# EHD

# Annual Report 2016

ciberehd

Centro de Investigación Biomédica en Red
Enfermedades Hepáticas y Digestivas

# Index

**Jordi Bruix**, Scientific Director

# Scientific Director's Presentation

In 2016 a high level of scientific activity was maintained with a large number of publications in journals with great impact. This vouches for the consolidation of CIBEREHD as a powerful research structure which has been capable of overcoming budget difficulties and limitations for taking on new staff.

The annual report sets forth the most relevant results of the different programmes on which the CIBEREHD is structured and speaks for the gradual increase in cooperative studies with international impact. This feature can be seen in all the programmes in which both nationwide network research and successful internationalisation can be found in many projects. International cooperation is often led by CIBEREHD researchers, which speaks for the recognition attained.

Research has been relevant in basic aspects, but particularly in translation to patients affected by hepatic and digestive diseases. In this respect, it should be pointed out that in several fields clinical practice guides have been generated based on scientific evidence and on consensus documents in which the criteria and method that have to be implemented 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 projects at the same time as providing teaching activities in order for trainee researchers to gain the knowledge required for their work.

The renovation of the Scientific Management as well as of the Management Committee has led to designing an action plan for the next 4 years and at the same time to analysing the vital need to come to terms with a generation renovation. It has been decided to incorporate new research groups in complementary aspects and during 2017 the evaluation of the possible candidates must be carried out.

One relevant aspect that has been displayed is the need to move towards a gender balance on all levels and to identify young researchers with ambitions leaning towards scientific careers in order to ensure that the research culture in Biomedicine is maintained.

# 2

# Organisation

# Organisational Structure

CIBEREHD is one of the thematic areas forming the Centro de Investigación Biomédica en Red (CIBER), a Spanish research consortium in the field of biomedical research with great scientific capacity, under the Instituto de Salud Carlos III (ISCIII) – Ministry of the Economy and Competitiveness. In 2016 it was made up of 8 thematic areas, which were extended to 11 in 2017.

It is made up of 43 research groups, belonging to institutions of many different kinds: university hospitals, universities, Public Research Organizations (OPI), such as the Instituto de Salud Carlos III (ISCIII) itself and the Consejo Superior de Investigaciones Científicas (CSIC), and research centres of Spain's regional autonomous communities.

CIBEREHD has a large team of human resources consisting of over 500 people, including a sizeable staff of its own researchers and members of groups as personnel associated to the CIBEREHD. This extensive team is made up of basic and clinical biomedical researchers, research technicians and management staff.

As a thematic area of the CIBER, the CIBEREHD belongs to this public consortium and is thus governed by a Governing Body and a Permanent Committee (its governing and management bodies) in which the institutions in the consortium take part. The organisational structure is made up of the Scientific Management, under Dr Jordi Bruix, which along with the Management Committee coordinates the work done by the 4 Scientific Programmes into which CIBEREHD groups are split. The CIBER Technical Unit provides the administrative support required for the Institution to run.

## Steering Committee Members

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

| Name | Post |
|---|---|
| Jordi Bruix Tudó | Scientific Director |
| Joan Caballería Rovira | Traning Programme Coordinator |
| Rafael Bañares Cañizares | Liver damage mechanisms/evolution into advanced cirrhosis and transplants Coordinator |
| Pere Clavé Civit | Gastrointestinal physiopathology: inflammatory disease and motility disorders Coordinator |
| Xavier Forns Bernhardt | Epidemiology, prevention and treatment of hepatitis virus infection Coordinator |
| Bruno Sangro Gómez-Acebo | Hepatic and Digestive Oncology Coordinator |
| Manuel Sánchez Delgado | Manager |
| Mª Luz Martínez-Chantar | Transfer Coordinator |

Scientific Management Assistant: Clara Esteva

## External Advisory Scientific Committee

The External Advisory Scientific Committee is a body for scientific assessment and support, made up of relevant personalities in the field of health sciences who are well-known for their professional or scientific careers in line with the objectives of the centre. This is the body which carries out the annual appraisal of the work done by CIBEREHD and its research groups.

| Name | Post |
|---|---|
| Guadalupe García-Tsao | President. University of Yale |
| Michael Trauner | Member. University of Vienna |
| Alberto Sánchez-Fueyo | Member. King's College, UCL, London |
| Massimo Colombo | Member. University of Milan |
| Jan Tack | Member. University of Leuven |

## Technical Unit

See list of personnel: http://www.ciberehd.org/en/about-us/structure/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 (FIMABIS) | Hospital Virgen de la Victoria | Malaga |
| Armengol Niell, Carolina | Fundación Instituto de Investigación Germans Trias i Pujol | Hospital Germans Trias i Pujol | Barcelona |
| Azpiroz Vidaur, Fernando | Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR) | Hospital Vall d'Hebron | Barcelona |
| Bañares Cañizares, Rafael | Servicio Madrileño de Salud | Hospital Gregorio Marañón | Madrid |
| Berenguer Haym, Marina | Fundación para la Investigación del Hospital la Fe | Hospital Universitario de la Fe | Valencia |
| Bosch Genover, Jaume | Hospital Clínico y Provincial de Barcelona | Hospital Clínico y Provincial de Barcelona | Barcelona |
| Bruix Tudó, Jordi | Hospital Clínico y Provincial de Barcelona | Hospital Clínico y Provincial de Barcelona | Barcelona |
| Bujanda Fernández de Pierola, Luis | Asociación Instituto Biodonostia | Hospital Donostia | Guipúzcoa |
| Cabré Gelada, Eduard | Fundación Instituto de Investigación Germans Trias i Pujol | Hospital Germans Trias i Pujol | Barcelona |
| Calvet Calvo, Xavier | Corporación Sanitaria Parc Taulí | Corporacion Sanitaria Parc Taulí | Barcelona |
| Castell Ripoll, José Vicente | Fundación para la Investigación del Hospital la Fe | Hospital Universitario de la Fe | Valencia |
| Castells Garangou, Antoni | Hospital Clínico y Provincial de Barcelona | Hospital Clínico y Provincial de Barcelona | Barcelona |
| Clavé Civit, Pere | Fundación Privada Salud del Consorcio Sanitario del Maresme | Fundacion Privada Salud del Consorcio Sanitario del Maresme | Barcelona |
| Esplugues Mota, Juan Vicente | Universidad de Valencia | Facultad de Medicina de Valencia | Valencia |
| Esteban Mur, Juan Ignacio | Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR) | Hospital Vall d'Hebron | Barcelona |
| Esteban Mur, Rafael | Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR) | Hospital Vall d'Hebron | Barcelona |

| Group Leader | Institution | Centre | Prov. Centre |
|---|---|---|---|
| Fernández-Checa Torres, José Carlos | Agencia Estatal Consejo Superior de Investigaciones Científicas | Instituto de Investigaciones Biomédicas de Barcelona | Barcelona |
| Forns Bernhardt, Xavier | Hospital Clínico y Provincial de Barcelona | Hospital Clínico y Provincial de Barcelona | Barcelona |
| Francés Guarinos, Rubén | Fundación para la Investigación Sanitaria y Biomédica de la Comunidad Valenciana (FISABIO) | 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 | Universidad 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 (VHIR) | Hospital Vall d'Hebron | Barcelona |
| Gines Gibert, Pere | Hospital Clínico y Provincial de Barcelona | Hospital Clínico y Provincial de Barcelona | Barcelona |
| 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 Leon | Leon |
| Guarner Aguilar, Carlos | Instituto de Investigación del Hospital de la Santa Cruz y San Pablo | Instituto de Investigación del Hospital de la Santa Cruz y San Pablo | Barcelona |
| Lanas Arbeloa, Ángel | Instituto Aragonés de Ciencias de la Salud | Hospital Clínico Universitario Lozano Blesa | Zaragoza |
| Martín Sanz, Paloma | Agencia Estatal Consejo Superior de Investigaciones Científicas | Instituto de Investigaciones Biomedicas Alberto Sols | Madrid |
| Mata García, Manuel de la | Fundación para la Investigación Biomédica de Córdoba (FIBICO) | Hospital Universitario Reina Sofia | Córdoba |
| Mato de la Paz, José María | CIC BIOGUNE | Cic BioGUNE | Vizcaya |
| Navasa Anadon, Miquel Ángel | Hospital Clínico y Provincial de Barcelona | Hospital Clínico y Provincial de Barcelona | Barcelona |
| Panes Díaz, Julián | Hospital Clínico y Provincial de Barcelona | Hospital Clínico y Provincial de Barcelona | Barcelona |
| Parés Darnaculleta, Albert | Hospital Clínico y Provincial de Barcelona | Hospital Clínico y Provincial de Barcelona | Barcelona |
| Parrilla Paricio, Pascual | Fundación para la Formacion e Investigación Sanitarias de la Región de Murcia (FFIS) | Hospital Universitario Virgen de la Arrixaca | Murcia |
| Pastor Anglada, Marçal | Universidad de Barcelona | Facultad de Biología. Universidad de Barcelona | Barcelona |
| Pérez Gisbert, Javier | Servicio Madrileño de Salud | Hospital Universitario La Princesa | Madrid |
| Romero Gómez, Manuel | Fundación Pública Andaluza para la 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 (FIBAO) | 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 | | | | | |
|---|---|---|---|---|---|
| ISCIII TRANSFER | GRANTS PROJECTS | SERVICES RENDERED | OTHER INCOME | CARRYOVERS | TOTAL |
| 3.653.580,00 | 369.506,45 | 33.387,33 | 226.768,97 | 85.788,96 | 4.369.031,71 |

| EXPENDITURE | | | | |
|---|---|---|---|---|
| Project | Inventoriable | Provisions and other activity expenses | Personnel | TOTAL |
| Management, Scientific Secretariat, Communication | 0,00 | 82.383,09 | 37.967,78 | 120.350,87 |
| Groups | 149.449,42 | 168.322,32 | 2.759.758,36 | 3.077.530,13 |
| Training | 0,00 | 23.053,38 | 0,00 | 23.053,38 |
| Platform | 1.121,67 | 40.577,87 | 100.112,37 | 141.811,94 |
| Transfer | 0,00 | 14.215,57 | 0,00 | 14.215,57 |
| Intramural projects | 0,00 | 90.350,92 | 0,00 | 90.350,92 |
| External projects | 4.915,74 | 426.327,56 | 470.475,45 | 901.718,90 |
| **TOTAL** | **155.486,83** | **845.230,71** | **3.368.313,96** | **4.369.031,71** |

# Personnel

Personnel taken on during the year as of 31 December, classified by categories:

| | MEN | WOMEN | Total general |
|---|---|---|---|
| Diploma holders | 1 | 8 | 9 |
| Doctors | 16 | 23 | 39 |
| Graduates | 18 | 43 | 61 |
| Technical staff | 4 | 13 | 17 |
| **TOTAL** | **39** | **87** | **126** |

# Significant Activities

## Projects

### NATIONAL

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

Understanding obesity (Ob), metabolic syndrome (MetS), type 2 diabetes (T2DM) and fatty liver disease (FL): a multidisciplinary approach (PIE14/00031).

Implementation of a tool based on ultra-sequencing for determining sub-genotypes of hepatitis C virus: optimisation of the treatment (PI14/01349).

Virological and immunological factors connected with anti-viral treatment and recurrence of hepatitis C after liver transplantation (PI13/00155).

Characterisation of microRNAs in pancreas cancer: from new biomarkers to therapeutic targets (PI13/02192).

Implication of activity of the extracellular matrix in the appearance of evolutionary complications in Crohn's disease and in the development of new therapeutic proposals (PI12/0621).

Prospective clinical assessment of the genetic-immune/ inflammatory profile in the treatment of hepatocellular carcinoma with sorafenib to predict tolerance and survival. (PI15/00145).

Safety and clinical efficacy of intralesional administration of dendritic cells in patients with refractory Crohn's disease.

Impact on the treatment of new antiviral agents in the natural history of cirrhosis by the hepatitis c virus. Identification of the factors predicting no response. Part A: Impact of the treatment with the new direct-acting antiviral agents on the natural history of advanced chronic liver disease (cirrhosis) and pathogenic mechanisms.

Impact on the treatment of new antiviral agents in the natural history of cirrhosis by the hepatitis c virus. Identification of the factors predicting no response. Part B: optimisation of the direct antiviral treatment of chronic Hepatitis C in clinical practice and identification of the factors associated with the lack of response.

State sub-programme on training contracts Río Hortega granted by the ISCIII (CM15/00050). Safety and clinical efficacy of intralesional administration of tolerogenic dendritic cells in patients with refractory Crohn's disease (PI13/01585).

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

Development of a kit for early diagnosis of colorectal cancer – Detection in plasma (miRNAs) (RTC-2015-3850-1).

**Other financing agencies:**

Fundació la Marató on TV3 television station: "Anàlisi per biología de sistemes de la tolerància immunitària en trasplantament d'òrgans." (122130/31/32).

AECC project

## Transfer

One of the CIBER's main aims is the transfer of the knowledge generated by its researchers, so that its research results can be developed in protocols, services and products for improving clinical practice and people's quality of life. To this end the CIBER Technology Transfer department acts as a liaison between our researchers and companies, private institutions, public research centres and other innovation agents to make cooperation with them more effective and ensure that the results of research are actually applied. Work is done in several lines in order to achieve this aim:

- Continuous contact with our researchers to monitor their results and train them in management of innovation.

In this respect, on 29 and 30 November 2016 a Technology Transfer Session was arranged as part of the 30th anniversary of ISCIII. Experts in different areas shared their knowledge on industrial property, company creation, licencing processes, venture capital, grants for internationalisation, etc. at this event.

- Protection of the results of research and management of cooperation with other agents, as displayed by the application for patents and signing licence contracts, amongst other agreements.
  Hence, in 2016 eleven new patent applications and a registration of software were submitted at the CIBER. Seven inventions are also in the patentability study and one in the drafting stage, and these are expected to be submitted in early 2017.
- Apart from this, eight licence contracts have been signed. In 2016 furthermore, different negotiations that are expected to end successfully in the first quarter of 2017 were also got under way.
  In the EHD area four applications for priority patents were registered in 2016 and work began on drawing up a patent report which will be submitted in early 2017. A patent licence contract has also been signed as well as an agreement for valorisation of a technology in this field.
- The presentation of the results of research and technological capacities of our groups in technology transfer sessions. Amongst many other measures, and merely as an example of this, CIBER had a stand with institutional presence at BIOSPAIN 2016 (28-30 September, Bilbao).
- Support for technology-based company creation stemming from CIBER groups.
- Other activities connected with innovation, public-private cooperation and industrial and intellectual property

## Dissemination

In 2016 the CIBER'S Communication Department carried out different measures for dissemination and disclosure in order to raise awareness about the Centre, as well as to spread knowledge about the research work done by the groups in its eight thematic areas.
The main highlights of the Communication work done by CIBEREHD in 2016 are as follows.

- **The CIBEREHD in the media:**
  67 CIBER press releases were issued in this period, 3 of these from CIBEREHD and one in cooperation between several CIBER areas.

| Date | Thematic area | Holder |
|---|---|---|
| 10/03/2016 | CIBEREHD | Presentan un consenso para mejorar el tratamiento de la bacteria 'Helicobacter pylori', que afecta a la mitad de la población española |
| 30/06/2016 | CIBEREHD | Se publica el consenso para optimizar el tratamiento de la bacteria 'Helicobacter pylori', que afecta a la mitad de la población española |
| 16/11/2016 | VARIOS CIBER | El CIBER acerca su investigación a la sociedad de la mano de la improvisación teatral en #ImproCiencia |
| 07/12/2016 | CIBEREHD | The Lancet publica los resultados positivos de un fármaco en cáncer de hígado cuando otras alternativas fallan |

270 appearances in the media were also recorded:

| 2016 | News items | Audience |
|---|---|---|
| CIBEREHD | 270 | 22.060.300 |

- **CIBER Newsletter**
  This year 5 CIBER newsletters were published and disseminated, including relevant content about the CIBEREHD and other thematic areas. The digital newsletters were sent to around 4000 subscribers. http://www.ciberisciii.es/en/press/newsletter

- **CIBEREHD Newsletter**
  In 2016 the CIBEREHD newsletter was started up as a new tool for communication about this area. Every month, the newsletter contains an interview of a researcher and gives the news on the CIBEREHD for that period http://www.ciberehd.org/en/press/ciberehd-newsletter At present the newsletters are sent via e-mail to all the members of the area.

- **CIBEREHD Web page**
  55 news items and 38 events on the agenda were published on the CIBEREHD web page in 2016.

| Statistics on visits on the web page 2016 | | | | | | | |
|---|---|---|---|---|---|---|---|
| | No. of visits to page | Sessions* | Users | Pages / session | Average duration of session | % rebound** | % new sessions |
| CIBEREHD | 44.874 | 18.004 | 12.703 | 2,49 | 1:51 | 68,95 | 69,52 |

(*) Sessions: a session is a set of interactions taking place on this website in a certain period. For example, a single session may involve several pages being viewed.
(**) Rebound: the rebound percentage is the percentage of sessions of a single page, i.e. the sessions in which the user has left the site on the entry page without interacting with this.

- **Social Networks**
  Main indicators of CIBEREHD presence on Twitter:

| | Followers | | Updates | | Klout (Influence) | |
|---|---|---|---|---|---|---|
| | January | December | January | December | January | December |
| CIBEREHD | 394 | 603 | 337 | 511 | 42 | 43 |

- **CIBEREHD Annual Report**
  The CIBER Communication area, in cooperation with the CIBEREHD, coordinated the content of the CIBEREHD Report 2015 in Spanish/English, drawing up and disseminating 2 reports in interactive (flipbook) format and pdf. These reports have been distributed over the web page and through the Twitter account: http://www.ciberisciii.es/en/press/annual-report

- **CIBER Science Week #ImproCiencia**
  The #ImproCiencia dissemination event, held on 16 November in Madrid, combined science and theatre improvisation to give a light-hearted explanation of the biomedical research work done by the CIBER in its eight thematic areas. CIBEREHD presented the Project on detection in the blood of the risk of undergoing pancreas cancer, coordinated by researcher Meritxell Gironella.

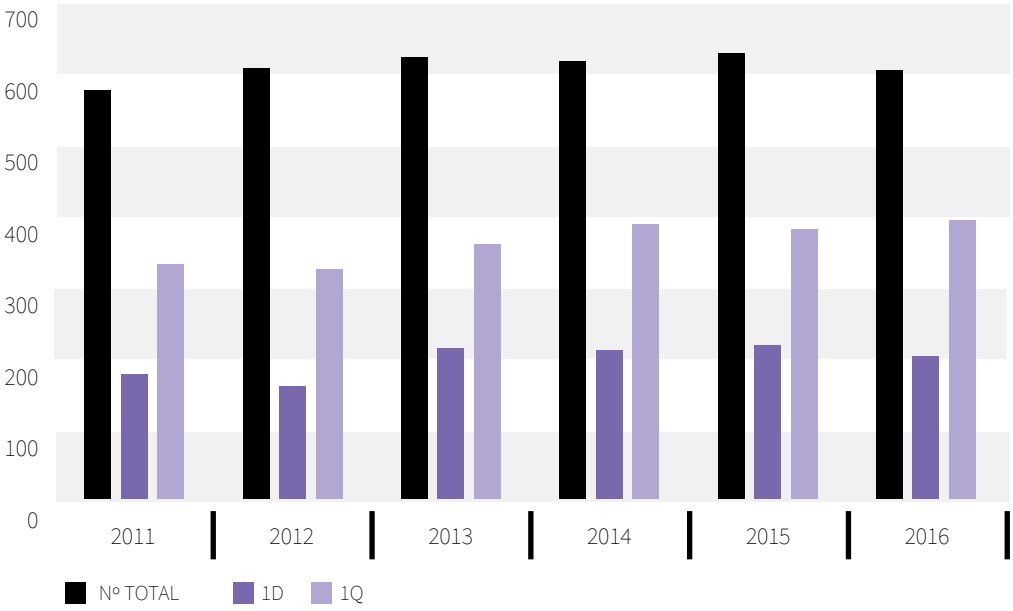
- **CIBEREHD Scientific Sessions**
  The Hotel Barceló Sants in Barcelona was the venue for the X Jornadas Científicas del CIBEREHD on 24 and 25 October. As a new aspect brought in this year, this involved the possibility of the research groups presenting their work in poster form, and prizes were given to the best four.

# Scientific Production

The evolution undergone by CIBEREHD publications can be seen from the following tables, in which the data from 2010 to 2016 is analysed. The publications per group for this year are also itemised, as well as the interCIBER and intraCIBER cooperation work.

| Publications per year | | | | | | |
|---|---|---|---|---|---|---|
| CIBEREHD | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 |
| Total numbers | 579 | 611 | 626 | 621 | 632 | 607 |
| 1D | 176 | 160 | 213 | 210 | 218 | 202 |
| 1Q | 332 | 325 | 361 | 389 | 382 | 395 |

EVOLUTION OF CIBEREHD PUBLICATIONS 2011-2016




# Most relevant publications of the CIBEREHD during 2016 according to their Impact Factor

| Publication | Impact Factor |
|---|---|
| Bonaccorsi-Riani E., Pennycuick A., Londono M.-C., Lozano J.-J., Benitez C., Sawitzki B. et al. Molecular Characterization of Acute Cellular Rejection Occurring during Intentional Immunosuppression Withdrawal in Liver Transplantation. American Journal of Transplantation. 2016;16(2):484-496. | 5,669 |
| Fernandez-Calotti P., Casulleras O., Antolin M., Guarner F., Pastor-Anglada M. Galectin-4 interacts with the drug transporter human concentrative nucleoside transporter 3 to regulate its function. FASEB Journal. 2016;30(2):544-554. | 5,299 |
| 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. 2016. | 14,921 |
| Manns M., Samuel D., Gane E.J., Mutimer D., McCaughan G., Buti M. et al. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial. The Lancet Infectious Diseases. 2016;16(6):685-697. | 21,372 |
| Blaya D., Coll M., Rodrigo-Torres D., Vila-Casadesus M., Altamirano J., Llopis M. et al. Integrative microRNA profiling in alcoholic hepatitis reveals a role for microRNA-182 in liver injury and inflammation. Gut. 2016. | 14,921 |
| Urtasun R., Elizalde M., Azkona M., Latasa M.U., Garcia-Irigoyen O., Uriarte I. et al. Splicing regulator SLU7 preserves survival of hepatocellular carcinoma cells and other solid tumors via oncogenic miR-17-92 cluster expression. Oncogene. 2016;35(36):4719-4729. | 7,932 |
| Carballal S., Rodriguez-Alcalde D., Moreira L., Hernandez L., Rodriguez L., Rodriguez-Moranta F. et al. Colorectal cancer risk factors in patients with serrated polyposis syndrome: A large multicentre study. Gut. 2016. | 14,921 |
| Reig M., Marino Z., Perello C., Inarrairaegui M., Ribeiro A., Lens S. et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. Journal of Hepatology. 2016;65(4):719-726. | 10,59 |
| Gisbert J.P., Marin A.C., Chaparro M. The risk of relapse after Anti-TNF discontinuation in inflammatory bowel disease: Systematic review and meta-analysis. American Journal of Gastroenterology. 2016;111(5):632-647. | 10,383 |
| Panes J., Garcia-Olmo D., Van Assche G., Colombel J.F., Reinisch W., Baumgart D.C. et al. Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: A phase 3 randomised, double-blind controlled trial. The Lancet. 2016. | 44,002 |

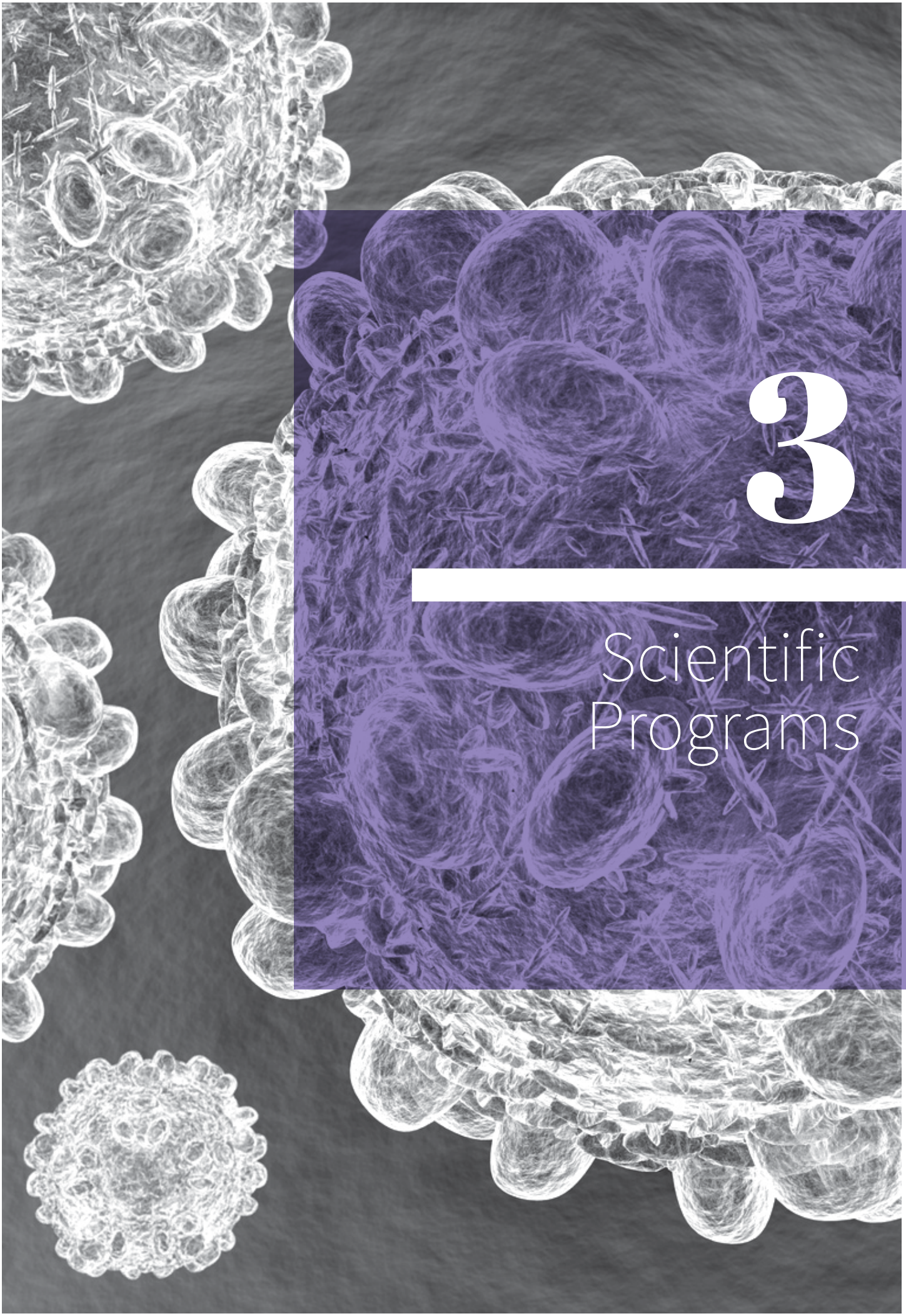
# Nº. of publications per group 2016

| Group Leader | Total Publications | Q1 | D1 |
|---|---|---|---|
| Albillos Martínez, Agustín | 11 | 11 | 8 |
| Andrade, Raúl | 19 | 9 | 4 |
| Armengol Niell, Carolina | 12 | 7 | 5 |
| Azpiroz Vidaur, Fernando | 26 | 12 | 4 |
| Bañares Cañizares, Rafael | 13 | 11 | 6 |
| Berenguer Haym, Marina | 18 | 12 | 10 |
| Bosch Genover, Jaume | 31 | 27 | 21 |
| Bruix Tudó, Jordi | 27 | 21 | 18 |
| Bujanda Fernández de Pierola, Luis | 34 | 23 | 15 |
| Cabré Gelada, Eduard | 24 | 13 | 4 |
| Calvet Calvo, Xavier | 25 | 10 | 3 |
| Castell Ripoll, José Vicente | 11 | 10 | 4 |
| Castells Garangou, Antoni | 42 | 31 | 20 |
| Clavé Cívit, Pere | 26 | 8 | 3 |
| Esplugues Mota, Juan Vicente | 11 | 11 | 2 |
| Esteban Mur, Juan Ignacio | 21 | 13 | 6 |
| Esteban Mur, Rafael | 21 | 12 | 7 |
| Fernández-Checa Torres, José Carlos | 11 | 8 | 4 |
| Forns Bernhardt, Xavier | 27 | 21 | 15 |
| Francés Guarinos, Rubén | 14 | 9 | 5 |
| García Buey, Luisa | 4 | 1 | 0 |
| García Marín, José Juan | 11 | 8 | 3 |
| García-Samaniego Rey, Javier | 3 | 1 | 0 |
| Genesca Ferrer, Joan | 24 | 18 | 12 |
| Gines Gibert, Pere | 33 | 25 | 15 |
| Gómez Castilla, Jordi | 10 | 7 | 0 |
| González Gallego, Javier | 8 | 6 | 3 |
| Guarner Aguilar, Carlos | 14 | 11 | 7 |
| Guarner Aguilar, Francisco | 8 | 6 | 3 |
| Lanas Arbeloa, Ángel | 39 | 25 | 16 |
| Martín Sanz, Paloma | 3 | 3 | 1 |

| Group Leader | Total Publications | Q1 | D1 |
|---|---|---|---|
| Mata García, Manuel de la | 17 | 12 | 6 |
| Mato de la Paz, José María | 18 | 16 | 7 |
| Navasa Anadon, Miquel Ángel | 28 | 15 | 11 |
| Panes Díaz, Julián | 29 | 26 | 14 |
| Pares Darnaculleta, Albert | 7 | 5 | 2 |
| Parrilla Paricio, Pascual | 14 | 9 | 6 |
| Pastor Anglada, Marçal | 10 | 10 | 2 |
| Pérez Gisbert, Javier | 55 | 29 | 17 |
| Romero Gómez, Manuel | 19 | 14 | 8 |
| Salmerón Escobar, Francisco Javier | 6 | 3 | 0 |
| Sánchez de Medina López Huertas, Fermín | 18 | 16 | 7 |
| Sangro Gómez-Acebo, Bruno Carlos | 33 | 25 | 14 |

## COLLABORATIVE WORK

| Collaborative work | 2015 | 2016 |
|---|---|---|
| IntraCIBER publications | 150 | 174 |
| InterCIBER publications | 61 | 45 |



# 3

# Scientific Programs

# Liver Damage Mechanisms/Evolution into Advanced Cirrhosis and Transplant

Coordinator: **Rafael Bañares Cañizares**

In 2016 the scientific work done in programme 1 was implemented in the framework of the CIBEREHD's strategic orientation in its different spheres.

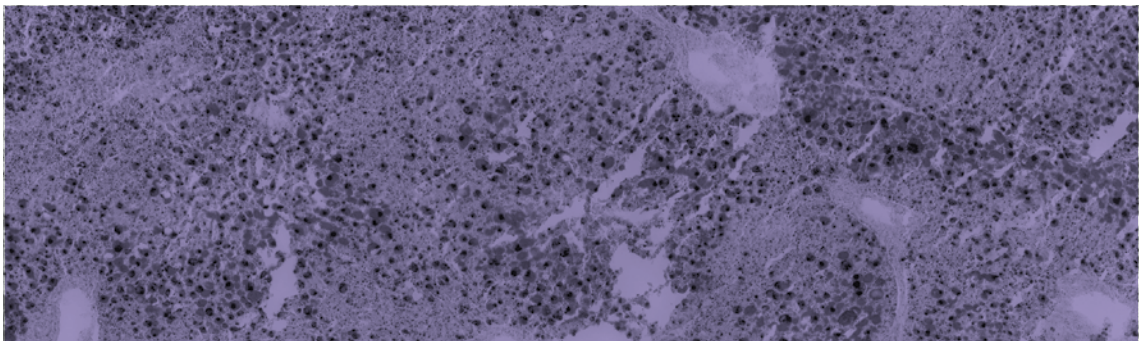
First of all, from the standpoint of the internationalisation of its research work, cooperation with groups from other countries has been consolidated in the setting of different multicentre studies in the field of liver transplantation (tolerance of the implant after transplantation), of acutely decompensated liver disease (new devices for artificial liver support) as well as in international networks of immune-mediated liver diseases, amongst others. In the same approach of recruiting research resources, all the groups in the programme have been able to maintain their own lines for project financing and recruiting human resources in competitive calls, which has meant that the critical research mass of the programme could be maintained. Likewise, the groups in the programme have transferred a good deal of their research work to the technology sector, stressing for example the participation in programmes for developing nanomedicines based on peptides of the major histocompatibility complex; considerable progress has also been made in the transfer of inventions such as the development of microfluidic chambers enabling simulating the physiological setting of the human liver endothelium exploring the paracrine relations between the different cell types involved.

From the standpoint of the necessary development of cooperative research different strategic actions financed by the CIBER itself have been carried out with the intention of making the groups' joint activity more dynamic, especially that of the basic groups, whose tradition in this respect usually has a lower profile. In this respect they have proceeded to develop a mouse model with humanised liver, whose application to the research lines of different groups in the programme has great potential scope.

A cooperative research line is also being developed covered by another strategic action intended to determine the role of exosomes in a wide range of experimental models of acute and chronic liver diseases.

One important aspect now characteristic of the programme is physiopathological research from the dual, clinical and laboratory angle. Progress has thus been made in knowledge of the close relationship between the intestinal barrier and its regulation with inflammatory and immune-mediated mechanisms of advanced liver disease.

From the viewpoint of Clinical research cooperative projects have been maintained and reinforced, including progress in the applicability of non-invasive diagnostic strategies in chronic liver disease, consolidation of the role of statins in treatment of advanced liver disease or extension of knowledge of the action mechanisms of beta blocker medications in early stages of the disease. The overall results of the programme have been noteworthy from the standpoint of scientific production with a large number of publications in the first decile of the speciality and different clinical practice guides being drafted as a final expression of the capacity for translation of the wide range of research done by the programme to the patient.



# Gastrointestinal Physiopathology: Inflammatory Disease and Motility Disorders

Coordinator: **Pere Clavé Civit**

The work for 2016 in programme 2 was done in the 3 Major Research Sub-programmes in this programme and in a new transversal strategic action intended to promote cooperative research also between basic researchers in all the groups and to encourage its translation. The major active research sub-programmes are: 1) Oesophageal-gastroduodenal pathology; 2) Inflammatory bowel disease and 3) Gastrointestinal motility disorders and Neuro-gastroenterology; and the transversal action "Developing collaborative networks for basic research with human tissue". From a quantitative angle, scientific production involved in the three major sub-programmes was highly intense; from the qualitative standpoint, the strategic transversal action has enabled us to reinforce the cooperative structure between basic researchers of all the groups in the programme, and to reproduce in basic research the CIBEREHD success model of cooperative research.

In the oesophageal-gastroduodenal sub-programme we should stress the translation of several epidemiological, diagnostic and therapeutic studies on gastrointestinal diseases associated with Helicobacter pylori, which has enabled holding the IV Conferencia de Consenso estatal en el Tratamiento de la Infección por HP, which affects roughly 50% of the Spanish population, and the Toronto Consensus on the treatment of the infection in adults. The studies characterising gastrointestinal risk of the use of NSAIDS and the adaptation of the recommendations for use of PPI should also be highlighted, as studies with an extremely high potential for translation to clinical practice.

The Inflammatory bowel sub-programme has continued with the development of a project for cell therapy and autologous transplantation of hematopoietic progenitor cells for treatment of refractory Crohn's disease and development of mesenchymal stem cells for treatment of fistulising perianal disease. On the physiopathological side we should emphasise: a) studies on the relevance of the macrophagic phenotype in human and murine colitis and the role of autophagy in the intestinal epithelial cell; b) the importance of the microbiota in the intestinal inflammatory response, in its dual aspect of source of immunological stimulation and regulation of epithelial dynamics; and c) by means of studies based on using organoids it has been shown that there are permanent changes in the epithelium of patients with ulcerous colitis, which are conditioned by disorders in the conduct of intestinal stem cells and which could contribute to perpetuating the disease. The groups have also provided significant contributions to improving clinical practice by taking part in writing the clinical guide of the European Crohn's and Colitis Organization on the use of biosimilar medications.

The work done in 2016 in the sub-programme on motility disorders and neurogastroenterology including the development of a sensorial neuromodulation protocol for treatment of oropharyngeal dysphagia after strokes; the development and validation by means of a pilot study of "Minimum-Massive Interventions" enabling reducing readmissions through respiratory nutritional complication in the elderly with dysphagia at General Hospitals, We have contributed to the development of two systematic reviews establishing clinical guides for handling Dysphagia after two years of interaction between two European scientific associations (ESSD/EUGMS), and which recognise oropharyngeal dysphagia as a geriatric syndrome and establish the bases for the treatment. Groups in the programme have contributed to the development of Rome IV Criteria for diagnosis of functional digestive disorders. Lastly, the implementation of the Strategic Action entitled Networks for Basic Research with Human Tissue in the Area 2 of the Ciberehd has enabled three young CIBER researchers to lead and develop a network of 18 cooperative projects in basic research of the programme.

# Epidemiology, Prevention and Treatment of Hepatitis Virus Infection

Coordinator: **Xavier Forns Bernhardt**

In 2016, programme 3 has made some significant progress in different fields. It is important to stress that some of the headway was made in the framework of the Strategic Plan for Hepatitis, including cooperation with groups belonging to other programmes.

The data registered in HEPA-C (a joint CIBER-AEEH register) has meant that data on the efficacy and safety of large real-life cohorts could be compiled. The efficacy results are excellent and highly similar to the ones reported in the register tests published on the combinations of medications (both for the set of patients and for the ones with liver cirrhosis). As well as the elimination of the virus, another of the aims of the treatment is to prevent or reduce the incidence of decompensations. In a study that included over 200 patients with clinically significant portal hypertension and cirrhosis it was observed that after PVR the hepatic vein pressure dropped from 15.8. to 13.5 mmHg (average change -2.3 mm Hg), with a considerable percentage of patients reaching a portal pressure gradient under 10 mm Hg (and thus clear of any risk of decompensation).

In cooperation with the hepatic oncology programme, it has been observed that treatment with DAA in patients with hepatocellular carcinoma (CHC) in remission could be associated with a higher CHC recurrence rate. This finding has generated a great deal of controversy and further multi-centre studies have been got under way to go more deeply into this area.

Another of the aspects on which work has been done in 2016 is the subtyping of samples of patients of the HEPA-C cohort, in which over 35 centres in Spain have cooperated. They also proceeded to standardise in-depth sequencing to detect resistant mutants in regions NS3, NS5A and NS5B. In fact, 165 samples from patients with virological failure in different patterns,. have been processed: In respect of the diagnostic use of high-resolution Hepatitis C virus subtyping by massive-sequencing, the exploitation of European patent (EU PATENT No. WO2015001068 A1) has been consolidated, which will entail royalties for the CIBER.

In the field of epidemiology, an analysis has been made of the hepatitis B and C chronification rates in children of infected pregnant mothers, to analyse the factors involved in this and evaluate whether there are biomarkers which could identify the mothers at greatest risk of vertical transmission.

As aspects of translational research, we should stress: 1- the study of the induction in the expression of Angiopoyetin-2 in the liver of patients with hepatitis C, and its correlation with the state of the illness and the capacity of different genomic regions of the HCV; 2- the study of the polymorphisms of Aurora Kinase B activity in the progression of hepatic fibrosis in patients with chronic hepatitis C. 3- validation of the system for analysis of RNA-HCV at points of care, 4- the study of the role of favipiravir for potential treatment of hepatitis C, taking advantage of its effect on the viral quasispecies (lethal mutagenesis).

In the area of hepatitis B it is worthwhile mentioning a study of cohorts which included over 600 patients treated with entecavir and tenofovir and who were monitored for over 5 years to assess the effect of treatment on clinical events.

# Hepatic and Digestive Oncology

Coordinator: **Bruno Sangro Gómez-Acebo**

In 2016 the groups kept up their excellence activity in both clinical and translational research. In the field of hepatocellular carcinoma, studies have been published investigating the usefulness of liver transplantation for prevention of post-resection recurrence, the laparoscopic approach in liver donation for transplantation from live donors, options of adjuvant therapy for treatment with chemoembolisation, characterisation of computational models of intra-arterial administration of particles, utility of radioembolisation in subgroups of patients in advanced stages, and genomic hepatic characterisation with possible targets for preventive or therapeutic interventions. It is important to stress that an alarm signal of oncogenic risk associated with treatment of hepatitis C has been identified in the context of studies undertaken in the National Hepatitis Plan. In cholangiocarcinoma, the possible utility of liver transplantation for very early-stage tumours has been published or the characterisation of the change in tumour microenvironment during cholangiocarcinogenesis. The results of therapeutic interventions on rare liver diseases such as fibropolycystic liver diseases or acute intermittent porphyria have been made known, including advanced gene and cell therapy strategies, and a genetic alteration has been identified which could explain some case of hypertransaminasemia of unknown origin. In the context of colorectal cancer the EPoS project has been got under way, a multi-centre, international, controlled and randomised study intended to establish the best strategy for monitoring patients who develop high and low-risk adenomas, as well as serrated lesions. The results obtained in projects stemming from the ColonPreve project have been published, including the identification of the characteristics of endoscopists which may have an influence on the quality of endoscopy, or the assessment of the potential aid for electronic alerts in the clinical history of Primary Care for improving adhesion to screening programmes. Progress is being made in the development and validation of biomarkers of early diagnosis of colorectal cancer (EPICOLON project). Results of the research into mechanisms of resistance to chemotherapy in gastric cancer have been published as well as an analysis of the impact of the transportome in the response of gastrointestinal cancer to chemotherapy.

As regards the transfer of results, the Guides for Diagnosis and Treatment of Hepatocellular Carcinoma have been published, included in the portfolio of services of the Ministry of Health, Consumption and Equality; an international consensus document has been published on Cholangiocarcinoma and the risk stratification criteria proposed by the European Colorectal Cancer Screening Guide have been reassessed. A new method of diagnosis for pancreas cancer has been patented, and different scientific meetings have been arranged to disclose the knowledge generated. One of these deserving mention through its innovative quality is the "*I International Congress of Cholangiocarcinoma*". The development of the European Network for the Study of Cholangiocarcinoma (www.enscca.org), now grouping 30 European groups and 7 North American ones, has been led, and we are taking part in the first international GWAS study on this disease.

# 4

# Transversal Programmes

# Training Programme

One of the objectives of the CIBEREHD is to promote the training of our researchers, (associated and contracted staff: postdoctoral, predoctoral, nurses and technical staff) to increase the level of research and facilitate the 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 on Liver and Digestive Diseases is implemented in the following actions:

- Training stays at CIBEREHD centres
- Short training stays in Spain or abroad (maximum 8 weeks and exceptionally up to 3 months)
- Visiting intramural teachers programmes
- Carrying out training courses or activities considered of interest for the CIBEREHD
- Promoting scientific activities organised by members of the CIBEREHD (sponsoring and financing seminars, symposia, courses for postgraduates) cooperation with training activities of scientific associations and virtual training activities through the web page.

In 2016, a total number of 44 grants for our researchers were assigned for different activities according to the Training Plan Programme. The beneficiaries of the aid were 19 attached members and 25 contracted staff. The activities financed were 2 short stays abroad (London-England and Ghent-Belgium), 1 national (CIMA, Pamplona), 3 stays in groups CIBEREHD, 27 training courses and activities in Spain and 7 courses abroad.

Some of these activities that we would like to stress are the training stays at CIBEREHD Centres: Sergi Vila (Dr Bosch's group) at the group of Dr Albillos (Madrid), Sergi Guixé (Dr Bosch's group) in Dr Mato's group (Vizcaya) with Dr Juan Manuel Falcón and Dr Mª Dolores Ortiz (Dr Esplugues' group) at Dr Pérez-Gisbert's group (Madrid).

We have also cofinanced the following four courses arranged by members of this centre:

- *Spring SIOPEL Meeting, Barcelona from 21 to 23 April 2016, organised by Dr Carolina Armengol.*
- *XIV Congreso Nacional de Virología, Cadiz from 11 to 14 June 2017, organised by Dr Josep Quer Silva.*
- *XV Jornadas de Avances en Hepatología, Malaga on 20-21 May 2016, organised by Raúl J. Andrade.*
- *Workshop entitled "Translating colorectal cancer research", Porto on 9-10 February 2017, arranged by Dr Sergi Castellví-Bel*

Through the training plan the CIBEREHD furthermore sponsored the Postgraduate Course of the Asociación Española para el Estudio del Hígado (AEEH) which took place during the celebration of the 42 Congreso Anual de la AEEH and of the Asociación Española de Gastroenterología (AEG).

# Strategic Actions

Three Strategic Actions were granted in 2016:

## *FRG mice with humanized liver to study human liver diseases and drug-induced liver injury.*

Principal Investigator: **JC Fernández-Checa**

GROUPS PARTICIPATING:

- Raúl Andrade Group
- Carmelo García Monzón Group
- Pere Gines Group (PIs, Joan Claria and Pau Sancho Bru)
- Xavi Forns Group

## *Use of human tissue in translational gastroenterology research.*

Principal Investigator: **P Clavé**

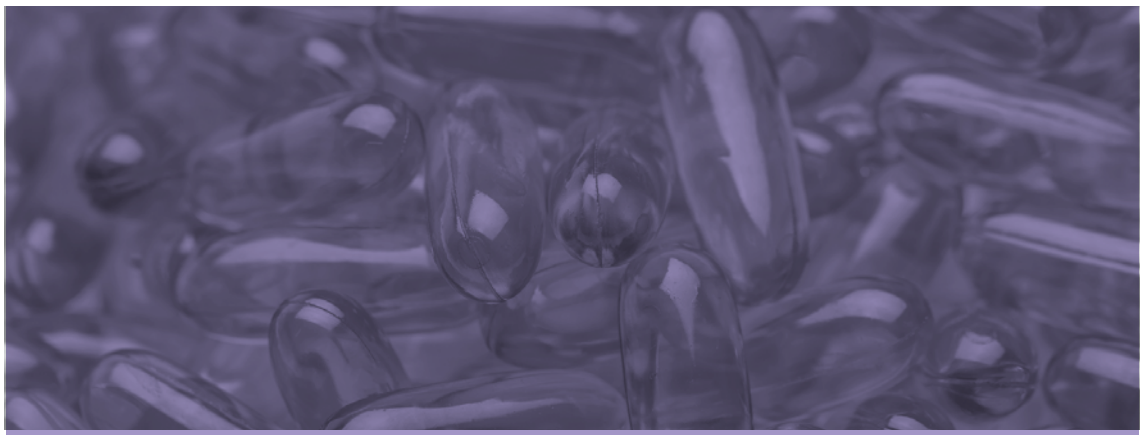
COORDINATORS: M. Vicario (H. Vall d'Hebron), R. Farré (KU Leuven), D. Álvarez-Berdugo (H. Mataró)

GROUPS PARTICIPATING: J. Manyé (IGTP, Badalona), D. Bernardo (H. La Princesa, Madrid), A. Salas (H. Clínic, Barcelona), S. Lario (Parc Taulí, Sabadell), E. Piazuelo (H. Clínico, Zaragoza), F. Sánchez de Medina (Granada), D. Barrachina (U. Valencia), A. Carrasco (M. Terrassa).

## Study of cell communication via exosomes in liver disease.

GROUPS PARTICIPATING:

- G0017 – Dr Juan Manuel Falcón-Pérez (JM Mato Group). Implementer of sub-project 1.
- G0082 – Dr Javier Vaquero (R Bañares) Group. Head of sub-project 2.
- G0026 – Dr Jordi Gracia-Sancho (J Bosch Group). Head of implementation of sub-projects 3 and 4.
- G0024 – Dr Agustín Albillos. Head of translational aspect of this proposal and of implementation of sub-project 5.




Test
Hepatitis
HBsAg (cobas)
Anti-HBs (cobas)
Anti-HBc (cobas)
HIV

# 5

# Platforms

# Biobank: Biobanc Clínic and Collection of Steatotic Livers

## Biobank of the Hospital Clinic de Barcelona (Biobanc Clinic)

The CIBEREHD has set up a platform which collects, stores and distributes biological samples connected with digestive diseases, and supported by the infrastructure of the IDIBAPS Biobank.

The work done by the CIBEREHD Biobank Platform includes two types of collections: gastrointestinal and pancreatic oncology (OGP) and inflammatory intestinal diseases (IID). The samples are deposited at the HCB-IDIBAPS Biobank.

GASTROINTESTINAL AND PANCREATIC ONCOLOGY (OGP). The Biobank has samples of plasma, serum, DNA and peripheral blood mononuclear cells (PBMC) from the following donors:

- Colorectal cancer: 283 donors.
- Patient with intermediate risk of colorectal cancer: 6296 donors.
- Patient or relative with high risk of colorectal cancer (polyposic or non-polyposic syndrome): 760 donors.
- Patient or relative with a moderate risk of colorectal cancer (familial colorectal cancer): 65 donors.
- Pancreas cancer: 7 donors.
- Intraductal papillary mucinous tumour or mucinous cystic tumour: 22 donors.
- Chronic pancreatitis: 25 donors.
- Gastric cancer: 10 donors.

904 new donors were received only from the Hospital Clínico de Barcelona in 2016 and work has been done on improving the circuit for management of the samples in order to speed up their processing, as well as registration of the consents covering the samples.

Similarly, a total number of 1142 different aliquots were assigned in the following projects:

- Tackling key aspects in the virotherapy of cancer with adenovirus: arrival of systemic viruses in tumours, replication, dissemination and immunity. Cristina Fillat, assignment of 51 serums.
- Designing and adjusting kits for diagnosis of colon cancer in the blood based on multiplex platforms (COLONTEST Project). Antoni Castells, assignment of 233 plasmas.
- Identification of new biomarkers for prevention of colorectal cancer. Antoni Castells, assignment of 528 serums.
- Metabolomics-based detection of early stage cancers. Antoni Castells and UniversalDx, assignment of 330 serums.

INFLAMMATORY INTESTINAL DISEASES (IID). The Biobank mainly has samples of DNA (in some cases, also plasma and PBMC) from the following donors:

- Crohn's disease: 2086 donors.
- Ulcerous colitis: 1643 donors.
- Indeterminate colitis: 29 donors.
- Lymphocytic colitis: 67 donors.
- Collagenous colitis: 77 donors.

In this period 347 new donors were received, 186 of whom (53.6%) are Catalonia health centres other than the Hospital Clínic de Barcelona, and 89 of whom (25.6%) are from health centres outside Catalonia.

A great effort has also been made to improve the management of collection of IID along with the Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa (GETECCU). This effort has resulted in drafting an agreement for establishing the IID bank, an improvement in the coordination of the shipments of samples collected nationwide, as well as proper administration of the information associated with the

samples (exhaustive review of the diagnoses of donors and of the informed covering the samples).

Samples of DNA have similarly been requested for the project entitled 'Identification of new genetic variants associated with myelotoxicity from thiopurines in patients with IID and normal thiopurine S-methyltransferase: study of the full genome association' (principal investigator: Javier Pérez Gisbert). This application is currently still under way.

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

La Fe Biobank is an authorised and consolidated service in the Hospital and the Instituto de Investigación Sanitaria. It was authorised in 2013 according to Royal Decree 1716/2011, of 18 November, by means of which the basic operating requirements of biobanks for purposes of biomedical research are established.

In 2016, La Fe Biobank received 4955 donations of the collections that it has open until now, specifically 52 under the biobank system, having a stock of almost 90,000 samples available for research, 3000 samples having been used in 2016. As of this date, the collection has 175 livers characterised and managed according to normative and quality criteria and several research groups have displayed interest, through the Plataforma Nacional de Biobancos. The Biobank has developed an internal programme of molecular characterisation of samples kept and is carrying out quality studies of these samples.

This Platform certified its Quality Management System (QMS) in January 2016, in line with the standards of ISO 9001:2008 and acquired a management software for its transition to ISO 9001:2015 Standard. In keeping with this philosophy. La Fe Biobank is implementing an Information Security Management System to ISO 27001 standard and working on the use of specific sample coding for registration of pre-analytical variables, the SPREC code.

La Fe Biobank forms part of the "Biobank Platform (PT13/0010/0026. AES-2013)" cooperating in four currently active programmes/work lines: "Programme of collections with strategic value", "Management of Network Services", "R+D+i  Programmes (Management Technologies and Quality Control Programmes)" and "Training".

# Bioinformatics

The Bioinformatics platform is actively cooperating in the operation of this CIBER, as shown by the 17 publications resulting from its support in 2016. Special mention should be given to the contribution made in the areas of colon cancer, specifically 4 high-impact articles in close cooperation with the group led by Dr Antoni Castells (G0016) in consortiums with (3) national and (1) international institutions. Two important publications resulting from bioinformatic analyses by massive sequencing are:

- *The Fanconi anemia DNA damage repair pathway in the spotlight for germline predisposition to colorectal cancer.* Esteban-Jurado C, Franch-Expósito S, Muñoz J, Ocaña T, Carballal S, López-Cerón M, Cuatrecasas M, Vila-Casadesús M, Lozano JJ, Serra E, Beltran S, Brea-Fernández A, Ruiz-Ponte C, Castells A, Bujanda L, Garre P, Caldés T, Cubiella J, Balaguer F, Castellví-Bel S.Eur J Hum Genet. 2016 Oct;24(10):1501-5. doi: 10.1038/ejhg.2016.44. Epub 2016 May 11.
- *MicroRNAs for Detection of Pancreatic Neoplasia: Biomarker Discovery by Next-generation Sequencing and Validation in 2 Independent Cohorts.* Vila-Navarro E, Vila-Casadesús M, Moreira L, Duran-Sanchon S, Sinha R, Ginés À, Fernández-Esparrach G, Miquel R, Cuatrecasas M, Castells A, Lozano JJ, Gironella M. Ann Surg. 2016.May 26. [Epub ahead of print].

It should be stressed that a project with Dr Francesc Balaguer as Principal Investigator, forming the platform as research team, under the title of Analysis of the field defect mediated by aberrant DNA methylation in the serrated polyposis syndrome, will be financed by the Instituto de Salud Carlos III in the next three yearly periods.

In the area of alcoholic hepatitis research our platform has cooperated with Dr Pau Sancho's research team for discovery of a major microRNA biomarker involved.

- *Integrative microRNA profiling in alcoholic hepatitis reveals a role for microRNA-182 in liver injury and inflammation.* Blaya D, Coll M, Rodrigo-Torres D, Vila-Casadesús M, Altamirano J, Llopis M, Graupera I, Perea L, Aguilar-Bravo B, Díaz A, Banales JM, Clària J, Lozano JJ, Bataller R, Caballería J, Ginès P, Sancho-Bru P. Gut. 2016 Sep;65(9):1535-45.

The same area has managed to discover a new marker (KRT23) of alcoholic hepatitis after an international cooperation scheme led by Dr Ramón Bataller.

- *LPS-TLR4 Pathway Mediates Ductular Cell Expansion in Alcoholic Hepatitis.* Odena G, Chen J, Lozano JJ, Altamirano J, Rodrigo-Torres D, Affo S, Morales-Ibanez O, Matsushita H, Zou J, Dumitru R, Caballeria J, Gines P, Arroyo V, You M, Rautou PE, Valla D, Crews F, Seki E, Sancho-Bru P, Bataller R.Sci Rep. 2016 Oct 18;6:35610.

In the area of hepatic haemodynamics cooperation work has been carried out, with publication in two first quartile journals. Firstly, a diagnostic tool for idiopathic portal hypertension and also describing the role of simvastatin drug in a model of biliary cirrhosis.

It should lastly be pointed out that our platform has cooperated by offering services to groups not belonging to the CIBEREHD (Dr Antonio Alcaraz) which have resulted in several publications in the first quartile. On an internal level our small group has developed and published a new bioinformatic tool (MIRComb) to study interactions between the microRNA and its target genes.

- *MiRComb: An R Package to Analyse miRNA-mRNA Interactions. Examples across Five Digestive Cancers.* Vila-Casadesús M, Gironella M, Lozano JJ.PLoS One. 2016 Mar 11;11(3):e0151127.

# CIBERHEP.
# Chronic Hepatitis B Platform

The CIBERHEP chronic hepatitis B platform is a cooperation scheme between the CIBER and the Asociación Española para el Estudio del Hígado (AEEH). This is currently the main database for patients being treated for chronic hepatitis B in Spain: in 2016 the data for 1427 patients monitored at 29 centres in 9 different autonomous communities was recorded.

In 2016, the studies performed from this data focussed above all on safety and effectiveness in front-line therapeutic options against the hepatitis B virus, entecavir (ETV) and tenofovir (TDF), and on the progression to hepatocellular carcinoma (HCC) of the patients undergoing treatment with these antiviral agents. In this respect the cases in which HCC was developed during antiviral treatment were analysed to compare these with the ones predicted by

the PAGE-B score, for prediction of the development of HCC in Caucasian patients treated with ETV and TDF. The aim of this study was to validate this system of scoring in the Spanish population of chronic hepatitis B patients in antiviral treatment. The results of the study were presented as an oral paper at the 41 Congreso Anual de la AEEH (Madrid, 17-19 February 2016) and as a poster at the 51 Annual Congress of the European Association for the Study of the Liver (EASL) (Barcelona, 13–17 April 2016).This study was later extended with the analyses of the efficacy and renal safety of ETV and TDF in this cohort of patients for the validation of the PAGE-B score. The final results of the article were accepted for publication in the Digestive Diseases and Sciences journal [Riveiro- Barciela, M., Tabernero, D., Calleja, J.L. et al. Dig Dis Sci (2017). doi:10.1007/s10620-017-4448-7].

The renal level safety of ETV and TDF was also studied in patients with chronic hepatitis B over 65 years of age in routine clinical practice. The results of this study were presented as a poster at the 67 Annual Congress of the American Association for the Study of Liver Diseases (AASLD) (Boston, USA, 11-15 November 2016).

Lastly, the updating of the database and its associated web page were completed, thus extending the data collected to carry out more exhaustive studies on the monitoring of patients in antiviral treatment with ETV and TDF, especially focussing on their safety and side-effects, at the same time as recording this data.

# CIC bioGUNE.
# Plataform for Genomics, Proteomics, Metabolomics and Gene Silencing

## Genomics Platform

In 2016 the genome analysis platform carried out 77 characterisation services with a total number of 5786 samples for the description of their genotyping, transcriptomics, epigenomics or metagenomics. The platform also took part in 1 public tender for services, which meant a total sum invoiced of 70,000.00€.

As technological progress, the platform completed the adjustment of massive sequencing protocols with Oxford Nanopore Technologies (The MinION) technology.

Over this period. 4 articles were published in journals of international impact on research carried out in cooperation projects, and in June 2016, they published a book entitled “Field Guidelines for Experimental Genetic Designs in High-Throughput Sequencing”, as editors and authors of one of its chapters (8000 purchases of its chapters reissued in its first 7 months).

## Proteomics Platform

In 2016 the proteomics platform provided service for and cooperated with different CIBEREHD groups (Hospital Princesa, H. Clinic, ITGP, BioDonostia and CIC bioGUNE). Four articles were published in scientific journals with international impact. In cooperation with Dr J Bañales (BioDonostia), results were obtained in the preparation of exosomes extracted from the blood of patients with cholangiocarcinoma. In its line of implementing what is known as the "liquid biopsy" along with Dr María Chaparro and Dr Javier Gisbert (H. Princesa) markers were identified in exosomes taken from blood in Crohn's and inflammatory bowel diseases. By the detection and identification of endogenous peptides in urine by means of nLC MS/MS) cirrhotic patients with compromised kidney function were analysed (Dr Ginés, H. Cliníc). Finally in a piece of work led by Dr Martinez-Chantar an analysis was made of the mitochondrial respiratory supercomplexes chain formed after treatment with acetaminophen by means of nLC MS/MS.

## Metabolomics platform

The platform performed 20 services for research groups and pharmaceutical companies interested in quantifying the levels of metabolites of the methionine cycle and derivatives in the liver (Alonso C et al *Gastroenterology*). The biological matrices for determining this panel of metabolites in adipose tissue were also extended. The methodology for carrying out fluxomics studies in cells and in livers was developed. The measurements of metabolism of cholesterol have been incorporated in the platform's capacities, as well as NAPQI-GSH metabolites associated with liver toxicity. Apart from this, methods for specific and sensitive determination of MAT and COMT enzyme activities in samples of liver and serum have been developed and applied, and some of the results obtained form part of the publication *Frontiers in Pharmacology*, 2016.

## Metabolomics Platform (NMR)

The NMR metabolomics analysis of samples of serum has enabled establishing a protocol for separation between stages 1 and 4 of hepatic fibrosis (PLoS ONE) and (*Current Topics in Medicinal Chemistry*).

The current state of the platform's different projects is detailed below:

- **Determination of "metabolic health" in adults**. Monitoring normal and pathological profiles of a significant portion of the population of the CAV (Basque Community, as study region). 20000 samples were analysed over the 2016-2017 period.
- **Determination of biomarkers of the metabolic syndrome.** To this end samples of urine in patients with metabolic syndrome and with cardiovascular risk were analysed. A statistical multi-and univariate analysis of the profiles will be made. For this purpose a set of 3000 properly annotated samples, provided by the Universitat de València, is available.
- **Identification of congenital pathologies in the new-born baby.** In cooperation with the four hospitals with neonatology units of the CAPV the use of NMR for analysing urine of new-born babies was examined (500 samples) in order to detect any metabolic evidence resulting from a number of congenital diseases.

# e-CATCH Platform. Diagnosis and Treatment of Liver Cancer

The e-catch platform has the mission of offering diagnostic and therapeutic guidance services for patients with liver cancer by means of remote consultation. The possibility of evaluating both opinions and imaging technique enables reviewing the information available by the doctors consulted on a reliable basis, and offering guidance grounded on scientific evidence. In 2016 a contract was established with Bayer pharmaceutical company which financed the telemedicine activity.

In 2016 over 40 consultations were made over the platform and its review started in order to offer the consultation services internationally and thus ensure the sustainability of the platform.

Apart from the consultation services the platform has enabled transporting tomography or resonance images in order to validate the results of multicentre studies and thus ensure the validity of readings of images by independent radiologists.

# Hepa-C. National Database for Patients with Chronic Hepatitis C

Hepa-C is a cooperation project launched by the Asociación Española para el Estudio del Hígado (AEEH) in cooperation with the CIBEREHD. With the aims stipulated for 2016 as a guide, it has gone on with scientific production, making a significant contribution to this stage of consolidating knowledge about treatment of hepatitis C.

## Papers at congresses

- Poster presentation (AEEH 2016): *results of the efficacy of combining sofosbuvir y simeprevir with or without ribavirin in patients with genotype 1 and 4 hepatic cirrhosis in Spain.*
- Oral paper (AEEH 2016): *results of interferon-free antiviral therapy in patients with cirrhosis by virus c treated on the waiting list for liver transplants. Impact on exclusion from the list through improvement and post-transplant evolution.*
- Oral paper (AEEH 2016): *effectiveness and safety of treatment with sofosbuvir/ledipasvir, with/ without ribavirin in patients monoinfected with chronic hepatitis by hcv in real clinical practice.*
- Poster presentation (AEEH 2016): *effectiveness and safety of ombitasvir/paritaprevir/ritonavir with or without dasabuvir ribavirin in patients with genotype 1 and 4 hepatic cirrhosis. Results of the early access programme.*
- Oral paper (AEEH 2016): *efficacy and safety in clinical practice of the oral antiviral treatment in kidney transplant patients with hepatitis c: experience of liver registry.*
- Oral paper (AEEH 2016): *effectiveness and safety of treatment with direct-acting antiviral agents (daa) free of ifn, in patients with advanced kidney failure in real clinical practice.*
- Oral paper (AEEH 2016): *interferon-free treatment of c virus in patients with advanced cirrhosis: is this always justified? an analysis of the Hepa-C registry.*
- Poster presentation (AEEH 2016): *can we continue after kidney transplantation with virus c treatment started on the waiting list? (series of cases of Hepa-C).*

- Poster presentation (AEEH 2016): *results of efficacy and safety of combinations of direct-acting antivirals in patients with genotype 3 hepatitis c: Hepa-C cohort.*
- Poster presentation (and short oral paper in the "club joven AEEH" seminar 2016): *efficacy and safety of combinations of direct-acting antivirals in elderly patients: Hepa-C registry.*
- Oral paper (prize for "best clinical abstract" EASL 2016): *treatment of hepatitis c virus in patients with advanced cirrhosis: always justified? analysis of the Hepa-C registry.*
- Poster presentation (EASL 2016): *effectiveness and safety of sofosbuvir/ledipasvir treatment for monoinfected genotype 1 hcv patients in real-life clinical practice: results from Spanish Hepa-C cohort.*
- Poster presentation (EASL 2016): *effectiveness and safety of ombitasvir, paritaprevir, ritonavir and dasabuvir patients with genotype 1 chronic hepatitis c virus infection: results from the Spanish real-world cohort.*
- Poster presentation (EASL 2016): *can we continue after liver transplantation with hcv treatment started on list? (Hepa-C registry case series).*
- Poster presentation (EASL 2016): *efficacy and tolerability of interferon-free antiviral therapy in kidney transplant (kt) recipients with chronic hepatitis c: real-life data from the Spanish national registry (Hepa-C).*
- Poster presentation (EASL 2016): *safety and efficacy of sofosbuvir plus simeprevir in a Spanish cohort of 622 cirrhotic patients infected with genotypes 1 or 4.*

## Articles in scientific journals

- Carrillo CF, Crespo G, de la Revilla J, Castells L, Buti M, Montero JL, Fábrega E, Fernández I, Serrano-Millán C, Hernández V, Calleja JL, Londoño MC. *Successful continuation of HCV treatment following liver transplantation*. Transplantation. 2016 Dec 1.
- Alonso S, Riveiro-Barciela M, Fernandez I, Rincón D, Real Y, Llerena S, Gea F, Olveira A, Fernandez-Carrillo C, Polo B, Carrión JA, Gómez A, Devesa MJ, Baliellas C, Castro Á, Ampuero J, Granados R, Pascasio JM, Rubín A, Salmeron J, Badia E, Planas JM, Lens S, Turnes J, Montero JL, Buti M, Esteban R, Fernández-Rodríguez CM. *Effectiveness and safety of sofosbuvir-based regimens plus an NS5A inhibitor for patients with HCV genotype 3 infection and cirrhosis. Results of a multicenter real-life cohort*. J Viral Hepat. 2016 Dec 9.
- Three manuscripts were sent off in 2016 and accepted for early 2017, which will be included among the achievements for 2017.

## Others

- We have continued increasing the sample and promoting participation. There are at present over 6700 patients from 76 different national centres.
- The new Elbasvir/Grazoprevir and Sofosbuvir/Velpatasvir regimens have been included. A package of software improvements has been applied which will make a significant improvement to reducing biases and to improving user experience.

# 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 a 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 2017) over 500 patients were registered. In spite of their infrequency, 7 of these centres registered over 20 patients. The exploitation of the register and intercommunication between its members has also enabled cooperating with the European group for the study of vascular liver diseases (VALDIG) and as a result of this cooperation a work has recently been published on the use of the new direct anticoagulants in patients with liver diseases and a piece of work on Abernethy's disease which at the present time is in the drafting stage for its publication.


# 6

# Research Groups

LEAD RESEARCHER

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Group Website

PROGRAMMES
**P1**

GROUP MEMBERS

**Staff members:** Muñoz Zamarrón, Leticia | Úbeda Cantera, María P

**Associated members:** Álvarez de Mon Soto, Melchor | Gea Rodríguez, Francisco | Martínez González, Javier | Montserrat Sanz, Jorge | Prieto Martín, Alfredo | Tellez Villajos, Luis

# 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


- Abraldes JG, Villanueva C, Aracil C, Turnes J, Hernandez-Guerra M, Genesca J et al. Addition of Simvastatin to Standard Therapy for the Prevention of Variceal Rebleeding Does not Reduce Rebleeding but Increases Survival in Patients With Cirrhosis.Gastroenterology. 2016;150(5).
- Villanueva C., Albillos A., Genesca J., Abraldes J.G., Calleja J.L., Aracil C. et al. Development of hyperdynamic circulation and response to β-blockers in compensated cirrhosis with portal hypertension. Hepatology. 2016;63(1):197-206.
- Berzigotti A, Albillos A, Villanueva C, Genescá J, Ardevol A, Augustín S et al. Effects of an intensive lifestyle intervention program on portal hypertension in patients with cirrhosis and obesity: The sportdiet study.Hepatology (Baltimore, Md.). 2016.
- Bissonnette J., Carlos Garcia-Pagan J., Albillos A., Turon F., Ferreira C., Tellez L. et al. Role of the transjugular intrahepatic portosystemic shunt in the management of severe complications of portal hypertension in idiopathic noncirrhotic portal hypertension. Hepatology. 2016.
- Albillos A., Martinez J.. Prognostic value of bacterial infection in acute and chronic liver failure. Liver International. 2016;36(8):1090-1092.


# Hightlights

During the year 2016 the University of Alcalá-Ramón y Cajal University Hospital group has worked on projects aimed at modulating the damage of the intestinal barrier in rats with cirrhosis and reducing the high rate of bacterial translocation observed in this model. In relation to the clinical projects we have studied the alterations of the T lymphocyte compartment in patients with chronic liver disease by alcohol and virus C, and the modifications in the latter compartment after the antiviral treatment. With regard to clinical projects we have participated in different cooperative studies including the analysis of changes in cardiac function during beta-blocker treatment in advanced cirrhosis, the clinical trial to evaluate the efficacy of rivaroxaban in the natural history of cirrhosis And the efficacy of the methacetin breath test to identify patients with significant portal hypertension and follow-up of those treated with antivirals and portal pressure gradient response in patients with C virus cirrhosis on antiviral therapy. In addition, we have worked with regulatory agencies in the trial to study the efficacy of rivaroxaban in the natural history of cirrhosis with portal venous thrombosis. Alongside this, our group has participated in national cooperative studies describing the extensive experience accumulated in Spain on the use of direct-acting antivirals and in clinical trials using different drugs against fatty liver disease. We have contributed to national guidelines for hepatic vascular disease.

LEAD RESEARCHER

## Andrade, Raúl

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Group Website

PROGRAMMES
**P1 | P3**

GROUP MEMBERS

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# Main lines of research

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

# Most relevant scientific articles


- Medina-Caliz I., Robles-Diaz M., Garcia-Munoz B., Stephens C., Ortega-Alonso A., Garcia-Cortes M. et al. Definition and risk factors for chronicity following acute idiosyncratic drug-induced liver injury. Journal of Hepatology. 2016.
- Stephens C, Castiella A, Gomez-Moreno EM, Otazua P, López-Nevot MÁ, Zapata E et al. Autoantibody presentation in drug-induced liver injury and idiopathic autoimmune hepatitis: the influence of human leucocyte antigen alleles.Pharmacogenetics and genomics. 2016.
- Bessone F., Isabel Lucena M., Roma M.G., Stephens C., Medina-Caliz I., Frider B. et al. Cyproterone acetate induces a wide spectrum of acute liver damage including corticosteroid-responsive hepatitis: Report of 22 cases. Liver International. 2016.
- Gallego-Duran R., Cerro-Salido P., Gomez-Gonzalez E., Pareja M.J., Ampuero J., Rico M.C. et al. Imaging biomarkers for steatohepatitis and fibrosis detection in non-alcoholic fatty liver disease. Scientific Reports. 2016;6.
- Robles-Diaz M., Medina-Caliz I., Stephens C., Andrade R.J., Lucena M.I.. Biomarkers in DILI: One more step forward. Frontiers in Pharmacology. 2016;7(AUG).


# Hightlights

Three new contracts have been obtained during this year in competitive calls: ISCiii (Juan Rodés) and SAS (Senior investigator Nicolás Monardes and Intensificación), and funding for three projects (FIS PI16/01748 Co-IPs: Maria Isabel Lucena y Camilla Stephens; Consejería de Salud PI-0274-2016 IP: Mercedes Robles Díaz; PI-0285-201 IP: Miren García Cortes).

We have continued the work of strengthening our hepatotoxicity registries and case collections from both national and international hospital units. Our leadership position in this area has resulted in that IP Raúl J Andrade has been selected by the EASL to coordinate the development of new clinical practice guidelines for this condition.

Other relevant results have been the definition and risk factors for chronicity in hepatotoxicity based on information from 298 cases with long term follow-up. Furthermore, the role of HLA alleles in hepatotoxicity development classified by the presence of autoantibodies during the episode has been characterised, as well as the influence of KIR genotype variations on the risk of hepatotoxicity induced by amoxicillin-clavulanate. At the initiative of the European Medicines Agency, our group has organized a seminar titled "Assessment of Drug-Induced Liver Injury (DILI): Key Rules and Common Pitfalls" aimed at evaluators and regulatory agencies with the objective to develop hepatotoxicity recognition skills. Finally, the updated version of the eDILI mobile application developed by our group has been launched. It is a mobile application for professional use that provides information on hepatotoxicity and allows the calculation of the most commonly used parameters.

LEAD RESEARCHER

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Group Website


PROGRAMMES
**P1 | P4**

GROUP MEMBERS

**Staff members:** Bartoli Sole, Ramón | Simón Coma, Marina

**Associated members:** Morillas Cunil, Rosa | Sala Llinas, Margarita | Sarrias Fornes, María Rosa

# Main lines of research

Our multidisciplinary group is characterized by their clinical, translational and experimental research of various liver diseases. Our main research lines are:

- Viral Hepatitis and Complications of Cirrhosis.
- Liver cancer: Hepatocellular Carcinoma and Hepatoblastoma.
- Innate Immunity in liver disease.

# Most relevant scientific articles


- Klionsky DJ, Abdelmohsen K, Abe A, Abedin MJ, Abeliovich H, Acevedo Arozena A et al. Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition). Autophagy. 2016;12(1):1-222.
- Nicolle D., Fabre M., Simon-Coma M., Gorse A., Kappler R., Nonell L. et al. Patient-derived mouse xenografts from pediatric liver cancer predict tumor recurrence and advise clinical management. Hepatology. 2016-.
- Escorsell A., Pavel O., Cardenas A., Morillas R., Llop E., Villanueva C. et al. Esophageal balloon tamponade versus esophageal stent in controlling acute refractory variceal bleeding: A multicenter randomized, controlled trial. Hepatology. 2016;63(6):1957-1967.
- Villanueva C., Albillos A., Genesca J., Abraldes J.G., Calleja J.L., Aracil C. et al. Development of hyperdynamic circulation and response to β-blockers in compensated cirrhosis with portal hypertension. Hepatology. 2016;63(1):197-206.
- Shiffman M.L., Rustgi V., Bennett M., Forns X., Asselah T., Planas Vila R. et al. Safety and efficacy of ombitasvir/paritaprevir/ritonavir plus dasabuvir with or without ribavirin in HCV-infected patients taking concomitant acid-reducing agents. American Journal of Gastroenterology. 2016;111(6):845-851.


# Hightlights

In 2016 the Group has seen a leader change, where Dr. Armengol replaced Dr. Planas after his retirement in June. Dr. C. Armengol is an i3 stabilized Ramon y Cajal researcher at IGTP, that will be leading a multidisciplinary team composed by 2 MD, 3 PhD - including a Miguel Servet researcher- and 1 pre-doc. The clinical and translational research of the group covered complications of cirrhosis, HCV, liver cancer and the involvement of innate immunity in these pathologies. We have obtained 3 competitive grants (2 FIS ISCIII and 1 MINECO), we have had active projects as PI or co-PI for a total of 1.738.618 EUR (Juan de la Cierva contract, 2 FIS ISCIII; 1 MTV3; 2 European projects EFSD and Horizon2020). Among these, the H2020 ChiLTERN project in which C. Armengol is leading one Work Package is focused on improving the clinical management of pediatric patients with liver cancer. Altogether, the activity of our group resulted in 16 publications including a guideline (total IF: 109,688). Furthermore, we have participated in 9 clinical trials and maintained a network of collaborators with 11 different groups of CIBEREHD, CIBERRES and CIBERDEM, allowing our participation in 5 multicentric projects. We have also consolidated our international collaborations and boosted our innovation and transfer activity by registering 1 patent (EP163823365, transference to market under study), and by collaborating with 2 international companies (XenTECH, Lionex). Concerning our educational activity, 2 doctoral thesis were defended in 2016, 2 pre-doctoral and 1 master students are working in our laboratories. Moreover, we particpated in several national and international conferences and organized a Symposium on “Advances in molecular profiling to improve clinical management of the patient with liver cancer” and an international meeting (http://www.siopelbarcelona2016.org/) that has been a complete success doubling the last attendances with more than 150 participants from 21 different countries.

LEAD RESEARCHER

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PROGRAMMES
**P2**

GROUP MEMBERS

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**Associated members:** Accarino Garaventa, Anna María | Alonso Cotoner, Carmen | Antolín Mate, María | Borruel Sainz, Natalia | Casellas Jorda, Francisco | Malagelada Benaprés, Juan Ramón | Malagelada Prats, Carolina | Manichanh, Chaysavanh | Molero Richard, Francesc Xavier | Santos Vicente, Javier | Vicario Pérez, María | Vilaseca Momplet, Jaime

# Main lines of research

- Gut sensitivity and viscerosomatic reflexes.
- Sensory and digestive responses to meals.
- Diet, microbiota, abdominal content and digestive function.
- Inflammatory mediators in functional gut disorders.
- Development of molecular and bioinformatic tools to study microbiome.
- Role of intestinal microbiota in specific gastrointestinal and liver diseases.
- Quality of life in chronic gastrointestinal diseases.
- Genetic and environmental factors in chronic pancreatitis.
- Experimental models of pancreatic cancer.

# Most relevant scientific articles


- Barba E., Accarino A., Soldevilla A., Malagelada J.-R., Azpiroz F. Randomized, Placebo-Controlled Trial of Biofeedback for the Treatment of Rumination. American Journal of Gastroenterology. 2016;111(7):1007-1013.
- Martinez X., Pozuelo M., Pascal V., Campos D., Gut I., Gut M. et al. MetaTrans: An open-source pipeline for metatranscriptomics. Scientific Reports. 2016;6.
- Rodriguez-Urrutia A., Eiroa-Orosa F.J., Accarino A., Malagelada C., Azpiroz F. Incongruence between clinicians' assessment and self-reported functioning is related to psychopathology among patients diagnosed with gastrointestinal disorders. Psychotherapy and Psychosomatics. 2016;85(4):244-245.
- Arias A., Lucendo A.J., Martinez-Fernandez P., Gonzalez-Castro A.M., Fortea M., Gonzalez-Cervera J. et al. Dietary treatment modulates mast cell phenotype, density, and activity in adult eosinophilic oesophagitis. Clinical and Experimental Allergy. 2016;46(1):78-91.
- Fernandez-Calotti P., Casulleras O., Antolin M., Guarner F., Pastor-Anglada M. Galectin-4 interacts with the drug transporter human concentrative nucleoside transporter 3 to regulate its function. FASEB Journal. 2016;30(2):544-554.


# Hightlights

## COLLABORATIONS

- 1. Intra-Ciber Collaborations (CIBEREHD).
  - Dr. P. Clavé: studies of digestive motility.
  - Dr. C.Guarner: microbioma analysis in patients with cirrhosis.
  - Dr. Pastor-Anglada (Oncology): molecular studies on digestive epithelial physiology.
  - ACCES-CIBEREHD strategic action project: P. Clave, M. Esteve, Dr. Cabré. Development of different basic-translational research studies.
- Inter-Ciber Collaborations.
  - CIBERDEM: Center for Omics Sciences, Universitat Rovira i Virgili, Tarragona. Studies on metabolomic pattern.
  - CIBERSAM: Department of Psychiatry, Vall d'Hebron Hospital. Study of the psychological alterations in patients with severe digestive dismotility.
  - CIBERBBN: Institute of Bioengineering of Catalonia, Dr. E. Martinez. Development of in-vitro 3D models of digestive mucosa.
  - CIBERER: Center for Biomedical Research on Rare Diseases (Dr Martinez-Fernandez). Analysis of mast cells in Eosinophilic Esophagitis.
  - INTERCIBER INFLAMES Project.

## SCIENTIFIC ACTIVITIES

- Publication of a guide on prebiotics and two book chapters, together with the Spanish Society of Pre- and Probiotics (Azpiroz, Guarner Board of Directors).
  - Joint UEG / AGA meeting. Gut Microbiota For Health Summit, Miami. Azpiroz, Guarner organizing committee.
  - Rome IV criteria for the diagnosis of functional digestive disorders. Azpiroz, Santos.
  - The week of science, CosmoCaixa.
  - Marie Curie Training Network on research in Neurogastroenterology.
  - Incorporation of Juan de la Cierva postdoctoral fellow.
  - Organization of the International Microbiotic and Probiotic Research Course.
  - International symposium Microbiome B-Debate sponsored by BIOCAT and CosmoCaixa. Co-direction.
  - 'WGO Probiotics and Prebiotics Guideline'. F Guarner chair.

LEAD RESEARCHER

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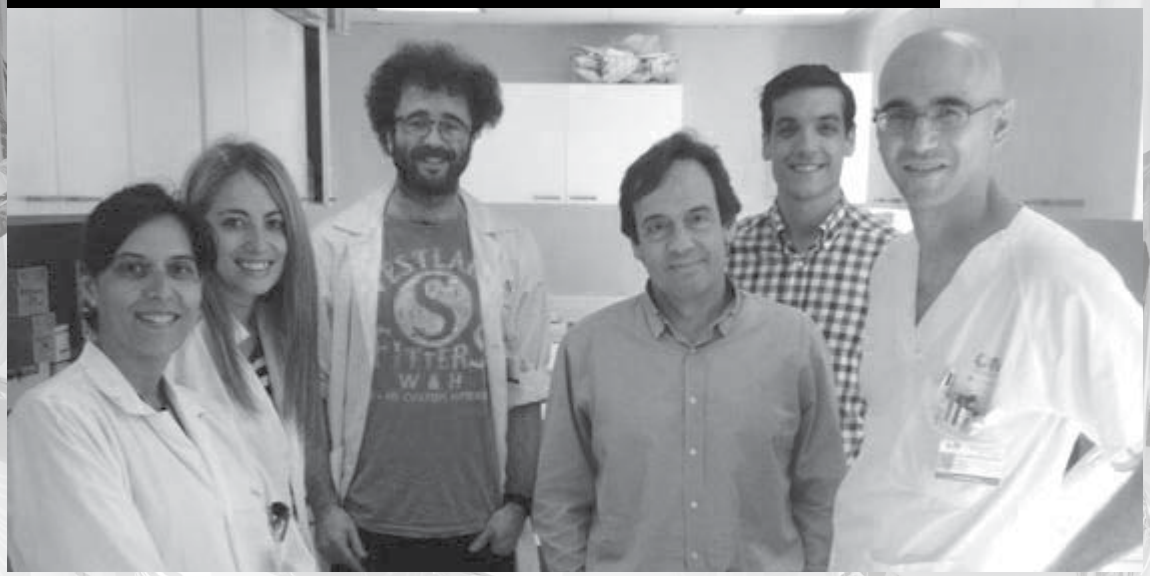
Group Website


PROGRAMMES
**P1**



GROUP MEMBERS

**Staff members:** Puerto Cantero, Marta

**Associated members:** Catalina Rodríguez, María De La Vega | Clemente Ricote, Gerardo | García Martínez, Rita | Ibañez Samaniego, Luis | 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).
  - Complicaitions of portal hypertension (clinical and experimental studies).
  - Implications of cirrhosis for the pathophysiology of other organs.
- Mechanisms of liver regeneration (experimental studies).
- Inflammatory bowel disease (clinical and experimental studies).
- Natural history after liver transplantation.

# Most relevant scientific articles


- Villanueva C., Albillos A., Genesca J., Abraldes J.G., Calleja J.L., Aracil C. et al. Development of hyperdynamic circulation and response to β-blockers in compensated cirrhosis with portal hypertension. Hepatology. 2016;63(1):197-206.
- Nehrhoff I., Bocancea D., Vaquero J., Vaquero J.J., Ripoll J., Desco M. et al. 3D imaging in CUBIC-cleared mouse heart tissue: Going deeper. Biomedical Optics Express. 2016;7(9):3716-3720.
- Asencio J.M., Garcia-Sabrido J.L., Lopez-Baena J.A., Olmedilla L., Peligros I., Lozano P. et al. Preconditioning by portal vein embolization modulates hepatic hemodynamics and improves liver function in pigs with extended hepatectomy. Surgery (United States). 2016.
- Aguero F., Forner A., Manzardo C., Valdivieso A., Blanes M., Barcena R. et al. Human immunodeficiency virus infection does not worsen prognosis of liver transplantation for hepatocellular carcinoma. Hepatology. 2016;63(2):488-498.
- Berzigotti A, Albillos A, Villanueva C, Genescá J, Ardevol A, Augustín S et al. Effects of an intensive lifestyle intervention program on portal hypertension in patients with cirrhosis and obesity: The sportdiet study.Hepatology (Baltimore, Md.). 2016.


# Hightlights

Our group has maintained its research projection in the clinical and experimental settings. It should be particularly noted the consolidation of the research laboratory, whose scientific production has experimented a notable advance during the last year with a considerable number of manuscripts in preparation.

From the funding perspective, it is noteworthy the maintenance of the funding from the national plan with the granting of the third consecutive project to Dr. Menchén Viso, whose work in the area of intestinal permeability is of great value towards the integration of the different laboratory research lines. Likewise, it should be noted the participation of our group in the “Proyecto Integrado de Excelencia” granted to our Instituto de Investigación Sanitaria Gregorio Marañón (WP-4: Microbiota and liver disease) as well as in the strategic action of the CIBERehd itself (exosomes, WP: liver regeneration). Finally, and for the first time in the history of the group, we will participate in a H2020 project (ALIVER Project) aimed at evaluating the efficacy of a new artificial liver device.

From the teaching perspective, we have directed several “end-of-degree” (Medicine) and “end-of-master” (Biology) projects; moreover, four Ph.D. thesis directed by group members have been defended in 2016.

The most relevant results of our group in 2016 are included in clinical research cooperative studies. It should be particularly noted the generation of the initial results of the PREDESCI study in relation with the haemodynamic basis that support the capacity of beta-blockers to prevent the decompensation of patients with cirrhosis, as well as the “proof-of-concept” study associating the weight loss by exercise and diet with the lowering of portal pressure.

LEAD RESEARCHER

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Group Website

PROGRAMMES
**P1**

GROUP MEMBERS

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**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. Collaboration with national and international groups aimed at defining the point of no return in patients with advanced disease. These studies/collaborations have resulted in several publications in first decile journals (some in preparation) and guidelines (national and international) regarding the treatment of HCV. 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. Participation in trials.
- **Non-cirrhotic and 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. Collaborations with national groups to improve the management of cirrhotic patients with portal hypertension and portal vein thrombosis.
- **Non-alcoholic steatosis**. Industry promoted studies. Clinical trials in liver transplant context. Participation in the Spanish registry. Collaboration in National guide.
- **Cholestasic liver diseases:** Industry promoted studies. Collaboration in the Spanish registry.

# Most relevant scientific articles


- Alvarez-Sotomayor D., Satorres C., Rodriguez-Medina B., Herrero I., De La Mata M., Serrano T. et al. Controlling Diabetes after Liver Transplantation: Room for Improvement. Transplantation. 2016;100(10): e66-e73.
- Manns M., Samuel D., Gane E.J., Mutimer D., McCaughan G., Buti M. et al. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial. The Lancet Infectious Diseases. 2016;16(6):685-697.
- Aguero F., Forner A., Manzardo C., Valdivieso A., Blanes M., Barcena R. et al. Human immunodeficiency virus infection does not worsen prognosis of liver transplantation for hepatocellular carcinoma. Hepatology. 2016;63(2):488-498.
- Addolorato G., Bataller R., Burra P., DiMartini A., Graziadei I., Lucey M.R. et al. Liver Transplantation for Alcoholic Liver Disease. Transplantation. 2016.
- Berenguer M. Last gasps of the hepatitis C virus dragon: Direct acting antiviral failures and hepatitis C virus–positive donors. Liver Transplantation. 2016; 22:47-51.


# Hightlights

This year our group on "Hepatology & Liver Transplantation" obtained the IIS La Fe accreditation. We were also able to recruit staff members; one clinical researcher (Rio Hortega grant), one technician (La Fe Bankia Training Program) & finally one experimental researcher through CIBEREHD. The most relevant results have been published in 23 scientific articles. Two doctoral and one master thesis also have been presented. Currently, the group has 12 active projects (4 competitive projects, 8 privately financed) and 17 clinical trials.

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PROGRAMMES
**P1**

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**Associated members:** Deulofeu Piguet, Ramón | Escorsell Mañosa, Ángeles | Fernández Iglesias, Anabel | 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
- 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 and In the development of liver-on-a-chip devices.
- Angiogenesis in advanced chronic liver disease: function, regulation, and therapeutic potential
- *Impact of obesity on chronic liver disease: pathogenic mechanisms and therapeutic implications.*
- *Molecular regulation of progression from hepatic steatosis to cirrhosis and liver cancer. Identification of therapeutic targets.*
- New methods of noninvasive evaluation in cirrhosis.
- Clinical trials of randomization of new treatments for portal hypertension and esophageal-gastric variceal hemorrhage.
- Hepatic vascular diseases. Prognostic studies and new diagnostic methods.

# Most relevant scientific articles


- Abraldes JG, Villanueva C, Aracil C, Turnes J, Hernandez-Guerra M, Genesca J et al. Addition of Simvastatin to Standard Therapy for the Prevention of Variceal Rebleeding Does not Reduce Rebleeding but Increases Survival in Patients With Cirrhosis.Gastroenterology. 2016;150(5).
- Calderone V, Gallego J, Fernandez-Miranda G, Garcia-Pras E, Maillo C, Berzigotti A et al. Sequential Functions of CPEB1 and CPEB4 Regulate Pathologic Expression of VEGF and Angiogenesis in Chronic Liver Disease.Gastroenterology. 2016;150(4).
- Berzigotti A, Albillos A, Villanueva C, Genescá J, Ardevol A, Augustín S et al. Effects of an intensive lifestyle intervention program on portal hypertension in patients with cirrhosis and obesity: The sportdiet study.Hepatology (Baltimore, Md.). 2016.
- Noronha Ferreira C., Seijo S., Plessier A., Silva-Junior G., Turon F., Rautou P.-E. et al. Natural history and management of esophagogastric varices in chronic noncirrhotic, nontumoral portal vein thrombosis. Hepatology. 2016;63(5):1640-1650.
- Escorsell A., Pavel O., Cardenas A., Morillas R., Llop E., Villanueva C. et al. Esophageal balloon tamponade versus esophageal stent in controlling acute refractory variceal bleeding: A multicenter randomized, controlled trial. Hepatology. 2016;63(6):1957-1967.


# Hightlights

## PUBLICATIONS

The group has published a total of 32 publications (19 Originals, 6 Reviews, 2 Editorials, 2 Letters and 3 Clinical Trials), and also 2 Clinical Guidelines. Of these publications, 18 were collaborative, 21 were in magazines of the first decile and 28 in magazines of the first quartile.

## PROJECTS

The group has 12 active competitive projects, in charge of the following IP:

- **Bosch J**: a. Contrast-enhanced uLtrasound for livEr-disease eValuation: development and validation of a novel E-Health-software for Risk-stratification (CLEVER). 612273. European Commission. b. Understanding obesity (Ob), metabolic syndrome (MetS), type 2 diabetes (T2DM) and fatty liver disease (FL): a multidisciplinary approach. PIE14/00031.With 4 CIBER group participating.. c. Hepatic hemodynamics and portal hypertension in cirrhosis. Advances in pathophysiology and treatment (Clinical and experimental studies). ISCIII. PI13/00341.
- **García Pagán JC**: a. Targeting endothelial dysfunction in highly prevalent diseases: characterization and validation of prognostic biomarkers and identification of potential therapeutic strategies. PIE15/00027. b. Multivessel, randomized prospective study of the effect of Rivaroxaban on the survival and development of portal hypertension complications in patients with cirrhosis. ISCIII. ICI14/00133. c. Molecular mechanisms involved in structural and functional alterations in the liver in the progression to cirrhosis with portal hypertension. SAF2013-44723-R.
- **Fernández M**: a. Molecular regulation of the interaction between obesity and chronic liver disease. BES2015-071399. b. Molecular and cellular mechanisms involved in the interaction between obesity and chronic liver disease: role and therapeutic potential of angiogenesis and CPEB proteins. SAF2014-55473-R
- **Gracia-Sancho J**: a. The hepatic sinusoid in old age: characterization of pathophysiological cellular mechanisms for the development of new therapeutic strategies. FIS PI14/00029. b. BioLiver: Deconstruction applied to Hepatology. MINECO. Explora BIO2014-61377-EXP.
- **Hernández-Gea V**: Role of autophagy in the modulation of endothelial dysfunction and fibrosis: characterization of a new therapeutic target for the development of new antifibrotic treatments. FIS PI14/00182.
- **Escorsell A**: Efficacy of intrahepatic portosystemic shunt (TIPS) in the treatment of acute gastric variceal hemorrhage: a randomized controlled trial versus conventional treatment. FIS PI14/00392.

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PROGRAMMES
**P4**

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# Main lines of research

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

The BCLC group has received wide international recognition for its work at all levels. At the clinical level the group established the relevance of hepatitis C virus infection as a risk factor for liver cancer, defined the imaging criteria for imaging diagnosis of liver cancer, defined the role of portal pressure measurement in the selection of candidates for surgery, established the benefits of ablation for early stage cancers and, more importantly, demonstrated the benefit of chemoembolization and sorafenib through phase 3 randomised trials.

Furthermore, the BCLC strategy for prognosis assessment and treatment allocation has been endorsed by major scientific associations and research consortia. The BCLC contributions have laid the foundation for the development of international practice guidelines based on scientific evidence as done by EASL, AASLD, WGO, ESMO and ILCA. Indeed, most guidelines have been lead by BCLC investigators.
The activity in translational research has primed the establishment of a molecular classification of liver cancer and elucidated some of the most relevant signalling pathways involved in tumour progression. In addition, studies have identified genomic signatures associated with different outcome either due to tumor progression or to liver disease progression. As a whole, the combined clinical and translational research is paving the path for stratified medicine.
The BCLC group work has resulted, along the years, in more than 600 publications, with an Impact Factor higher than 3.000, and a total citations number higher than 36.000.

# Most relevant scientific articles


- Ferrer-Fabrega J., Forner A., Liccioni A., Miquel R., Molina V., Navasa M. et al. Prospective validation of ab initio liver transplantation in hepatocellular carcinoma upon detection of risk factors for recurrence after resection. Hepatology. 2016.
- Reig M., Marino Z., Perello C., Inarrairaegui M., Ribeiro A., Lens S. et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. Journal of Hepatology. 2016;65(4):719-726.
- Forner A., Reig M., Varela M., Burrel M., Feliu J., Briceno J. et al. Diagnosis and treatment of hepatocellular carcinoma. Update consensus document from the AEEH, SEOM, SERAM, SERVEI and SETH. Medicina Clinica. 2016.
- Nakagawa S., Wei L., Song W.M., Higashi T., Ghoshal S., Kim R.S. et al. Molecular Liver Cancer Prevention in Cirrhosis by Organ Transcriptome Analysis and Lysophosphatidic Acid Pathway Inhibition. Cancer Cell. 2016;30(6):879-890.
- Martinez-Quetglas I., Pinyol R., Dauch D., Torrecilla S., Tovar V., Moeini A. et al. IGF2 Is Up-regulated by Epigenetic Mechanisms in Hepatocellular Carcinomas and Is an Actionable Oncogene Product in Experimental Models. Gastroenterology. 2016;151(6):1192-1205.


# Hightlights

The research activity of the Hepatic Oncology team has continued to focus on clinical and translational research in liver cancer. At the clinical level, it has been demonstrated the possibility of indicating liver transplantation in patients with early stage cholangiocarcinoma and this has led to the implementation of a clinical trial at an international level led by Barcelona. At the same time, the utility of liver transplantation has been validated in patients with a high risk of relapse after surgical resection. In addition, an international trial led by our group has shown the usefulness of systemic treatment of liver cancer with regorafenib in the second line, which represents a great milestone in the treatment of this neoplasm.
Finally, thanks to the National Hepatitis Plan, an alarm signal has been identified regarding the treatment of the hepatitis C virus with direct antiviral agents. An excessively high rate of tumor recurrence has been detected in these patients and this has initiated a broader assessment of the safety of these agents internationally.
A major achievement has been the updating of clinical practice guidelines for hepatocellular carcinoma that have been adopted by different scientific societies (AEEH, SEOM, SETH, SERVEI and SERAM) and which are finally part of the portfolio of clinical guidelines of the Ministry of Health.
At the translational level, the molecular abnormalities that characterize liver tumors have continued to be characterized in a way that has continued to provide relevant information for a better understanding of the mechanisms that lead to the development and progression of this neoplasm. In this way, it is advanced for the future incorporation of new parameters for a personalized management of the patients in terms of both prevention and treatment.

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PROGRAMMES
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# Main lines of research

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

# Most relevant scientific articles


- Bujanda L., Rodriguez-Gonzalez A., Sarasqueta C., Eizaguirre E., Hijona E., Marin J.J.G. et al. Effect of pravastatin on the survival of patients with advanced gastric cancer. Oncotarget. 2016;7(4):4379-4384.
- Banales J.M., Cardinale V., Carpino G., Marzioni M., Andersen J.B., Invernizzi P. et al. Expert consensus document: Cholangiocarcinoma: current knowledge and future perspectives consensus statement from the European Network for the Study of Cholangiocarcinoma (ENS-CCA). Nature Reviews Gastroenterology and Hepatology. 2016;13(5):261-280.
- Quintero E., Carrillo M., Leoz M.-L., Cubiella J., Gargallo C., Lanas A. et al. Risk of Advanced Neoplasia in First-Degree Relatives with Colorectal Cancer: A Large Multicenter Cross-Sectional Study. PLoS Medicine. 2016;13(5).
- D'Agnolo H.M.A., Kievit W., Takkenberg R.B., Riano I., Bujanda L., Neijenhuis M.K. et al. Ursodeoxycholic acid in advanced polycystic liver disease: A phase 2 multicenter randomized controlled trial. Journal of Hepatology. 2016.
- Cubiella J., Vega P., Salve M., Diaz-Ondina M., Alves M.T., Quintero E. et al. Development and external validation of a faecal immunochemical test-based prediction model for colorectal cancer detection in symptomatic patients. BMC Medicine. 2016;14(1).


# Hightlights

Dr. Luis Bujanda is the President of the Spanish Association of Gastroenterology since March 2016. Our group coordinates the "European Network for the Study of Cholangiocarcinoma (ENSCCA: www.enscca.org)", composed by 30 groups / research centers in the European Union and 7 in USA. In 2016 received the "EASL Registry Award " by the European Association for the Study of the Liver (EASL) for create a European database of patients with cholangiocarcinoma (CCA), which will contain clinical information as well as biological samples. The groups of the Oncology Area –CIBEREHD also participating, for example, Jordi Bruix (Hospital Clinic), Bruno Sangro (CUN) and José Juan Garcia Marin (IBSAL).
On the other hand, our group organized in May 2016 the "I International Congress of CCA" in San Sebastian). In addition, our group participates in the "International Registry of Polycystic Liver Diseases" (EASL Registry Award 2014) and in the Spanish Registry of Liver Metabolic Diseases (HEPAMET). Our group also participates in the first international GWAS study on CCA (http://cholangiocarcinoma.org/professionals/action-alert-mayo-clinic-study/)
In addition, Dr. Bañales is the Editor of 40 manuscripts for a "Special Issue in Cholangiocytes in Health and Disease" for BBA- molecular basis of disease (1Q).

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PROGRAMMES
**P2**

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# Main lines of research

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

# Most relevant scientific articles


- Garcia-Planella E., Manosa M., Cabre E., Marin L., Gordillo J., Zabana Y. et al. Fecal calprotectin levels are closely correlated with the absence of relevant mucosal lesions in postoperative Crohn's Disease. Inflammatory Bowel Diseases. 2016;22(12):2879-2885.
- Julia A., Vinaixa M., Domenech E., Fernandez-Nebro A., Canete J.D., Ferrandiz C. et al. Urine metabolome profiling of immune-mediated inflammatory diseases. BMC Medicine. 2016;14(1).
- Llao J., Naves J.E., Ruiz-Cerulla A., Gordillo J., Manosa M., Maisterra S. et al. Improved outcome of acute severe ulcerative colitis while using early predictors of corticosteroid failure and rescue therapies. Digestive and Liver Disease. 2016;48(6):608-612.
- Marin-Jimenez I., Nos P., Domenech E., Riestra S., Gisbert J.P., Calvet X. et al. Diagnostic Performance of the Simple Clinical Colitis Activity Index Self-Administered Online at Home by Patients With Ulcerative Colitis: CRONICA-UC Study. American Journal of Gastroenterology. 2016.
- Carpio D, Jauregui-Amezaga A, de Francisco R, de Castro L, Barreiro-de Acosta M, Mendoza JL et al. Tuberculosis in Anti-Tumor Necrosis Factor Treated Inflammatory Bowel Disease Patients after the Implementation of Preventive Measures: Compliance with Recommendations and Safety of Retreatment.Journal of Crohn's & colitis. 2016.


# Hightlights

In 2016, four FIS **grants** have been managed, and we have obtained an additional grant for a new project. In addition, we also participate in the intramural project of CIBEREHD, ACCES. IPs of our group lead the FIS projects mentioned above, which are in accordance with the master plan, and 3 of them are clearly collaborative with other CIBEREHD groups. The main **results** of the scientific activity can be summarized as follows: i) Prediction of therapeutic response in steroid-treated moderate-to-severe ulcerative colitis (UC); ii) Identification of the mechanism of action linked to UC steroid-refractoriness; iii) Characterization of metabolic profiles in urine related to chronic inflammatory diseases; iv) Data compilation on natural history of postoperative Crohn's disease (CD) under IMS prevention and design of new preventive strategies, as well as identification of new therapeutic targets; v) Description of the biological activity influenced by microorganisms in the CD; vi) Improvement in colonoscopy preparation for diabetic patients; vii) Characterization of variables associated to oesophageal motility disorders; and viii) Identification of patients with irritable bowel syndrome sensitive to therapeutic intervention on the intestinal microbiota. Some of these results have generated **patents**, such as the bioactive platform for wound healing of endoscopic lesions (EP163823365), or for drug release, as well as a panel of plasmatic biomarkers of corticosteroid failure in UC (last ones submitted). In the **transfer activities**, a collaboration agreement has been signed with Epithelion S.L. (Barcelona), and a study has been completed where we have transferred know-how to the industry (Lorén V, et al., 2016). Finally, the new edition of the international course "Miquel A. Gassull" on inflammatory bowel diseases (Badalona, 2016) is to be highlighted among the various formative activities.

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PROGRAMMES
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# Main lines of research

- *Helicobacter pylori* and associated diseases.
- Non-variceal upper gastrointestinal bleeding.
- Social and laboral aspects of inflammatory bowel disease.
- Quality of care in Inflammatory Bowel Disease.

# Most relevant scientific articles


- Vergara M., Sicilia B., Prieto L., Casellas F., Ramos A., Gomollon F. et al. Development and validation of the short Crohn's disease work disability questionnaire. Inflammatory Bowel Diseases. 2016;22(4):955-962.
- Palau M., Kulmann M., Ramirez-Lazaro M.J., Lario S., Quilez M.E., Campo R. et al. Usefulness of Housekeeping Genes for the Diagnosis of Helicobacter pylori Infection, Strain Discrimination and Detection of Multiple Infection. Helicobacter. 2016.
- Puig I., Baylina M., Sanchez-Delgado J., Lopez-Gongora S., Suarez D., Garcia-Iglesias P. et al. Systematic review and meta-analysis: Triple therapy combining a proton-pump inhibitor, amoxicillin and metronidazole for Helicobacter pylori first-line treatment. Journal of Antimicrobial Chemotherapy. 2016;71(10):2740-2753.
- Ramírez-Lázaro MJ, Lite J, Lario S, Pérez-Jové P, Montserrat A, Quílez ME et al. Good diagnostic accuracy of a chemiluminescent immunoassay in stool samples for diagnosis of Helicobacter pylori infection in patients with dyspepsia.Journal of investigative medicine : the official publication of the American Federation for Clinical Research. 2016;64(2):388-91.
- Kuligowski J., Sanjuan-Herraez D., Vazquez-Sanchez M.A., Brunet-Vega A., Pericay C., Ramirez-Lazaro M.J. et al. Metabolomic analysis of gastric cancer progression within the Correa's cascade using ultraperformance liquid chromatography-mass spectrometry. Journal of Proteome Research. 2016;15(8):2729-2738.


# Hightlights

The most relevant achievements of 2016 of the Research Group of Parc Taulí Hospital of Sabadell were as follows:

Regarding the **development of projects**, we would highlight the different group's lines of work: In the line of research on infection by Helicobacter, we would highlight the development of a systematic review on the utility of increasing the dose of PPI for *Helicobacter pylori* eradication. Regarding the projects of the research line on quality of life, we would highlight the development of indicators of quality of care for patients with inflammatory bowel disease, developed and evaluable by patients without intervention of care providers.

Regarding the description of the **results** obtained, we would highlight the first publications of CIBEREHD researchers with other basic research groups, from University of Barcelona and University of Valencia. These publications reflect, on the one hand, the consolidation of the basic and translational research group and, on the other hand, the establishment of a network with basic researchers from the rest of the state to promote research on *H. pylori* and on the early detection of gastric cancer. Another important achievement to note is that the Spanish Working Group on Crohn's Disease and Ulcerative Colitis has adapted the quality standards established by our group, in collaboration with other groups from CIBEREHD, to certify the units of care attention in inflammatory bowel disease. **Guidelines**: During 2016, members of the group participated in the IV Spanish Consensus on the treatment of *H. pylori* (Emili Gené, Xavier Calvet), and in the following position papers of the Societat Catalana de Digestologia: upper non-variceal haemorrhage ( Rafel Campo, coordinator, Xavier Calvet, Emili Gene participants), management of *H. pylori* infection (Jordi Sánchez, Emili Gene participants, Xavier Calvet, coordinator), autoimmune liver diseases (Mercè Vergara).

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PROGRAMMES
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# Main lines of research

The **Experimental Hepatology and Liver Transplantation Group** is an accredited research group of the IIS Hospital La Fe, which was established in 2008 as a Joint Research Unit between the University of Valencia and the Foundation Hospital La Fe, and which includes research-teaching staff from both the Department of Biochemistry and Molecular Biology and the IIS Hospital La Fe.

Its main objective is the translational research in hepatology. Based on the study of the cellular and molecular biology of hepatocytes, and using complex cellular models capable of mimicking the behavior of the human liver along with the support of advanced analytical technologies, it investigates challenging problems with clinical relevance in order to develop new diagnostic and therapeutic strategies (cellular therapy).

In this context, the group has carried out a very relevant and pioneering work in the study of the molecular bases of drug metabolism and hepatotoxicity, and the regulation of the genes involved. It has also pioneered the development of differentiated liver cell models that mimic the behavior of the human liver, as well as hepatic cell therapy and cell transplantation research.

Among the current lines of research we highlight:

- Development of new human hepatic cell models with differentiated hepatic phenotype and able to mimic idiosyncratic responses.
- Hepatotoxicity by drugs: Molecular mechanisms and new biomarkers for their translation into the clinic in iatrogenic steatosis and cholestasis.
- Etiology of nonalcoholic fatty liver: transcriptional mechanisms involved.
- Advanced diagnosis, monitoring, prognosis and clinical trials in drug hepatotoxicity.
- Cell transplantation and other personalized hepatic cell therapies.

# Most relevant scientific articles


- Prieto J., Leon M., Ponsoda X., Sendra R., Bort R., Ferrer-Lorente R. et al. Early ERK1/2 activation promotes DRP1-dependent mitochondrial fission necessary for cell reprogramming. Nature Communications. 2016;7.
- Garcia-Canaveras J.C., Castell J.V., Donato M.T., Lahoz A.. A metabolomics cell-based approach for anticipating and investigating drug-induced liver injury. Scientific Reports. 2016;6.
- Gomez-Lechon M.J., Tolosa L.. Human hepatocytes derived from pluripotent stem cells: a promising cell model for drug hepatotoxicity screening. Archives of Toxicology. 2016;:1-13.
- Bozic M., Guzman C., Benet M., Sanchez-Campos S., Garcia-Monzon C., Gari E. et al. Hepatocyte vitamin D receptor regulates lipid metabolism and mediates experimental diet-induced steatosis. Journal of Hepatology. 2016.
- Tolosa L., Gomez-Lechon M.J., Lopez S., Guzman C., Castell J.V., Donato M.T. et al. Human upcyte hepatocytes: Characterization of the hepatic phenotype and evaluation for acute and long-term hepatotoxicity routine testing. Toxicological Sciences. 2016;152(1):214-229.


# Hightlights

PROJECTS

- *Fast metabolomic assessment of donor liver quality prior to transplant*. Roche Organ Transplant Research Foundation (2014-2016)
- *Aproximaciones metabonómicas para el estudio de la hepatotoxicidad idiosincrásica con base metabólica y la identificación del agente causal*. Instituto de Salud Carlos III-FIS. Proyecto PI 13/00986 (2014-2016).
- *Esteatosis hepática por medicamentos: nuevos mecanismos y biomarcadores aplicables al desarrollo farmacéutico y a una terapia más racional en pacientes con síndrome metabólico*. Instituto de Salud Carlos III-FIS. Proyecto PI13/01470 (2014-2016)
- *An integrated european 'flagship' program driving mechanism-based toxicity testing and risk assessment for the 21st century* (EU-ToxRisk) H2020 EU Research Project 681002 (2016-2020)
- *Hepatotoxicidad idiosincrásica por fármacos: estrategias in vitro para un diagnóstico retrospectivo, atribución de la causalidad y evaluación del potencial riesgo clínico en pacientes susceptibles*. Instituto de Salud Carlos III-FIS. Proyecto PI 16/00333 (2017-2019).
- *Improving feasibility of liver cell therapy: new cell sources and strategies to improve the clinical outcome*. Instituto de Salud Carlos III-FIS. Proyecto CP16/0097 (2017-2019).

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PROGRAMMES
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# Main lines of research

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

# Most relevant scientific articles


- de Barrios O., Gyorffy B., Fernandez-Acenero M.J., Sanchez-Tillo E., Sanchez-Moral L., Siles L. et al. ZEB1-induced tumourigenesis requires senescence inhibition via activation of DKK1/mutant p53/Mdm2/CtBP and repression of macroH2A1. Gut. 2016.
- Carballal S., Maisterra S., Lopez-Serrano A., Gimeno-Garcia A.Z., Vera M.I., Marin-Garbriel J.C. et al. Real-life chromoendoscopy for neoplasia detection and characterisation in long-standing IBD. Gut. 2016.
- Quintero E., Carrillo M., Leoz M.-L., Cubiella J., Gargallo C., Lanas A. et al. Risk of Advanced Neoplasia in First-Degree Relatives with Colorectal Cancer: A Large Multicenter Cross-Sectional Study. PLoS Medicine. 2016;13(5).
- Vila-Navarro E., Vila-Casadesus M., Moreira L., Duran-Sanchon S., Sinha R., Gines A. et al. MicroRNAs for Detection of Pancreatic Neoplasia: Biomarker Discovery by Next-generation Sequencing and Validation in 2 Independent Cohorts. Annals of Surgery. 2016.
- Dragani T.A., Castells A., Kulasingam V., Diamandis E.P., Earl H., Iams W.T. et al. Major milestones in translational oncology. BMC Medicine. 2016;14(1).


# Hightlights

The research lines of our group are focused on characterizing those mechanisms involved in the development and progression of premalignant and malignant gastrointestinal and pancreatic lesions, in order to establish new diagnostic, therapeutic and preventive strategies. The main milestones achieved in the year 2016 are framed in the context of cooperative projects led by our group in the field of colorectal cancer (CRC) prevention, either screening or surveillance.

Regarding CRC surveillance, it is important to mention the initiation of the EPoS project, a multicenter, international, randomized controlled study aimed at establishing the best strategy for the surveillance of patients who develop high- and low-risk adenomas, as well as serrated lesions. In addition, the risk stratification criteria proposed by the European Screening Guidelines have been reassessed.

With respect to CRC screening, we are continuing working in the context of the ColonPrev project, a prospective, randomized controlled study comparing fecal immunochemical testing and colonoscopy. After presenting the baseline results (N Engl J Med 2012, 366: 697-706), this year's results have been focused on nested projects, including the identification of endoscopists' characteristics influencing the quality of colonoscopy, or the evaluation of electronic alert assistance in the Primary Care history to improve adherence to screening programs.

Finally, the development and validation of biomarkers of early cancer diagnosis, framed in the EPICOLON project, constitutes a strategic transversal action of several CIBEREHD groups. In this field, it is important to mention the aid granted by the Spanish Association against Cancer (1,200,000€) and the patent for a new diagnostic method in pancreatic cancer.

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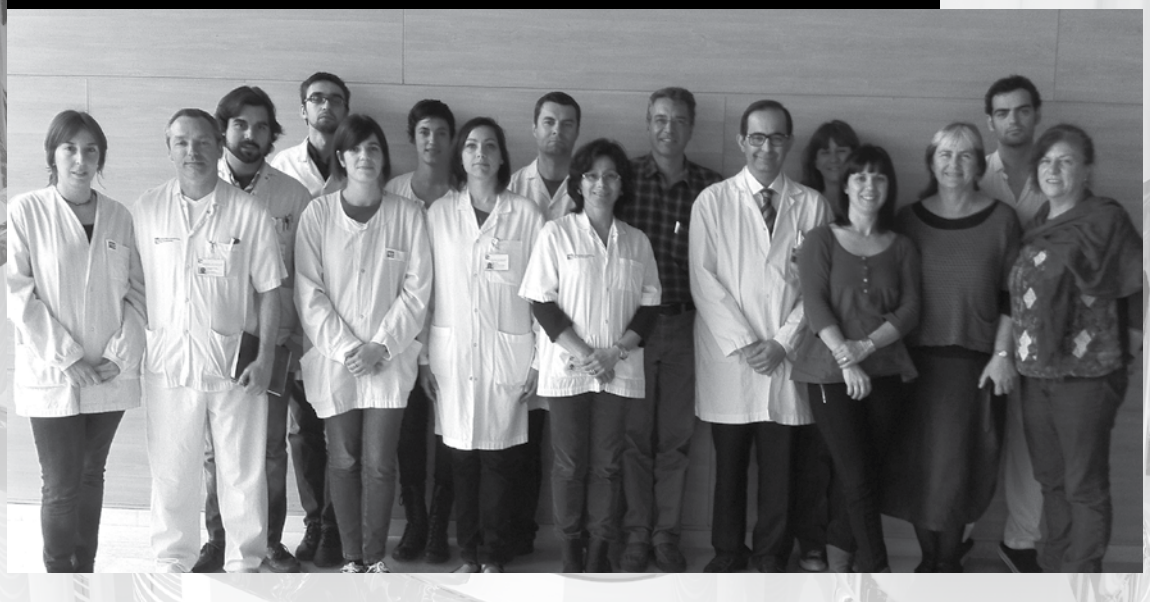
PROGRAMMES
**P2**



GROUP MEMBERS

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**Associated members:** Arreola Garcia, Olga Viridiana | Carrion Bolorino, Silvia | Espin Alvarez, Francisco José | Farré Martí, Ricard Lluis | Jiménez Farrerons, Marcelo | Mans Muntwyler, Ester | Martín Ibáñez, María Teresa | Martínez Perea, Vicente | Serra Prat, Mateur | Vergara Esteras, Patrocinio

# Main lines of research

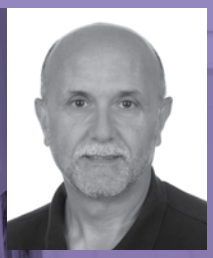
- Oropharyngeal and gastroesophageal motility. Pathophysiology, diagnosis and treatment of oropharyngeal and esophageal dysphagia. Pharmacology of swallow response. Oropharyngeal dysphagia and ageing. Neurogenic dysphagia. Brain plasticity.
- Gastrointestinal peptides, control of appetite in ageing and 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


- Farre R.. Evaluating the esophageal epithelial integrity: More complex than it seems. American Journal of Gastroenterology. 2016;111(2):295-296.
- Bath P.M., Scutt P., Love J., Clave P., Cohen D., Dziewas R. et al. Pharyngeal Electrical Stimulation for Treatment of Dysphagia in Subacute Stroke: A Randomized Controlled Trial. Stroke. 2016.
- Mane N., Jimenez-Sabado V., Jimenez M.. BPTU, an allosteric antagonist of P2Y1 receptor, blocks nerve mediated inhibitory neuromuscular responses in the gastrointestinal tract of rodents. Neuropharmacology. 2016;110:376-385.
- Alvarez-Berdugo D., Rofes L., Casamitjana J.F., Padron A., Quer M., Clave P.. Oropharyngeal and laryngeal sensory innervation in the pathophysiology of swallowing disorders and sensory stimulation treatments. Annals of the New York Academy of Sciences. 2016;1380(1):104-120.
- Carrion S., Roca M., Costa A., Arreola V., Ortega O., Palomera E. et al. Nutritional status of older patients with oropharyngeal dysphagia in a chronic versus an acute clinical situation. Clinical Nutrition. 2016.


# Hightlights

The Group has developed four groups of projects in 2016. The first, entitled "D*evelopment of a sensory neuromodulation protocol to treat post-stroke oropharyngeal dysphagia*", has allowed the addition through a grant of a clinical neurophysiologist, raising the technical level of our studies on the CNS. The second is the development and validation through a study pilot of the "Minimal-Massive Intervention" designed to reduce the nutritional and respiratory complications and the readmission rate of elderly people with oropharyngeal dysphagia to General Hospitals and the development of a stable cooperation with Investen and CIBER on Frailty to disseminate and validate this therapeutic strategy. Our group also investigates the relationship between frailty, anorexia and sarcopenia and has begun a new study on the relationship between obesity, sarcopenia and diabetes in elderly people and its treatment by physical exercise and dietary intervention. We have contributed to the development of two systematic reviews that have established clinical guidelines for the management of dysphagia; the first one after two years of interaction between two European scientific societies (ESSD/EUGMS), considering oropharyngeal dysphagia as a geriatric syndrome and setting the bases of its treatment; the second is a systematic review on the effect of changes rheology of the food bolus in patients with dysphagia, and establishes the optimal characteristics for the patients. Finally the fourth group of projects is a strategic action of called "*Acces-ciberehd developing collaborative networks for basic research with human tissue in the area 2 of the ciberehd*" which has allowed three young researchers from the CIBER to lead and develop a network of 18 cooperative projects in basic research involving all the groups of the area 2 of the CIBEREHD. The group has completed its activity of 2016 with relevant basic studies on neurogastroenterology, multiple clinical trials and several relevant participations in international meetings.



LEAD RESEARCHER

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PROGRAMMES
**P2 | P6**

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# Main lines of research

- Modulation of autophagy in epithelial cells by macrophages: relevance in Crohn's disease and in non-steroidal anti-inflammatory drug-induced gastroenteropathy.
- Nitric oxide and oxygen consumption: physiological and pathophysiological implications.
- Mitochondrial dysfunction in inflammatory processes.
- Role of endothelial-mitochondrial dysfunction in obesity.
- Mechanisms of toxicity and adaptive responses induced by antiretroviral drugs: role of mitochondrial dysfunction, autophagy, reticular stress and inflammation.

# Most relevant scientific articles


- Ortiz-Masia D., Cosin-Roger J., Calatayud S., Hernandez C., Alos R., Hinojosa J. et al. M1 macrophages activate notch signalling in epithelial cells: Relevance in Crohn's disease. Journal of Crohn's and Colitis. 2016;10(5):582-592.
- Blas-Garcia A., Marti-Rodrigo A., Victor V.M., Polo M., Alegre F., Funes H.A. et al. The purine analogues abacavir and didanosine increase acetaminophen-induced hepatotoxicity by enhancing mitochondrial dysfunction. Journal of Antimicrobial Chemotherapy. 2016;71(4):916-926.
- Escribano-Lopez I., Diaz-Morales N., Rovira-Llopis S., de Maranon A.M., Orden S., Alvarez A. et al. The mitochondria-targeted antioxidant MitoQ modulates oxidative stress, inflammation and leukocyte-endothelium interactions in leukocytes isolated from type 2 diabetic patients. Redox Biology. 2016; 10:200-205.
- Macias-Ceja D.C., Cosin-Roger J., Ortiz-Masia D., Salvador P., Hernandez C., Calatayud S. et al. The flesh ethanolic extract of Hylocereus polyrhizus exerts anti-inflammatory effects and prevents murine colitis. Clinical Nutrition. 2016.
- Klionsky DJ, Abdelmohsen K, Abe A, Abedin MJ, Abeliovich H, Acevedo Arozena A et al. Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition).Autophagy. 2016;12(1):1-222.


# Hightlights

In 2016 the group has had 6 competitive research projects underway and has been granted 3 new state-funded projects, two consolidated research group projects (FISABIO) and various young researcher contracts (two Sara Borrell, one Juan de la Cierva Formación, one Val i+d).
Members of our group participate in the "Strategic action 2016: Developing collaborative networks for basic research with human tissue in the area 2 of the CIBEREHD" Use of human tissue in translational gastroenterology research. (PI: Pere Clavé)
Two collaborations have arisen as a result of this project:
With the group led by Dr. Gisbert, Hospital La Princesa, Madrid, where Dr. Mª Dolores Ortiz Masiá received training in flow cytometry.
With the group led by Dr. Cabré, Fundación Instituto de Investigación Germans Trias i Pujol Dr. Many, Badalona, which has provided us with samples from Crohn's patients to analyse markers of fibrosis and y macrophages.
Publication in collaboration with the CIBEREHD group led by Dr. Angel Lanas: Chueca E., Apostolova N., Esplugues J.V., Garcia-Gonzalez M.A., Lanas A., Piazuelo E. Proton pump inhibitors display antitumor effects in barrett's adenocarcinoma cells. Frontiers in Pharmacology. 2016;7(NOV):1-1.
Inter-CIBER collaborations with the groups led by:
Dr. Ángela M. Martínez Valverde, Instituto de Investigaciones Biomédicas Alberto Sols, Madrid (CIBERDEM).
Dr. Ana Blas García completed a six-month stay during which she collaborated in different projects studying the molecular mechanisms associated with non-alcoholic fatty liver disease and new therapies for this disease.
Dra. Caty Casas, del Instituto de Neurociencias de la UAB (CIBERNED).
Members of the group are part of the European Project COST Action TRANSAUTOPHAGY: European Network of Multidisciplinary Research and Translation of Autophagy Knowledge.
Dr. Nadezda Apostlova leads a NEAR (Network of Excellence for Autophagy Research) group, a national network of groups that study autophagy.

LEAD RESEARCHER

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PROGRAMMES
**P3**

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# Main lines of research

- Translational Research:
  HCV SUBTYPING: Development of a High resolution HCV subtyping method for clinical diagnosis based on massive sequencing and molecular phylogeny.
  HCV RESISTANCE MUTATIONS by ultra-deep massive sequencing.
  Treatment of HCV infection in different clinical situations: after liver transplant, coinfection with other viruses (HIV, HBV).
  Studies of new infections by molecular phylogeny. Outbreaks and Nosocomial transmission.
  National Strategic Plan for HCV infection 2015. RAS studies in patients that have failed to antiviral treatments.
- 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.

Study of exosomes before, during and after treatment of HCV infection.

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

# Most relevant scientific articles


- Campos-Varela I., Moreno A., Morbey A., Guaraldi G., Hasson H., Bhamidimarri K.R. et al. Treatment of severe recurrent hepatitis C after liver transplantation in HIV infected patients using sofosbuvir-based therapy. Alimentary Pharmacology and Therapeutics. 2016.
- Perales C., Domingo E.. Antiviral strategies based on lethal mutagenesis and error threshold. Current Topics in Microbiology and Immunology. 2016;392:323-339.
- Gregori J., Perales C., Rodriguez-Frias F., Esteban J.I., Quer J., Domingo E.. Viral quasispecies complexity measures. Virology. 2016;493:227-237.
- De Avila A.I., Gallego I., Soria M.E., Gregori J., Quer J., Ignacio Esteban J. et al. Lethal mutagenesis of hepatitis C virus induced by favipiravir. PLoS ONE. 2016;11(10).
- Gallego I, Sheldon J, Moreno E, Gregori J, Quer J, Esteban JI et al. Barrier-Independent, Fitness-Associated Differences in Sofosbuvir Efficacy against Hepatitis C Virus.Antimicrobial agents and chemotherapy. 2016;60(6):3786-93.


# Hightlights

- Our group had led a consortium that has obtained the approval of the CDTI Project IDI20151125 with a total Budget of 8M€ for the next years in collaboration with Roche Sant Cugat: “Plataforma de Medicina de Precisión basada en el desarrollo y uso asistencial de aplicaciones y tecnología de Next-next generation sequencing (NNGS)”.
- Routine clinical use of High-resolution HCV subtyping methodology and exploitation of the EU PATENT No.WO2015001068 A1 will report royalties to CIBER institution in the next weeks.
- We have started studies to patent primers and methods for identification of resistance-associated substitution (RAS) to direct acting antivirals (DAA) used to treat HCV infected patients. CIBER will be well represented. At present, agreements and technical patent documents are being written.
- Our group has centralized the studies of RAS to DAA treatments, based on massive sequencing from the National Strategic Plan for HCV infection 2015. At this moment, 155 RAS reports have been generated for patients from 33 different Hospitals from 9 autonomous communities.
- The methodology of High-resolution HCV subtyping and studies of RAS have been successfully transferred to MiSeq sequencing platform.
- Several studies of accidental Nosocomial HCV transmission have been performed, giving support to the Health Care System.
- A new line of research has been opened; it consists in the study of exosome in serum samples from patients, before, during and after stopping DAA-based treatments.
- Members of the group have actively participated in meetings, congresses and scientific societies.

LEAD RESEARCHER

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Group Website

PROGRAMMES
**P3**

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**Associated members:** Buti Ferrer, María Asunción | Riveiro Barciela, María del Mar | Rodríguez Frías, Francisco

# Main lines of research

- Platform for chronic hepatitis B patients data collection (CIBEREHP).
- Study of hepatitis B virus (HBV) quasispecies using massive sequencing:
  - Study of the regions of HBV envelope proteins involved in the interaction and entry of HBV and hepatitis delta virus (HDV) into hepatocytes (preS1 region).
  - Study of regulatory regions from HBV genome (basal core promoter, enhancer II...).
  - Study of the different viral populations with substitutions, insertions or deletions in the HBV X protein promoter and coding regions, to locate conserved regions that can be used as potential therapeutic targets.
- Study of the clinical application of new markers of chronic HBV infection:
  - Quantification of circulating HBV core protein related antigens (HBcrAg).
  - Quantification of HBV surface antigen (qnHBsAg).
  - Quantification of circulating pregenomic HBV RNA (pgRNA).
- Study of replication of different HBV of genomes in vitro.
- Study of HDV quasispecies by massive sequencing:
  - Evolution rate of circulating HDV RNA in patients with chronic delta hepatitis.
  - Quantification of circulating edited [amber stop codon at position 196 of the delta antigen (HDAg)] and unedited genomes (tryptophan codon at position 196 of the HDAg).
  - Complexity of viral population.
  - Search for interaction mechanisms between HBV and HDV.
- Collaboration with the hepatitis delta international network (HDIN).
- Infection with hepatitis E virus (HEV).

# Most relevant scientific articles


- Manns M., Samuel D., Gane E.J., Mutimer D., McCaughan G., Buti M. et al. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial. The Lancet Infectious Diseases. 2016;16(6):685-697.
- Marcellin P., Ahn S.H., Ma X., Caruntu F.A., Tak W.Y., Elkashab M. et al. Combination of Tenofovir Disoproxil Fumarate and Peginterferon α-2a Increases Loss of Hepatitis B Surface Antigen in Patients with Chronic Hepatitis B. Gastroenterology. 2016;150(1):134-144.e10.
- Homs M., Rodriguez-Frias F., Gregori J., Ruiz A., Reimundo P., Casillas R. et al. Evidence of an exponential decay pattern of the hepatitis delta virus evolution rate and fluctuations in quasispecies complexity in long-term studies of chronic delta infection. PLoS ONE. 2016;11(6):-.
- Riveiro-Barciela M., Sauleda S., Quer J., Salvador F., Gregori J., Piron M. et al. Red blood cell transfusion-transmitted acute hepatitis E in an immunocompetent subject in Europe: A case report. Transfusion. 2016.
- Quer J., Rodriguez-Frias F., Gregori J., Tabernero D., Soria M.E., Garcia-Cehic D. et al. Deep sequencing in the management of hepatitis virus infections. Virus Research. 2016.


# Hightlights

In 2016 our group has continued to actively participate in different international multicenter clinical trials about hepatitis B (HBV) and hepatitis C (HCV) virus treatment. The data recorded on the CIBEREHP platform has been analyzed to evaluate the utility of the PAGE-B score, to estimate the likelihood of developing hepatocellular carcinoma in patients treated with entecavir or tenofovir for more than 4 years in routine clinical practice. In the patients selected for this evaluation we also studied the virological, biochemical and serological response, and the renal safety of the long-term therapy. Moreover, we analysed the utility of HBsAg and HBcrAg levels for the correct classification of HBeAg negative patients in inactive HBV carriers and HBeAg negative chronic hepatitis B. This characterization is important since the clinical management of both patients' groups is different. The impact of HBV genotype on serum levels of both markers and the evolution of HBsAg levels in HBeAg negative patients during their follow-up has also been assessed.

Regarding clinical laboratory and basic research, the subgenotypic classification of HCV by massive sequencing has been consolidated, and we have begun collaborating in the adaptation of this technology for detection of HCV resistance to the new antiviral treatments. Finally, it is also noteworthy the study for the first time of the evolution rate of the hepatitis delta virus (HDV) for more than 10 years by massive sequencing. This technology has also been applied to the quantitative study of edited and unedited circulating HDV genomes, as well as changes in complexity of the HBV quasispecies due to the interaction with HDV.

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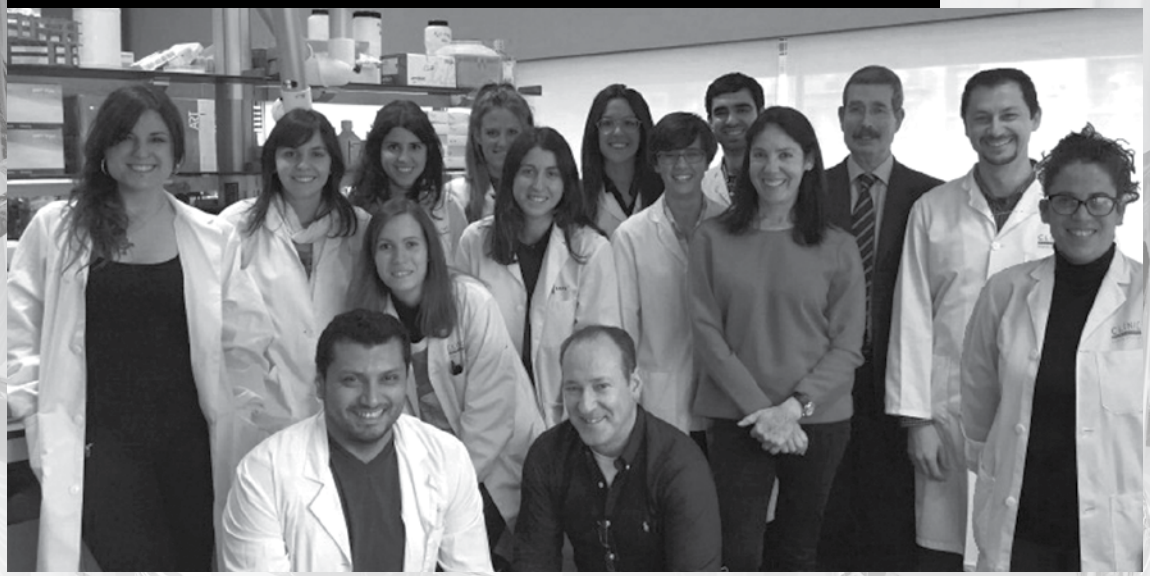
PROGRAMMES
**P1**



GROUP MEMBERS

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**Associated members:** Caballería Rovira, Joan | García Ruiz, María del Carmen | Lluis Duquez, 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.
- Identification of novel therapeutic targets in patients with alcoholic liver disease.
- Characterization of  mechanisms involved in sorafenib cytotoxicity in hepatocellular carcinoma.

# Most relevant scientific articles


- Klionsky DJ, Abdelmohsen K, Abe A, Abedin MJ, Abeliovich H, Acevedo Arozena A et al. Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition). Autophagy. 2016;12(1):1-222.
- 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. 2016.
- Prieto-Dominguez N., Ordonez R., Fernandez A., Mendez-Blanco C., Baulies A., Garcia-Ruiz C. et al. Melatonin-induced increase in sensitivity of human hepatocellular carcinoma cells to sorafenib is associated with reactive oxygen species production and mitophagy. Journal of Pineal Research. 2016.
- Blaya D., Coll M., Rodrigo-Torres D., Vila-Casadesus M., Altamirano J., Llopis M. et al. Integrative microRNA profiling in alcoholic hepatitis reveals a role for microRNA-182 in liver injury and inflammation. Gut. 2016.
- Nuno-Lambarri N., Dominguez-Perez M., Baulies-Domenech A., Monte M.J., Marin J.J.G., Rosales-Cruz P. et al. Liver Cholesterol Overload Aggravates Obstructive Cholestasis by Inducing Oxidative Stress and Premature Death in Mice. Oxidative Medicine and Cellular Longevity. 2016;2016.


# Hightlights

The most relevant activities performed during 2016 centered on the identification of new therapeutic targets in patients with alcoholic steatohepatitis and the characterization of new cytotoxic mechanisms of sorafenib and events associated with its resistance in hepatocellular carcinoma, including the disruption of mitophagy and the catabolism of the ceramide through glucosilceramide synthase induction. In relation with the processes of autophagy, we have participated in an international initiative to elaborate the guides for the assays and interpretation of autophagy and its implications in physiopathological processes. Furthermore, we have identified that hepatocellular free cholesterol plays a key role in obstructive cholestasis due to the increase of the mitochondrial oxidative stress and alterations in the expression of the antioxidant defenses. During 2016 we have received financial support from the NIH/NIAAA through an agreement with the University of Southern California (USC Los Angeles, CA) to investigate the role of mitochondrial cholesterol and StARD1 in alcoholic liver disease. As a result of the above-mentioned action, we have generated a chimeric StARD1 floxed mice that have been crossed with Alb-Cre or Mxl-Cre to produce mice with selective deficiency of StARD1 in hepatocytes or myeloid cells, respectively and these results are now in consideration. Finally, one of the most prominent aspects during 2016 has been the development of a mouse (FRGN) that allows the repopulation of the mouse liver with human hepatocytes and human hematopoietic cells, which will serve as a great translational research tool for the study of human liver diseases, an activity that has been partly supported from a strategic action from the CIBEREHD.

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## Main lines of research

- Efficacy of new antiviral regimens against HCV and relevance of resistance-associated variants in treatment failure.
- Dynamics of resistance-associated variants during therapy with direct-acting antivirals by massive sequencing.
- Study of the innate immune response in patients with chronic hepatitis C receiving direct-acting antivirals.
- 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.
- 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.

# Most relevant scientific articles


- Gambato M., Perez-del-Pulgar S., Hedskog C., Svarovskia E.S., Brainard D., Denning J. et al. Hepatitis C Virus RNA Persists in Liver Explants of Most Patients Awaiting Liver Transplantation Treated With an Interferon-Free Regimen. Gastroenterology. 2016;151(4):633-636.e3.
- Reig M., Marino Z., Perello C., Inarrairaegui M., Ribeiro A., Lens S. et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. Journal of Hepatology. 2016;65(4):719-726.
- Perello M. C., Fernandez-Carrillo C., Londono M.-C., Arias-Loste T., Hernandez-Conde M., Llerena S. et al. Reactivation of Herpesvirus in Patients With Hepatitis C Treated With Direct-Acting Antiviral Agents. Clinical Gastroenterology and Hepatology. 2016;14(11):1662-1666.e1.
- Manns M., Samuel D., Gane E.J., Mutimer D., McCaughan G., Buti M. et al. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial. The Lancet Infectious Diseases. 2016;16(6):685-697.
- Lens S., Torres F., Puigvehi M., Marino Z., Londono M.-C., Martinez S.M. et al. Predicting the development of liver cirrhosis by simple modelling in patients with chronic hepatitis C. Alimentary Pharmacology and Therapeutics. 2016.


# Hightlights

Participation and coordination of the Spanish Strategic Plan of Hepatitis C, aimed at assessing the impact of treatment with direct acting antivirals on the natural history of advanced liver disease. Among the most relevant achievements are: a) the effect of sustained virological response on portal hypertension (presented at the AASLD meeting 2016), b) the impact of antiviral therapy on hepatocellular carcinoma recurrence (Reig, Mariño et al. J Hepatol 2016), and c) the effect of sustained virological response in patients with decompensated cirrhosis awaiting liver transplantation (Pascasio et al., EASL 2016)

Participation and leadership of international clinical trials and investigator initiated studies to assess the efficacy and safety of new direct acting antivirals against hepatitis C virus in special populations: 1) renal transplant recipients (Fernández et al. J Hepatol in press), 2) patients with decompensated cirrhosis (Fernández-Carrillo et al. Hepatology in press; Manns et al. Lancet Infectious Dis 2016) and 3) patients in the waiting list for liver transplantation (Gambato et al. Gastroenterology 2016).

Contribution in de development of clinical guidelines: “EASL Clinical Practice Guidelines: Liver Transplantation” (J. Hepatol. 2016) and “EASL Recommendations on Treatment of Hepatitis C 2016” (J. Hepatol. 2016).

Following the stay of Dr. Sofía Pérez del Pulgar in Dr. Fabien Zoulim’s Lab (INSERM U1052, CRCL, Lyon, France), we have successfully established the HBV cell culture system and started a project aimed to study cccDNA persistence during HBV infection in vivo, and in vitro using a bioreactor that mimics the liver microenvironment (ISCIII PI16/00111). This translational project will be developed in collaboration with Dr. Barbara Testoni and Dr. Fabien Zoulim (INSERM U1052, CRCL, University of Lyon, France), Dr. Jordi Gracia-Sancho (IDIBAPS, Hospital Clinic de Barcelona, CIBEREHD) and Dr. Francisco Rodríguez-Frías (Fundación Hospital Univesitario Vall d’Hebron–Institut de Recerca, CIBEREHD).

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PROGRAMMES
**P1 | P2**

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# 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


- Ramos J.M., Vidal I., Bellot P., Gomez-Hurtado I., Zapater P., Such J. Comparison of the in vitro susceptibility of rifaximin versus norfloxacin against multidrug resistant bacteria in a hospital setting. A proof-of-concept study for use in advanced cirrhosis. Gut. 2016;65(1):182-183.
- Gutierrez A., Zapater P., Juanola O., Sempere L., Garcia M., Laveda R. et al. Gut Bacterial DNA Translocation is an Independent Risk Factor of Flare at Short Term in Patients With Crohn's Disease. American Journal of Gastroenterology. 2016.
- Juanola O., Gomez-Hurtado I., Zapater P., Moratalla A., Caparros E., Pinero P. et al. Selective intestinal decontamination with norfloxacin enhances a regulatory T cell-mediated inflammatory control mechanism in cirrhosis. Liver International. 2016.
- Julia A., Vinaixa M., Domenech E., Fernandez-Nebro A., Canete J.D., Ferrandiz C. et al. Urine metabolome profiling of immune-mediated inflammatory diseases. BMC Medicine. 2016;14(1).


# Hightlights

During 2016, our Group has performed its research activity within the 4 ongoing national projects and has continued its collaborations with different national and international research groups. Group's activity has been present in all international meetings during the year and has followed in its young researchers formative activity. In 2016, the Group has been involved in the organization of V Curso de Gastroenterología y XI Curso de Hematología "Miguel Pérez-Mateo", supported by CIBEREHD and celebrated in Hospital General Universitario de Alicante.

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PROGRAMMES
**P3**

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# Main lines of research

- Angiogenesis and fibrogénesis in chronic liver diseases of viral etiology.
- Identification of prognostic biomarkers of chronic liver diseases progression.
- Monitoring immune response during chronic hepatitis C treatment with direct acting antivirals: relevance in the advent/recurrence of hepatic and extrahepatic complications.
- Viral and cellular determinants in hepatitis C virus infection.
- Hepatitis B Virus X protein in hepatocellular carcinoma.

# Most relevant scientific articles


- Hernández-Bartolomé Á, López-Rodríguez R, García-Buey L, Martín-Vílchez S, Rodríguez-Muñoz Y, Borque MJ et al. Intrahepatic angiopoietin-2 correlates with chronic hepatitis C progression and is induced in hepatitis C virus replicon systems. Liver international: official journal of the International Association for the Study of the Liver. 2016.
- Hernández-Bartolome A., Lopez-Rodriguez R., Borque M.J., Gonzalez-Moreno L., Real-Martinez Y., Garcia-Buey L. et al. Angiopoietin-2/angiopoietin-1 as non-invasive biomarker of cirrhosis in chronic hepatitis C. World Journal of Gastroenterology. 2016;22(44):9744-9751.
- Madejon A., Romero M., Hernández A., Garcia-Sanchez A., Sanchez-Carrillo M., Olveira A. et al. Hepatitis B and D viruses replication interference: Influence of hepatitis B genotype. World Journal of Gastroenterology. 2016;22(11):3165-3174.
- Martin-Dominguez V., Diaz-Menendez A., Santander C., Garcia-Buey L.C. Portal hypertensive polyps, a new entity? Revista Espanola de Enfermedades Digestivas. 2016;108(5):279-280.


# Hightlights

During last year we have been mainly focused on investigating the impact of Hepatitis C Virus (HCV) on the expression of angiopoietins (Ang1 and Ang2) by hepatocytes, the meaning of these factors on chronic hepatitis C (CHC) progression and the possible involved signaling routes. Interestingly, our recent findings have shown that intrahepatic levels of Ang2 significantly correlate with the necro-inflammatory activity index of the liver as well as with the fibrosis stage of CHC patients. Furthermore, the in vitro expression of Ang2 by different HCV replicons was notably stimulated by the influence of either structural or nonstructural HCV genomic regions but encouragingly reduced by the inhibition of PI3K signaling, highlighting its relevance as a target for therapeutic intervention.
Furthermore, concerning to the HCV strategic line of CIBEREHD we have been studying potential immune factors related to the emergence/recurrence of hepatic and extrahepatic manifestations associated with chronic HCV infection after direct acting antivirals (DAA) therapy. Despite this treatment causes a significant reduction of these complications, not all patients benefit equally, especially those with advanced fibrosis, thus requiring a close monitoring of its progression. In this regard, owing to the central role played by the immune system in the therapeutic response and the appearance of various disorders associated with CHC, we are monitoring the peripheral immunologic profile of patients before, during and after treatment with AADs by a wide cytokine array of more than 100 factors in order to detect any anomalies that help to establish a more accurate prognosis for these patients.

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PROGRAMMES
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# 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


- Monte M.J., Alonso-Pena M., Briz O., Herraez E., Berasain C., Argemi J. et al. ACOX2 deficiency: An inborn error of bile acid synthesis identified in an adolescent with persistent hypertransaminasemia. Journal of Hepatology. 2016.
- Banales J.M., Cardinale V., Carpino G., Marzioni M., Andersen J.B., Invernizzi P. et al. Expert consensus document: Cholangiocarcinoma: current knowledge and future perspectives consensus statement from the European Network for the Study of Cholangiocarcinoma (ENS-CCA). Nature Reviews Gastroenterology and Hepatology. 2016;13(5):261-280.
- Marin J.J.G., Lozano E., Perez M.J. Lack of mitochondrial DNA impairs chemical hypoxia-induced autophagy in liver tumor cells through ROS-AMPK-ULK1 signaling dysregulation independently of HIF-1α. Free Radical Biology and Medicine. 2016; 101:71-84.
- Gonzalez-Sanchez E., Perez M.J., Nytofte N.S., Briz O., Monte M.J., Lozano E. et al. Protective role of biliverdin against bile acid-induced oxidative stress in liver cells. Free Radical Biology and Medicine. 2016; 97:466-477.
- Abu-Hayyeh S., Ovadia C., Lieu T., Jensen D.D., Chambers J., Dixon P.H. et al. Prognostic and mechanistic potential of progesterone sulfates in intrahepatic cholestasis of pregnancy and pruritus gravidarum. Hepatology. 2016.


# Hightlights

During 2016, the research group in Experimental Hepatology and Drug Targeting (HEVEFARM) has collaborated with other members of the CIBEREHD- Bujanda and Bañales (San Sebastián), Prieto, Ávila and Sangro (Pamplona), Mato and Martínez-Chantal (Bilbao ), Muntané (Sevilla), Sánchez de Medina and Martínez Augustín (Granada), Armengol, Bruix and Fernandez-Checa (Barcelona) - and with other European groups, which has resulted in the staying in the HEVEFARM during much of 2016 of two Researchers from Italy and the Netherlands. In the educational field, HEVEFARM has coordinated a Doctorate Program and a University Master's Degree in Pathophysiology and Cellular and Molecular Pharmacology. Activities within the framework of the European network for the study of cholangiocarcinoma (ENS-CCA) have also been intensified. The work in the research lines of the HEVEFARM has allowed to achieve advances related to chemoresistance and the development of chemosensitization strategies in liver and gastric cancer. Regarding the characterization of hepatocarcinogenesis processes, two studies have been completed that regard the hepatoprotective capacity of endogenous molecules with antioxidant capability, such as biliverdin and the deregulation in liver tumor cells of mitochondrial genome-mediated retrograde control of the nuclear genome in the alteration of autophagy induced by hypoxia. On the other hand, a research study carried out in collaboration with Dr. Jesús Prieto (Pamplona) has led to the identification of a novel nosological entity called "ACOX2 deficiency". This is due to a genetic alteration that affects the normal function of hepatocyte peroxisomes, which results in enhanced liver fragility of the patient. Individuals suffering from ACOX2 deficiency present higher predisposition to develop hepatocellular injury when they are exposed to drugs that induce low hepatotoxicity in normal liver. In this study the molecular bases of the disorder have been identified, which will permit an early diagnosis and an effective treatment of this pathology.

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**P3**

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# Main lines of research

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

# Most relevant scientific articles


- Madejon A., Romero M., Hernandez A., Garcia-Sanchez A., Sanchez-Carrillo M., Olveira A. et al. Hepatitis B and D viruses replication interference: Influence of hepatitis B genotype. World Journal of Gastroenterology. 2016;22(11):3165-3174.
- Sarrazin C., Manns M., Calleja J.L., Garcia-Samaniego J., Forns X., Kaste R. et al. HCVerso3: An open-label, phase IIb study of faldaprevir and deleobuvir with ribavirin in hepatitis C virus genotype-1b-infected patients with cirrhosis and moderate hepatic impairment. PLoS ONE. 2016;11(12).
- Buti M., Calleja J.L., Garcia-Samaniego J., Serra M.A., Crespo J., Romero M. et al. Elimination of hepatitis C in Spain: Adaptation of a mathematical model based on the public health strategic plan for addressing hepatitis C in the National Health System. Medicina Clinica. 2016.
- Rodríguez-Nóvoa S, García-Samaniego J, Prieto M, Calleja JL, Pascasio JM, Delgado Blanco M et al. Altered Underlying Renal Tubular Function in Patients With Chronic Hepatitis B Receiving Nucleos(t)ide Analogs in a Real-World Setting: The MENTE Study.Journal of clinical gastroenterology. 2016;50(9):779-89.


# Hightlights

Completion of the technology transfer process to ARCIS Ltd of SNPs detection models coupled to simplified nucleic acid extraction systems for its use at diagnostic points of care. (Project EHD15PE16: "Development of a detection system of the IL28B single nucleotide polymorphism (rs12979860) coupled to a simplified method of DNA extraction").
Completion of project FIS PI12 / 02146 entitled "Identification in plasma and PBMCs of resistance variants to treatment with telaprevir or boceprevir against HCV by cold-PCR. Use in Treatment Response Monitoring, "designed for the identification of drug resistant variants in patients with chronic hepatitis C treated with direct acting antiviral drugs.
Participation in the 2nd call for the program "Aid for the Execution of Projects and Activities of Medical Education" promoted by Gilead Science S.L.U. In the "Program for detection of HBV and HCV Infection in Primary Care. Referral to Specialized Hospital Consultation", with the project entitled" Training Activities Directed to Medical Staff of Primary Care for the Update of Strategies for Approach of Chronic Hepatitis C after the Implantation of New Treatments with Directives Direct Antivirals".
Direction of two Final Degree projects entitled "Functional analysis of hepatitis C virus in lymphocytes of patients with chronic hepatitis C responders to antiviral treatment. Implications in the concept of viral eradication induced by therapy "and" Design of a database of genetic markers and clinical parameters to identify prognostic markers of progression to liver fibrosis in patients with viral hepatopathy " as well as the Master degree final project titled" Analysis Of cellular epigenetic modifications induced by hepatitis B virus (HBV) infection."
Participation in clinical trials of direct action drugs against HCV.

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**P1**


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# Main lines of research

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

# Most relevant scientific articles


- Villanueva C., Albillos A., Genesca J., Abraldes J.G., Calleja J.L., Aracil C. et al. Development of hyperdynamic circulation and response to β-blockers in compensated cirrhosis with portal hypertension. Hepatology. 2016;63(1):197-206.
- Conejo I., Augustin S., Pons M., Ventura-Cots M., Gonzalez A., Esteban R. et al. Alcohol consumption and risk of infection after a variceal bleeding in low-risk patients. Liver International. 2016.
- Nevens F., Andreone P., Mazzella G., Strasser S.I., Bowlus C., Invernizzi P. et al. A Placebo-controlled trial of obeticholic acid in primary biliary cholangitis. New England Journal of Medicine. 2016;375(7):631-643.
- Ventura-Cots M., Concepcion M., Arranz J.A., Simon-Talero M., Torrens M., Blanco-Grau A. et al. Impact of ornithine phenylacetate (OCR-002) in lowering plasma ammonia after upper gastrointestinal bleeding in cirrhotic patients. Therapeutic Advances in Gastroenterology. 2016;9(6):823-835.
- Abraldes J.G., Bureau C., Stefanescu H., Augustin S., Ney M., Blasco H. et al. Noninvasive tools and risk of clinically significant portal hypertension and varices in compensated cirrhosis: The “Anticipate” study. Hepatology. 2016;64(6):2173-2184.


# Hightlights

In 2016 the most relevant feature of our group is the substantial increase in clinical cooperative studies, both at the national and international level. It is worht to mention the participation of our group in an international clinical trial funded by the European Union.

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# 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


- Pauta M., Rotllan N., Fernandez-Hernando A., Langhi C., Ribera J., Lu M. et al. Akt-mediated foxo1 inhibition is required for liver regeneration. Hepatology. 2016.
- Fernandez-Varo G., Oro D., Cable E.E., Reichenbach V., Carvajal S., de la Presa B.G. et al. Vasopressin 1a receptor partial agonism increases sodium excretion and reduces portal hypertension and ascites in cirrhotic rats. Hepatology. 2016;63(1):207-216.
- Claria J., Stauber R.E., Coenraad M.J., Moreau R., Jalan R., Pavesi M. et al. Systemic inflammation in decompensated cirrhosis: Characterization and role in acute-on-chronic liver failure. Hepatology. 2016;64(4):1249-1264.
- Ariza X., Graupera I., Coll M., Sola E., Barreto R., Garcia E. et al. Neutrophil gelatinase-associated lipocalin is a biomarker of acute-on-chronic liver failure and prognosis in cirrhosis. Journal of Hepatology. 2016.
- Huelin P., Piano S., Sola E., Stanco M., Sole C., Moreira R. et al. Validation of a Staging System for Acute Kidney Injury in Patients With Cirrhosis and Association With Acute-on-Chronic Liver Failure. Clinical Gastroenterology and Hepatology. 2016.


# Hightlights

The group's clinical and translational research has described new biomarkers to evaluate the progression of cirrosis and the development of ACLF, of these NGAL is the most promising. We have also described the role of systemic inflammation and molecular pathways of liver injury in the pathophysiology of cirrhosis progression. The clinical investigation has led to the validation of a new classification of AKI.
We have provided solid evidence that systemic inflammation, and the cytokine storm in particular, is the main driver of Acute-on-Chronic Liver Failure in patients with decompensated cirrhosis. In addition, we have unveiled the mechanisms by which specialized pro-resolving lipid mediators modulate the cell signaling of the anti-inflammatory cytokine IL-10, and thus promote the resolution of inflammation in visceral adipose tissue from obese individuals at risk of developing non-alcoholic fatty liver disease.

## PROJECTS

- Jiménez W and Fernández-Varo G. Utilidad terapéutica de las nanopartículas de óxido de cerio en las enfermedades hepáticas. Sponsored by MINECO/SAF15-64126-R. Duration: 1/1/2016-31/12/2018.
- Morales-Ruiz M. Potencialidad terapéutica del fosfoproteoma de Akt/PKB en la regeneración hepática y en la cirrosis. Sponsored by MINECO/SAF13-41840-R. Duration: 1/1/2014-31/5/2017.
- Casals G. Evaluación de las propiedades antioxidantes y antiinflamatorias de las nanopartículas de óxido de cerio como nueva estrategia terapéutica en la esteatosis hepática. Sponsored by MINECO/PI15/00777. Duration: 1/1/2016-31/12/2018
- Finally, during 2016 has led the design of a new European Horizon 2020 Project, aimed at evaluating the utility of combined rifaximin and statin therapy to prevent the progression of Cirrhosis.

## EUROPEAN PATENT

Jiménez W, Puntes VF and Fernández-Varo G. Ceria nanoparticles for use in the treatment of hepatocellular carcinoma. Application number: EP16163838.2. Date: 5/4/2016.

LEAD RESEARCHER

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PROGRAMMES
**P3**

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# Main lines of research

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

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

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


- De Avila A.I., Gallego I., Soria M.E., Gregori J., Quer J., Ignacio Esteban J. et al. Lethal mutagenesis of hepatitis C virus induced by favipiravir. PLoS ONE. 2016;11(10).
- Ariza-Mateos A., Diaz-Toledano R., Block T.M., Prieto-Vega S., Birk A., Gomez J. Geneticin stabilizes the open conformation of the 5' region of hepatitis C virus RNA and inhibits viral replication. Antimicrobial Agents and Chemotherapy. 2016;60(2):925-935.
- Gregori J., Perales C., Rodriguez-Frias F., Esteban J.I., Quer J., Domingo E. Viral quasispecies complexity measures. Virology. 2016; 493:227-237.
- Gallego I, Sheldon J, Moreno E, Gregori J, Quer J, Esteban JI et al. Barrier-Independent, Fitness-Associated Differences in Sofosbuvir Efficacy against Hepatitis C Virus.Antimicrobial agents and chemotherapy. 2016;60(6):3786-93.
- Quer J., Rodriguez-Frias F., Gregori J., Tabernero D., Soria M.E., Garcia-Cehic D. et al. Deep sequencing in the management of hepatitis virus infections. Virus Research. 2016.


# Hightlights

The joint CSIC molecular virology group was formed in 2007 to bring together scientists investigating the structural and evolutionary aspects of the hepatitis C virus in terms of viral targets, their therapeutic agents and the resistances HCV acquieres to therapeutic agents. Most reported activities are collaborations with a number of CIBEREHD members from other research groups. Concerned with the quasispecies nature of the HCV genome and its high rate of evolution, our studies focus on two main premises: firstly, that HCV fitness may play a part in reducing viral sensitivity to the drug sofosbuvir; and secondly, that favipiravit, a new drug used to treat influenza, offers a novel option for HCV treatment. This is because its mechanism of action acts at least partially through a lethal mutagenesis during RNA replication. With regard to RNA structures present in the 5' region of the HCV genome, we found that Geneticin®, a well-known antibiotic agent that binds to the bacterial ribosomal RNA, can also impede the structural switch of HCV RNA in the 5' region and inhibit viral replication.

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PROGRAMMES

**P1 | P3 | P4**

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# Main lines of research

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

# Most relevant scientific articles


- Bozic M., Guzman C., Benet M., Sanchez-Campos S., Garcia-Monzon C., Gari E. et al. Hepatocyte vitamin D receptor regulates lipid metabolism and mediates experimental diet-induced steatosis. Journal of Hepatology. 2016.
- Prieto-Dominguez N., Ordonez R., Fernandez A., Mendez-Blanco C., Baulies A., Garcia-Ruiz C. et al. Melatonin-induced increase in sensitivity of human hepatocellular carcinoma cells to sorafenib is associated with reactive oxygen species production and mitophagy. Journal of Pineal Research. 2016.
- Crespo I., San-Miguel B., Sanchez D.I., Gonzalez-Fernandez B., Alvarez M., Gonzalez-Gallego J. et al. Melatonin inhibits the sphingosine kinase 1/sphingosine-1-phosphate signaling pathway in rabbits with fulminant hepatitis of viral origin. Journal of Pineal Research. 2016.
- Booth L., Roberts J.L., Ecroyd H., Tritsch S.R., Bavari S., Reid S.P. et al. AR-12 Inhibits Multiple Chaperones Concomitant With Stimulating Autophagosome Formation Collectively Preventing Virus Replication. Journal of Cellular Physiology. 2016;231(10):2286-2302.
- Prieto-Dominguez N., Ordonez R., Fernandez A., Garcia-Palomo A., Muntane J., Gonzalez-Gallego J. et al. Modulation of autophagy by sorafenib: Effects on treatment response. Frontiers in Pharmacology. 2016;7(JUN).


# Hightlights

The research group has published seven articles in indexed journals (three in collaboration with other CIBEREHD groups); five are 1st quartile (including three 1st decile). Among competitive research projects developed, it is worth mentioning those related with the effect of intestinal microbiota modulation by flavonoid treatment, microbiota transplant and exercise in experimental models of non-alcoholic fatty liver disease (financed by the Plan Estatal de Investigación Científica y Técnica and the Junta de Castilla y León), or the therapeutic role of melatonin in experimental models of liver fibrosis and hepatocarcinoma. Moreover, studies have been carried out on the role of vitamin D receptor in the appearance and progression of hepatic steatosis or the antiviral efficacy of new chaperone inhibitors. Concerning translation of results to clinical practice we have participated in one clinical assay on the efficacy and safety of ABT-493/ABT-530 in adults with chronic infection by HCV GT1 and cooperate with the European Prospective Drug-Induced Liver Injury Registry (Pro-Euro-DILI Registry). During this period we have collaborated with the following CIBEREHD groups: Program 1 (J. V. Castell, J. C. Fernández-Checa, R. Andrade, M. de la Mata, C. García-Monzón), Program 3 (M. Romero, J. García-Samaniego), Program 4 (F. J. Padillo, P. Parrilla). We have also maintained international collaborations with the Universities of Arizona, Virginia Commonwealth and Georgia Regents (USA), the Army Medical Research Institute of Infectious Diseases (USA), the University de Wollongong (Australia), the University of Buenos Aires (Argentina), the Universidad Autónoma of Chile and the Federal Universities of Santa María and Rio Grande do Sul (Brazil).

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# Main lines of research

The Research Group on Complications of Cirrhosis at the Hospital de Sant Pau in Barcelona has followed two fundamental lines of research. We have 13 publications in journals, corresponding 11 of them to international journals and we have multicenter studies with different CIBEREHD groups involved.
Dr. Germán Soriano has directed publications to evaluate predictive factors of mortality in patients with spontaneous bacterial peritonitis, a study of the human serum microbiome in patients with cirrhosis, and the effect of exercise on the patient with cirrhosis on their functional capacity and the risk of falls.
We are collaborating with the Immunology Service of our hospital, Research Group of Dr. F. Azpiroz of the Hospital Vall d'Hebron and CLIF Consortium. Currently we are studying various factors of intestinal barrier and microbiota, both in an experimental model in cirrhosis and also in patients with cirrhosis. We have two national research projects and one private research project. Dr. Soriano has collaborated in two publications of hepatotoxicity of the group of Dr. R. Andrade and one publication on chronic liver failure of the CLIF Consortium.
The other research line of the group is directed by Dr. Villanueva and is dedicated to the study and management of portal hypertension. This research line in our group is essentially clinical. Dr. Villanueva and his collaborators have followed their own research and have collaborated with other groups on this field, such as: Hospital Clinic, Hospital Gregorio Maranon, Hospital Vall d'Hebron, Puerta de Hierro, etc. Two publications correspond to multicenter studies of prevention of variceal hemorrhage with drugs and the publication related to the control variceal hemorrhage by balloon vs stents. Dr. Villanueva has obtained the grant of intensification awarded by the Hospital de Sant Pau and has a national research fellowship.

# Most relevant scientific articles


- Villanueva C., Albillos A., Genesca J., Abraldes J.G., Calleja J.L., Aracil C. et al. Development of hyperdynamic circulation and response to β-blockers in compensated cirrhosis with portal hypertension. Hepatology. 2016;63(1):197-206.
- Poca M., Alvarado-Tapias E., Concepcion M., Perez-Cameo C., Canete N., Gich I. et al. Predictive model of mortality in patients with spontaneous bacterial peritonitis. Alimentary Pharmacology and Therapeutics. 2016;44(6):629-637.
- Abraldes JG, Villanueva C, Aracil C, Turnes J, Hernandez-Guerra M, Genesca J et al. Addition of Simvastatin to Standard Therapy for the Prevention of Variceal Rebleeding Does not Reduce Rebleeding but Increases Survival in Patients With Cirrhosis.Gastroenterology. 2016;150(5).
- Berzigotti A, Albillos A, Villanueva C, Genescá J, Ardevol A, Augustín S et al. Effects of an intensive lifestyle intervention program on portal hypertension in patients with cirrhosis and obesity: The sportdiet study.Hepatology (Baltimore, Md.). 2016.
- Santiago A., Pozuelo M., Poca M., Gely C., Nieto J.C., Torras X. et al. Alteration of the serum microbiome composition in cirrhotic patients with ascites. Scientific Reports. 2016;6.


# Hightlights

PROJECTS

- Study of the fragility syndrome in patients with hepatic cirrhosis. Relationship with cognitive impairment and quality of life.
- Treatment of hepatorenal syndrome with terlipressin associated with hemodynamic response.
- Study of the effect of VSL#3 on cognitive function, risk of falls and quality of life in patients with cirrhosis.
- Albumin administration in the prevention of hepatorenal syndrome and death in patients with cirrhosis, bacterial infections other than spontaneous bacterial peritonitis and high risk of hospital mortality.
- Study of the alterations of the intestinal barrier in patients and experimental models of cirrhosis.
- Composition of the microbiota of gallbladder bile in an experimental model in C57BL / 6 mouse and study the effect of different diets.

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# Main lines of research

- **Diseases of the digestive tract associated with acid inhibition of COX or *H. Pylori* infection.**
  Identification of environmental and genetic risk factors for injuries and complications of gastro-intestinal mucosa, development of prevention and treatment strategies. • Biological and molecular mechanisms of neoplastic progression in Barrett's esophagus: identification of new biomarkers and therapeutic targets for chemoprevention. • Identification of effective bactericide compounds against *Helicobacter pylori* infection.
- **Genetic and environmental determinants involved on inflammatory or tumour processes of the digestive tract.**
  Genetic susceptibility and Helicobacter pylori infection associated with the development and prognosis of gastric cancer. • Study of the genetic basis of susceptibility to hereditary and familial colon cancer. • Diagnostic and Therapeutic Targets.
- **Stem cells and cell therapy for different digestive and liver gastrointestinal diseases.**
  Identification, separation and molecular characterization of cancer stem cells in esophageal cancer. • Optimization of isolation and culture of human hepatocytes to be used for cell therapy source. Investigation of the role of bone marrow stem cells in liver regeneration in different human models of disease. • Bioengineering of organs and tissues (hepatic and pancreatic). Cellular therapies are being developed in patients, in a clinic level just like expansion of human stem cells of fetal and adult liver.
- **Identification of bioactive compounds against protein targets related with digestive pathologies.**
  Transport and selective release by using multifunctional nanoparticles and nanosphere/nanoaggregated polymers • Selected targets are associated with colon cancer (BFT), pancreatic cancer (NUPR1), Clostridium difficile infection (DPC) and viral hepatitis C (HCV NS3 protease). We work with gold nanoparticles (NP) as nanospheres /nanoclusters of polymers for drug transport and release.

# Most relevant scientific articles


- Chueca E., Apostolova N., Esplugues J.V., Garcia-Gonzalez M.A., Lanas A., Piazuelo E. Proton pump inhibitors display antitumor effects in barrett's adenocarcinoma cells. Frontiers in Pharmacology. 2016;7(NOV):1-1.
- Rodriguez L.A.G., Martin-Perez M., Hennekens C.H., Rothwell P.M., Lanas A. Bleeding risk with long-term low-dose aspirin: A systematic review of observational studies. PLoS ONE. 2016;11(8).
- Scarpignato C, Dolak W, Lanas A, Matzneller P, Renzulli C, Grimaldi M et al. Rifaximin Reduces Number and Severity of Intestinal Lesions Associated With use of Non-steroidal Anti-inflammatory Drugs in Humans.Gastroenterology. 2016.
- Vaduganathan M., Bhatt D.L., Cryer B.L., Liu Y., Hsieh W.-H., Doros G. et al. Proton-Pump Inhibitors Reduce Gastrointestinal Events Regardless of Aspirin Dose in Patients Requiring Dual Antiplatelet Therapy. Journal of the American College of Cardiology. 2016.
- Halvorsen S, Storey RF, Rocca B, Sibbing D, Ten Berg J, Grove EL et al. Management of antithrombotic therapy after bleeding in patients with coronary artery disease and/or atrial fibrillation: expert consensus paper of the European Society of Cardiology Working Group on Thrombosis. European heart journal. 2016.


# Hightlights

## PROJECTS

- Asunción García. PI15/00331. Innate and adaptive immunity in gastric cancer. Relevance of gene-gene and gene-environmentinteractions on the risk and prognosis of the disease.
- Olga Abián. PI15/00663. Calorimetric analysis of protein interaction with plasma metabolites: A fast and noninvasive test for the early diagnosis and follow-up of gastrointestinal tumors (DIGCal).
- Pedro Baptista. PI15/00563. Ex vivo Re-vascularization in Porcine Liver Bioengineering – A critical First Step Towards Effective Transplantation on Bioengineered Livers.
- 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. IBD-CHARACTER, Grant agreement no: 305676.
- Pedro Baptista. Proposal 660554. Marie Curie 2015 Liver Bioengineering. "Ex vivo Re-vascularization in Porcine Liver Bioengineering – A critical First Step Towards Effective Transplantation on Bioengineered Livers".

## CLINICAL GUIDELINES

- Halvorsen S,.…. Lanas A, ESC Working Group on Thrombosis. Management of antithrombotic therapy after bleeding in patients with coronary artery disease and/or atrial fibrillation: expert consensus paper of the European Society of Cardiology Working Group on Thrombosis. Eur Heart J. 2016 Oct27.
- Gisbert JP, ..,…Gomollón F, Lanas Á,... IV Spanish Consensus Conference on Helicobacter pylori infection treatment. Gastroenterol Hepatol. 2016; 39:697-721
- González-Lama , ….J.P. Gisbert , M. Chaparro , E. Domènech , M. Esteve y F. Gomollón . Recommendations by the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU) about management of patients with spondyloarthritis associated to inflammatory bowel disease. Current IBD 2016
- Dr. Lanas is Associated Editor of Am J Gastroenterol (D1), Frontiers in Pharmacology (Q1), member of the Editorial Board of Clin Gastroenterol Hepatol (Q1), and Scientific Director of the Health Research Institute of Aragon. Dr. Gomollon is member of the Editorial Board of J Crohns Colitis (Q1).

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PROGRAMMES
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# Main lines of research

- **Dual Role of COX-2 in hepatic pathophysiology:** Given the protective role of COX-2 in many of the studied diseases but also taking into account its role as inflammatory agent; it is clear that COX-2 exerts various effects depending on the time and cell type that expresses. Our goal is to further deepen this topic. For this we have transgenic animals and cell models for COX-2.
- **Contribution of COX-2-dependent prostaglandins to the onset and progression of non-alcoholic fatty liver disease (NAFLD):** Our results have shown that COX-2 protects against early stages of the disease. Our goal is to advance the study evaluating the role of COX-2 in the progression to steatohepatitis and fibrosis, analyzing involved signaling pathways and molecular mechanisms, as well as the expression of COX-2 in human samples of NAFLD and its relationship with the disease.
- **COX-2 and mitochondrial function. Role in ischemia reperfusion (I/R) in the liver:** Our goal is to elucidate the regulation of mitochondrial function, oxidative stress and damage by I/R in response to COX-2. In this line, we analyze the correlation between levels of prostaglandins and expression of COX-2 and liver function after OLT in order to check whether the presence of prostaglandins in the graft may be a marker of prognosis in recovery of function liver in the transplanted organ.
- **COX-2 and liver miRNAs:** In previous studies we have shown modulation of miRNAs on the expression of COX-2 as well as the regulatory role of COX-2 itself exerts on the expression pattern of liver miRNAs involved in insulin signaling. Our interest is to continue studying the role of COX-2 in miRNAs associated with various pathologies and to search for possible mechanisms of action.

# Most relevant scientific articles


- Motino O., Agra N., Brea Contreras R., Dominguez-Moreno M., Garcia-Monzon C., Vargas-Castrillon J. et al. Cyclooxygenase-2 expression in hepatocytes attenuates non-alcoholic steatohepatitis and liver fibrosis in mice. Biochimica et Biophysica Acta - Molecular Basis of Disease. 2016;1862(9):1710-1723.
- Singh P., Gonzalez-Ramos S., Mojena M., Rosales-Mendoza C.E., Emami H., Swanson J. et al. GM-CSF Enhances macrophage glycolytic activity in vitro and improves detection of inflammation in vivo. Journal of Nuclear Medicine. 2016;57(9):1428-1435.
- Klionsky DJ, Abdelmohsen K, Abe A, Abedin MJ, Abeliovich H, Acevedo Arozena A et al. Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition). Autophagy. 2016;12(1):1-222.


# Hightlights

During 2016 we have focused on studying the contribution of cyclooxygenase-2-dependent prostaglandins to the pathogenesis of steatohepatitis and hepatic fibrosis in collaboration with Carmelo García-Monzón from Ciberehd and Ángela Valverde from Ciberdem. Our study demonstrated that, hCOX-2-Tg mice fed MCD diet showed lower grades of steatosis, ballooning and inflammation than Wt mice, in part by reduced recruitment and infiltration of hepatic macrophages, with a corresponding decrease in serum levels of pro-inflammatory cytokines. Furthermore, hCOX-2-Tg mice showed a significant attenuation of the MCD diet-induced increase in oxidative stress and hepatic apoptosis observed in Wt mice. Even more, hCOX-2-Tg mice treated with CCl4 had significantly lower stages of fibrosis and less hepatic content of collagen, hydroxyproline and pro-fibrogenic markers than Wt controls. Collectively, our data indicates that constitutive hepatocyte COX-2 expression ameliorates NASH and liver fibrosis development in mice by reducing inflammation, oxidative stress and apoptosis and by modulating activation of hepatic stellate cells, respectively, suggesting a possible protective role for COX-2 induction in NASH/NAFLD progression.
In collaboration with Lisardo Boscá we have studied the effect of granulocyte-macrophage colony-stimulating factor (GM-CSF), a clinically used cytokine in the glycolytic activity of macrophages and the conclusion is that GM-CSF augments glycolytic flux in vitro and increases 18F-FDG uptake within inflamed atheroma in vivo. These findings demonstrate that GM-CSF can be used to enhance detection of inflammation.
In this year we have got a new Project from MINECO “Role of COX-2 in hepatic ischemia/reperfusion injury. Study of mitochondrial function” (2017-19).

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## Main lines of research

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

# Most relevant scientific articles


- Claria J., Stauber R.E., Coenraad M.J., Moreau R., Jalan R., Pavesi M. et al. Systemic inflammation in decompensated cirrhosis: Characterization and role in acute-on-chronic liver failure. Hepatology. 2016;64(4):1249-1264.
- Gonzalez-Rubio S., Linares C.I., Aguilar-Melero P., Rodriguez-Peralvarez M., Montero-Alvarez J.L., De la Mata M. et al. AP-1 Inhibition by SR 11302 protects human hepatoma HepG2 cells from bile acid-induced cytotoxicity by restoring the NOS-3 expression. PLoS ONE. 2016;11(8).
- Jurado-Garcia J., Garcia-Borruel M.M., Rodriguez-Peralvarez M.L., Ruiz-Cuesta P., Poyato-Gonzalez A., Barrera-Baena P. et al. Impact of MELD allocation system on waiting list and early post-liver transplant mortality. PLoS ONE. 2016;11(6).
- Rodriguez-Peralvarez M., Rico-Juri J.M., Tsochatzis E., Burra P., De la Mata M., Lerut J.. Biopsy-proven acute cellular rejection as an efficacy endpoint of randomized trials in liver transplantation: A systematic review and critical appraisal. Transplant International. 2016.
- Castells L., Rimola A., Manzardo C., Valdivieso A., Montero J.L., Barcena R. et al. Corrigendum to “Pegylated interferon plus ribavirin in HIV-infected patients with recurrent hepatitis C after liver transplantation: A prospective cohort study” [J Hepatol 2015;62:92-100]. Journal of Hepatology. 2016


# Hightlights

In 2016, our research group has focused its efforts in developing high quality translational/ clinical research and networking, thus aligning with CIBEREHD priorities. The main actions are summarized below:

- Development of two research projects funded by the Instituto de Salud Carlos III. FIS PI11/02867 evaluates the impact of immunosupressive regimen with mTOR inhibitor in liver transplant patients with hepatocarcinoma. The preliminary results of thsi project have been presented at AEEH-EASL meetings, both in 2016 and also accepted for 2017 and in an article. FIS PI14/01469, a more recently funded research project to investigate the role of immune system in the removal of circulating tumor cells and the hepatocarcinoma recidiva. This project is on its recruitment phase.
- Collaboration in multicentre randomized trials evaluating therapeutic options for patients with advanced hepatocellular carcinoma, HCV and liver transplant: A total of 4 Phase I-II randomized clinical trials, and 6 Phase III randomized trials.
- Participation in an European clinical guideline on modifiable risk factors in liver transplantation (COMMIT guidelines to be published in “Transplantation”). Participation in the new version of the clinical guideline on Diagnosis and Treatment of Hepatocellular Carcinoma (Medicina Clínica 2016).
- Creation of an international consortium coordinated by our research group, including 3 groups from CIBEREHD, and 3 additional institutions across Europe (Royal Free Hospital London, Padova University Hospital and Cliniques Universitaires Sant Luc, leuven). The consortium aims to reassess the prognostic impact of T-cell mediated rejection in liver transplantation under current immunosuppression protocols, and has applied recently for one of the EASL registry grants 2017.
- Three new patents have been registrated.

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## Main lines of research

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

- We investigate the regulation of S-adenosylmethionine (SAMe) biosynthesis in mammalian cells and the function of SAMe in fatty liver disease, liver cirrhosis, and cancer.
- New molecular mechanisms in the development and progression of nonalcoholic fatty liver disease (NAFLD) to liver cancer: unraveling the impact of the post-translational modifications.
- Application of “omics” technologies to the study of the composition and function of hepatic exosomes: application to the identification of new 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


- Mato J.M., Lu S.C.. Liver receptor homolog 1 and transmethylation fluxes in nonalcoholic steatohepatitis. Hepatology. 2016;63(1):17-19.
- Murray B., Antonyuk S.V., Marina A., Lu S.C., Mato J.M., Hasnain S.S. et al. Crystallography captures catalytic steps in human methionine adenosyltransferase enzymes. Proceedings of the National Academy of Sciences of the United States of America. 2016;113(8):2104-2109.
- Stuart D.I., Subramaniam S., Abrescia N.G.A.. The democratization of cryo-EM. Nature Methods. 2016;13(8):607-608.
- Yang H., Liu T., Wang J., Li T.W., Fan W., Peng H. et al. Deregulated methionine adenosyltransferase α1, c-Myc, and Maf proteins interplay promotes cholangiocarcinoma growth in mice and humans. Hepatology. 2016


# Hightlights

- CIC bioGUNE has lisenced two patents about the treatment of NASH and cirrhosis to Mitotherapeutix.
- CIC bioGUNE and OWL have developed a metabolic non invasive test for the identification of NASH subtypes.
- Galmed Pharmaceuticals and CIC bioGUNE have signed a contract to deteminate the mechanism of action of Aramchol in the treatment of NASH.
- Dr. JM Falcón, Deputy President of GEIVEX and Board member of ISEV.
- Dr. ML Martínez- Chanta member of Women in Hepatology organization.

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## 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


- Aguero F., Forner A., Manzardo C., Valdivieso A., Blanes M., Barcena R. et al. Human immunodeficiency virus infection does not worsen prognosis of liver transplantation for hepatocellular carcinoma. Hepatology. 2016;63(2):488-498.
- Cornide-Petronio M.E., Negrete-Sanchez 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. 2016.
- Aguero F., Rimola A., Stock P., Grossi P., Rockstroh J.K., Agarwal K. et al. Liver Retransplantation in Patients with HIV-1 Infection: An International Multicenter Cohort Study. American Journal of Transplantation. 2016;16(2):679-687.
- Ferrer-Fabrega J., Forner A., Liccioni A., Miquel R., Molina V., Navasa M. et al. Prospective validation of ab initio liver transplantation in hepatocellular carcinoma upon detection of risk factors for recurrence after resection. Hepatology. 2016.


# Hightlights

As a consequence of the results of the different studies realized by the group in relationship with the liver graft tolerance, a new prospective, multicentre, European trial has been started to translate the results of the studies to the clinical practice. The trial (LIFT) is conducted by Dr. Alberto Sanchez-Fueyo (King's College, London) and includes our participation.
In the field of organ retrieval and utilization of donor organs with expanded criteria, we have followed with the studies characterizing new targets based on adipocytokines modulation. We have also followed the investigation with polyethilenglycol in the preservation solutions. In addition, a new device for static preservation has been developed by Dr. Carmen Peralta, based on the control of temperature and the use of ultrasounds. Finally, in the field of dynamic preservation we are participating in a European trial and we are conducting several studies evaluating ex-vivo perfusion devices.
Three important studies have to be underlined: treatment and indications for retransplantation of coinfected patients (HIV-HVC), evaluation of the hepatorenal syndrome in patients in the wainting list for liver transplantation and the validation of the selection criteria for liver transplantation in patients with hepatocelular carcinoma.

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# Main lines of research

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

# Most relevant scientific articles


- Jauregui-Amezaga A., Rovira M., Marin P., Salas A., Pino-Donnay S., Feu F. et al. Improving safety of autologous haematopoietic stem cell transplantation in patients with Crohn's disease. Gut. 2016.
- Danese S., Fiocchi C., Panes J.. Drug development in IBD: From novel target identification to early clinical trials. Gut. 2016.
- Mora-Buch R., Dotti I., Planell N., Calderon-Gomez E., Jung P., Masamunt M.C. et al. Epithelial IL-1R2 acts as a homeostatic regulator during remission of ulcerative colitis. Mucosal Immunology. 2016;9(4):950-959.
- Panes J., Garcia-Olmo D., Van Assche G., Colombel J.F., Reinisch W., Baumgart D.C. et al. Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: A phase 3 randomised, double-blind controlled trial. The Lancet. 2016.
- Dotti I., Mora-Buch R., Ferrer-Picon E., Planell N., Jung P., Masamunt M.C. et al. Alterations in the epithelial stem cell compartment could contribute to permanent changes in the mucosa of patients with ulcerative colitis. Gut. 2016.


# Hightlights

The inflammatory bowel disease Group at Hospital Clínic de Barcelona has continued the development of an active program of cell therapy. It is now the groups with the largest experience in autologous hematopoietic stem cell transplant for the treatment of refractory Crohn's disease worldwide, and we have provided significant contributions to the field that increase the safety of the procedure without compromising efficacy. We have also had a significant contribution in collaboration with the industry in the development of Mesenchymal stem cell therapy for treatment fo perianal fistulizing disease. This innovative therapeutic approach affords closure of fistula to patients that previously failed all available medical options.

Our group has also provided new insights into inflammatory bowel disease pathogenesis based on the use of organoids. We have shown that permanent changes in the colonic epithelium of patients with ulcerative colitis can be promoted by alterations imprinted in the intestinal stem cell compartment. These changes may contribute to perpetuation of the disease.

Significant contributions to optimization of clinical practice include the participation in the development of the European Crohn's and Colitis guideline on the use of biosimilars in inflammatory bowel disease, as well as in consensus documents on the assessment of disease severity and outcomes over time.

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# Main lines of research

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

# Most relevant scientific articles


- Trivedi P.J., Corpechot C., Pares A., Hirschfield G.M. Risk stratification in autoimmune cholestatic liver diseases: Opportunities for clinicians and trialists. Hepatology. 2016;63(2):644-659.
- Nevens F., Andreone P., Mazzella G., Strasser S.I., Bowlus C., Invernizzi P. et al. A Placebo-controlled trial of obeticholic acid in primary biliary cholangitis. New England Journal of Medicine. 2016;375(7):631-643.
- Bolier R, Tolenaars D, Kremer AE, Saris J, Parés A, Verheij J et al. Enteroendocrine cells are a potential source of serum autotaxin in men.Biochimica et biophysica acta. 2016;.
- Guañabens N, Mumm S, Gifre L, Ruiz-Gaspà S, Demertzis JL, Stolina M et al. Idiopathic Acquired Osteosclerosis in a Middle-Aged Woman with Systemic Lupus Erythematosus.Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research. 2016;.
- Guañabens N, Ruiz-Gaspà S, Gifre L, Miquel R, Peris P, Monegal A et al. Sclerostin Expression in Bile Ducts of Patients with Chronic Cholestasis May Influence the Bone Disease in Primary Biliary Cirrhosis. Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research. 2016.


# Hightlights

Participation in a project of excellence funded by Carlos III Health Institute aimed at building a framework for the design of nanomedicines based on major histocompatibility complex peptides (pMHC) for different autoimmune diseases including primary biliary cholangitis, to demonstrate that they can be used in humanized mice for the selection of pMHC-based cells with nanomedicines for future clinical trials, and to identify patients who most likely would to respond to this therapy.
The Spanish registry of cholestatic and autoimmune hepatic diseases (ColHai) has been established within the Spanish Association for the Study of the Liver (AEEH) in collaboration with CIBEREHD.
Members of the research group have participated in the international networks of primary biliary cholangitis (Global-PBC), primary sclerosing cholangitis (IPSCSG) and the international group of autoimmune hepatitis, which has established a worldwide AIH registry. Dr. Parés is also a member of the steering committee of the European Reference Network on Rare Hepatological Diseases (RARE-LIVER) approved by the Committee of Member States for European Reference Networks (ERN).
Dr. Nuria Guañabens has been awarded with the Steven Boonen Research Award by the European Calcified Tissue Societey (ECTS) during the annual meeting held in Rome (Italy).

LEAD RESEARCHER

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PROGRAMMES
**P4**

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# Main lines of research

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

# Most relevant scientific articles


- Robles-Campos R, Brusadin R, López-Conesa A, Parrilla P. Modified ALPPS Procedures Avoiding Division of Portal Pedicles. Ann Surg. 2017 Feb;265(2): e21
- Cascales-Campos PA, Sánchez-Fuentes PA, Gil J, Gil E, López-López V, Rodriguez Gomez-Hidalgo N, Fuentes D, Parrilla P. Effectiveness and failures of a fast track protocol after cytoreduction and hyperthermic intraoperative intraperitoneal chemotherapy in patients with peritoneal surface malignancies. Surg Oncol. 2016 Dec;25(4):349-354
- Tyrkalska SD, Candel S, Angosto D, Gómez-Abellán V, Martín-Sánchez F, García-Moreno D, Zapata-Pérez R, Sánchez-Ferrer Á, Sepulcre MP, Pelegrín P, Mulero V. Neutrophils mediate Salmonella Typhimurium clearance through the GBP4 inflammasome-dependent production of prostaglandins. Nat Commun. 2016 Jul 1; 7:12077.
- de Torre-Minguela C, Barberà-Cremades M, Gómez AI, Martín-Sánchez F, Pelegrín P. Macrophage activation and polarization modify P2X7 receptor secretome influencing the inflammatory process. Sci Rep. 2016 Mar 3; 6:22586.
- Martínez-Bosch N, Fernández-Zapico ME, Navarro P, Yélamos J. Poly(ADP-Ribose) Polymerases: New Players in the Pathogenesis of Exocrine Pancreatic Diseases. Am J Pathol. 2016 Feb;186(2):234-41.


# Hightlights

Our group is focus in five closely related research areas: Barrett oesophagus and the development of oesophagus adenocarcinoma, Inflammation and cancer, Poly(ADP-ribose) polymerases and cancer, Liver regeneration and liver tumour, and Liver transplantation. During 2016, we have continue to study the Barrett oesophagus stability after radiofrequency treatment and the identification of genetic alterations induced by this treatment. In relation with inflammation and cancer, we are studying the regulation of inflammatory response to extracellular ATP and P2X7 receptor signalling: through and beyond the inflammasome. As a main achieve in this area, we have demonstrated that the NLRP3 inflammasome is released as a particulate danger signal, acting as an extracellular oligomeric complex, that amplifies the inflammatory response. In relation to the study play by Poly(ADP-ribose) polymerase enzymes in cancer, we are exploring the lethal interactions between PARP proteins and the DNA damage response in cancer treatment. Among the data obtained, we have demonstrated that PARP-1 plays a key role in pancreatic cancer. Recently, we have started a research focus in understanding the immunomodulatory role of PARP proteins and it implication in the immune response to tumours. Other achievements of our group are related to liver tumour and tumoral progression after portal occlusion in patients with liver resection in two times. Finally, we continue working in liver tolerance after liver transplant, aim to analysis immunological factors and gene expression profiles involved in liver tolerance.

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PROGRAMMES
**P4**

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**Associated members:** Casado Merediz, Francisco Javier

# 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


- Fernandez-Calotti P., Casulleras O., Antolin M., Guarner F., Pastor-Anglada M. Galectin-4 interacts with the drug transporter human concentrative nucleoside transporter 3 to regulate its function. FASEB Journal. 2016;30(2):544-554.
- Catala A., Pastor-Anglada M., Caviedes-Cardenas L., Malatesta R., Rives S., Vega-Garcia N. et al. FLT3 is implicated in cytarabine transport by human equilibrative nucleoside transporter 1 in pediatric acute leukemia. Oncotarget. 2016;7(31):49786-49799.
- Grane-Boladeras N., Perez-Torras S., Lozano J.J., Romero M.R., Mazo A., Marin J.J.G. et al. Pharmacogenomic analyzis of the responsiveness of gastrointestinal tumor cell lines to drug therapy: A transportome approach. Pharmacological Research. 2016; 113:364-375.
- Grane-Boladeras N., Spring C.M., Hanna W.J.B., Pastor-Anglada M., Coe I.R.. Novel nuclear hENT2 isoforms regulate cell cycle progression via controlling nucleoside transport and nuclear reservoir. Cellular and Molecular Life Sciences. 2016;73(23):4559-4575.
- Pérez-Torras S, Iglesias I, Llopis M, Lozano JJ, Antolín M, Guarner F et al. Transportome Profiling Identifies Profound Alterations in Crohn's Disease Partially Restored by Commensal Bacteria.Journal of Crohn's & colitis. 2016.


# Hightlights

During 2016 we have reported new gene networks incorporating a variety of plasma membrane transporters which, as a whole, build up what we call the cellular transportome. The transportome is tightly linked to a variety of intracellular machineries implicated in cell proliferation, including drug and druggable targets. These networks might be critically altered in inflammatory diseases, such as Crohn's disease, being these alterations partially reversed by commensal bacteria. They also incorporate a subset of genes and proteins, the purinome, similarly altered in inflammation and cancer. Moreover, a major progress has been made by applying MYTH (Membrane Yeast Two Hybrid) to unveil novel partner proteins for selected membrane transporters thus defining their interactome. MYTH has been used to identify hENT2 protein partners which build up functional heteromers in the cell nucleus, thereby determining nucleotide availability and cell cycle progression. This opens for the forthcoming years the possibility of analyzing how this machinery might contribute to oncogenesis. Galectin-4 has also been identified, albeit with more classical approaches (proteomics) as a partner protein of the purine and thiopurine transporter hCNT3, being Galectin-4 able to regulate its function in a way that might be relevant to anti-inflammatory drug bioavailability. The use of MYTH to undertake further analysis of selected membrane proteins interactome has been recently awarded a Fundación Ramón Areces project (granted in 2016) to be developed during the forthcoming three years, starting January 2017. Most of these studies have also involved researchers from CIBEREHD. An inter-CIBER collaboration (CIBEREHD – CIBERER), has also helped to understand how combined therapies involving selected tyrosine kinase inhibitors (i.e. FLT3 inhibitors) and conventional anticancer drugs (i.e. cytarabine) might compromise drug responsiveness depending upon drug administration protocols, simply because tyrosine kinase inhibitors might eventually impact on the cellular pathways associated with drug action.

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# Main lines of research

The Gastrointestinal Inflammatory Disease Group, from La Princesa University Hospital in Madrid (and its network of affiliated researcher), focuses on the understanding and management of Inflammatory Bowel Disease (IBD) and *Helicobacter pylori* infection.

MILESTONES

- AEG-REDCap Platform
  - Direction and coordination of the Online Platform for Collaborative Research AEG-REDCap (>50 projects and 1,000 researchers).
  - Management of the AEG-REDCao strategic line and agreement at CIBEREHD.
- H. pylori infection
  - International coordination of the European Registry on H. pylori management (250 hospitals, 27 Countries).
  - In situ and in vivo detection and treatment with multifunctional nanomaterials.
  - Effect of eradication treatment on intestinal microbiota.
  - Validation of new diagnostic methods.
  - Prevalence/transmission/resistance, and sociosanitary factors of infection.
- Inflammatory Bowel Disease
  Clinical research. Coordination and participation in over 20 clinical trials and studies in different phases, with the participation of numerous CIBER centers; the most outstanding ones are:
  - "Prospective and multicentre study on the epidemiology and "omic" characteristics of newly diagnosed IBD in Spain" (FIS16/01296). / "Withdrawal of anti-TNF treatment in patients with IBD: Multicenter, prospective and randomized clinical trial" (FIS15/00560). / "Predicting short- and long-term response to treatment with anti-TNF drugs in patients with Crohn's disease. Predicrohn Study (FIS12/02557). / "Long-

term safety of anti-TNF treatment in children" (coordinating 30 European centers). / Epidemiologic study about IBD incidence in Spain (coordinating over 200 centers).

- Investigación traslacional. Desde el laboratorio de este grupo actualmente se dirigen proyectos relacionados con:
  Immune response / Mechanisms of production of antibodies against anti-TNF treatments, and their relation with treatment response. / Characterization of circulating and intestinal dendritic cells and monocytes in IBD patients. / Identification of the mechanisms mediating the mucosa recruitment of circulating dendritic cell and monocyte subsets. / Identification and characterization of novel bioactive peptides secreted by the commensal microbiota with immunomodulatory properties over the intestinal mucosa. / Novel Biomarkers based on: - Homing profile of circulating dendritic cell and monocyte subsets. - Circulating antibodies against microbiota peptides. / Therapeutic targets / Identification of the mechanisms driving the altered phenotype and functional and intestinal dendritic cells and macrophages.

# Most relevant scientific articles


- Fallone C.A., Chiba N., van Zanten S.V., Fischbach L., Gisbert J.P., Hunt R.H. et al. The Toronto Consensus for the Treatment of Helicobacter pylori Infection in Adults. Gastroenterology. 2016;151(1):51-69.e14.
- Nyssen O.P., McNicholl A.G., Megraud F., Savarino V., Oderda G., Fallone C.A. et al. Sequential versus standard triple first-line therapy for Helicobacter pylori eradication. Cochrane Database of Systematic Reviews. 2016;2016(6).
- Gisbert J.P., Marin A.C., Chaparro M.. The risk of relapse after Anti-TNF discontinuation in inflammatory bowel disease: Systematic review and meta-analysis. American Journal of Gastroenterology. 2016;111(5):632-647.
- Fernandez-Banares F., Casanova M.J., Arguedas Y., Beltran B., Busquets D., Fernandez J.M. et al. Current concepts on microscopic colitis: Evidence-based statements and recommendations of the Spanish Microscopic Colitis Group. Alimentary Pharmacology and Therapeutics. 2016;43(3):400-426.
- Feagan B.G., Sandborn W.J., Gasink C., Jacobstein D., Lang Y., Friedman J.R. et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. New England Journal of Medicine. 2016;375(20):1946-1960.


# Hightlights

In 2016, at the initiative of this group, an agreement was signed with the Platform for Collaborative Research AEG-REDCap (directed from this group) to establish a Strategic Line at CIBEREHD. This platform includes over 50 research projects and 1,000 researchers.
The group has consolidated its leadership in clinical research in Inflammatory Bowel Disease (IBD) and H. pylori infection, coordinating several national and international multicenter studies, with the participation of several CIBEREHD centers.
In the area of H. pylori, we have coordinated and participated in several consensus conferences (Canadian/ European/Spanish). The European Registry on Helicobacter has reached the 20.000 registered patients, and this data has been monitored and analyzed.
In IBD, the group has coordinated and participated in several clinical trials at different stages as well as on observational studies. We have obtained public funds in several competitive calls. At present, the group is coordinating studies aiming to know the epidemiology of IBD, as well as generating a wide collection of biological samples. In addition, it is currently coordinating several studies aiming to optimize the therapy with biologics, as well as to identify when the treatment can be discontinued. All this research is being carried out within the framework of the CIBEREHD-Strategic-Line of research in IBD. Finally, the group participated in various clinical guidelines on IBD.
In the laboratory, the group has established several collaborations with National and International centres, and obtained funding from some scientific associations. It has incorporated a post-doctoral researcher and 2 research technicians, allowing a deeper insight on the study of the phenotype and function of human intestinal dendritic cell and macrophage subsets, as well as on the mechanisms mediating their recruitment towards the mucosa from their circulating precursors and the identification of novel microbiota-secreted immunomodulatory peptides.

LEAD RESEARCHER

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PROGRAMMES
**P3**

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# Main lines of research

- The research group at Valme Hospital is focused on two main lines: Hepatitis C and Non-alcoholic fatty liver disease (NAFLD). The development of hepatocellular carcinoma from these diseases also currently represents a priority area of research for the group. On the other hand, several projects deal with other areas within the liver and digestive diseases (complications of cirrhosis, hepatic encephalopathy, Helicobacter pylori infection and inflammatory bowel disease).
- Regarding hepatitis C, our projects aimed to identify elements (genes and/or proteins) that may represent new therapeutic targets. To achieve this goal we perform two complementary approaches: one is based on an association analysis of the entire genome (GWAS), and the other in the study of molecular interactions between viral and host, with special emphasis on proteins related with the insulin-signaling pathway.

# Most relevant scientific articles


- Ratziu V., Harrison S.A., Francque S., Bedossa P., Lehert P., Serfaty L. et al. Elafibranor, an Agonist of the Peroxisome Proliferator-Activated Receptor-α and -δ, Induces Resolution of Nonalcoholic Steatohepatitis Without Fibrosis Worsening. Gastroenterology. 2016;150(5):1147-1159e5.
- Eslam M., Mangia A., Berg T., Chan H.L.Y., Irving W.L., Dore G.J. et al. Diverse impacts of the rs58542926 E167K variant in TM6SF2 on viral and metabolic liver disease phenotypes. Hepatology. 2016;64(1):34-46.
- Vilar-Gomez E, Yasells-Garcia A, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B et al. Development and validation of a noninvasive prediction model for nonalcoholic steatohepatitis resolution after lifestyle intervention.Hepatology (Baltimore, Md.). 2016.
- Medina-Caliz I., Robles-Diaz M., Garcia-Munoz B., Stephens C., Ortega-Alonso A., Garcia-Cortes M. et al. Definition and risk factors for chronicity following acute idiosyncratic drug-induced liver injury. Journal of Hepatology. 2016.
- Vilar-Gomez E., Adams L.A. Pioglitazone: An addition to our toolbox for patients with diabetes and nonalcoholic steatohepatitis?Annals of Internal Medicine. 2016;165(5):373-374.


# Hightlights

The group have been granted various projects, such as: “Transición esteatohepatitis no alcohólica-hepatocarcinoma: biomarcadores y dianas terapéuticas” by Instituto Carlos III (PI16-01842), or “Uso de terápia epigenética avanzada para el tratamiento de la enfermedad hepática por deposito de grasa no alcohólica” by the Consejería de Salud de la Junta de Andalucía (PC-0148-2016-0148). It has been also awarded a prize from the Asociación de Celíacos y Sensibles al Gluten for “Estudio epigenético de la enfermedad celíaca. Nuevos métodos de diagnóstico y de seguimiento de la dieta sin gluten”.
Regarding HCV, we have studied the different steps in the viral life cycle and the role that quercetin has on it. Our colaboration in the International Liver Disease Genetics Consortium have allowed to identify several genetic factors associated to progression, and to stablish an algorithm for stratifying fibrosis. The cardiovascular risk on HCV patients is also being studied (HepCar), which preliminar results had been already presented.
In the study of NAFLD, a new model for predicting reversion after life-style modification has been developed. We have validated imaging biomarkers (DEMILI®) and the use of PPAR agonists as a new therapy. Epigenetics biomarkers (miRNAs) have been identified and are under valitation.
Another epigenetic factor, lncRNA-H19, was found upregulated in liver cancer, and its role in the pathophisiology of the disease is being studied. We have also developed a non-invasive model for predicting HCC development.
Concerning hepatic encephalopathy, we have associated the critical flicker frequency with disease progression and accidental falls. The oral glutamine challenge has been related to the risk of overt hepatic encephalopathy. Finally, a large scale genetic studio was performed for detecting predictive genetic factors of the disease.

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PROGRAMMES
**P3**

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# 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


- Munoz-Gamez J.A., Lopez Viota J., Barrientos A., Carazo A., Sanjuan-Nunez L., Quiles-Perez R. et al. Synergistic cytotoxicity of the poly (ADP-ribose) polymerase inhibitor ABT-888 and temozolomide in dual-drug targeted magnetic nanoparticles. Liver International. 2016;35(4):1430-1441.
- Alonso S., Riveiro-Barciela M., Fernandez I., Rincon D., Real Y., Llerena S. et al. Effectiveness and safety of sofosbuvir-based regimens plus an NS5A inhibitor for patients with HCV genotype 3 infection and cirrhosis. Results of a multicenter real-life cohort. Journal of Viral Hepatitis. 2016.
- Ocete-Hita E., Salmeron-Fernandez M.J., Urrutia-Maldonado E., de Rueda P.M., Salmeron-Ruiz M., Martinez-Padilla M.C. et al. Analysis of Immunogenetic Factors in Idiosyncratic Drug-Induced Liver Injury in the Paediatric Population. Journal of Pediatric Gastroenterology and Nutrition. 2016.
- Munoz-Gamez J.A., Salmeron J., Ruiz-Extremera A. Hepatitis C during pregnancy, vertical transmission and new treatment possibilities. Medicina Clinica. 2016.
- Blanco-Reina E., Medina-Claros A.F., Vega-Jimenez M.A., Ocana-Riola R., Marquez-Romero E.I., Ruiz-Extremera A. Drug utilization pattern in children and off-label use of medicines in a pediatric intensive care unit. Medicina Intensiva. 2016;40(1):1-8.


# Hightlights

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.
- 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 initiated two other projects: PI05152014, Junta de Andalucía, and PI1501361, FIS, related with the line of research “Relación de las Poblaciones de Pre-Adipocitos y el Infiltrado Inmunológico del Tejido Adiposo Con la Enfermedad del Hígado Graso No Alcohólico en Obesos Mórbidos”.

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).

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# 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, particularly changes in alkaline phosphatase expression and disturbances in hydroelectrolytic transport.
- Targeting obesity and metabolic syndrome: influence of intestinal microbiota.
- Alterations of intestinal barrier in acute pancreatitis.
- Biosimilars.

# Most relevant scientific articles


- Martin M., Rodriguez-Nogales A., Garces V., Galvez N., Gutierrez L., Galvez J. et al. Magnetic study on biodistribution and biodegradation of oral magnetic nanostructures in the rat gastrointestinal tract. Nanoscale. 2016;8(32):15041-15047.
- Ocon B., Aranda C.J., Gamez-Belmonte R., Suarez M.D., Zarzuelo A., Martinez-Augustin O. et al. The glucocorticoid budesonide has protective and deleterious effects in experimental colitis in mice. Biochemical Pharmacology. 2016.
- Algieri F., Rodriguez-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. 2016.
- Carrasco-Benso M.P., Rivero-Gutierrez B., Lopez-Minguez J., Anzola A., Diez-Noguera A., Madrid J.A. et al. Human adipose tissue expresses intrinsic circadian rhythm in insulin sensitivity. FASEB Journal. 2016;30(9):3117-3123.
- Hidalgo-Cantabrana C., Algieri F., Rodriguez-Nogales A., Vezza T., Martinez-Camblor P., Margolles A. et al. Effect of a ropy Exopolysaccharide-producing Bifidobacterium animalis subsp. Lactis strain orally administered on dss-induced colitis mice model. Frontiers in Microbiology. 2016;7(JUN).


# Hightlights

The research activity of the group has resulted in 18 articles, some of them the stemming from partnerships with other national and international research groups. It is noteworthy that most publications are framed in the first quartile, including 7 in the first decile.

Among the highlights of our research in 2016 are the following. We have established the importance of the microbiota in the intestinal inflammatory response, in terms of both immunological stimulus and input for modulation of epithelial dynamics. We have explored the harmful effects of corticoids in experimental colitis, and a mouse conditional knock out glucocorticoid receptor model has been generated. We have characterized the distribution and degradation of magnetic nanoparticles in the murine intestine. We have additionally studied the intestinal antiinflammatory activity of the bisphosphonate pamidronate in experimental models, as well as that of calcium pyruvate. Also, a variety of studies focused on the intestinal antiinflammatory effects of natural products, including prebiotics and probiotics, and natural extracts, has been carried out.

Our research work has been funded by several research projects, both public (MINECO, Junta de Andalucía) and private. In 2016 the group has been awarded two new national/regional projects.

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PROGRAMMES
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## Main lines of research

- Study of the cellular and molecular mechanisms of liver response to acute and chronic injury, and hepatocarcinogenesis .
- Design of hepatoprotective strategies against situations of injury/acute liver failure and identification of therapeutic targets to slow the progression of chronic liver disease and its malignant transformation.
- Development of hepatoprotective therapies including insulin-like growth factor type 1 (IGF1) and cell therapy with endothelial cell progenitors.
- Characterization of the effects of amino-terminal protein modifications and their implications for the development of hepatocellular carcinoma and liver regeneration, and development of inhibitors of these enzymes as novel 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


- D'Avola D., Lopez-Franco E., Sangro B., Paneda A., Grossios N., Gil-Farina I. et al. Phase I open label liver-directed gene therapy clinical trial for acute intermittent porphyria. Journal of Hepatology. 2016.
- de la Torre M.A., Buades-Mateu J., de la Rosa P.A., Lue A., Bustamante F.J., Serrano M.T. et al. A comparison of survival in patients with hepatocellular carcinoma and portal vein invasion treated by radioembolization or sorafenib. Liver International. 2016.
- Urtasun R., Elizalde M., Azkona M., Latasa M.U., Garcia-Irigoyen O., Uriarte I. et al. Splicing regulator SLU7 preserves survival of hepatocellular carcinoma cells and other solid tumors via oncogenic miR-17-92 cluster expression. Oncogene. 2016;35(36):4719-4729.
- Forner A., Reig M., Varela M., Burrel M., Feliu J., Briceno J. et al. Diagnosis and treatment of hepatocellular carcinoma. Update consensus document from the AEEH, SEOM, SERAM, SERVEI and SETH. Medicina Clinica. 2016.
- Bigaud E., Corrales F.J.. Methylthioadenosine (MTA) regulates liver cells proteome and methylproteome: Implications in liver biology and disease. Molecular and Cellular Proteomics. 2016;15(5):1498-1510.


# Hightlights

The research activity of the group has remained intense in all fields. Competitive funding has been obtained from national agencies and the European Commission, and collaborations with foreign and national groups have been strengthened, both within and outside CIBEREHD. We continue to work on mechanisms of carcinogenesis, elucidating the role of molecules such as SLU7 or YAP1 and their epigenetic regulation, a research line on the role of lncRNA has been opened, and work has begun on a tool to predict response to treatment in hepatocellular carcinoma with targeted molecules. Based on the strategic action granted, collaborative studies of molecular classification of cholangiocarcinoma and identification of therapeutic targets are being carried out. In immunology and immunotherapy of hepatocellular carcinoma, we collaborate in the identification of the possible immunological mechanism of induction of relapse after treatment with direct acting antivirals in patients with hepatocellular carcinoma, we will communicate the final results of clinical trials with immune checkpoints inhibitors, we will begin the recruitment of a clinical trial using a multi-peptide vaccine, and we have organized early trials of combinations of these molecules with other agents, seeking therapeutic synergies. The collaboration with engineers for the development of computational fluid dynamics systems for the improvement of intra-arterial treatments is still active. The results of the first clinical trial of the treatment of acute intermittent porphyria have been reported and progress is being made in the development of an improved gene transfer system, which is intended to lead to clinical experimentation in the near future. Collaborative studies aim at improving the results of liver transplantation, especially in patients with liver cancer. Finally, we have collaborated in the update of the Spanish Guidelines for the Treatment of Hepatocellular Carcinoma, which will be part of the portfolio of Clinical Practice Guidelines of the Ministry of Health.

# Linked Groups

## Liver Damage Mechanisms/Evolution into Advanced Cirrhosis and Transplant Programme


### Llorenç Caballería Rovira
Universitat Autònoma de Barcelona

### Carmelo García Monzón
Servicio Madrileño de Salud, Madrid

### Alfredo Minguela Puras
Fundación para la Formacion e Investigacion Sanitarias de la Región de Murcia (FFIS), Murcia


## Gastrointestinal Physiopathology: Inflammatory Disease and Motility Disorders Programme


### Ana Belén Beltrán Niclós
Fundación para la Investigación del Hospital la Fe, Valencia

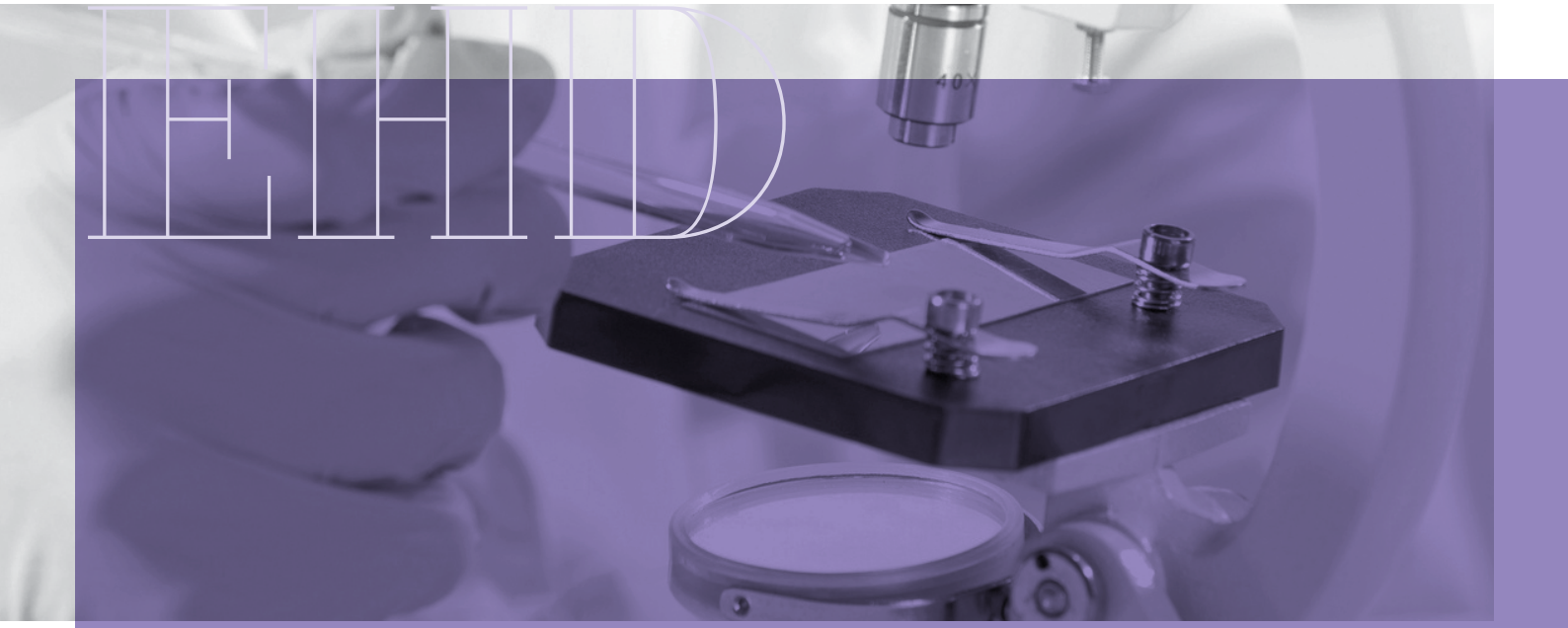
### María Esteve Comas
Fundación privada Institut de Recerca Biomèdica, Barcelona


## Epidemiology, Prevention and Treatment of Hepatitis Virus Infection Programme


### Jose Luis Calleja
Universidad de Alcalá, Madrid


## Hepatic and Digestive Oncology Programme


### Francisco Javier Padillo Ruiz
Fund. Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla



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*Enfermedades Hepáticas y Digestivas*

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