# EF Clif

EUROPEAN
**FOUNDATION**
FOR THE STUDY
OF CHRONIC
LIVER FAILURE

# SUMMARY OF ACTIVITIES **2017**

# Contents

Mission, vision and values . . . . . 6

Our organization . . . . . 8

Board of trustees . . . . . 9

The EASL Chair . . . . . 10

The Grifols Chair . . . . . 11

Our staff . . . . . 12

Facts and figures . . . . . 13

Scientific publications . . . . . 14

The Clif Consortium hospital network & associated investigators . . . . . 16

News and activities . . . . . 22

New studies calendar . . . . . 24

The EASL Chair Studies . . . . . 26

- Ongoing studies . . . . . 26
- New studies . . . . . 29

The Grifols Chair Studies . . . . . 30

- Albumin as a drug research program . . . . . 30
- Ongoing studies . . . . . 30
- New studies . . . . . 32

External projects . . . . . 36

- Finalized studies . . . . . 36
- Ongoing studies . . . . . 37
- New studies . . . . . 39

Future challenges . . . . . 41

- EASL Chair . . . . . 41

Financial report . . . . . 43

# Letter of the Chairman

2017 was the second full year of the European Foundation for the Study of Chronic Liver Failure (EF Clif). During this time, our research activity experienced a significant increase, thanks to the effort and dedication of the investigators of the EASL Chair for clinical studies and the Grifols Chair for translational studies.

In the clinical area and under the leadership of Prof Jonel Trebicka, the EF Clif launched the PREDICT Study, a large observational research project in more than 50 European hospitals aimed to define the main indicators which could predict the development of ACLF. This ambitious project is a clear example of the Foundation's main research interest, which is to achieve a comprehensive characterization of ACLF. In addition, we istarted preparation of the ACLARA study, aimed at the same patient population as the CANONIC study, which will be performed in 54 Latin American university hospitals. Its objective is to evaluate if ACLF in these regions is different compared to Europe and whether the differences could be influenced by regional, ethnic, racial and/or other factors. With this project, the EASL CLIF Consortium wants to progressively expand its research initiatives beyond the European region.

In the translational research area and under the leadership of Professors Richard Moreau and Joan Clària, we completed several studies focused on the effects of using albumin in cirrhotic patients. In addition, we decided to go a bit further in this type of studies by using part of the financial reserves we had kept during the previous two years and broaden our research in the area of metabolomics, lipidomics and genomics.

Late in the year, we designed a new 3-year research plan that includes a new global observational study and a number of new OMICS studies, taking advantage of the large amount of samples we expect to collect from the ongoing observational studies. This plan was presented to the Board of Trustees and, after having been approved, we secured a significant increase of resources from our main donor, that will allow us to double our research budget in 2018 and, most probably, in the following two years.

**Vicente Arroyo**

# Mission, vision and values



**The EF Clif is intended to improve the quality of life and to increase the survival of patients with liver cirrhosis.**

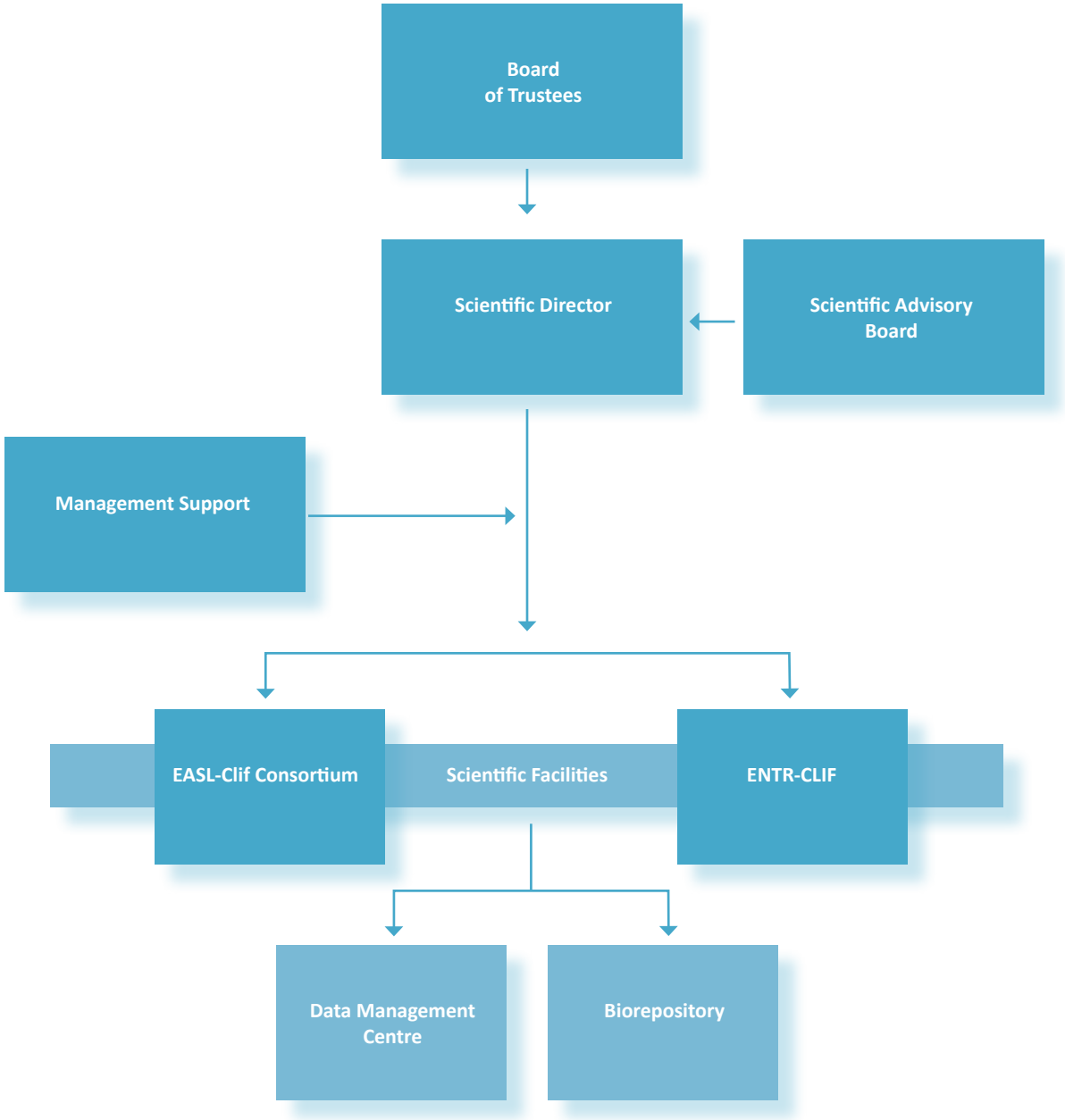
**Supporting high quality research and education on Chronic Liver Failure is our way to pursue it.**

service
dynamism
education
compromise
innovation
unity
dedication
research
health
commitment
independence
transparency
accuracy
welfare
healthiness
quality of life

**Our aim is helping investigators to achieve their objectives and getting the best results.**

**We want to build together an organization that inspires and that is able to contribute to improve the life of cirrhotic patients.**

# Our organization



# Board of Trustees

## VICENTE ARROYO
M.D.

Emeritus Professor of Medicine, University of Barcelona Medical School, Spain.

Chairman of the EASL Clif Consortium.

Recognition Award. European Association for the Study of the Liver.

**Main research interest:**

Chronic Liver Failure, ascites, acute bacterial infection in cirrhosis and Acute-on-Chronic Liver Failure.

## MAURO BERNARDI
M.D.

Professor of Internal Medicine at Bologna University, Italy.

Director, Postgraduate School in Internal Medicine.

Treasurer, European Association for the Study of the Liver.

Vice-Chairman of the EASL Clif Consortium.

Distinguished Service Award, Italian Association for the Study of the Liver.

**Main research fields:**

Cirrhosis and related complications, hepatocellular carcinoma, chronic viral hepatitis, liver transplantation clinical aspects and treatment of alcoholism.

## ANTONIO PÁEZ
M.D. B. Sc.

Director, Medical & Technical Department. Grifols Bioscience Industrial Group.

Graduated in Medicine and Surgery from the Autonomous University of Barcelona.

Graduated in Physical Science. Open University (United Kingdom)

**Main research fields:**

New functions of plasma proteins.

## IGNACIO CALERO
Lawyer

Lawyer at Osborne Clarke.

Graduated in Law from the Autonomous University of Madrid.

Master's Degree in Corporate Legal Advice from the Instituto de Empresa Business School (Madrid, 2003).

**Main research fields:**

He specializes in Company Law, Competition and Industrial Property.

# The EASL Chair

## EASL Clif Consortium Steering Committee

The scientific activities of the network of hospitals organized in the setting of the EASL Chair are performed under the direction of a Chairman and a Vice-Chairman and of an EASL-Clif Consortium Steering Committee of 15 additional members.

**Paolo Angeli /** University of Padova

**Vicente Arroyo /** EF Clif, Barcelona (Chairman of the EASL Clif Consortium)

**Mauro Bernardi /** Policlinico S Orsola-Malpighi - University of Bologna (Vice-Chairman of the EASL Clif Consortium)

**Alexander Gerbes /** Munich University Hospital

**Pere Ginès /** Hospital Clínic, Barcelona

**Thierry Gustot /** Erasme University Hospital, Bruxelles

**Rajiv Jalan /** Royal Free Hospital, London

**Richard Moreau /** Hôpital Beaujon, Clichy

**Frederik Nevens /** Gasthuisberg University Hospital, Leuven

**Marco Pavesi /** EF Clif, Barcelona

**Thomas Reiberger /** Medical University of Vienna

**Francesco Salerno /** Policlinico San Donato - University of Milan

**Faouzi Saliba /** Hôpital Paul Brousse, Villejuif

**Fin Stolze Larsen /** Rigshospitalet -University of Copenhagen

**Jonel Trebicka /** Bonn University Hospital

**Julia Wendon /** King's College Hospital, London

**Reiner Wiest /** University Clinic of Visceral Surgery and Medicine-Inselspital, Berne

# The Grifols Chair

## European Clif Network of Translational Research (Clif- ENTR). Governing Board

The scientific activities of the European Clif Network of Translational Research centres, organized in the setting of the Grifols Chair are performed under the direction of a Director, a Deputy Director and a Secretary.

*Director*
**Vicente Arroyo /** Ef Clif, Barcelona

*Deputy Director*
**Richard Moreau /** Hôpital Beaujon, Clichy

*Secretary*
**Joan Clària /** Hospital Clínic, Barcelona

# Our staff

## Management

*Managing Director*
**Josep Mª Torner**

*Administrative Assistant*
**Montserrat Carreras**

*Scientific Assistant*
**Yolanda Godoy**

## Data Management Centre

*Head*
**Marco Pavesi**

*Data Manager*
**Carme Deulofeu**

*Statisticians*
**Ferran Aguilar, Àlex Amorós, Elisabeth García**

*Trainee*
**Carla Pitarch**

## Research Associates

*PI Predict Study*
**Jonel Trebicka**

*PI Apache Study*
**Javier Fernández**

*Grifols Chair Secretary*
**Joan Clària**

# Facts and figures

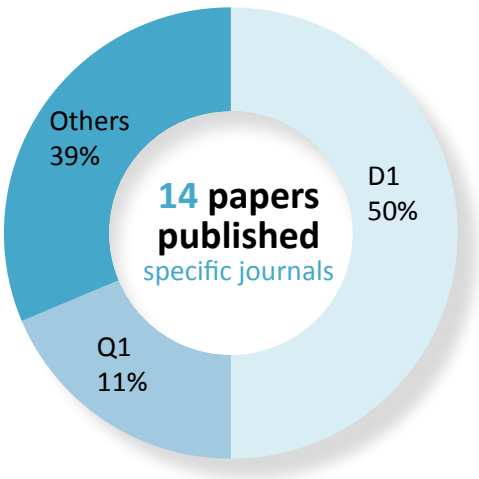
A network of **100 hospitals** in Europe

In **26 European countries**

More than **200 investigators** working on EF Clif Sponsored projects

Supporting **research projects** with more than 1,500,000 €/year

**14 papers** published in 2017




**7 papers**
**IF* > 10**

**Total mean**
**IF* = 7,02**

***IF**: Impact factor

# Scientific publications

The scientific outcome in 2017 has consisted of 14 published articles: 8 originals, 1 reviews, 1 snapshot, 1 seminar and 3 editorials.

1. POLYMORPHISMS IN THE INTERLEUKIN (IL-1) GENE CLUSTER INFLUENCE SYSTEMIC INFLAMMATION IN PATIENTS AT RISK FOR ACUTE-ON-CHRONIC LIVER FAILURE. Alcaraz-Quiles J, Titos E, Casulleras M, Pavesi M, López-Vicario C et al Hepatology 2017;65:202-216.

2. ACUTE-ON-CHRONIC LIVER FAILURE – AN UPDATE. Hernaez R, Solà E, Moreau R, Ginès P. Gut 2017 March 27. - Published by group.bmj.com REV

3. DIAGNOSIS AND PROGNOSIS OF ACUTE ON CHRONIC LIVER FAILURE (ACLF) IN CIRRHOSIS. Arroyo V, Moreau R. J Hepatol 2017; 66:451-453 SNAP

4. USING EQ-5D-3L AND OAB-5D TO ASSESS CHANGES IN THE HEALTH-RELATED QUALITY OF LIFE OF MEN WITH LOWER URINARY TRACT SYMPTOMS ASSOCIATED WITH BENIGN PROSTATIC HYPERPLASIA. Hakimi Z, Herdman M, Pavesi M, Devlin N, Nazir J et al Qual Life Res. Published 28 November 2016.

5. IMPACT OF GENETIC VARIATION IN THE VASOPRESSIN 1a RECEPTOR ON THE DEVELOPMENT OF ORGAN FAILURE IN PATIENTS ADMITTED FOR ACUTE DECOMPENSATION OF LIVER CIRRHOSIS. Kerbert AJC, Schaapman JJ, Van der Reifden JJ, Amoros A, McCormick A et al Eur J Gastroenterol Hepatol 2017;29:535-538.

6. MICROALBUMINURIA, SYSTEMIC INFLAMMATION, AND MULTIORGAN DYSFUNCTION IN DECOMPENSATED CIRRHOSIS: EVIDENCE FOR A NONFUNCTIONAL MECHANISM OF HEPATORENAL SYNDROME. Arroyo V. Hepatol Int. 2017;11:242-244. ED

7. AQUAPORIN-2 EXCRETION IN HOSPITALIZED PATIENTS WITH CIRRHOSIS: RELATION TO DEVELOPMENT OF RENAL INSUFFICIENCY AND MORTALITY. Busk TM, Moller S, Pedersen EB, Gerbes A, Krag A et al J Gastroenterol Hepatol 2017;32:1087-1093.

8. NEW LIVER – FRESH MICROBIOME: IMPLICATIONS ON BRAIN FUNCTION. Reiberger T, Trebicka J. Liver Transpl. 2017; 23:873-874. ED

9. BACTERIAL AND FUNGAL INFECTIONS IN ACUTE-ON-CHRONIC LIVER FAILURE – PREVALENCE, CHARACTERISTICS AND IMPACT ON PROGNOSIS. Fernandez J, Acevedo J, Weist R, Gustot T, Amoros A et al Gut. 2017 Aug 28. pii: gutjnl-2017-314240.

10. PLASMA CYSTATIN C IS A PREDICTOR OF RENAL DYSFUNCTION, ACLF AND MORTALITY IN PATIENTS WITH ACUTELY DECOMPENSATED LIVER CIRRHOSIS. Markwardt D, Holdt L, Steib Ch, Benesic A, Bendtsen F et al Hepatology 2017; 66:1232-1241.

11. MOLECULAR ADSORBENT RECIRCULATING SYSTEM CAN REDUCE SHORT-TERM MORTALITY AMONG PATIENTS WITH ACLF. A RETROSPECTIVE STUDY. Gerth HU, Pohlen M, Thölking G, Pavenstadt H, Brand M et al Crit Care Med. 2017; 45:1616-1624.

12. SEPSIS IN ALCOHOL-RELATED LIVER DISEASE. Gustot T, Fernández J, Szabo G, Albillos A, Louvet A et al J Hepatol 2017; 67:1031-1050. SEM

13. SELECTED PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE GRDE 3 ARE NOT TOO SICK TO BE CONSIDERED FOR LIVER TRANSPLANTATION. Gustot T, Agarwal B. J Hepatol 2017;67:667-668. ED

14. COPEPTIN IN ACUTE DECOMPENSATION OF LIVER CIRRHOSIS: RELATIONSHIP WITH ACUTE-ON-CHRONIC LIVER FAILURE AND SHORT-TERM SURVIVAL. Kerbert AJC, Verspaget HW, Navarro À, Jalan R, Solà E, Benten D, Durand F, Ginès P, van der Reijden JJ, van Hoek 2, Coenraad MJ; CANONIC Study Investigators of the EASL-CLIF Consortium. Crit Care. 2017 21;21(1):321

# The Clif Consortium hospital network & associated investigators

| | |
|---|---|
| **AUSTRIA** | |
| MEDICAL UNIVERSITY OF GRAZ | **Rudolf Stauber**<br>Karl Oettl<br>Walter Spindelboeck |
| MEDICAL UNIVERSITY OF INSBRUCK | **Wolfang Vogel**<br>**Heinz Zoller**<br>Livia Dorn<br>Ivo Graziadei |
| KLAGENFURT AM WÖRTHESEE HOSPITAL | **Markus Peck Radosavljevic** |
| MEDICAL UNIVERSITY OF VIENNA | **Thomas Reiberger** |
| **BELGIUM** | |
| ERASME HOSPITAL. UNIVERSITÉ LIBRE DE BRUXELLES | **Thierry Gustot**<br>**Christophe Moreno**<br>Massimo Bocci<br>Antonella Putignano |
| UNIVERSITY HOSPITAL ANTWERP<br>GHENT UNIVERSITY HOSPITAL | **Sven Francque**<br>**Hans Van Vlierberghe**<br>Isabelle Colle<br>Anja Geerts<br>Xavier Verhelst |
| UZ GASTHUISBERG LEUVEN | **Frederik Nevens**<br>Wim Laleman<br>Jelle Matthijnssens<br>Len Verbeke<br>Alexander Willmer |
| **CROATIA** | |
| ZAGREB UNIVERSITY HOSPITAL | **Irena Hrstic** |
| **CZECH REPUBLIC** | |
| INSTITUTE FOR CLINICAL AND EXPERIMENTAL MEDICINE | **Jan Sperl** |
| **DENMARK** | |
| AARHUS UNIVERSITY HOSPITAL | Henning Groenbaek<br>Hendrik Vilstrup<br>Niels Kristian AAgaard<br>Stine Karlsen<br>Moestrup oren Kragh<br>Sidsel Rødgaard-Hansen |
| RIGSHOSPITALET | **Fin Stolze Larsen**<br>Christian Mortensen |
| HVIDOVRE UNIVERSITY HOSPITAL | **Flemming Bendtsen** |
| NYKOEBING FALSTER HOSPITAL | **Lars Martinsen**<br>Stig Bondesen |
| ODENSE UNIVERSITY HOSPITAL | **Aleksander Krag** |
| **ESTONIA** | |
| WEST TALLIN CENTRAL HOSPITAL | **Vadim Brjalin**<br>**Külliki Suurmaa** |
| **FRANCE** | |
| CHU AMIENS –PICARDIE | **Nguyen-Khac** |
| CHU ANGERS | **Frédéric Oberti** |
| HÔPITAL MINJOZ | **Thierry Thevenot** |
| HÔPITAL AVICENNE BOBIGNY | **Dominique Roulot** |
| HÔPITAL JEAN VERDIER | **Roland Amathieu** |
| HÔPITAL BEAUJON | **Claire Francoz**<br>François Durand |

BLUE TEXT - New centres
**BOLD TEXT** - Principal Investigator

| | |
|---|---|
| | Richard Moreau |
| | Pierre-Emmanuel Rautou |
| | Dominique Valla |
| HÔPITAL HENRI MONDOR | **Christophe Duvoux** |
| HÔPITAL CLAUDE HURIEZ | **Philippe Mathurin** |
| HÔPITAL TENON- PARIS | **Jean Didier Grange** |
| HÔPITAL PITIÉ SALPÊTRIÈRE - PARIS | **Dominique Thabut** |
| RENNES UNIVERSITY HOSPITAL | **Pierre Brissot** |
| CHU TOULOUSE | **Christophe Bureau** |
| | **Jean-Marie Peron** |
| HÔPITAL PAUL BROUSSE | **Faouzi Saliba** |
| | Audrey Coilly |
| | Eric Levesque |
| | Didier Samuel |
| **GEORGIA** | |
| GEORGIAN NATIONAL HEPATOBILIARY CENTRE | **V Katsarava** |
| | **Gocha Barbakadze** |
| **GERMANY** | |
| AACHEN UNIVERSITY HOSPITAL | **Christian Trautwein** |
| | Pavel Strnad |
| UNIVERSITY OF BONN | **Jonel Trebicka** |
| | Frank Usner |
| DUSSELDORF UNIVERSITY HOSPITAL | **Dieter Häussinger** |
| UNIVERSITY HOSPITAL OF ESSEN | **Guido Gerken** |
| J W GOETHE UNIVERSITY HOSPITAL-FRANKFURT | **Stefan Zeuzem** |
| | George Dultz |
| | Christian Lange |
| | Oliver Waidmann |
| | Martin-Walter Welker |
| | Tania Welzel |
| UNIVERSITY HOSPITAL OF FREIBURG | **Robert Thimme** |
| UNIVERSITY HOSPITAL HALLE-WITTENBERG | **Alexander Zipprich** |
| HAMBURG-EPPENDORF UNIVERSITY HOSPITAL | **Ansgar Lohse** |
| | **Valentin Fuhrmann** |
| | Daniel Benten |
| | Henning Wege |
| HANNOVER MEDICAL SCHOOL | **Thomas von Hahn** |
| | **Michael Manns** |
| UNIVERSITY HOSPITAL OF HEIDELBERG | Wolfgang Stremmel |
| | Uta Merle |
| UNIVERSITY HOSPITAL OF HOMBURG | Frank Lammert |
| JENA UNIVERSITY HOSPITAL | **Tony Bruns** |
| UNIVERSITY HOSPITAL LEIPZIG | **Cornelius Engelmann** |
| UNIVERSITY OF MAINZ HOSPITAL | **Peter R. Galle** |
| | **Marcus-A. Wörns** |
| MUNICH UNIVERSITY HOSPITAL | **Alexander Gerbes** |
| | Corinna Hopf |
| MÜNSTER UNIVERSITY HOSPITAL | **Hartmut Schmidt** |
| UNIVERSITY HOSPITAL OF MAGDEBURG | **Ali Canbay** |
| UNIVERSITY HOSPITAL WÜRZBURG | **Andreas Geier** |
| **HUNGARY** | |
| UNIVERSITY OF DEBRECEN | **Mária Papp** |

| | |
|---|---|
| **ICELAND** | |
| LANDSPITALI UNIVERSITY HOSPITAL | **Sigurdur Olafsson** |
| **IRELAND** | |
| ST VINCENT'S UNIVERSITY HOSPITAL | **Aiden McCormick**<br>Jun Liong Chin |
| **ITALY** | |
| ALMA MATER STUDIORUM. UNIVERSITÀ DI BOLOGNA | **Mauro Bernardi**<br>**Paolo Caraceni**<br>Marco Domenicali<br>Filippo Morando<br>Giacomo Zaccherini |
| ASL BRINDISI | **Pietro Gatti** |
| OSPEDALE NIGUARDA, MILAN | **Luca Saverio Belli** |
| POLICLINICO SAN DONATO- UNIVERSITY OF MILAN | **Francesco Salerno** |
| AZIENDA OSPEDALIERA DI PADOVA | **Paolo Angeli**<br>Elisabetta Gola<br>Carlo Merkel<br>Sara Montagnese<br>Salvatore Piano<br>Antonietta Romano |
| POLICLINICO OF PALERMO | **Vito di Marco** |
| UNIVERSITY OF ROME | **Manuela Merli**<br>Oliviero Riggio |
| AZIENDA OSPEDALIERA CITTÀ DELLA SALUTE E DELLA SCIENZA DI TORINO | **Carlo Alessandria**<br>Alfredo Marzano<br>Alessandro Risso<br>Mario Rizzetto<br>Giorgio M Saracco |
| INTERNAL MEDICINE- UNIVERSITY OF UDINE | **Pierluigi Toniutto** |
| **LATVIA** | |
| RIGA EAST UNIVERSITY HOSPITAL | **Ieva Tolmane** |
| **LITHUANIA** | |
| HOSPITAL OF LITHUANIAN UNIVERSITY OF KAUNAS | **Limas Kupcinskas** |
| SIAULIAI HOSPITAL | **Gitana Acute** |
| **NETHERLANDS** | |
| LEIDEN UNIVERSITY MEDICAL CENTRE | **Minneke J Coenraad** |
| ERASMUS UNIVERSITY MEDICAL CENTRE ROTTERDAM | **Rob de Man**<br>Rosalie Oey |
| **NORWAY** | |
| OSLO UNIVERSITY HOSPITAL | **Zbigniew Konopski** |
| **POLAND** | |
| POMERIAN MEDICAL UNIVERSITY | **Anna Borón Kaczmarska** |
| **PORTUGAL** | |
| HOSPITAL SANTA MARIA. FACULTADE DE MEDICINA DA UNIVERSIDADE DE LISBOA | **José Velosa** |
| CENTRO HOSPITALAR DO PORTO | Filipe Nery |
| CHTMAD VILA REAL | José A Presa Ramos |
| **SLOVACK REPUBLIC** | |
| PAVOL JOZEF SAFARIK UNIVERSITY IN KOSICE | **Peter Jarcuska**<br>Martin Janicko |
| ROOSEVELT UNIVERSITY HOSPITAL. BANSKA BYSTRICA | **Lubomir Skladany** |

| | |
|---|---|
| **SPAIN** | |
| HOSPITAL UNIVERSITARI GERMANS TRIAS I PUJOL | **Rosa Mª Morillas** |
| HOSPITAL CLINIC BARCELONA | **Pere Ginès**<br>José Alcaraz-Quiles<br>Xavier Ariza<br>Rogelio Barreto<br>Joan Clària<br>Javier Fernández<br>Isabel Graupera<br>Mónica Guevara<br>Wladimiro Jiménez<br>Manuel Morales Ruiz<br>Elsa Solà<br>Esther Titos |
| HOSPITAL DE LA SANTA CREU I SANT PAU | **German Soriano**<br>Concepción Mª del Mar<br>Maria Poca Sans |
| FUNDACIÓ HOSPITAL UNIVERSITARI<br>VALL D'HEBRON- INSTITUT DE RECERCA | **Víctor Vargas**<br>Joan Genescà<br>Macarena Simon-Talero |
| HOSPITAL UNIVERSITARIO REINA SOFÍA | **Manuel de la Mata**<br>Patricia Aguilar Melero<br>José Luis Montero Álvarez |
| HOSPITAL UNIVERSITARI BELLVITGE | **José Castellote**<br>Xavier Xiol |
| HOSPITAL UNIVERSITARIO RAMÓN Y CAJAL | **Agustín Albillos**<br>Javier Martínez<br>Francisco Mesonero |
| HOSPITAL GENERAL UNIVERSITARIO GREGORIO MARAÑÓN | **Rafael Bañares**<br>María Vega Catalina<br>Rita García |
| CLINICA UNIVERSITARIA NAVARRA | **Jorge Quiroga** |
| HOSPITAL VIRGEN DEL ROCÍO | **Manuel Romero Gómez**<br>Javier Ampuero<br>Jordi Muntané |
| **SWEDEN** | |
| LINKÖPIN UNIVERSITY HOSPITAL | **Stergios Kechagias** |
| **SWITZERLAND** | |
| INSELSPITAL BERNE | **Andrea De Gottardi**<br>Jean François Dufour<br>Bernhard Morrell<br>Reiner Wiest |
| UNIVERSITY HOSPITAL OF GENEVE | **Laure Elkrief** |
| LAUSANNE UNIVERSITY HOSPITAL CHUV | **Pierre Deltenre** |
| ST GALL CANTONAL HOSPITAL | **Christine Bernsmeier**<br>Anne Kristin Hausen |
| ZÜRICH UNIVERSITY HOSPITAL | **Beat Mühlhaupt** |
| **TURKEY** | |
| ANKARA UNIVERSITY FACULTY OF MEDICINE | **Ramazan Idilman** |
| MARMARA UNIVERSITY SCHOOL OF MEDICINE | **Osman Ozdogan** |
| KARADENIZ SCHOOL OF MEDICINE | **Mehmet Arslan** |
| **UKRAINE** | |
| IVANO-FRANKIVSK NATIONAL MEDICAL UNIVERSITY | **Virstyk Nataliya** |

### UNITED KINGDOM

| | |
|---|---|
| UNIVERSITY HOSPITALS BIRMINGHAM | **Ahmed Elsharkawy**<br>Neil Rajoriya |
| GLASGOW ROYAL INFIRMARY | **Ewan Forrest**<br>Adrian Stanley |
| IMPERIAL COLLEGE | **Harry Antoniades (†)** |
| KING'S COLLEGE HOSPITAL | **Julia Wendon**<br>Caterina Maggioli<br>Chris Willars<br>Daniel Markwardt<br>Debbie Shawcross<br>Pablo Solís-Muñoz<br>William Bernal |
| ROYAL FREE HOSPITAL | **Rajiv Jalan**<br>**Raj Mookerjee**<br>Banwari Aqarwal<br>Gautam Mehta<br>Jane Macnaughtan<br>Karen Thomsen<br>María Yago Baenas<br>Nathan Davies<br>Nigel Beaton<br>Patrick Kamath<br>Peter Holland-Fisher<br>Rohit Sawhney |
| UNIVERSITY HOSPITALS NOTTINGHAM | Stephen Ryder |
| PLYMOUTH HOSPITAL TRUST | **Juan Acevedo**<br>**Matthew Cramp** |
| QUEEN ALEXANDRA HOSPITAL -PORTSMOUTH | **Richard Aspinall** |

## EXTERNAL COLLABORATORS

| | |
|---|---|
| Ramón Bataller | *University of Pittsburgh* |
| Flair Carrilho | *Hospital de Clínicas de São Paulo* |
| Alberto Farias | *Hospital de Clínicas de São Paulo* |
| Cristophe Junot | *CEA* |
| David Gómez-Cabrero | *University of Navarra* |

# News and activities

Dr. Trebicka at the meeting

**18 January 2017**

## THE PREDICT STUDY KICK-OFF MEETING HELD IN BARCELONA

The meeting took place at the EF Clif offices in Barcelona on 18 January. PI's from the 48 participating centres gathered to discuss the execution of the first stage of the project and to share their views and thoughts on the development of the PREDICT Study.

On the basis of the experience of the CANONIC Study, the discussion focused on the main working lines of PREDICT and then moved to the different aspects of the Study. Special attention was given to the eCRF and how to make it user-friendly and competitive. Other relevant aspects, such as the pathogenetic background and the management of the samples by the biobank, took up another part of the session. The PREDICT kick-off meeting finished with an overview on the ancillary studies and their developments, which will be further discussed.

**27 March 2017**

## THE INCLUSION OF PATIENTS IN THE PREDICT STUDY BEGAN

In 18 hospitals.

**19–22 April 2017**

## EASL CLIF CONSORTIUM MEETINGS AT THE EASL ANNUAL CONGRESS 2017

Dr Paolo Angeli

During the EASL Congress (Amsterdam, 19–23 April) we held the Annual meeting of the CLIF Consortium Steering Committee and the General Assembly.

In both meetings, a general overview was presented on all the activities done during the previous year. We also focused on the development of the EF Clif and the enlargement of the CLIF Consortium hospital network (100 hospitals). In addition, we spent some time in presenting new projects and ideas, in both clinical and translational research, to be developed in the short and medium term.

During the Steering Committee Meeting, Dr Vicente Arroyo presented his resignation as Chairman of the CLIF Consortium, after having served in this position for eight years. Among the potential candidates to succeed him (Steering Committee members), only Dr Paolo Angeli (University of Padova) applied for this position and, later on, his candidacy was unanimously approved by the Committee. Two days later, the General Assembly of the CLIF Consortium confirmed this appointment. And, after that, in accordance with the Rules for Regulation of the EASL-CLIF Consortium, the EASL Governing Board was informed accordingly for its final designation.
Dr Angeli took over the position of Chairman of the CLIF Consortium on 1 January, 2018.

The participants at the Aclara first meeting at the Hospital das Clinicas, Sao Paulo

**31 August to 1 September 2017**

## THE ACLARA STUDYTAKES ITS FIRST STEPS

The Aclara Study aims to characterize the mechanisms of ACLF in Latin America and compare its results with the data obtained from other previous similar studies.

Dr Flair Carrilho from the Hospital das Clínicas and Dr Richard Moreau from the Centre de Recherche sur l'Inflammation (INSERM) are the PI's of the study, and Dr Alberto Farias is the Project Manager. Under their direction, 54 hospitals from Argentina, Brazil, Chile, Colombia, Mexico, Panama and Peru participated in the first PI's meeting of the Study, sponsored by the EF Clif, on 31 August and 1 September in Sao Paulo.

Members of the EF Clif in Barcelona travelled to Sao Paulo to share their expertise with the participant centres representatives in the ACLARA study. During the two-day meeting, the main strategy, goals and operational plan of the project were discussed with all the participants.

**21 December 2017**

## DR ALBERTO FARIAS HAS VISITED THE EF CLIF HEADQUARTERS

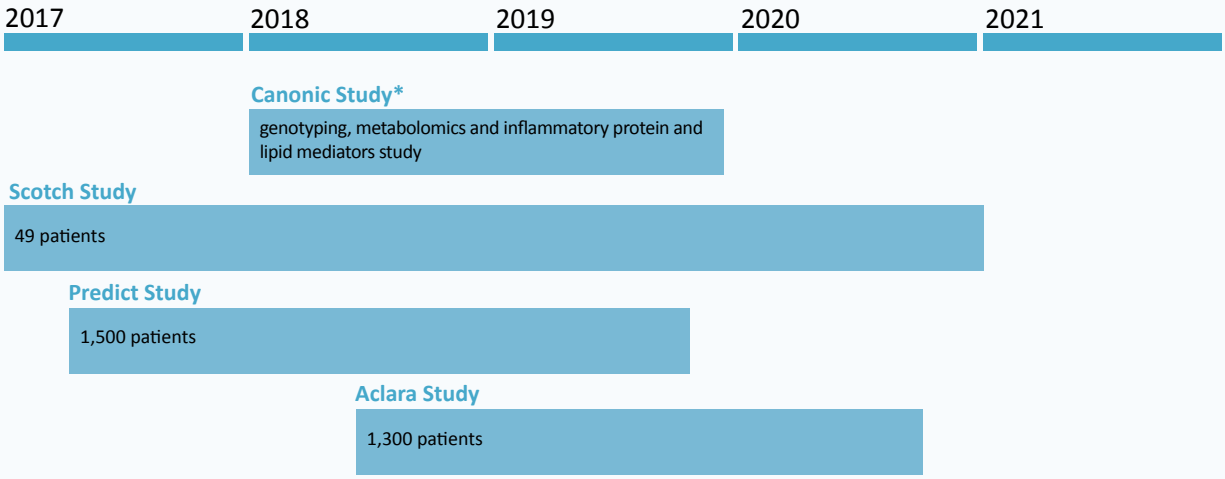
Dr Alberto Farias

Professor of Gastroenterology and Hepatology at the Sao Paulo University Medical School, he is the Clinical Coordinator of the Liver Transplant Programme at the Hospital das Clínicas and the Project Manager of the EF Clif sponsored ACLARA study.
His four-day visit to EF Clif headquarters served to start coordinating efforts in the ACLARA Study preparation, following the plan designed at the PI's meeting held in Sao Paulo in September.
During the working sessions, we focused on several aspects of the study, particularly the organizational and clinical ones. Our approach in these sessions was to cover the main lines discussed already at the PI's meeting, paying special attention to the needs of both the PIs and their institutions, and the EF Clif itself.
A major emphasis has been put on enhancing the relationship between the ACLARA team members in Barcelona and the ACLARA office in Sao Paulo, in order to provide the best support to all participating centres.

# New studies calendar

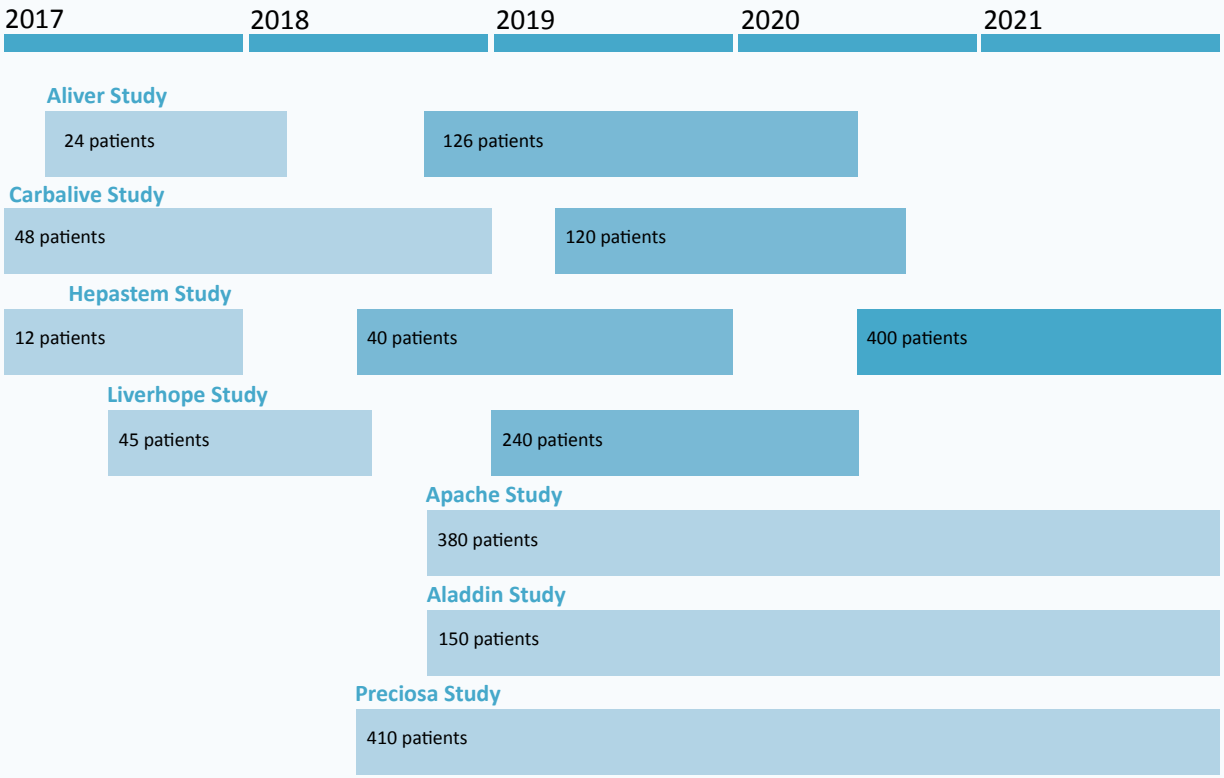
## The EASL Chair Studies

Schedule for inclusion of patients in Scotch, Predict and Aclara Studies and final analysis in biobank samples of Canonic Study

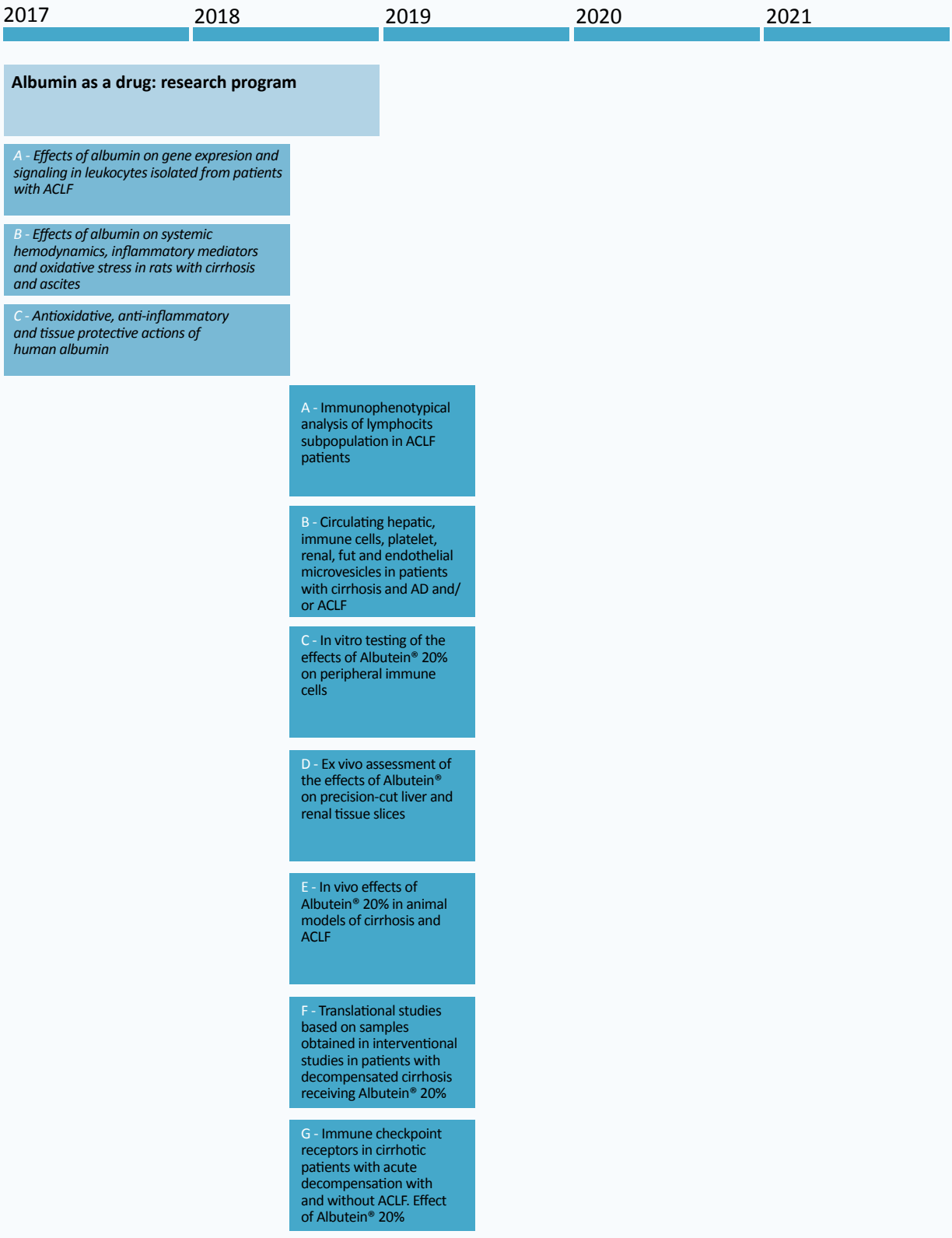



** Study inclusion finished in 2012*

## Collaboration in external Projects



## The Grifols Chair Studies



# The EASL Chair Studies

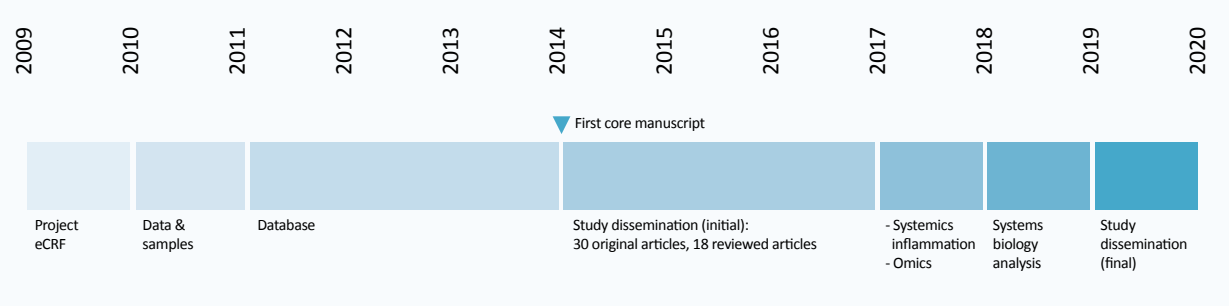
## Ongoing studies

### CANONIC Study

**Follow up projects**

***Principal Investigators: Christophe Junot (CEA, Saclay, France), Richard Moreau (Hôpital Beaujon, Clichy, France), Joan Clària (Hospital Clínic, Barcelona, Spain) and David Gómez-Cabrero (University of Pamplona, Pamplona, Spain)***

We are in the process of assessing the genotyping, metabolomics and targeted lipidomics of the samples obtained from the CANONIC study patients and data integration cell system biomedical analysis




We estimate to finalize all these analyses and corresponding articles at the end of 2019. The CANONIC study will then be closed.

SCotCH

**(June 2015-December 2020))**

**Study designed to assess the clinical relevance, efficacy and safety in the treatment of hypotensive Cirrhotic Patients with suspicion of sepsis by using low dose cortisone (Supplemental Corticosteroids in Cirrhotic Hypotensive Patients with Suspicion of Sepsis. The SCOTCH – trial).**

*Principal Investigators: Alexander Willmer (Gasthuisberg University Hospital, Leuven, Belgium) and Javier Fernández (Hospital Clínic, Barcelona, Spain).*

This is a phase IV, double-blind, randomized, placebo-controlled, multicentre trial, in cirrhotic patients with septic shock aimed to assess if stress dose steroids treatment improves 28-day mortality in cirrhotic patients with septic shock

Ten centres are currently active to recruit: Spain (n=4), Belgium (n=2), United Kingdom (n=2) and Italy and Czech Republic (n=1, each). Regulatory issues are pending in Germany (n=1) and Austria (n=1). Until now, 213 patients have been screened and 49 patients (23%) were included. We estimate that the inclusion will finish at the end of 2020. An interim analysis has been scheduled after the inclusion of the first 100 patients

PREDICT

**Predicting Acute-on-Chronic Liver Failure in Cirrhosis (PREDICT)**

**(January 2017-September 2019)**

**The PREDICT Study is designed to prospectively observe patients with cirrhosis and Acute Decompensation (AD) at risk of developing ACLF within three months, and to discover new clinical and laboratory predictors of ACLF development, patho-physiological mechanism (using prospective ancillary studies) and potential treatment to prevent ACLF.**

*Principal Investigator: Jonel Trebicka (Cellex Visiting Professor at the EF-Clif; Bonn University Hospital, Germany).*

The first patient was included on 31 March, 2017 and the first phase of the study was completed in September, after an analysis of the first 400 patients included consecutively (without prior selection). The objective of this initial analysis was to differentiate highly predisposed patients to develop ACLF in a short period of time (3 months) (Group 1) from those who were not very predisposed (Group 2).

Based on this analysis, we initiated the second phase of the study, which will focus on patients in group 1 and patients who already have the syndrome at the time of admission. Therefore, this second phase will include only 2 groups of patients: 1. Patients at high risk of developing ACLF in 3 months (Group 1); 2. A control group of patients who already suffer from the ACLF syndrome at the time of admission, whose inclusion was initiated at the beginning of the second phase of the study.

The Cellex Foundation contributes to the realization of the project by means of a contribution that covers the expenses incurred by the Principal Investigator of the study in terms of personnel and travel.

# New studies

ACLARA

**(May 2018-September 2020)**

**The ACLF-ACLARA study is a prospective follow-up observational investigation in 1300 patients with cirrhosis hospitalized for AD with and without ACLF at 48 hospitals, designed to assess the characteristics of the ACLF syndrome in Latin America.**

*Principal Investigator: Flair Carrilho (Hospital das Clinicas, Sao Paulo, Brasil) and Richard Moreau (INSERM, Paris and Hôpital Beaujon, Clichy, France).*

The aims of the ACLF-ACLARA project are:

- To investigate the characteristics of the ACLF syndrome in Latin America (including its clinical course, severity and mortality) by sequential assessment of multi-organ failure, specific biomarkers of systemic inflammation and oxidative stress, effective arterial blood volume, immune cell function and cell death, exogenous precipitating factors, and genotyping (assessed only at enrolment), transcriptomics and metabolomics.
- To investigate the relationship between the prevalence of ACLF and of potential specific phenotypes (subtypes) with pathogenic, ethnic, lifestyle and other features related to geographic and environmental variations.
- To perform systems biology modeling analysis for better understanding of the ACLF mechanisms and identification of new predictive biomarkers and potential therapeutic targets.
- To integrate the Latin-America cohort with other prospective highly harmonizable international cohorts developed with the CANONIC template for comparative assessment.
- To obtain blood samples for future metagenomics analysis.
- The logistic expenses (electronic CRF, specific tubes for the samples, and samples shipment and biobanking), the assessment of clinical data and biomarkers and the economical compensation to the centres will be supported by the EF Clif.

During 2017, the EF Clif has designed the protocol and CRF and finalized the selection of centres. In August 2017 the first PI's meeting was held, to discuss the set-up of the study, which will start in 2018. Patient inclusion is expected to be completed in 9 months and data analysis will probably start at the end of 2019.

# The Grifols Chair Studies

## Albumin as a drug research program

## Ongoing studies

### a) EFFECTS OF ALBUMIN ON GENE EXPRESSION AND SIGNALING IN LEUKOCYTES ISOLATED FROM PATIENTS WITH ACLF.

*Principal Investigator: Richard Moreau (Hôpital Beaujon, Clichy, France).*
(June 2016-June 2018)

The clinical relevance of albumin is supported by studies showing improved survival in cirrhotic patients receiving albumin infusions. Mechanisms accounting for these beneficial actions suggest that albumin modulates a vast network of gene implicated in the control of systemic oxidative stress and inflammation. The main goal of this project is to shed new light on the mechanisms underlying the biological properties of albumin by assessing the effects of albumin on gene expression in leukocytes isolated from patients with decompensated cirrhosis and ACLF.

### b) EFFECT OF ALBUMIN ON SYSTEMIC HEMODYNAMICS, INFLAMMATORY MEDIATORS AND OXIDATIVE STRESS IN RATS WITH CIRRHOSIS AND ASCITES.

*Principal Investigator: Wladimiro Jiménez (Hospital Clínic, Barcelona, Spain).*
(June 2016-June 2018)

Mechanisms accounting for the beneficial actions of albumin have been investigated in experimental models of cirrhosis and sepsis, with results suggesting that albumin modulates systemic inflammation, oxidative and cellular stress by its ability to bind and sequester soluble mediators. The main goal of this project is to compare the effects of a new formulation of albumin on systemic hemodynamics, inflammation and oxidative stress in rats with cirrhosis and ascites with those using the conventional formulation.

## c) ANTIOXIDATIVE, ANTI-INFLAMMATORY AND TISSUE PROTECTIVE ACTIONS OF HUMAN ALBUMIN.

*Principal Investigator: Joan Clària (Hospital Clínic, Barcelona, Spain).*
(June 2016- June 2018)

Albumin plays a modulatory role in systemic inflammation and oxidative stress through its ability to bind and sequester soluble mediators. In this project, we have collected evidence indicating that albumin exerts anti-inflammatory actions in human leukocytes, effects that reflect the ability of this molecule to attenuate the activation of the immune cells in the systemic circulation. This project also has obtained data indicating that albumin protects liver tissue slices from TNF-alpha cytotoxicity.

# New studies

## a) Immunophenotypical analysis of lymphocyte subpopulations in peripheral blood of cirrhotic patients with acute decompensation with and without ACLF.

*Principal Investigator Francisco Lozano (Innate Immunity unit, Hospital Clínic, Barcelona, Spain).*
(January 2018-June 2019)

This project will provide the first immunophenotypical characterization of adaptive immune cells in patients with decompensated cirrhosis with and without ACLF. This proposal includes ex vivo immunophenotypical analyses of functionally relevant lymphocyte subpopulations from peripheral blood of patients with compensated cirrhosis (without current or prior decompensation) (n=30), and decompensated cirrhosis with (n=30) and without (n=30) ACLF recruited from five different hospitals (TBD). The immunophenotyping will be performed in a centralized laboratory (Hospital Clínic) and will include the following T and B cell panels: 1) TBNK (CD4+T, CD8+T, NK, and B cells); 2) T (TCRαβ, TCRγδ, naïve T, memory T, activated T; 3) B (naïve B, switch memory B, un-switch memory B, transitional B, plasmablasts, CD21loCD38lo B, and regulatory CD38hiCD24hi B); and 4) regulatory T (CD3+CD4+CD25hiCD127-).

## b) Circulating hepatic, immune cells, platelet, renal, gut and endothelial microvesicles in patients with cirrhosis and AD and/or ACLF. Effects of human albumin (Albutein®20%).

*Principal Investigator Pierre-Emmanuel Rautou (Inserm U970 and Hepatology department at Beaujon Hospital, Clichy, France).*
(January 2018-June 2019)

Extracellular vesicles are membrane vesicles released by cells in the extracellular space. They are formed of a lipid bilayer enclosing soluble cytosolic material. They include apoptotic bodies, microvesicles, also known earlier as microparticles, and exosomes. Apoptotic bodies are larger than 1 µm, include apoptotic nuclear material and are surrounded by a permeable membrane. Microvesicles are distinguished from other vesicles by their size (≈100–1000 nm) and by the mechanisms regulating their formation, which include cytoskeleton remodeling and externalization of phosphatidylserine. Exosomes (≈40 to 100 nm) are the smallest extracellular vesicles, although there is no clear cut-off value separating microvesicles from exosomes. Previous findings indicate that plasma microvesicles contribute to portal hypertension associated with cirrhosis and that hepatocyte microvesicle levels increase with the severity of cirrhosis. Moreover, hepatocyte microvesicle levels increase with cirrhosis severity and can predict survival independently of MELD score, particularly in patients with severe cirrhosis. It can be hypothesized that circulating extracellular vesicle levels can be early markers of organ dysfunction in patients with acute decompensation of cirrhosis and highlight pathophysiological processes explaining the transition

from acute decompensation to ACLF. This project objective is to measure the levels of exosomes and microvesicles derived from hepatocytes, immune cells (neutrophils, CD66b; leukocytes, CD11a) in plasma samples from patients included in the CANONIC study and INFECIR study.

## c) In vitro testing of the effects of Albutein® 20% on peripheral immune cells

*Principal Investigator Joan Clària (Hospital Clínic, Barcelona).*
(January 2018-June 2019)

Immune cells (i.e., polymorphonuclear leukocytes (PMN), monocytes and T and B lymphocytes) are the principal cellular players in systemic inflammation. The assessment of the effects of albumin on the biology of these cells either under resting conditions or under inflammatory conditions will allow us to explore the effects of albumin on systemic inflammation at the cellular level. Comparison of the effects of an albumin solution with purity higher than 95% (Albutein®) with those of an albumin solution with purity lower than 85% (Plasmanate®) and a recombinant human albumin (96% purity) from transgenic rice will be performed. This comparison will make it possible to establish what part of the biological effects of albumin solutions is attributable to the albumin molecule and which is attributable to other compounds (proteins and/or lipids) that are either directly bound to human albumin or in solution. The main objective of this project is to dissect and gain knowledge of the mechanisms of action of albumin on peripheral blood leukocytes that can be of use in explaining its anti-inflammatory role in several diseases that have systemic inflammation as a common underlying cause.

## d) Ex vivo assessment of the effects of Albutein®20% on precision-cut liver and renal tissue slices

*Principal Investigator Joan Clària (Hospital Clínic, Barcelona).*
(January 2018-June 2019)

In addition to systemic inflammation, factors such as cell death (necrosis and/or apoptosis), endoplasmic reticulum (ER) stress and mitochondrial dysfunction also play a major role in tissue damage and organ failure. Since albumin is of clear therapeutic value in preventing organ failure(s) in several clinical settings, it is of interest to investigate the effects of different albumin formulations on tissue biology. Precision-cut slices of liver and kidney represent an established experimental model that allows the assessment of the direct effects of a drug on a tissue without the influence of circulating factors. Importantly, precision-cut slices preserve the original cell-cell interactions existing in a tissue. In these experiments, we will compare the effects of an albumin solution with a purity higher than 95% (Albutein®) with those of an albumin solution with a

purity lower than 85% (Plasmanate®) and a recombinant human albumin with 96% purity will be performed. The overall aim of this project is to dissect and gain knowledge about the mechanisms of action of albumin on isolated precision-cut tissue slices of liver and kidney that can be useful to explain the protective effects of albumin against tissue damage and organ dysfunction.

## e) In vivo effects of Albutein® 20% in animal models of cirrhosis and ACLF

*Principal Investigator Joan Clària (Hospital Clínic, Barcelona, Jonel Trebicka, University of Bonn, Germany).*
(January 2018-June 2019)

The investigation of the mechanism of action of albumin in vivo is limited by the absence of a reliable animal model that could serve as a useful experimental platform to test the effects observed in vitro in cells and tissues. This is particularly critical in the case of decompensated liver cirrhosis and ACLF. Although it is true that several models of liver cirrhosis have been described and used for many years, at present there is not a single animal model reproducing the clinical characteristics of ACLF in humans. This is truly poignant in terms of the most important feature of ACLF: the presence of systemic inflammation and its role in the development of organ failure(s). Therefore, generation of an animal model reproducing the complete pathophysiological process of human ACLF is needed. Moreover, the availability of such a model represents a priority to confirm the therapeutic properties of albumin in preclinical studies. The objective of this project is to develop optimal preclinical murine models reproducing the clinical features of patients with decompensated cirrhosis and ACLF.

## f) Translational studies based on samples obtained in interventional studies in patients with decompensated cirrhosis receiving intravenous human serum albumin (Albutein®, 20%)

*Principal Investigators Joan Clària and Javier Fernández (Hospital Clínic, Barcelona, Spain).*
(January 2018-June 2019)

The major goal of this project is to translate the findings described at cellular, tissue and experimental level to the clinical level. To achieve this, we will collect mechanistic evidence in serum/plasma samples obtained from a pilot study in which albumin dose was titrated for long-term treatment in patients with decompensated cirrhosis (pilot PRECIOSA study) and from a randomized control trial (INFECIR study) in patients with decompensated cirrhosis and bacterial infections other than spontaneous bacterial peritonitis in which albumin was administered to reduce risk of organ failure. The end-point of this proposal is to provide clinical evidence and proof-of-concept of the mechanisms underlying the therapeutic properties of human albumin

## g) Immune checkpoint receptors in cirrhotic patients with acute decompensation with and without ACLF. Effect of albumin (Albutein®20%) treatment (study using samples from the CANONIC AND INFECIR cohorts).

*Principal Investigator Shilpa Chokshi (Institute of Hepatology, Foundation for Liver Research, London, UK).*

(January 2018-June 2019)

Immune checkpoint receptors are inhibitory receptors that physiologically regulate the balance between protective anti-pathogen/tumor immunity and immune-mediated tissue damage. Recently, it was demonstrated that patients with decompensated cirrhosis show an increased expression of IP-10 (C-X-C motif chemokine 10) – a potent T-cell chemoattractant and T-cell activator in the plasma of patients with ACLF with increasing concentrations with increase in severity. Moreover, a decrease in the interferon (IFN)γ/IL-10 ratio was reported, which we previously showed to be a correlate of decreased anti-bacterial T-cell functionality. This data suggests that the T-cell response may be critical in ACLF. Therefore, it can be hypothesized that checkpoint receptors mediate the immune damage and immunodeficiency in ACLF and may represent both prognostic markers and therapeutic targets. The aim of this project is to measure the presence of soluble checkpoint receptors in plasma during ACLF and correlate with disease outcome and progression in order to assess surface bound checkpoint receptor expression on peripheral blood mononuclear cells in patients with ACLF and correlate with soluble plasma receptors; correlate all finding with markers of gut bacterial translocation; assess the role of interferons in ACLF and their relationship with checkpoint receptors and assess the effects of albumin (Albutein®20%) treatment on the circulating levels of checkpoint receptors.

# External projects

## Finalized studies


**Study focused on the effects of albumin administration in the prevention of hepato-renal syndrome and death in patients with cirrhosis, bacterial infections other than spontaneous bacterial peritonitis and high risk of hospital mortality.**

*Principal Investigator: Javier Fernández (Hospital Clínic, Barcelona, Spain)..*
(April 2014-December 2016)

This was a phase IV, open-label, multicentre European RCT aimed at evaluating if albumin administration impacts survival in patients with advanced cirrhosis and non-SBP infections. From April 2014 to December 2016, 776 patients were screened and 119 patients (15.3%) were included in the study. Hospital Clinic of Barcelona (n=33), University of Padova (n=9), Sapienza University in Rome (n=9), University Hospital in Bonn (n=9), San Giovanni Battista Hospital, Turin (n=7) and Erasme Hospital, Brussels and Aarhus University Hospital (n=6 each) were the centres with the highest patient inclusion. The study was prematurely interrupted in December 2016 due to low recruitment rate, lower than expected hospital mortality and expiration of the study drug.
A preliminary analysis of the database has been performed. Sixty subjects were finally randomized to receive antibiotics+albumin within the first 72h after infection diagnosis and 59 to receive antibiotics. Baseline clinical and analytical characteristics were similar between groups with no differences in Child-Pugh, MELD score, type of infection (pneumonia: 28% vs. 37%, UTI: 27% vs. 20%, bacteremia: 23% vs. 19% in the albumin and non-albumin groups, respectively) and severity (nosocomial: 30% vs. 32%; ACLF: 25% vs. 18%). Hospital (13% vs. 10%), 28-d (15% vs. 10%) and 90-d mortality rates (28% vs. 22%) were similar between the albumin and the non-albumin group. Four patients receiving albumin (7%) developed pulmonary edema during hospitalization compared to none in the non-albumin group. The main conclusion of the study is that albumin administration does not improve short-term survival in patients with advanced cirrhosis and non-SBP infections. These results will be presented at the upcoming EASL meeting in Paris in April 2018.

# Ongoing studies


## (European Union Horizon 2020 Programme)

**This is a multicentre, randomised controlled study, to evaluate the safety and performance of The DIALIVE Liver Dialysis Device (LDD) in patients with Acute on Chronic Liver Failure (ACLF) versus standard of care (SOC).**

*Principal Investigator: Rajiv Jalan (Royal Free Hospital, London, UK).*
(2017-2018)

In the expectation of successful completion of the DIALIVE Safety & Performance study, a second study is planned to assess the efficacy of the DIALIVE to treat ACLF patients. The study hypothesis of the EFFICACY study will be defined based on the outcome of the ongoing SAFETY & PERFORMANCE trial.


## (European Union Horizon 2020 Programme)

**The aim of the CARBALIVE project is to further develop and validate a novel nanoporous carbon adsorbent (Yaq-001) capable of removing bacterial endotoxin and other metabolic toxins relevant to the progression of bacterial translocation and endotoxemia in patients with cirrhosis and NAFLD.**

*Principal Investigator: Rajiv Jalan (Royal Free Hospital, London, UK).*
(2017-2018)

The expected outcome would be a new therapeutic strategy for the treatment of cirrhosis and NAFLD patients ready for further development and clinical application.

## HEPASTEM

**Promethera Biosciences is a start-up pharmaceutical company that develops innovative therapies for the treatment of liver diseases like HepaStem (Heterologous Human Adult Liver-derived Progenitor Cells).**

*Principal Investigator: Frederik Nevens (UZ Gasthuisberg, Leuven, Belgium).*
(2016-2017)

The EF Clif has collaborated in the design, statistical planning and safety study and afterwards in the Study Safety Monitoring Board.

## (European Union Horizon 2020 Programme)

**The objective of the LIVERHOPE project is to evaluate a novel therapeutic strategy for patients with cirrhosis based on a combination of rifaximin and simvastatin, targeting the main pathophysiological mechanisms of disease progression, namely the impairment in the gut-liver axis and the persistent hepatic and systemic inflammatory response.**

*Principal Investigator: Pere Ginès (Hospital Clínic, Barcelona, Spain).*
(2017-2018)

This dual therapeutic approach is supported by preclinical data showing very promising results.

# New studies

## The APACHE TRIAL (Promoter: Grifols)

**The APACHE TRIAL is aimed to study the effects of plasma exchange on short-term survival in patients with ACLF and high risk of mortality.**

*Principal Investigators: Javier Fernández (Hospital Clínic, Barcelona, Spain) and Fin Stolze Larsen (Rigshospitalet, Copenhagen, Denmark).*
(2018-2021)

This is a phase III, multicentre, randomized, open-label trial in 380 patients with ACLF-1b, ACLF grade 2 or ACLF-3a aimed to determine whether plasma exchange with 5% albumin (from 4 to 9 plasma exchange sessions) improves 90-day survival in comparison with standard medical therapy. The study will be performed in around 40 centres in Europe and North America. The first draft of the study was sent to the FDA in December 2017. The submission process will start within the second/third quarter of 2018. The estimated duration of the study is 36-48 months.

## The ALADDIN STUDY (Promoter: Grifols)

**The ALADDIN STUDY is a complementary study to the APACHE, aimed to assess the mechanisms of systemic inflammation and ACLF in patients with and without ACLF.**

*Principal Investigators: Joan Clària (Hospital Clínic, Barcelona, Spain), Richard Moreau (Hôpital Beaujon, Clichy, France) and Ramon Bataller (University of Pittsburgh, USA).*
(2017-2020)

The ALADDIN Study is a translational research project coupled to the APACHE Study. It will be performed in blood samples and monocytes and polymorphonuclear leukocytes obtained from patients with ACLF included in the APACHE Study and from an additional group of 150 patients with acute decompensated cirrhosis but without ACLF that will serve as control group. The ALADDIN Study will be performed at the European centres participating in the APACHE Study.

The ALADDIN Study also includes three ancillary investigations aimed at exploring several specific mechanisms of systemic inflammation, the role of coagulopathy as a potential mechanism of organ failure, and albumin function in decompensated cirrhosis with and without ACLF. This later project will assess the potential role of albumin dysfunction in ACLF, the effect of Plasma Exchange (PE) on albumin function and the potential value of albumin function as a marker of response to PE.

## The PRECIOSA STUDY (Promoter: Grifols)

**The PRECIOSA STUDY is focused on exploring the albumin dosage for long-term treatment in patients with decompensated cirrhosis.**

*Principal Investigator: Paolo Caraceni (Policlinico S Orsola-Malpighi, Bologna, Italy).*
(2018-2021)

This is a phase IV, European and American, multicentre, randomized open-label trial in 410 patients with decompensated liver cirrhosis with ascites aimed to determine whether long-term albumin administration (1.5 g/kg body weight every 10 days for 12 months) improves 1-year transplant-free survival in comparison with standard medical therapy.
The study will be performed in about 40 centres in Europe and USA. The submission process started in the fourth quarter of 2017. The first patient will be included within the second quarter of 2018. The estimated duration of the study is 36-48 months.

# Future challenges

## EASL Chair

### The OBSERVAH Study

**Observational study in alcoholic hepatitis: identification of predisposing factors, diagnostic criteria, and determinants of complications and mortality**

*Principal Investigators: Christophe Moreno (Erasme University Hospital, Bruxelles, Belgium) and Ramon Bataller (Medical Center, University of Pittsburgh, USA)*

The OBSERVAH study will be a global, large, observational, multi-centre study designed to prospectively observe patients with alcoholic hepatitis. The overall aim of this study will be to better characterize the natural history of AH, to develop non-invasive methods for diagnosis as well as identifying the main determinants of complications, ACLF development and mortality, with the ultimate goal to favour the development of targeted therapies that reduce mortality. Moreover, the global biological material that will be obtained during the OBSERVAH study will be an exciting source for pathophysiological studies.
As it will be an observational study, this study will not exclude other studies in parallel.
The OBSERVAH study plan is to include approximately 2000 patients from Europe, North and South America and Asia within 2 years.
The plan of the EF Clif is to cover the elaboration of the project, data collection (including electronic CRF), logistics for sample collection and travelling, biobanking facilities, data management and a limited economic compensation to the centres.

### The GIC Project

**Global Integrated Cohort**

*Principal Investigators: Paolo Angeli (University of Padova, Italy) and Rajiv Jalan (University College London, UK)*

The recognition and characterization in 2013 of the ACLF syndrome by the CANONIC study was a breakthrough in the knowledge of the pathophysiology and natural history of cirrhosis. Widely accepted concepts on the mechanism of AD and extra-hepatic organ failure in cirrhosis, targets for innovative treatments and predictive prognostic models have since then been seriously challenged. As a consequence of this, major networking research activities have started in patients with decompensated cirrhosis. New regional and national Consortiums (including North American Consortium for the Study of End Stage Liver Disease, Latin-American CLIF Consortium and Chinese CLIF Consortium) have been organized and seven large post-CANONIC prospective observational studies in Korea, China, India, Europe and Latin America based on the CANONIC methodology have been completed or are in the process of development in patients with ACLF. Most of these studies have also collected biobanking material. Additionally, several randomized controlled interventional trials in large series of patients with AD with and without ACLF are currently being performed. Since most of these studies follow the CANONIC study methodology, they are easy to harmonize and therefore constitute an invaluable material for the creation of a global integrated cohorts to promote research in AD and ACLF in cirrhosis.

The aim of this project is to merge the CANONIC, PREDICT and ACLARA data (4 500 patients) with data from other prospective cohorts into a single coordinated cohort called GLOBAL INTEGRATED COHORT (GIC) under the umbrella of EF Clif (2 prospective cohorts from China with a total of 2467 patients, have already formally agreed to participate in the project).

The GIC should initially include more than 10 000 patients with AD (>3000 with ACLF) with homogeneous global distribution and complete set of harmonized clinical and standard laboratory data, inflammatory markers and omics data. Optimally it should allow:

1. Continuous comprehensive reassessment of concepts on AD and ACLF based on data coming from patient cohorts;
2. Enhancement or development of innovative tools for maximizing results of clinical relevance to understand mechanisms and update predictive models;
3. Cohort enrichment with new selected patient cohorts for continuous assessment of the impact of new diagnostics and therapies on the natural history of the disease;
4. Identification of common phenotypic characteristics and phenotypic variations (subtypes) of ACLF and the global and regional prevalence and epidemiology in connection with ethnic, pathogenic, lifestyle, societal and environmental determinants;
5. Identification of specific signatures of ACLF and ACLF as an independent syndrome and development of a globally accepted definition and stratification of ACLF;
6. Identification of genetic determinants, pathophysiological pathways and therapeutic targets of ACLF;
7. Comparative analysis of the GIC with cohort patients with other diseases associated with systemic inflammation, multi-organ failure and high short-term mortality, to share efforts for the identification of common pathogenic pathways and therapeutic targets;
8. Identification of criteria for intensive care treatment, artificial liver support and liver transplantation in patients with ACLF.

The elaboration of the GIC project would require not only a major challenge in terms of data harmonization and integration by investigators, biostatisticians and bioinformaticians, but also a great effort by lawyers and experts in ethics, intellectual property and scientific international cooperation among others to elaborate the rules and government structure of the GIC.

EF Clif

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