José Carlos**

## Group members



STAFF MEMBERS: Baulies Domènech, Anna | Núñez Pozuelo, Susana | Zurita García, Esther.

ASSOCIATED MEMBERS: Caballería Rovira, Joan | García Ruiz, María del Carmen | Lluis Dúquez, José María | Ribas Serra, Vicente.

## Main lines of research

- Contribution of lysosomal cholesterol, sphingolipids and autophagy in steatohepatitis and rare diseases.
- Development of non-invasive diagnostic methods for diagnosis and prognosis in alcohol-induced liver disease.
- Hepatic cholesterol as a predictive factor for liver transplantation.
- Mechanisms of ischemia/reperfusion liver injury and their regulation based on antioxidant and antinflammatory strategies.
- Mitochondrial glutathione transporters and their implication in liver cancer.
- Regulation of cholesterol homeostasis in patients and experimental models of non-alcoholic steatohepatitis and ischemia-reperfusion injury.
- Role of cholesterol in aging and Alzheimer disease.
- Sphingolipid and mitochondrial oxidative-stress regulation of cell death.

# Most relevant scientific articles

MAEHARA Y., FERNÁNDEZ-CHECA J.C.. Augmenter of liver regeneration links mitochondrial function to steatohepatitis and hepatocellular carcinoma. Gastroenterology. 2015;148(2):285-288.

CABALLERIA J.. Is petoxifylline still an option in severe alcoholic hepatitis?. Hepatology. 2015;61(4):1425-1427.

BAULIES A., RIBAS V., NUNEZ S., TORRES S., ALARCON-VILA C., MARTÍNEZ L. ET AL. Lysosomal Cholesterol Accumulation Sensitizes to Acetaminophen Hepatotoxicity by Impairing Mitophagy. Scientific Reports. 2015;5.

MARTÍNEZ L., TORRES S., BAULIES A., ALARCON-VILA C., ELENA M., FABRIAS G. ET AL. Myristic acid potentiates palmitic acid-induced lipotoxicity and steatohepatitis associated with lipodystrophy by sustaning de novo ceramide synthesis. Oncotarget. 2015;6(39):41479-41496.

WIN S., THAN T.A., LE B.H.A., GARCÍA-RUIZ C., FERNÁNDEZ-CHECA J.C., KAPLOWITZ N.. Sab (Sh3bp5) dependence of JNK mediated inhibition of mitochondrial respiration in palmitic acid induced hepatocyte lipotoxicity. Journal of Hepatology. 2015;62(6):1367-1374.

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# G0004

Programme: **Viral Hepatitis**

Lead Researcher: **Forns Bernhardt, Xavier**

## Group members


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

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

## Main lines of research

- Efficacy of new antiviral regimens against HCV and relevance of resistance-associated variants in treatment failure.
- Impact of HCV elimination on the natural history of the disease.
- Natural history of chronic hepatitis C: development of predictive models of risk of progression to cirrhosis.
- Genetic evolution and quasispecies dynamics of HCV in the liver transplant setting using ultra-deep pyrosequencing.
- Study of the innate immune response in patients with chronic hepatitis C receiving direct-acting antivirals.
- Characterization of viral and cellular factors involved in HCV infection using cell culture models in vitro.
- Molecular epidemiology and phylogenetic analysis of acute hepatitis C in HIV-coinfected patients.
- Influence of viral and host factors in the natural history and response to treatment in chronic hepatitis B.
- Molecular mechanisms and clinical significance of cccDNA persistence in HBV infection.
- Natural history of chronic HBV infection in inactive carriers and patients in the “gray zone”.
- Validation of non-invasive diagnostic methods of liver fibrosis in HBV-infected patients.
- Epidemiology of HEV infection.

# Most relevant scientific articles

CURRY MP, FORNS X, CHUNG RT, TERRAULT NA, BROWN R JR, FENKEL JM ET AL. Sofosbuvir and ribavirin prevent recurrence of HCV infection after liver transplantation: an open-label study.Gastroenterology. 2015;148(1):100-107.e1.

LONDONO M.-C., PERELLO C., CABEZAS J., CANETE N., LENS S., MARINO Z. ET AL. The addition of a protease inhibitor increases the risk of infections in patients with hepatitis C-related cirrhosis. Journal of Hepatology. 2015;62(2):311-316.

PÉREZ-DEL-PULGAR S., GREGORI J., RODRÍGUEZ-FRIAS F., GONZÁLEZ P., GARCÍA-CEHIC D., RAMIREZ S. ET AL. Quasispecies dynamics in hepatitis C liver transplant recipients receiving grafts from hepatitis C virus infected donors. Journal of General Virology. 2015;96(12):3493-3498.

CHARLTON M, GANE E, MANNS MP, BROWN RS JR, CURRY MP, KWO PY ET AL. Sofosbuvir and ribavirin for treatment of compensated recurrent hepatitis C virus infection after liver transplantation. Gastroenterology. 2015;148(1):108-17.

FORNS X., GORDON S.C., ZUCKERMAN E., LAWITZ E., CALLEJA J.L., HOFER H. ET AL. Grazoprevir and elbasvir plus ribavirin for chronic HCV genotype-1 infection after failure of combination therapy containing a direct-acting antiviral agent. Journal of Hepatology. 2015;63(3):564-572.

# 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. In 2015, we finished the first international study evaluating the compassionate use of sofosbuvir in liver transplant patients in life-threatening situation (Hepatology 2015). This key study clearly shows the positive impact of HCV eradication on the natural history of cirrhosis, which allows in some cases the withdrawal of patients from the waiting list for liver transplantation.
- The project "Virological and immunological factors associated with HCV and HBV infection recurrence after treatment discontinuation" (Ref. GLD15 / 00274) led by Dr. Xavier Forns has been funded on the 3rd Call for Research Projects on HIV, Hepatitis and Hematology-Oncology, "Fellowship Programme" sponsored by GILEAD ESPAÑA and the Instituto de Salud Carlos III.
- Development of clinical guidelines: "EASL Clinical Guidelines Practice: Liver Transplantation", "EASL Recommendations on Treatment of Hepatitis C 2015" and "Guia per a la prevenció i el control de l'hepatitis C" (Departament de Salut de la Generalitat de Catalunya).
- Dr. Xavier Forns has been awarded the Josep Trueta 2015 Scientific Research Award of the Acadèmia de Ciències Mèdiques i de la Salut de Catalunya i Balears ("L'Academia") and the Professional Excellence Award COMB (Col·legi de Metges de Barcelona) for his scientific career and for his outstanding clinical and scientific work on the management and treatment of hepatitis C.
- Dr. Sofía Pérez del Pulgar has performed a stay in Dr. Fabien Zoulim's laboratory at the Cancer Research Center (CRCL), Lyon, France, thanks to the funding granted by the CIBERehd and the scholarship for the Training in New Technologies granted by the AEEH.

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# G0041

Programme: **Portal Hypertension & Mechanisms of Transition to Cirrhosis**
Lead Researcher: **Francés Guarinos, Rubén**

## Group members

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

ASSOCIATED MEMBERS: Bellot García, Pablo | González Navajas, José Manuel | Palazón Azorín, José María | Pascual Bartolomé, Sonia | Zapater Hernández, Pedro.

## Main lines of research

MAIN RESEARCH LINES:

- Immunobiology of bacterial translocation in cirrhosis.
- Inflammatory response and immunomodulatory action of antibiotics, immune suppressors and biologic agents.
- Gut homeostasis recovery in cirrhosis by biologic agents.
- Role of inflammasomes in immune response in cirrhosis.
- Regulatory role of sympathetic nervous system in inflammation and hepatocarcinoma.

INTERACTIONS:

- Bacterial translocation in IBD and metabolic syndrome.
- Inflammation and heptocarcinoma.

# Most relevant scientific articles

MORATALLA A., CAPARROS E., JUANOLA O., PORTUNE K., PUIG-KROGER A., ESTRADA-CAPETILLO L. ET AL. Bifidobacterium pseudocatenulatum CECT7765 induces an M2 anti-inflammatory transition in macrophages from patients with cirrhosis. Journal of Hepatology. 2015.

JUANOLA O., MORATALLA A., GUTIERREZ A., SEMPERE L., ZAPATER P., GIMÉNEZ P. ET AL. Anti-TNF-alpha loss of response is associated with a decreased percentage of FoxP3+ T cells and a variant NOD2 genotype in patients with Crohn's disease. Journal of Gastroenterology. 2015;50(7):758-768.

RAMIREZ-BOSCA A., NAVARRO-LÓPEZ V., MARTÍNEZ-ANDRES A., SUCH J., FRANCES R., DE LA PARTE J. ET AL. Identification of bacterial DNA in the peripheral blood of patientswith active psoriasis. JAMA Dermatology. 2015;151(6):670-671.

MORATALLA A., GÓMEZ-HURTADO I., MOYA-PÉREZ A., ZAPATER P., PEIRO G., GONZÁLEZ-NAVAJAS J.M. ET AL. Bifidobacterium pseudocatenulatum CECT7765 promotes a TLR2-dependent anti-inflammatory response in intestinal lymphocytes from mice with cirrhosis. European Journal of Nutrition. 2015.

GARCÍA-MARTÍNEZ I., FRANCES R., ZAPATER P., GIMÉNEZ P., GÓMEZ-HURTADO I., MORATALLA A. ET AL. Use of proton pump inhibitors decrease cellular oxidative burst in patients with decompensated cirrhosis. Journal of Gastroenterology and Hepatology (Australia). 2015;30(1):147-154.

# Highlights

During 2015, the CIBEREHD Group at Hospital General Universitario de Alicante has conducted his research primarily within its 4 national ongoing projects and intramural active studies to tackle several aspects of the immunobiology of bacterial translocation in cirrhosis and how to restore intestinal homeostasis as a central step in the inflammatory control of these patients. The characterization of regulatory T-cell role in the immunomodulatory mechanism of norfloxacin and of a probiotic strain capable of redirecting ascitic fluid macrophages towards an anti-inflammatory state in patients with cirrhosis, the description of the AIM2 inflammasome as a mediator of the inflammatory response in sterile ascitic fluid of patients with decompensated cirrhosis, or identification of bacterial DNA translocation as a marker of short-term relapse in patients with Crohn's disease are among the most important results of the Group in the past year.

The Group has also put its efforts in developing an intense training schedule for new researchers and has enjoyed from three new predoctoral positions funded by different agencies. Finally, the startup of new partnerships and the consolidation of existing ones, both with other CIBEREHD groups and with international groups, has also constituted an important part of the cooperative research work of the Group.

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# G0048

Programme: **Viral Hepatitis**

Lead Researcher: **García Buey, Luisa**

## 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.

## 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

QUER J., GREGORI J., RODRÍGUEZ-FRIAS F., BUTI M., MADEJON A., PÉREZ-DEL-PULGAR S. ET AL. High-resolution hepatitis C virus subtyping using NS5B deep sequencing and phylogeny, an alternative to current methods. Journal of Clinical Microbiology. 2015;53(1):219-226.

SARRAZIN C, DIERYNCK I, CLOHERTY G, GHYS A, JANSSEN K, LUO D ET AL. An OPTIMIZE Study Retrospective Analysis for the Management of Telaprevir-Treated HCV Patients Using the Abbott RealTime HCV RNA Assay.Journal of clinical microbiology. 2015.

AMPUERO J., DEL CAMPO J.A., ROJAS L., GARCÍA-LOZANO R.J., BUTI M., SOLA R. ET AL. Fine-mapping butyrophilin family genes revealed several polymorphisms influencing viral genotype selection in hepatitis C infection. Genes and Immunity. 2015;16(5):297-300.

BENEDICTO I., GONDAR V., MOLINA-JIMÉNEZ F., GARCÍA-BUEY L., LÓPEZ-CABRERA M., GASTAMINZA P. ET AL. Clathrin mediates infectious hepatitis C virus particle egress. Journal of Virology. 2015;89(8):4180-4190.

STRIPPOLI R., LOUREIRO J., MORENO V., BENEDICTO I., PÉREZ LOZANO M.L., BARREIRO O. ET AL. Caveolin-1 deficiency induces a MEK-ERK1/2-Snail-1-dependent epithelial-mesenchymal transition and fibrosis during peritoneal dialysis. EMBO Molecular Medicine. 2015;7(1):102-123.

# Highlights

Our research group is focused on identifying non-invasive 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.

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 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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# G0023

Programme: **Hepatic & Gastrointestinal Oncology**

Lead Researcher: **García Marín, José Juan**

## Group members

STAFF MEMBERS: Briz Sánchez, Óscar | Lozano Esteban, Elisa

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

- 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.
- Bile acids in physiology, pathology and pharmacology. Cholestasis.

# Most relevant scientific articles

LOZANO E., MONTE M.J., BRIZ O., HERNÁNDEZ-HERNÁNDEZ A., BANALES J.M., MARIN J.J.G. ET AL. Enhanced antitumour drug delivery to cholangiocarcinoma through the apical sodium-dependent bile acid transporter (ASBT). Journal of Controlled Release. 2015;216:93-102.

ESTIU M.C., MONTE M.J., RIVAS L., MOIRON M., GÓMEZ-RODRÍGUEZ L., RODRÍGUEZ-BRAVO T. ET AL. Effect of ursodeoxycholic acid treatment on the altered progesterone and bile acid homeostasis in the mother-placenta-foetus trio during cholestasis of pregnancy. British Journal of Clinical Pharmacology. 2015;79(2):316-329.

MUNOZ-GARRIDO P., MARIN J.J.G., PERUGORRIA M.J., URRIBARRI A.D., ERICE O., SAEZ E. ET AL. Ursodeoxycholic acid inhibits hepatic cystogenesis in experimental models of polycystic liver disease. Journal of Hepatology. 2015;63(4):952-961.

MARIN J.J.G., HOUWEN R.H.J.. Treatment of paediatric cholestasis due to canalicular transport defects: Yet another step forward. Gut. 2015;64(1):6-8.

MASCARAQUE C., LÓPEZ-POSADAS R., MONTE M.J., ROMERO-CALVO I., DADDAOUA A., GONZÁLEZ M. ET AL. The small intestinal mucosa acts as a rutin reservoir to extend flavonoid anti-inflammatory activity in experimental ileitis and colitis. Journal of Functional Foods. 2015;13:117-125.

# Highlights

During 2015, the group of research on Experimental Hepatology and Drug Targeting (HEVEFARM) has maintained the collaboration with other members of the CIBERehd, such as Drs. Bujanda and Bañales (San Sebastián), Prieto, Avila and Sangro (Pamplona), Mato and Martínez-Chantal (Bilbao), Muntané (Sevilla) and Sánchez de Medina and Martínez-Augustín (Granada). Likewise, the HEVEFARM has potentiated the collaboration with groups from Germany, Italy, Netherlands, Norway and UK which have included the exchange of researchers and the participation in a funding application to the EASL, as well as the foundation of an European research network in which the HEVEFARM plays an important role in the study of chemoresistance of cholangiocarcinoma. In this area, the HEVEFARM has characterized the potential diagnostic interest and the usefulness as molecular target in cholangiocarcinoma of the bile acid transporter ASBT, which has led to file a Spanish patent application on the "use of ASBT protein as a tumour marker of cholangiocarcinoma".

Moreover, we investigated the genetic and epigenetic mechanisms responsible for the impaired expression of the gene SLC22A1 that are associated with the lack of cellular uptake and hence sensitivity of hepatocellular carcinoma to sorafenib. Advances have also been done in the development of biotechnological strategies to overcome the resistance of hepatocellular carcinoma and cholangiocarcinoma to chemotherapy. To potentiate this line of investigation two new researchers, funded by FPU fellowships, have joined the HEVEFARM. A significant effort has been invested in the study of the effect of glucocorticoid treatment on the communication between the intestine and the liver via the enterohepatic signalling mediated by the tandem FXR/FGF19. Regarding education activities, the HEVEFARM has hosted long stays (>6 months) of young researchers from the Universities of Barcelona, Groningen and Rome, and has coordinated a Doctoral Program and a Master's Degree on Cellular and Molecular Pathophysiology and Pharmacology.

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# G0083

Programme: **Viral Hepatitis**

Lead Researcher: **García-Samaniego Rey, Javier**

## Group members

STAFF MEMBERS: Gil García, Ana Isabel | 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

MADEJON A., SHELDON J., FRANCISCO-RECUERO I., PERALES C., DOMINGUEZ-BEATO M., LASA M. ET AL. Hepatitis C virus-mediated Aurora B kinase inhibition modulates inflammatory pathway and viral infectivity. Journal of Hepatology. 2015;63(2):312-319.

QUER J., GREGORI J., RODRÍGUEZ-FRIAS F., BUTI M., MADEJON A., PÉREZ-DEL-PULGAR S. ET AL. High-resolution hepatitis C virus subtyping using NS5B deep sequencing and phylogeny, an alternative to current methods. Journal of Clinical Microbiology. 2015;53(1):219-226.

ROMERO-GÓMEZ M., TURNES J., AMPUERO J., OYAGUEZ I., CUENCA B., GONZÁLEZ-GARCÍA J. ET AL. Prediction of week 4 virological response in hepatitis C for making decision on triple therapy: The optim study. PLoS ONE. 2015;10(3).

AMPUERO J., DEL CAMPO J.A., ROJAS L., GARCÍA-LOZANO R.J., BUTI M., SOLA R. ET AL. Fine-mapping butyrophilin family genes revealed several polymorphisms influencing viral genotype selection in hepatitis C infection. Genes and Immunity. 2015;16(5):297-300.

BUTI M., MORILLAS R.M., PÉREZ J., PRIETO M., SOLA R., PALAU A. ET AL. Entecavir has high efficacy and safety in white patients with chronic hepatitis B and comorbidities. European Journal of Gastroenterology and Hepatology. 2015;27(1):46-54.

# Highlights

RESEARCH PROJECTS. In 2015 the research team has developed the project entitled "Detection by Cold-PCR, of HCV resistance-variants to treatment with telaprevir or boceprevir in plasma and PBMCs. Usefulness in monitoring antiviral response", funded by the Fondo de Investigación Sanitaria (FIS PI12/02146). In addition, it has been started a new project, funded by ARCIS, S.A., aimed to develop a simplified system of point mutations (SNPs) detection in both human and viral genomes, entitled "Development of a detection system of IL28B the single nucleotide polymorphism (rs12979860) coupled to a simplified method of DNA extraction".

RESULTS. The ability of HCV to induce epigenetic changes in the host cell has been confirmed in a collaborative project involving a CIBERehd group and other group from the Medicine School of the Universidad Autónoma de Madrid (UAM) . Based on these results we have started a project to analyze the effect that the variability of the genes involved in such changes may have on the progression of liver fibrosis in patients with chronic hepatitis C. On the other hand, research focused on chronic hepatitis B has confirmed the presence of a significant rate of patients in the so-called "grey zone" of treatment carrying HBV strains associated with high risk of developing hepatocellular carcinoma (HCC). These data suggest the possibility of identifying subgroups of patients requiring special monitoring.

TRAINING ACTIVITIES. The group has organized a conference of international training entitled "Hepatitis C in 2015" held on February 5, 2015 at the Hospital Universitario La Paz (HULP) and in the facilities of the Instituto de Investigación del Hospital La Paz (FIBHULP), and funded by the publishing group ACINDES.

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# G0007

Programme: **Portal Hypertension & Mechanisms of Transition to Cirrhosis**
Lead Researcher: **Genesca Ferrer, Joan**

## Group members

STAFF MEMBERS: García Lezana, Teresa | Raurell Saborit, Imma.

ASSOCIATED MEMBERS: Agustín 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

RODRÍGUEZ S., RAURELL I., EZKURDIA N., AUGUSTIN S., ESTEBAN R., GENESCA J. ET AL. The renal effects of droxidopa are maintained in propranolol treated cirrhotic rats. Liver International. 2015;35(2):326-334.

CHAVARRIA L., CORDOBA J.. Magnetic resonance imaging and spectroscopy in hepatic encephalopathy. Journal of Clinical and Experimental Hepatology. 2015;5(S1):S69-S74.

CERINI F., GONZÁLEZ J.M., TORRES F., PUENTE A., CASAS M., VINAIXA C. ET AL. Impact of anticoagulation on upper-gastrointestinal bleeding in cirrhosis. A retrospective multicenter study. Hepatology. 2015;62(2):575-583.

AMPUERO J., SIMON M., MONTOLIU C., JOVER R., SERRA M.A., CORDOBA J. ET AL. Minimal Hepatic Encephalopathy and Critical Flicker Frequency Are Associated with Survival of Patients with Cirrhosis. Gastroenterology. 2015;149(6):1483-1489.

GUSTOT T., FERNÁNDEZ J., GARCÍA E., MORANDO F., CARACENI P., ALESSANDRIA C. ET AL. Clinical Course of acute-on-chronic liver failure syndrome and effects on prognosis. Hepatology. 2015;62(1):243-252.

# Highlights

During 2015, 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. Notably, the group has participated with a presentation at the *International Consensus Meeting Baveno VI*.

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# G0020

Programme: **Portal Hypertension & Mechanisms of Transition to Cirrhosis**
Lead Researcher: **Ginès Gibert, Pere**

## Group members

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

ASSOCIATED MEMBERS: Bataller Arberola, Ramon | Casals Mercadal, Gregori | Claria Enrich, Joan | Coll Loperena, Mar | Fernández Gómez, Javier | Graupera García Mila, Isabel | Guevara Montserrat, Mónica | 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 inflammatory lipid mediators produced by Kupffer cells
- Resolution of inflammation in chronic liver diseases: mechanism and mediators
- 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

ELIA C., GRAUPERA I., BARRETO R., SOLA E., MOREIRA R., HUELIN P. ET AL. Severe acute kidney injury associated with non-steroidal anti-inflammatory drugs in cirrhosis: A case-control study. Journal of Hepatology. 2015;63(3):593-600.

ANGELI P., GINÈS P., WONG F., BERNARDI M., BOYER T.D., GERBES A. ET AL. Diagnosis and management of acute kidney injury in patients with cirrhosis: Revised consensus recommendations of the International Club of Ascites. Gut. 2015;64(4):531-537.

LÓPEZ-VICARIO C., ALCARAZ-QUILES J., GARCÍA-ALONSO V., RIUS B., HWANG S.H., TITOS E. ET AL. Inhibition of soluble epoxide hydrolase modulates inflammation and autophagy in obese adipose tissue and liver: Role for omega-3 epoxides. Proceedings of the National Academy of Sciences of the United States of America. 2015;112(2):536-541.

PAUTA M., ROTLLAN N., FERNÁNDEZ-HERNANDO A., LANGHI C., RIBERA J., LU M. ET AL. Akt-mediated foxo1 inhibition is required for liver regeneration. Hepatology. 2015.

PAUTA M., RIBERA J., MELGAR-LESMES P., CASALS G., RODRÍGUEZ-VITA J., REICHENBACH V. ET AL. Overexpression of angiopoietin-2 in rats and patients with liver fibrosis. Therapeutic consequences of its inhibition. Liver International. 2015;35(4):1383-1392.

# Highlights

Studies and Results from basic and translational studies directed at studying the physiopathology of Acute-on Chronic Liver Failure (ACLF) of EASL CLIF Consortium.

New biomarkers studies to define the evolution and prognosis of patients with cirrhosis. Continuing with the research into AKI we have completed and evaluated a study of those patients with HRS who are on the transplant waiting list. New Studies to characterize the classification in more detail are underway. We have described the chemokines receptors CCR6 and Kinase p90RSK play in Alcoholic Hepatitis, as well as the role of MicroRNAs in activated hepatic stellate cells.

Research has focused on the resolution mechanisms of inflammation: the main results highlight the therapeutic potential of inhibiting the enzyme soluble epoxide hydrolase in non-alcoholic fatty liver disease. The selective inhibition of this enzyme stabilizes the tissue levels of omega-3-derived epoxides, which attenuate endoplasmic reticulum stress and regulate autophagy in insulin-sensitive tissues, especially the liver, counteracting metabolic disorders associated with obesity. Patent: Compositions comprising omega-3 fatty acids, 17-HDHA and 18-HEPE and methods of using same, United States Patent Office Application No. 62213958.

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# G0086

Programme: **Viral Hepatitis**
Lead Researcher: **Gómez Castilla, Jordi**

## Group members

STAFF MEMBERS: Ariza Mateos, M. Ascensión.
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].

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 hepatitis C virus in cell culture.

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

# Most relevant scientific articles

PERALES C., MORENO E., DOMINGO E.. Clonality and intracellular polyploidy in virus evolution and pathogenesis. Proceedings of the National Academy of Sciences of the United States of America. 2015;112(29):8887-8892.

GARCÍA-SACRISTAN A., MORENO M., ARIZA-MATEOS A., LÓPEZ-CAMACHO E., JAUDENES R.M., VAZQUEZ L. ET AL. A magnesium-induced RNA conformational switch at the internal ribosome entry site of hepatitis C virus genome visualized by atomic force microscopy. Nucleic Acids Research. 2015;43(1):565-580.

DIAZ-TOLEDANO R., GÓMEZ J.. Messenger RNAs bearing tRNA-like features exemplified by interferon alfa 5 mRNA. Cellular and Molecular Life Sciences. 2015;72(19):3747-3768.

MADEJON A., SHELDON J., FRANCISCO-RECUERO I., PERALES C., DOMINGUEZ-BEATO M., LASA M. ET AL. Hepatitis C virus-mediated Aurora B kinase inhibition modulates inflammatory pathway and viral infectivity. Journal of Hepatology. 2015;63(2):312-319.

DELGADO S., MORAN F., MORA A., MERELO J.J., BRIONES C.. A novel representation of genomic sequences for taxonomic clustering and visualization by means of self-organizing maps. Bioinformatics. 2015;31(5):736-744.

# Highlights

The group is founded by two Grants from the Plan Nacional and a Grant from Junta de Andalucía.

During 20015 and the first weeks of 2016, three doctoral dissertations have been registered.

- An evaluation of the impact of recombination for virus adaptability, pathogenesis and evolution of highly variable viruses. A distinction between biologically meaningful and inconsequential recombination.
- This article describes the use of atomic force microscopy (AFM) to visualize for the first time the HCV IRES structure in different sequence contexts and ionic conditions. We reported a magnesium-induced switch between two alternative 3D conformations: from 'open' morphologies to a 'closed', comma-shaped conformation. This sharp transition, confirmed by gel-shift analysis and partial RNase T1 cleavage, is hindered by the microRNA miR-122. Our results reinforce the structural/functional continuity between the HCV IRES and its flanking domains within the 5'UTR of the viral genomic RNA.
- The study describes a tRNA-like structure present within the coding region of the mRNA of the antiviral defence gene IFN5 alfa, the liver subtype. This structure, which is highly similar to the one present around the AUG start codon, opens a new way of understanding the viral capacity to evade the host immune response and to stablish a persistent infection.
- A study of epigenetic factors taht influence the infection by HCV. In this study it is shown that a core protein-mediated decrease of aurora B kinase activity may play arle in the inflamatory pathway during the initial steps of infection , and permit viral infectivity.
- This work presents a novel method for coding and classifying genomic sequence data using two numeric self-organizing map (SOM) models. The method anticipates a broad applicability of this codification method in the fields of virology and genomic.

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# G0013

Programme: **Hepatotoxicity, Cholestasis & 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., FERNÁNDEZ A., PRIETO-DOMINGUEZ N., MARTÍNEZ L., GARCÍA-RUIZ C., FERNÁNDEZ-CHECA J.C. ET AL. Ceramide metabolism regulates autophagy and apoptotic cell death induced by melatonin in liver cancer cells. Journal of Pineal Research. 2015;59(2):178-189.

PISONERO-VAQUERO S., MARTÍNEZ-FERRERAS A., GARCÍA-MEDIAVILLA M.V., MARTÍNEZ-FLOREZ S., FERNÁNDEZ A., BENET M. ET AL. Quercetin ameliorates dysregulation of lipid metabolism genes via the PI3K/AKT pathway in a diet-induced mouse model of nonalcoholic fatty liver disease. Molecular Nutrition and Food Research. 2015;59(5):879-893.

SAN-MIGUEL B., CRESPO I., SÁNCHEZ D.I., GONZÁLEZ-FERNÁNDEZ B., ORTIZ DE URBINA J.J., TUNON M.J. ET AL. Melatonin inhibits autophagy and endoplasmic reticulum stress in mice with carbon tetrachloride-induced fibrosis. Journal of Pineal Research. 2015;59(2):151-162.

BENET M., GUZMAN C., PISONERO-VAQUERO S., GARCÍA-MEDIAVILLA M.V., SÁNCHEZ-CAMPOS S., MARTÍNEZ-CHANTAR M.L. ET AL. Repression of the nuclear receptor small heterodimer partner by steatotic drugs and in advanced nonalcoholic fatty liver disease. Molecular Pharmacology. 2015;87(4):582-594.

CRESPO I., SAN-MIGUEL B., FERNÁNDEZ A., ORTIZ DE URBINA J., GONZÁLEZ-GALLEGO J., TUNON M.J.. Melatonin limits the expression of profibrogenic genes and ameliorates the progression of hepatic fibrosis in mice. Translational Research. 2015;165(2):346-357.

# Highlights

The research group has published 13 articles (6 in collaboration with other CIBEREHD groups); 10 are 1st quartil, including 6 1st decile, with an accumulated impact factor of 71.7.

There were 7 competitive research projects in development, including those related with effects of quercetin treatment and intestinal microbiota transplantation on experimental models of NAFLD (financed by the Plan Estatal de Investigación Científica y Técnica and the Junta de Castilla y León), the therapeutic role of melatonin on the mechanisms of liver fibrosis (Junta de Castilla y León and AECC), and the assessment of the immunomodulatory activity of bioactive compound from mushrooms (Plan Estatal de Investigación Científica y Técnica).

Concerning translation of results to clinical practice we have participated in 3 clinical assays related to adherence to triple therapy and to the use of telaprevir, boceprevir, ABT-493 and ABT-530 in the treatment of chronic infection by HCV GT1.

Within the formation area, a doctoral thesis has been presented on the pathogenic mechanisms of NAFDL in a nutritional murine model.

During this period we have collaborated with the following CIBEREHD groups: Program 1 (José V Castell, José C Fernández-Checa, José María Mato, Marina Berenguer, Ramón Planas, Raúl Andrade), Program 3 (Manuel Romero, Javier Salmerón, Rafael Esteban), Program 4 (Bruno Sangro, Pascual Parrilla). We have also maintained a collaboration with Laura Lechuga, from the CIBER-BBN. Finally, international collaborations existed with the University of Texas Health Science Center (USA), the University Medical Center Groningen (Holanda), and the Universidade Federal do Rio Grande do Sul (Brasil).

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# G0030

Programme: **Portal Hypertension & Mechanisms of Transition to Cirrhosis**
Lead Researcher: **Guarner Aguilar, Carlos**

## Group members

STAFF MEMBERS: Ardevol Ribalta, Alba | Sánchez Ardid, Elisabet.

ASSOCIATED MEMBERS: Poca Sans, María | 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

GRAUPERA I, PAVEL O, HERNÁNDEZ-GEA V, ARDEVOL A, WEBB S, URGELL E ET AL. Relative adrenal insufficiency in severe acute variceal and non-variceal bleeding: influence on outcomes.Liver international : official journal of the International Association for the Study of the Liver. 2015.

SÁNCHEZ E, NIETO JC, BOULLOSA A, VIDAL S, SANCHO FJ, ROSSI G ET AL. VSL#3 probiotic treatment decreases bacterial translocation in rats with carbon tetrachloride-induced cirrhosis.Liver international : official journal of the International Association for the Study of the Liver. 2015;35(3):735-45.

ESCORSELL À, PAVEL O, CÁRDENAS A, MORILLAS R, LLOP E, VILLANUEVA C ET AL. Esophageal balloon tamponade Vs esophageal stent in controlling acute refractory variceal bleeding: A multicenter RCT.Hepatology (Baltimore, Md.). 2015.

Nieto J.C., Sánchez E., Romero C., Roman E., Poca M., Guarner C. et al. Impaired innate immune response of leukocytes from ascitic fluid of patients with spontaneous bacterial peritonitis. Journal of Leukocyte Biology. 2015;98(5):819-825.

GÓMEZ-ANSON B., ROMAN E., DE BOBADILLA R.F., PIRES-ENCUENTRA P., DIAZ-MANERA J., NUEZ F. ET AL. Alterations in cerebral white matter and neuropsychology in patients with cirrhosis and falls. PLoS ONE. 2015;10(3).

# Highlights

The research group of complications of cirrhosis of the Hospital de la Santa Creu i Sant Pau, Barcelona has two main lines. Dr. Germán Soriano directs the line of complications of cirrhosis, especially ascites and renal function, bacterial infections, hepatic encephalopathy and quality of life. This line has conducted clinical and experimental work some published and others in progress. Especially it is working with the Immunology Department of our hospital and the research group of Dr. F. Guarner Valle Hebron Hospital, evaluating the effect of probiotics on the intestinal barrier and the microbiota, initially in an experimental model in cirrhosis and currently in patients with cirrhosis. We have two national research projects and two other private. We work with other groups CIBEREHD and especially with the Consortium of CLIF. Elizabeth Sanchez, contracted by the CIBEREHD of our group, has read her doctoral thesis on "Experimental models of bacterial peritonitis in rats with cirrhosis and new therapeutic strategies," obtaining the highest rating of "Excellent cum laude".

The other line of the group led by Dr. Villanueva is devoted to the study and management of portal hypertension. This line of research of our group is essentially clinical. Dr. Villanueva and his colleagues have followed his own research and in collaboration with the groups in this field as the Clinical H., H. Gregorio Maranon, Valle Hebron, Puerta de Hierro etc. Scientific production has been considerable, especially as a group and have funded research projects. Continued cooperation with the working group of Baveno.

Dr. X. Torras of our team is also leading another area on viral hepatitis with collaborative publications this year.

Results have also been obtained in the form of funded projects and articles in other lines of inquiry that belong to other areas of CIBEREHD such as inflammation and endoscopy.

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http://www.ciberehd.org/grupos/grupo-de-investigacion?id=16105

# G0062

Programme: **Inflammation & Gastrointestinal Motility**

Lead Researcher: **Guarner Aguilar, Francisco**

## Group members


STAFF MEMBERS: Varela Castro, Encarnación.

ASSOCIATED MEMBERS: Antolín Mate, María | Borruel Sainz, 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., GONZÁLEZ 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.

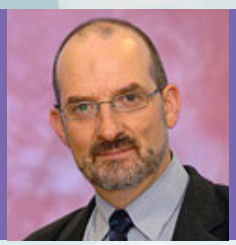
NIELSEN H.B., ALMEIDA M., JUNCKER A.S., RASMUSSEN S., LI J., SUNAGAWA S. ET AL. Identification and assembly of genomes and genetic elements in complex metagenomic samples without using reference genomes. Nature Biotechnology. 2014;32(8):822-828.

CENDROWSKI J., SÁNCHEZ-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.

**Institution:** Fundación Hospital Universitario Vall d´Hebron - Institut de Recerca (VHIR)
**Contact:** Hospital Vall d'Hebron. Passeig Vall d'Hebron, 119-129. 08035 Barcelona.
E.mail: fguarner@vhebron.net · Website: http://www.vhir.org

# G0066

Programme: **Inflammation & Gastrointestinal Motility**
Lead Researcher: **Lanas Arbeloa, Ángel**



## Group members

STAFF MEMBERS: Arechavaleta Tabuenca, Samanta P. | Chueca Lapuente, Eduardo.

ASSOCIATED MEMBERS: Abián Franco, Olga | 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 | Roncalés Lázaro, Pilar | 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 infec-

tion (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


SOSTRES C., CARRERA-LASFUENTES P., BENITO R., RONCALES P., ARRUEBO M., ARROYO M.T. ET AL. Peptic ulcer bleeding risk. the role of helicobacter pylori infection in NSAID/low-dose aspirin users. American Journal of Gastroenterology. 2015;110(5):684-689.

LANAS A., BOERS M., NUEVO J.. Gastrointestinal events in at-risk patients starting non-steroidal anti-inflammatory drugs (NSAIDs) for rheumatic diseases: The EVIDENCE study of European routine practice. Annals of the Rheumatic Diseases. 2015;74(4):675-681.

VEGA S., GARCÍA-GONZÁLEZ M.A., LANAS A., VELAZQUEZ-CAMPOY A., ABIAN O.. Deconvolution analysis for classifying gastric adenocarcinoma patients based on differential scanning calorimetry serum thermograms. Scientific Reports. 2015;5.

GARCÍA-GONZÁLEZ M.A., BUJANDA L., QUINTERO E., SANTOLARIA S., BENITO R., STRUNK M. ET AL. Association of PSCA rs2294008 gene variants with poor prognosis and increased susceptibility to gastric cancer and decreased risk of duodenal ulcer disease. International Journal of Cancer. 2015;137(6):1362-1373.

CLAVERIA-GIMENO R., VEGA S., GRAZU V., DE LA FUENTE J.M., LANAS A., VELAZQUEZ-CAMPOY A. ET AL. Rescuing compound bioactivity in a secondary cell-based screening by using γ-cyclodextrin as a molecular carrier. International Journal of Nanomedicine. 2015;10:2249-2259.


# Highlights

## PROJECTS

Angel Lanas. PI14/01218. Acetil salicilic acid and platelets in colon cancer.

Elena Piazuelo. PI14/01931. Proton transport inhibition for chemoprevention and treatment of esophageal adenocarcinoma.

Fernando Gomollón. European 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. Coordinatorr:Dr. Aber NADIR.

Olga Abián. Analysis of protein/metabolites interactions in plasma serum using calorimetry: application as a quick and noninvasive diagnostic method for early detection and monitoring of tumoral digestive diseases (DIGCAL).

Pedro Baptista. Proposal 660554. Liver Bioengineering. Marie Curie 2015 Liver Bioengineering. "Ex vivo Re-vascularization in Porcine Liver Bioengineering – A critical First Step Towards Effective Transplantation on Bioengineered Livers".

## CLINICAL GUIDES

Gomollón F, Rubio S, Charro M, García-López S, Muñoz F, Gisbert JP, et al; En Representación de GETECCU. [Reccomendations of the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU) on the use of methotrexate in inflammatory bowel disease]. Gastroenterol Hepatol. 2015;38:24-30.

Van Assche G, Dignass A, Bokemeyer B, Danese S, Gionchetti P, Moser G, Beaugerie L, Gomollón F, et al. [Second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 3: Special situations. Rev Gastroenterol Mex. 2015 ;80:74-106.

Dignass AU, Gasche C, Bettenworth D, Birgegård G, Danese S, Gisbert JP, Gomollon F, et al.; European Crohn's and Colitis Organisation [ECCO]. European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases. J Crohns Colitis. 2015 ;9(3):211-22.

Gralnek IM, Dumonceau JM, Kuipers EJ, Lanas A, Sanders DS, Kurien M, et al. Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2015;47(10):a1-a46.

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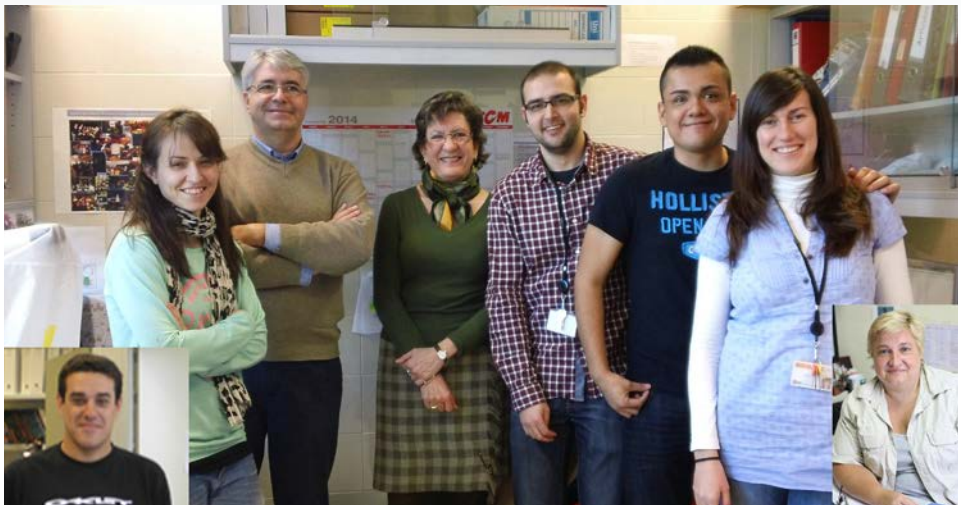
# G1069

Programme: **Hepatotoxicity, Cholestasis & Metabolic Disorders**
Lead Researcher: **Martín Sanz, Paloma**

## Group members



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

## Main lines of research

Basic Research Group associated to Ciberehd

Research Lines:

- 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 and CIBERDEM.

# Most relevant scientific articles

MOTINO O., FRANCES D.E., MAYORAL R., CASTRO-SÁNCHEZ L., FERNÁNDEZ-VELASCO M., BOSCA L. ET AL. Regulation of microRNA 183 by cyclooxygenase 2 in liver is DEAD-box helicase p68 (DDX5) dependent: Role in insulin signaling. Molecular and Cellular Biology. 2015;35(14):2554-2567.

PRIETO P., ROSALES-MENDOZA C.E., TERRON V., TOLEDANO V., CUADRADO A., LÓPEZ-COLLAZO E. ET AL. Activation of autophagy in macrophages by pro-resolving lipid mediators. Autophagy. 2015;11(10):1729-1744.

TAWAKOL A., SINGH P., MOJENA M., PIMENTEL-SANTILLANA M., EMAMI H., MACNABB M. ET AL. HIF-1α and PFKFB3 mediate a tight relationship between proinflammatory activation and anerobic metabolism in atherosclerotic macrophages. Arteriosclerosis, Thrombosis, and Vascular Biology. 2015;35(6):1463-1471.

MAYORAL R., OSBORN O., MCNELIS J., JOHNSON A.M., OH D.Y., IZQUIERDO C.L. ET AL. Adipocyte SIRT1 knockout promotes PPARγ activity, adipogenesis and insulin sensitivity in chronic-HFD and obesity. Molecular Metabolism. 2015;4(5):378-391.

GONZÁLEZ-RUBIO S., LÓPEZ-SÁNCHEZ L., MUNOZ-CASTANEDA J., LINARES C.I., AGUILAR-MELERO P., RODRÍGUEZ-PERALVAREZ M. ET AL. GCDCA down-regulates gene expression by increasing Sp1 binding to the NOS-3 promoter in an oxidative stress dependent manner. Biochemical pharmacology. 2015;96(1):39-51.

# Highlights

During 2015, we have focused on studying the contribution of cyclooxigenase-2-dependent prostaglandins to the initiation and progression of non-alcoholic fatty liver disease in collaboration with Carmelo García-Monzón from CIBEREHD and Ángela Valverde from Ciberdem. Our study demonstrated that constitutive expression of human COX-2 (hCOX-2) in hepatocytes protects against adiposity, inflammation, and hence insulin resistance induced by high fat diet. hCOX-2 transgenic mice exhibited increased whole body energy expenditure due in part by induction of thermogenesis and fatty acid oxidation. The analysis of hepatic insulin signaling revealed an increase in insulin receptor-mediated Akt phosphorylation in hCOX-2-Tg. In conclusion, our results point to COX-2 as a potential therapeutic target against obesity-associated metabolic dysfunction (Diabetes, 2015, 64:1522-1531). Furthermore, COX-2 represses miR-23b, miR-146b and miR-183 expression in liver cells by increasing the level of DEAD-box helicase p68 (DDX5) through PI3K/p300 signaling and by modulating the enzymatic function of the Drosha complex through its physical association with DDX5. The decrease of miR-183 promotes protection against insulin resistance by increasing IRS1 levels. These results indicate that the modulation of miRNA processing by COX-2 is a key event in insulin signaling in liver and has potential clinical implications for the management of various hepatic dysfunctions.

In collaboration with Lisardo Boscá, we have studied the regulation of autophagy in macrophages by pro-resolving lipid mediators and we demonstrate that 15-epi-LXA4 and RvD1 promote autophagy in murine and human macrophages by the degradation of SQSTM1 as well as the formation of MAP1LC3+ autophagosomes. This autophagic response involves the activation of MAPK1 and NFE2L2 pathways. Therefore, 15-epi-LXA4 and RvD1 improved both survival and functionality of macrophages, which likely supports the recovery of tissue homeostasis and avoiding chronic inflammatory diseases.

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E.mail: pmartins@iib.uam.es

# G0077

Programme: **Immunology & Liver Transplantation**
Lead Researcher: **Mata García, Manuel de la**

## Group members

STAFF MEMBERS: Ferrin Sánchez, Gustavo.

ASSOCIATED MEMBERS: Barrera Baena, Pilar | Briceño Delgado, Francisco Javier | González Galilea, Ángel | González Ojeda, Raul | Hervás Molina, Antonio José | López Cillero, Pedro | Montero Álvarez, José Luis | Naranjo Rodríguez, Antonio | Poyato González, Antonio | Rodríguez Perálvarez, Manuel Luis.

## 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

LINARES C.I., FERRIN G., AGUILAR-MELERO P., GONZÁLEZ-RUBIO S., RODRÍGUEZ-PERALVAREZ M., SÁNCHEZ-ARAGO M. ET AL. Sensitivity to anti-Fas is independent of increased cathepsin D activity and adrenodoxin reductase expression occurring in NOS-3 overexpressing HepG2 cells. Biochimica et Biophysica Acta - Molecular Cell Research. 2015;1853(5):1182-1194.

FERRIN G., RODRÍGUEZ-PERALVAREZ M., AGUILAR-MELERO P., RANCHAL I., LLAMOZA C., LINARES C.I. ET AL. Plasma protein biomarkers of hepatocellular carcinoma in HCV-infected alcoholic patients with cirrhosis. PLoS ONE. 2015;10(3):-.

GONZÁLEZ-RUBIO S., LÓPEZ-SÁNCHEZ L., MUNOZ-CASTANEDA J., LINARES C.I., AGUILAR-MELERO P., RODRÍGUEZ-PERALVAREZ M. ET AL. GCDCA down-regulates gene expression by increasing Sp1 binding to the NOS-3 promoter in an oxidative stress dependent manner. Biochemical pharmacology. 2015;96(1):39-51.

RODRÍGUEZ-PERALVAREZ M., PÉREZ-MEDRANO I., GUERRERO-MISAS M., GONZÁLEZ V., POYATO A., BARRERA P. ET AL. Everolimus is safe within the first month after liver transplantation. Transplant Immunology. 2015;33(2):146-151.

RODRÍGUEZ-PERÁLVAREZ M, GARCÍA-CAPARRÓS C, TSOCHATZIS E, GERMANI G, HOGAN B, POYATO-GONZÁLEZ A ET AL. Lack of agreement for defining 'clinical suspicion of rejection' in liver transplantation: a model to select candidates for liver biopsy.Transplant international : official journal of the European Society for Organ Transplantation. 2015;28(4):455-64.

# Highlights

- The FIS Project entitled "Inhibición de la vía mTOR en pacientes trasplantados por carcinoma hepatocelular y su repercusión en la recidiva de la enfermedad", which was awarded in 2011 and further extended to December 2015, has been closed and its preliminary results published (Rodríguez-Perálvarez et al, Transplant Immunol 2015). In addition, the project was awarded by the European Association for the Study of the Liver (EASL) with the Physician scientist fellowship, and received the annual grant by the Sociedad Andaluza de Trasplante de Órganos y Tejidos (SATOT). Final results are to be published in 2016.
- A second FIS Project, tightly related with the former, and entitled "Importancia de la activación del sistema inmune para eliminar células tumorales circulantes y prevenir la recidiva del hepatocarcinoma tras el trasplante hepático" got funded and will start soon.
- Sandra González and Clara Linares, both PhD students at our department, published final results from their doctoral theses in first quartile journals. In such work, they investigated the role of biliary acids in hepatocellular damage mediated by oxidative stress, and explored hepatoprotective strategies.
- A "Río Hortega" post-Doc fellowship was awarded by the Instituto de Salud Carlos III (Candidate: Dr. Manuel Rodríguez-Perálvarez; PI: Dr. Manuel de la Mata).
- Intra CIBERehd networking was reinforced within the "Liver Transplant and Immunology" program by sharing a common research project in which a model to predict acute cellular rejection was designed and further validated. Additional European Liver Units were involved including the Royal Free Hospital (London, UK), the Cliniques Universitaires St. Luc (Leuven, Belgium) and the Padova University Hospital (Italy). This project will form the basis for a competitive European consortium to apply for one of the EASL registry grants in 2016 awarded by the European Association for the Study of the Liver (EASL).

**Institution:** Fundación para la Investigación Biomédica de Córdoba (FIBICO)
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# G0017

Programme: **Hepatotoxicity, Cholestasis & Metabolic Disorders**
Lead Researcher: **Mato de la Paz, José María**

## Group members

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

ASSOCIATED MEMBERS: Abrescia, Nicola Gerardo | Aransay Bañares, Ana María | 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

Baixauli F, Acín-Pérez R, Villarroya-Beltrí C, Mazzeo C, Nuñez-Andrade N, Gabandé-Rodríguez E et al. Mitochondrial Respiration Controls Lysosomal Function during Inflammatory T Cell Responses.Cell metabolism. 2015;22(3):485-98.

Barbier-Torres L, Beraza N, Fernández-Tussy P, Lopitz-Otsoa F, Fernández-Ramos D, Zubiete-Franco I et al. Histone Deacetylase 4 promotes cholestatic liver injury in the absence of Prohibitin-1.Hepatology (Baltimore, Md.). 2015;.

Martínez-Una M., Varela-Rey M., Mestre D., Fernández-Ares L., Fresnedo O., Fernández-Ramos D. et al. S-Adenosylmethionine increases circulating very-low density lipoprotein clearance in non-alcoholic fatty liver disease. Journal of Hepatology. 2015;62(3):673-681.

Zubiete-Franco I., García-Rodríguez J.L., Martínez-Una M., Martínez-López N., Woodhoo A., Juan V.G.D. et al. Methionine and S-adenosylmethionine levels are critical regulators of PP2A activity modulating lipophagy during steatosis. Journal of Hepatology. 2015.

Feitelson M.A., Arzumanyan A., Kulathinal R.J., Blain S.W., Holcombe R.F., Mahajna J. et al. Sustained proliferation in cancer: Mechanisms and novel therapeutic targets. Seminars in Cancer Biology. 2015.

# Highlights

In the NAFLD area we have established how the levels of S-adenosylmethionine regulate fat accumulation and steatohepatitis blocking the autophagy process through a defect in the lysosome autophagosome fusion (Zubiete- Franco et al; J Hepatol 2015 Feb; 64 (2): 409-18.

Also in the NAFLD area we have identified that an excess of hepatic SAMe 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 (Martínez-Uña M et al; J Hepatol. 2015 Mar;62(3):673-81).

In the cirrhosis area we have described how the absence of prohibitin a mitochondrial protein regulates the activity of Histone Deacetylase 4 causing the development of a cholestatic liver (Barbier-Torres Hepatology 2015 Oct; 62 (4):. 1237-1248).

In the Liver Cancer area we have been able to identify the implication that the post-translational modification Neddylation has in the development and progression of HCC (Barbier –Torres et al; Oncotarget. 2015 Feb 10;6(4):2509-23.

In the area of the exosomes, different isolation methods have been established to analyze exosomes in clinical settings (Royo et al., J. Extracellular Vesicles, 2016). A project named MICROXOM funded by the Basque Government has been initiated to develop a nano-device to isolate subpopulations of urinary exosomes. It has been finished the proteomics analysis of urinary exosomes from cirrhotic patients funded by the health department of Basque Government.

In the metabolomics area, during 2015 the methodology to analyze by UPLC-MS the polyamines and glutathione metabolisms were developed and integrated with the method to analyze methionine cycle metabolism. During 2015, these methods were applied to study the seric kinetic of SAMe, the alterations of these metabolisms ejected by different liver-damaging conditions and to evaluate the efficacy of different treatments against some of those conditions.

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# G0011

Programme: **Immunology & Liver Transplantation**
Lead Researcher: **Navasa Anadón, Miquel Àngel**

## Group members

STAFF MEMBERS: Cubero León, María Dolores | Millán López, Olga | Muñoz Luque, Javier.

ASSOCIATED MEMBERS: Brunet Serra, Mercedes | Colmenero Arroyo, Jordi Fèlix | Crespo Conde, Gonzalo | Fondevila Campo, Constantino | García-Valdecasas Salgado, Juan Carlos | Peralta Uroz, Carmen | Roselló 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

VENDRELL M, HESSHEIMER AJ, RUIZ A, DE SOUSA E, PAREDES D, RODRÍGUEZ C ET AL. Coagulation Profiles of Unexpected DCDD Donors Do Not Indicate a Role for Exogenous Fibrinolysis.American journal of transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2015;15(3):764-71.

CORNIDE-PETRONIO M.E., NEGRETE-SÁNCHEZ E., MENDES-BRAZ M., CASILLAS-RAMIREZ A., BUJALDON E., MERONO N. ET AL. The Effect of High-Mobility Group Box 1 in Rat Steatotic and Nonsteatotic Liver Transplantation From Donors After Brain Death. American Journal of Transplantation. 2015.

RODRÍGUEZ E., HENRIQUE PEREIRA G., SOLA E., ELIA C., BARRETO R., POSE E. ET AL. Treatment of type 2 hepatorenal syndrome in patients awaiting transplantation: Effects on kidney function and transplantation outcomes. Liver Transplantation. 2015;21(11):1347-1354.

BENITO N., GARCÍA-VAZQUEZ E., HORCAJADA J.P., GONZÁLEZ J., OPPENHEIMER F., COFAN F. ET AL. Clinical features and outcomes of tuberculosis in transplant recipients as compared with the general population: A retrospective matched cohort study. Clinical Microbiology and Infection. 2015;21(7):651-658.

BONACCORSI-RIANI E., DANGER R., LOZANO J.J., MARTÍNEZ-PICOLA M., KODELA E., MAS-MALAVILA R. ET AL. Iron deficiency impairs intra-hepatic lymphocyte mediated immune response. PLoS ONE. 2015;10(8).

# Highlights

Previous studies of our group showed that, before initiation of drug withdrawal, operationally tolerant and non-tolerant recipients differed in the intra-graft expression of genes involved in the regulation of iron homeostasis. Furthermore, as compared with non-tolerant recipients, operationally tolerant patients exhibited higher serum levels of hepcidin and ferritin and increased hepatocyte iron deposition. Finally, liver tissue gene expression measurements accurately predicted the outcome of immunosuppressive withdrawal. The group has demonstrated now that small changes in iron homeostasis can have a major effect in the regulation of intra-hepatic lymphocyte mediated responses and more specifically that iron deprivation impairs intra-hepatic lymphocyte activation and proliferation and results in a beneficial effect on immune mediated hepatitis.

In the field of organ retrieval and utilization of donor organs with expanded criteria, new therapetutic targets based on adipocytokines modulation has been established. This opens a new path for the use of estatosic liver grafts. We are participating in new programs directed to the translation of these experimental results to clinical practice. In addition, it has been established the role of polyethilenglycol in the preservation solutions, that results in a significant increase in the time of safe preservation of the graft.

Two studies represent an improvement in clinical liver transplantation: The actual situation of tuberculosis in liver transplant patients, with special interest in prophylaxis, and the management and prognosis of hepatorenal syndrome in patients awaiting for liver transplantation.

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# G0018

Programme: **Inflammation & Gastrointestinal Motility**

Lead Researcher: **Panes Díaz, Julián**

## Group members

STAFF MEMBERS: Benítez Ribas, Daniel | Esteller Viñal, Miriam | Giner Agudo, Ángel | Masamunt Estrella, M. Carme | Planell Picola, Nuria.

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 | Pino Donnay, Susana | Pique Badia, Josep María | 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

RIMOLA J., PLANELL N., RODRÍGUEZ S., DELGADO S., ORDAS I., RAMIREZ-MORROS A. ET AL. Characterization of inflammation and fibrosis in crohn's disease lesions by magnetic resonance imaging. American Journal of Gastroenterology. 2015;110(3):432-440.

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. 2015;64(2):233-242.

COLOMBEL J.-F., ORDAS I., ULLMAN T., RUTGEERTS P., CHAI A., O'BYRNE S. ET AL. Agreement Between Rectosigmoidoscopy and Colonoscopy Analyses of Disease Activity and Healing in Patients With Ulcerative Colitis. Gastroenterology. 2015.

COIMBRA A.J.F., RIMOLA J., O'BYRNE S., LU T.T., BENGTSSON T., DE CRESPIGNY A. ET AL. Magnetic resonance enterography is feasible and reliable in multicenter clinical trials in patients with Crohn's disease, and may help select subjects with active inflammation. Alimentary Pharmacology and Therapeutics. 2015;43(1):61-72.

SALAS A., PANES J.. IBD: Regulatory T cells for treatment of Crohn's disease. Nature Reviews Gastroenterology and Hepatology. 2015;12(6):315-316.

# Highlights

The inflammatory bowel disease Group at Hospital Clínic de Barcelona has focused on the development of new forms of cell therapies for inflammatory bowel Disease. The group described the methodology to generate tolerògenic dendritic cells, and the completion of the phase I trial, based entirely funded by national grants, is a major achievement. Demonstration of the safety of this form of cell therapy opens the door to using it also in other fields of medicine, and our group is already collaborating with testing this therapy in multiple sclerosis with a group of neurologists.

We made further progress in the use of imaging for diagnosis and prognosis in inflammatory bowel disease. We showed that MRI findings are even more valuable than endoscopy in identifying patients with a poor prognosis, making them candidates for the most effective therapies available. This as clinical as well as research significance when selecting populations for disease-modification trials. In the field of imaging, we characterized the features that allow differentiation of fibrotic from stenotic lesions in Crohn's disease, a finding with a considerable relevance because fibrotic lesions will not respond to medical interventions and need endoscopic or surgical approaches.

In the field of drug development, we made significant contributions in the identification of easily measurable parameters of disease activity and severity, such as calprotectin, showing that in the context of a randomized controlled trial measurements of this biomarker provides the same signals of therapeutic response that a combined clinical-endoscopic endpoint. Finally, patient reported outcomes, increasingly requested by regulatory authorities in clinical trials have to be developed and tested for accuracy and responsiveness, and we provided evidence of the operational characteristics of patient reported outcomes in the context of clinical trials, showing their validity as outcome measures.

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# G0015

Programme: **Hepatotoxicity, Cholestasis & Metabolic Disorders**
Lead Researcher: **Parés Darnaculleta, Albert**

## Group members

**Colestasis y Patología Ósea**

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

LAMMERS W.J., HIRSCHFIELD G.M., CORPECHOT C., NEVENS F., LINDOR K.D., JANSSEN H.L.A. ET AL. Development and Validation of a Scoring System to Predict Outcomes of Patients with Primary Biliary Cirrhosis Receiving Ursodeoxycholic Acid Therapy. Gastroenterology. 2015;149(7):1804-1812e4.

HIRSCHFIELD G.M., MASON A., LUKETIC V., LINDOR K., GORDON S.C., MAYO M. ET AL. Efficacy of obeticholic acid in patients with primary biliary cirrhosis and inadequate response to ursodeoxycholic acid. Gastroenterology. 2015;148(4):751-761.e8.

GUAÑABENS N, FILELLA X, MONEGAL A, GÓMEZ-VAQUERO C, BONET M, BUQUET D ET AL. Reference intervals for bone turnover markers in Spanish premenopausal women.Clinical chemistry and laboratory medicine : CCLM / FESCC. 2015.

VESTERHUS M., HOV J.R., HOLM A., SCHRUMPF E., NYGARD S., GODANG K. ET AL. Enhanced Liver Fibrosis Score Predicts Transplant-Free Survival in Primary Sclerosing Cholangitis. Hepatology. 2015;62(1):188-197.

BEUERS U, GERSHWIN ME, GISH RG, INVERNIZZI P, JONES DE, LINDOR K ET AL. Changing Nomenclature for PBC: From 'Cirrhosis' to 'Cholangitis'.Gastroenterology. 2015.

# Highlights

In the year 2015 the group has done further research on the effects of bezafibrate on the improvement of biochemical cholestasis in patients with primary biliary cirrhosis. The metabolomic analysis has taken the first data on potential molecules involved in the pathogenesis of cholestatic itch. In this concern, the group has obtained a competitive research project funded by the Instituto de Salud Carlos III. In collaboration with other international centres the group has described a new indicator index regarding prognosis and therapeutic response to ursodeoxycholic acid, which is better to those previously described.

Moreover, cooperative studies with other CIBEREHD groups are in progress aimed at defining targets responsible involved in cholestasis. Also in collaboration with international groups it has demonstrated the effectiveness of a biochemical index and the usefulness of transient elastography for the prognosis of primary sclerosing cholangitis.

With respect to the pathogenesis of osteoporosis in cholestatic diseases it has demonstrated the effect of bilirubin and lithocholic acid on the expression of genes involved in the mechanisms of apoptosis and cell differentiation as well as other related on bone formation and resorption. In this field the group has led a collaborative project to establish normal values of bone turnover markers, which are essential to assess bone formation and resorption and therapeutic response in patients with metabolic bone disease.

The group has actively participated in the proposal for renaming "primary biliary cirrhosis" to "primary biliary cholangitis", in order to eliminate the term of cirrhosis in this disease, taking into account that most patients never will develop cirrhosis.

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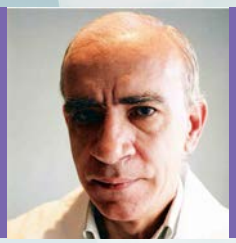
# G1092

**Programme:** Hepatic & Gastrointestinal Oncology
**Lead Researcher:** Parrilla Paricio, Pascual



## Group members

STAFF MEMBERS: Aparicio Alonso, Pedro | Bermejo López, Juan | Martínez Alarcón, Laura | Martínez Cáceres, Carlos Manuel | Martínez de Haro, Luisa Fernanda | Molina Martínez, Joaquín | Munitiz Ruiz, Vicente | Muñoz Luna, Antonio | Ortiz Escandell, Ángeles | Pelegrín Vivancos, Pablo | Pons Miñano, José Antonio | Ramírez Romero, Pablo | Revilla Nuin, Beatriz | Ríos Zambudio, Antonio | Robles Campos, Ricardo | Sánchez Bueno, Francisco | Yelamos López, José.

## 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., MARTÍN-SÁNCHEZ F., GÓMEZ A.I., MARTÍNEZ 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.

MARTÍNEZ-BOSCH N., IGLESIAS M., MUNNE-COLLADO J., MARTÍNEZ-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., JIMÉNEZ C., SÁNCHEZ-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., LÓPEZ-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., RODRÍGUEZ DE LOPE C., GASTACA M., ORTIZ DE URBINA J., SUAREZ 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.

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# G0063

Programme: **Hepatic & 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

- Role of the cellular transportome in oncogenesis and gastrointestinal inflammatory diseases. We will dissect the interactome of membrane proteins whose expression is known to be altered in inflamed tissue and 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 liver and gastrointestinal pathologies.
- 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

URTASUN N., VIDAL-PLA A., PÉREZ-TORRAS S., MAZO A.. Human pancreatic cancer stem cells are sensitive to dual inhibition of IGF-IR and ErbB receptors. BMC Cancer. 2015;15(1).

PASTOR-ANGLADA M., PÉREZ-TORRAS S.. Nucleoside transporter proteins as biomarkers of drug responsiveness and drug targets. Frontiers in Pharmacology. 2015;6(FEB).

CLAUDIO-MONTERO A., PINILLA-MACUA I., FERNÁNDEZ-CALOTTI P., SANCHO-MATEO C., LOSTAO M.P., COLOMER D. ET AL. Fluorescent nucleoside derivatives as a tool for the detection of concentrative nucleoside transporter activity using confocal microscopy and flow cytometry. Molecular Pharmaceutics. 2015;12(6):2158-2166.

ARIMANY-NARDI C., KOEPSELL H., PASTOR-ANGLADA M.. Role of SLC22A1 polymorphic variants in drug disposition, therapeutic responses, and drug-drug interactions. Pharmacogenomics Journal. 2015;15(6):473-487.

MINAMI K., SHINSATO Y., YAMAMOTO M., TAKAHASHI H., ZHANG S., NISHIZAWA Y. ET AL. Ribonucleotide reductase is an effective target to overcome gemcitabine resistance in gemcitabine-resistant pancreatic cancer cells with dual resistant factors. Journal of Pharmacological Sciences. 2015;127(3):319-325.

# Highlights

During 2015 we have been investigating some novel features of the pharmacology of pancreatic cancer treatment, focusing on the IGF-IR and ErbB receptors as stem cell targets, as well as on the nucleotide metabolism enzyme Ribonucleotide Reductase (RR) as a suitable target to overcome gemcitabine chemoresistance. We have also addressed from a critical point of view all available clinical studies focusing on the expression of Nucleoside Transporter (NT) proteins as probable biomarkers of drug responsiveness. During this year we have also consolidated the preclinical platform of cell clones stably expressing a broad set of drug transporters, including SLC22 family members, particularly SLC22A1 and its polymorphic variants showing the highest allelic frequency in humans. This panel of cell lines has proven suitable for drug-screening projects in collaboration with national pharma industry, under the framework of an Innpacto project funded by MINECO. We have also finished a collaborative study with scientists belonging to the Spanish cancer network (Retics) and organic chemists, aiming at obtaining novel fluorescent nucleoside analogs suitable for the functional study of NT proteins, both using confocal microscopy and flow cytometry. Within the framework of the current studies on the transportome and protein networks, and their role in oncogenesis and inflammation, we have organized a symposium on protein networks and disease, mostly funded by the Fundación Ramón Areces. This meeting gathered frontline international speakers and was advertised as a CIBEREHD activity in 2015.

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# G1088

Programme: **Inflammation & Gastrointestinal Motility**

Lead Researcher: **Pérez Gisbert, Javier**

## Group members

STAFF MEMBERS: Durán Vegue, Almudena | Marín Gómez, Alicia C. | McNicholl, Adrián Gerald | Muñoz Linares, Pablo | Rodríguez Perera, Eva María.

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 Biochemistry and Molecular Biology Department of Alcalá de Henares University, the Oncology Institute of Catalunya, the Galician Genomics Foundation, the National Center for Cardiovascular Research (CNIC) 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 / Characterization of circulating dendritic cells and monocytes and intestinal dendritic cells and macrophages in IBD patients with different affected tissues.

**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 / Characterization of circulating dendritic cell and monocyte subsets as novel biomarkers in IBD / Circulating antibodies against microbiota peptides as novel biomarkers 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*.

**Identification of new therapeutic targets in IBD (PSGL-1, MT1-MMP, IFG-1, ERß, CB1 and CB2).**

# Most relevant scientific articles

GISBERT J.P., MARIN A.C., MCNICHOLL A.G., CHAPARRO M.. Systematic review with meta-analysis: The efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed. Alimentary Pharmacology and Therapeutics. 2015;41(7):613-623.

MOLINA-INFANTE J., LUCENDO A.J., ANGUEIRA T., RODRÍGUEZ-TELLEZ M., PÉREZ-AISA A., BALBOA A. ET AL. Optimised empiric triple and concomitant therapy for Helicobacter pylori eradication in clinical practice: The OPTRICON study. Alimentary Pharmacology and Therapeutics. 2015;41(6):581-589.

GISBERT J.P., ROMANO M., GRAVINA A.G., SOLIS-MUNOZ P., BERMEJO F., MOLINA-INFANTE J. ET AL. Helicobacter pylori second-line rescue therapy with levofloxacin- and bismuth-containing quadruple therapy, after failure of standard triple or non-bismuth quadruple treatments. Alimentary Pharmacology and Therapeutics. 2015;41(8):768-775.

GISBERT J.P., MARIN A.C., CHAPARRO M.. Systematic review: factors associated with relapse of inflammatory bowel disease after discontinuation of anti-TNF therapy. Alimentary pharmacology & therapeutics. 2015;42(4):391-405.

ALONSO A., DOMENECH E., JULIA A., PANES J., GARCÍA-SÁNCHEZ V., MATEU P.N. ET AL. Identification of risk loci for crohn's disease phenotypes using a genome-wide association study. Gastroenterology. 2015;148(4):794-805.

# Highlights

The research group has continued its international expansion and networking throughout 2015:

With the European Helicobacter and Microbiota Study Group (EHMSG):

- Continue coordinating the "European Registry on the management of Helicobacter pylori infection" (Hp-EuREG): 300 researchers from 32 European countries with over 10,000 patients. / Coordinating the project "Effect of H. pylori eradication on the intestinal microbiota". / Coordinating the treatment working group from the European Helicobacter consensus (Maastrich V).

With the European Crohn´s and Colitis Organization (ECCO):

- Coordinating the European Project "long-term safety of anti-TNF therapy in pregnancy-exposed children" / Spanish coordinator of the research project "IBD, cancer and severe infections in Europe (I-CARE)". / Collaborating on the European consensus of anaemia in IBD.

The research group has also enhanced its collaborations with national and international institutions through different agreements, contracts and sponsorships to increase its visibility and improve its funding attracting capacity, highlighting:

- Increase of the GETECCU-CIBER agreement incorporating 2 new people to the scientific unit. / Coordination of the collaborative research online platform AEG-REDCap from the Spanish Society of Gastroenterology, which provides a free and useful online tool for the handling and management of multicentric research studies. / Starting the sponsorship of a research chair with Abvie-UAM for the study of IBD and obtaining the agreement to start a second one through the UAM. / Funds obtention from the EHMSG to coordinate the scientific research projects.

Last, but not least, the group has strengthen the basic and translational research laboratory incorporating a basic scientist who will coordinate the research laboratory starting with a grant on the study of "human intestinal dendritic cell compartmentalization in Crohn´s disease" funded by the "Convocatoria Retos Jóvenes Investigadores".

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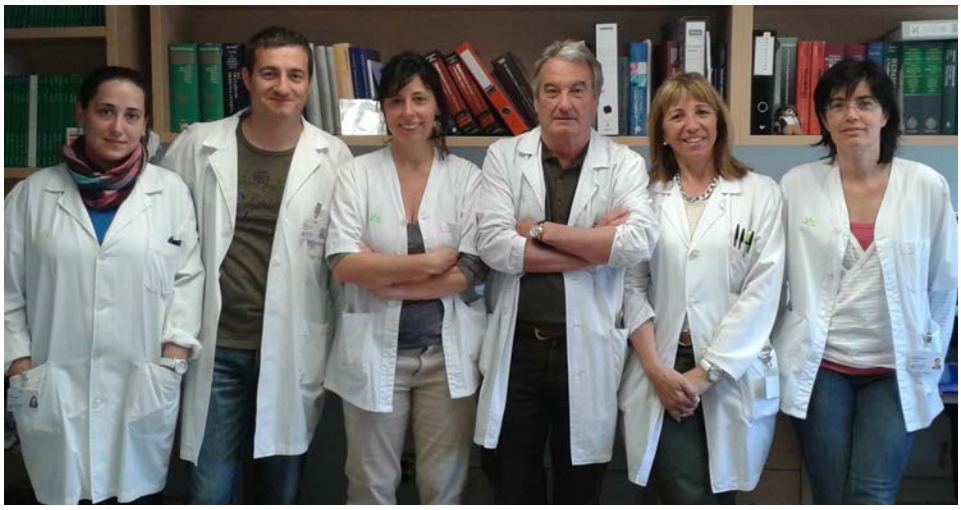
# G0033

Programme: **Portal Hypertension & Mechanisms of Transition to Cirrhosis**
Lead Researcher: **Planas Vilà, 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 Fornés, 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.
- Hepatoblastoma and hepatocellular cancer. Proteomic studies. Identification of diagnostic and prognostic markers.
- Innate immunity.

# Most relevant scientific articles

BUTI M., MORILLAS R.M., PÉREZ J., PRIETO M., SOLA R., PALAU A. ET AL. Entecavir has high efficacy and safety in white patients with chronic hepatitis B and comorbidities. European Journal of Gastroenterology and Hepatology. 2015;27(1):46-54.

CALLEJA J.L., PASCASIO J.M., RUIZ-ANTORAN B., GEA F., BARCENA R., LARRUBIA J.R. ET AL. Safety and efficacy of triple therapy with peginterferon, ribavirin and boceprevir within an early access programme in Spanish patients with hepatitis C genotype 1 with severe fibrosis: SVRw12 analysis. Liver International. 2015;35(1):90-100.

MORALES-IBANEZ O., AFFO S., RODRIGO-TORRES D., BLAYA D., MILLAN C., COLL M. ET AL. Kinase analysis in alcoholic hepatitis identifies p90RSK as a potential mediator of liver fibrogenesis. Gut. 2015.

SANJURJO L., AMEZAGA N., ARAN G., NARANJO-GÓMEZ M., ARIAS L., ARMENGOL C. ET AL. The human CD5L/AIM-CD36 axis: A novel autophagy inducer in macrophages that modulates inflammatory responses. Autophagy. 2015;11(3):487-502.

ESCORSELL À, PAVEL O, CÁRDENAS A, MORILLAS R, LLOP E, VILLANUEVA C ET AL. Esophageal balloon tamponade Vs esophageal stent in controlling acute refractory variceal bleeding: A multicenter RCT.Hepatology (Baltimore, Md.). 2015.

# Highlights

The group has maintained an intense activity during 2015 in several collaborative studies both portal hypertension and clinical encephalopathy and implementation studies of interferon-free therapies against HCV mono and co-infected patients, with 13 active trials. Also noteworthy is the consolidation of HEPACONTROL project (program improvement aftercare compensated cirrhotic patient care).

The line of innate immunity, with several ongoing studies and publications, presented its work in 4 international conferences and guest speakers. Funding this 2015 has been: Albert Renold Travel Fellowships EFSD / Lilly (8,000 €); Juan de la Cierva Training. MINECO. 50.000 € / 2 years; European Foundation for the Study of Diabetes ESFD. 2014-2017. € 400,000; Fundació Marató TV3. 2014-2017. € 190,000 and FIS PI13 / 1906. € 53,000. MR IP Sarrias.

The Childhood Liver Oncology group, led by Dr. C Armengol and integrated within our group, has secured funding (€ 964,206) by the European Commission (Horizon 2020) for the next five years (2016-2020 ) under the project "Children's Liver Tumour European Research Network (total funding: € 7,941,665). The group has established a collaboration with CIBER group led by Dra. Rocío Rodríguez Macías (U. Salamanca) and the company XenTECH (Evry). Finally, the findings of his investigation: a signature 3 protein that improves the clinical stratification of patients with hepatoblastoma, presented at the meeting Hepatinov (H. Paul Brousse) and the last congress ILCA (Paris).

The training activity has been important. We have organized two training courses for doctors in the area. In addition, the group has led five competitive projects.

Finally note that the group has participated in 15 publications, including 10 in international journals with total of 79.06 FI and filling a patent application.

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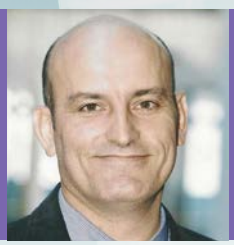
# G0047

Programme: **Viral Hepatitis**

Lead Researcher: **Romero Gómez, Manuel**



## Group members

STAFF MEMBERS: Gallego Durán, Rocío | Vilar Gómez, Eduardo.

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 | Rojas Álvarez-Ossorio, M. Ángeles | 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-PÉREZ 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-GÓMEZ 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-GÓMEZ 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-GÓMEZ 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.

**Institution:** Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla
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# G0044

Programme: **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

SALMERON J., VINAIXA C., BERENGUER R., PASCASIO J.M., RUANO J.J.S., SERRA M.A. ET AL. Effectiveness and safety of first-generation protease inhibitors in clinical practice: Hepatitis C virus patients with advanced fibrosis. World Journal of Gastroenterology. 2015;21(30):9163-9174.

QUER J., GREGORI J., RODRÍGUEZ-FRIAS F., BUTI M., MADEJON A., PÉREZ-DEL-PULGAR S. ET AL. High-resolution hepatitis C virus subtyping using NS5B deep sequencing and phylogeny, an alternative to current methods. Journal of Clinical Microbiology. 2015;53(1):219-226.

AMPUERO J., DEL CAMPO J.A., ROJAS L., GARCÍA-LOZANO R.J., BUTI M., SOLA R. ET AL. Fine-mapping butyrophilin family genes revealed several polymorphisms influencing viral genotype selection in hepatitis C infection. Genes and Immunity. 2015;16(5):297-300.

BUTI M., MORILLAS R.M., PÉREZ J., PRIETO M., SOLA R., PALAU A. ET AL. Entecavir has high efficacy and safety in white patients with chronic hepatitis B and comorbidities. European Journal of Gastroenterology and Hepatology. 2015;27(1):46-54.

ARTACHO-CORDON F., RIOS-ARRABAL S., OLIVARES-URBANO M.A., STORCH K., DICKREUTER E., MUNOZ-GAMEZ J.A. ET AL. Valproic acid modulates radiation-enhanced matrix metalloproteinase activity and invasion of breast cancer cells. International Journal of Radiation Biology. 2015.

# Highlights

In the year 2015, our research group has maintained active clinical and experimental projects related to our main line of research, "Viral Hepatitis in children and adults":

- Project Intrasalud PI10/00717 entitled "Estudio de la variabilidad genética del VHC y la respuesta inmune del hospedador en los pacientes tratados con interferón pegilado y ribavirina. Bases racionales para la obtención de una vacuna terapéutica"
- PI13/01925: Estudio de seguimiento de la transmisión vertical (TV) de los virus de la hepatitis C (VHC) y de la hepatitis B (VHB): análisis de factores implicados.
- GLD14-00292: Follow-up study of the vertical transmission (VT) of HCV and HBV: analysis of the risk factors involved.

The continuity of this line is guaranteed with a new project, GLD15-00307, "Validation study of biomarkers associated both with increased risk of mother-to-child HCV transmission and with increased risk of persistent HCV infection in children vertically transmitted". In addition, we have been granted two other projects: PI05152014, Junta de Andalucía, and PI1501361, FIS.

The collaborative research lines include the platform for the collection of data from patients with hepatitis B chronic (CIBERHEP), Hepatitis C (Hepa-C) national register and national register of Hepatocellular Carcinoma (HCC registration).

PATENTS: We have made a license agreement the supplier VIDIA HEALTH of patents:

1. P201530221: "Método de obtención de datos útiles para predecir o pronosticar la transmisión vertical del virus de la hepatitis C".
2. P201530222: "Método de obtención de datos útiles para predecir o pronosticar la cronificación de la hepatitis C y el aclaramiento del VHC".

In addition, 4 doctoral theses have been presented and the Official College of Medical of Granada has awarded us the prize "Juan Antonio García Torres" to the work entitled "Effectiveness and safety of first-generation protease inhibitors in clinical practice: HCV patients with advanced fibrosis".

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# G0042

Programme: **Inflammation & Gastrointestinal 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.
- Effect of corticoides con mucosal barrier function.
- 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

ALGIERI F., RODRÍGUEZ-NOGALES A., GARRIDO-MESA J., CAMUESCO D., VEZZA T., GARRIDO-MESA N. ET AL. Intestinal anti-inflammatory activity of calcium pyruvate in the TNBS model of rat colitis: Comparison with ethyl pyruvate. Biochemical Pharmacology. 2015.

UTRILLA M.P., PEINADO M.J., RUIZ R., RODRÍGUEZ-NOGALES A., ALGIERI F., RODRÍGUEZ-CABEZAS M.E. ET AL. Pea (Pisum sativum L.) seed albumin extracts show anti-inflammatory effect in the DSS model of mouse colitis. Molecular Nutrition and Food Research. 2015;59(4):807-819.

MASCARAQUE C., LÓPEZ-POSADAS R., MONTE M.J., ROMERO-CALVO I., DADDAOUA A., GONZÁLEZ M. ET AL. The small intestinal mucosa acts as a rutin reservoir to extend flavonoid anti-inflammatory activity in experimental ileitis and colitis. Journal of Functional Foods. 2015;13:117-125.

GÓMEZ-GUZMAN M., TORAL M., ROMERO M., JIMÉNEZ R., GALINDO P., SÁNCHEZ M. ET AL. Antihypertensive effects of probiotics Lactobacillus strains in spontaneously hypertensive rats. Molecular Nutrition and Food Research. 2015.

CAPITAN-CANADAS F., OCON B., ARANDA C.J., ANZOLA A., SUAREZ M.D., ZARZUELO A. ET AL. Fructooligosaccharides exert intestinal anti-inflammatory activity in the CD4+ CD62L+ T cell transfer model of colitis in C57BL/6J mice. European Journal of Nutrition. 2015.

# Highlights

The research activity of the group has resulted in 13 articles, some of them the stemming from partnerships with other CIBER groups, as well as with research groups of the Heracles network. It is noteworthy that most publications are framed in the first quartile, including 4 in the first decile.

We have published studies focusing on new intestinal anti-inflammatory effects of natural products , including pre- and probiotics , natural extracts and flavonoids, as well as other related studies. We have established the potential of the antibiotic doxycycline to work synergistically with S. boulardii and we have applied the lymphocyt transfer colitis model to investigate the therapeutic properties of natural products.

Our research work has been funded by several research projects, both public (MINECO, Junta de Andalucía) and private. In 2015 the group has been awarded two new national projects.

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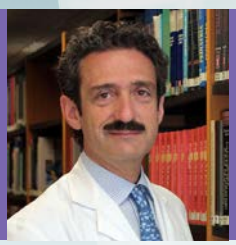
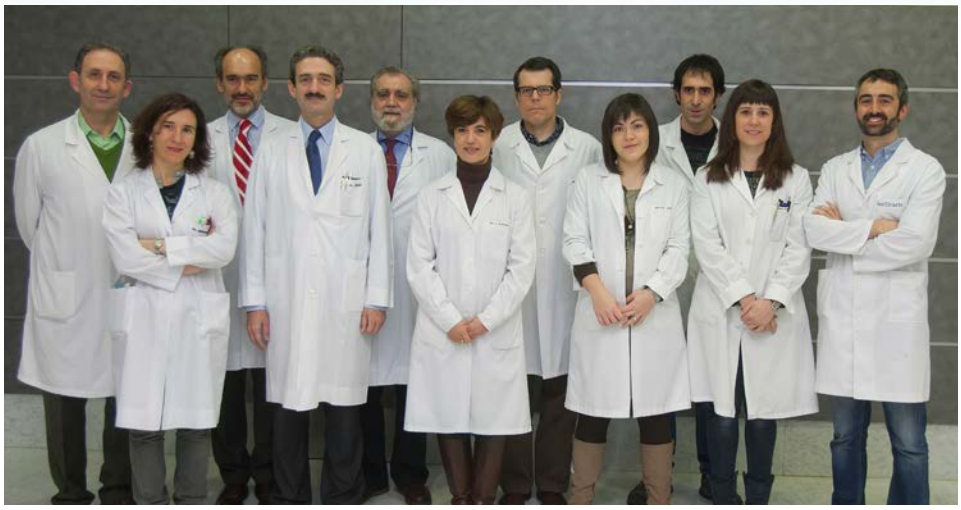
# G0006

Programme: **Hepatic & Gastrointestinal Oncology**

Lead Researcher: **Sangro Gómez-Acebo, Bruno Carlos**



## Group members



STAFF MEMBERS: Arcelus Echavarri, Sara | Barbero López, Roberto | D'avola, Delia | Santa María Monasterio, Eva | Uriarte Díaz Varela, Iker.

ASSOCIATED MEMBERS: Ávila Zaragoza, Matías Antonio | Berasain Lasarte, Carmen | Civeira Murillo, Mª Pilar | Concepción González, Axel Rolando | Corrales Izquierdo, Fernando José | Fontanellas Romas, Antonio | García Fernández de Barrena, Maite | García González, Javier Nicolás | Herrero Santos, José Ignacio | Iñarrairaegui Bastarrica, Mercedes | López Martínez, María | Quiroga Vila, Jorge | Rodríguez Ortigosa, Carlos Manuel | Sáez de Blas, Elena | Sarvide Plano, Sarai.

## 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

GARCÍA-IRIGOYEN O., LATASA M.U., CAROTTI S., URIARTE I., ELIZALDE M., URTASUN R. ET AL. Matrix Metalloproteinase 10 Contributes To Hepatocarcinogenesis in a Novel Crosstalk With the Stromal Derived Factor 1/C-X-C Chemokine Receptor 4 Axis. Hepatology. 2015;62(1):166-178.

PRIETO J., MELERO I., SANGRO B.. Immunological landscape and immunotherapy of hepatocellular carcinoma. Nature Reviews Gastroenterology and Hepatology. 2015;12(12):681-700.

JOHNSON PJ, BERHANE S, KAGEBAYASHI C, SATOMURA S, TENG M, REEVES HL ET AL. Assessment of Liver Function in Patients With Hepatocellular Carcinoma: A New Evidence-Based Approach-The ALBI Grade.Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015;33(6):550-8.

SERRANO-MENDIOROZ I., SAMPEDRO A., MORA M.I., MAULEON I., SEGURA V., ENRIQUEZ DE SALAMANCA R. ET AL. Vitamin D-binding protein as a biomarker of active disease in acute intermittent porphyria. Journal of Proteomics. 2015;127:377-385.

KOLLIGS F.T., BILBAO J.I., JAKOBS T., INARRAIRAEGUI M., NAGEL J.M., RODRÍGUEZ M. ET AL. Pilot randomized trial of selective internal radiation therapy vs. chemoembolization in unresectable hepatocellular carcinoma. Liver International. 2015;35(6):1715-1721.

# Highlights

In translational research we may highlight the progress made in different areas. In the field of the chronic liver disease associated with porphobilinogen deaminase enzyme deficiency characteristic of acute intermittent porphyria, we have identified a plasma marker of recurrent attacks of the disease. This marker corresponds to variable glycosylation forms of vitamin D binding protein, and could be developed as a diagnostic tool. We have made progress in the understanding of fundamental mechanisms of hepatocarcinogenesis, identifying a new role for metalloproteinase 10 in the neoplastic transformation of liver cells and the metastatic ability of hepatocellular carcinoma cells, and we have shown that fibroblast growth factor 15 (FGF15/19), derived from the intestinal tract, contributes to the neoplastic progression of the fibrotic liver. We have also identified the induction of mechanisms of liver regeneration after lobar radioembolisation, which may help exploiting this treatment as a method for surgical rescue. And finally, we have developed a radioembolisation model based on computational fluid dynamics that will help improve injection devices, catheters, etc.

Regarding clinical research, we have launched clinical trials exploring the effects of new immuno-oncology agents. In the field of locoregional treatment of hepatocellular carcinoma we have reported the results of the first randomized clinical trial comparing chemoembolization and radioembolization, which shows comparable results for both primary and secondary objectives. We have also contributed to develop a system of objective estimation of hepatic functional reserve (ALBI grade) in patients with hepatocellular carcinoma, which can replace the Child-Pugh classification due to better performance and objectivity. Finally, with regard to liver transplantation we have further characterized the effects of immunosuppression on two key factors in the long-term survival of patients, such as cardiovascular risk and impaired renal function.

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# Linked Research Groups

## VIRAL HEPATITIS RESEARCH PROGRAMME

• **José Luis Calleja Panero** (Universidad de Alcalá, Madrid).

## CHOLESTASIS AND METABOLIC DISORDERS RESEARCH PROGRAMME

• **Llorenç Caballería Rovira** (Universitat Autònoma de Barcelona).

• **Carmelo García Monzón** (Servicio Madrileño de Salud, Madrid).

## IMMUNOLOGY, CELL THERAPY AND LIVER TRANSPLANTATION RESEARCH PROGRAMME

• **Alfredo Minguela Puras** (Fundación para la Formación e Investigación Sanitarias de la Región de Murcia).

## HEPATIC AND GASTROINTESTINAL ONCOLOGY RESEARCH PROGRAMME

• **Francisco Javier Padillo Ruiz** (Fund. Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla).

## GASTROINTESTINAL INFLAMMATION AND MOTILITY RESEARCH PROGRAMME

• **Ana Belén Beltrán Niclós** (Fundación para la Investigación del Hospital la Fe, Valencia).

• **María Esteve Comas** (Fundación privada Institut de Recerca Biomèdica, Barcelona).

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