EF CLIF

EUROPEAN FOUNDATION
FOR THE STUDY OF
CHRONIC LIVER FAILURE

ANNUAL REPORT 2022

A year of cross-border collaboration

CONTENTS

Find the Annual Financial Report and Social Responsibility Report online at efclif.com

WHO WE ARE

EF CLIF's vision is to improve survival and the quality of life of patients with chronic liver failure

We forge links among researchers and professionals across disciplines and sectors to spark new ideas, redefine education and deliver impactful outcomes through collaborative projects.

The European Foundation for the Study of Chronic Liver Failure's fundamental purpose, reflected in its founding Statements of 2015, is to advance knowledge and promote research and education in liver disease to improve the prognosis of patients living with chronic liver failure.

WHAT WE DO

The Foundation has three roles that are key to performing its purpose:

European fellowship

As a fellowship of dedicated researchers and healthcare professionals across Europe, the Foundation recognizes clinical research excellence and every year nominates new members of the EASL-CLIF Consortium to contribute to advancing knowledge on the pathophysiology, diagnostics, and treatment of cirrhosis.

International academy

Through its global network, the Foundation fosters collaboration among international partners in conducting multicenter studies to further our understanding of liver function and disease, advise policymakers on new standards and protocols for the provision of critical care, and ultimately improve survival and the quality of life of patients with cirrhosis.

Knowledge transfer and innovation

As a knowledge provider, the Foundation facilitates the exchange of ideas across disciplines and geographical borders. We enable open collaboration to address global unmet needs for patients with cirrhosis. We are inspired to develop advanced diagnostic, prognostic and predictive tools for acute-on-chronic liver failure progression in patients with cirrhosis. We promote and conduct clinical studies to evaluate the efficacy and safety of novel therapeutic approaches that will ultimately improve survival and the quality of life of patients with cirrhosis. We engage with national and international liver disease patient communities and world-renown hepatology and liver transplant professional associations to raise awareness of the complications of cirrhosis and publish guidelines on good clinical practice to ensure that treatment and care of patients with liver disease is harmonized in Europe and around the world.

CORE VALUES

• We put patients at the heart of what we do

• We work for the benefit of society at large

• We combine scientific expertise and research excellence

• We openly communicate and share our knowledge, expertise and resources in a selfless manner

• We are determined to become a global reference for the study of chronic liver failure

• We accept all challenges that come our way in our pursuit of purpose and embrace them with passion

[1] Devarbhavi, H.; Asrani, S. K.; Arab, J. P., Nartey, Y. A.; Pose, E.; Kamath, P. S. Global burden of Liver Disease: 2023 Update. *J. Hepatol.* **2023**. DOI:10.1016/j.jhep.2023.03.017.

[2] Scalone, L.; Fagiuoli, S.; Ciampichini, R.; Gardini, I.; Bruno, R.; Pasulo, L.; Lucà, M.G.; Fusco, F.; Gaeta, L.; Del Prete, A.; Cesana, G.; Mantovani, L.G. The societal burden of chronic liver disease: Results from the COME study. *BMJ Open Gastroenterol.* **2015**, 2 (1), e000025. DOI:10.1136/bmjgast-2014-000025
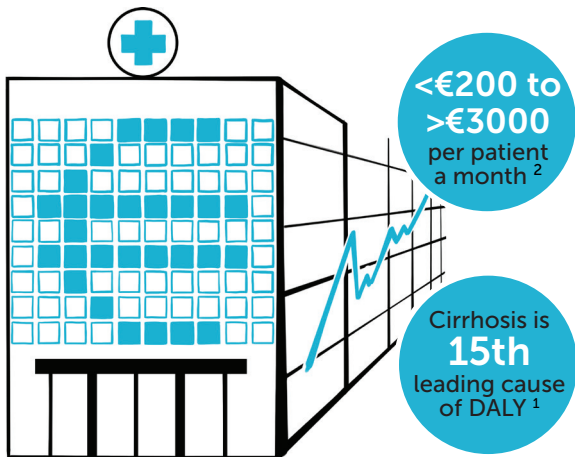
Why the study of liver disease matters
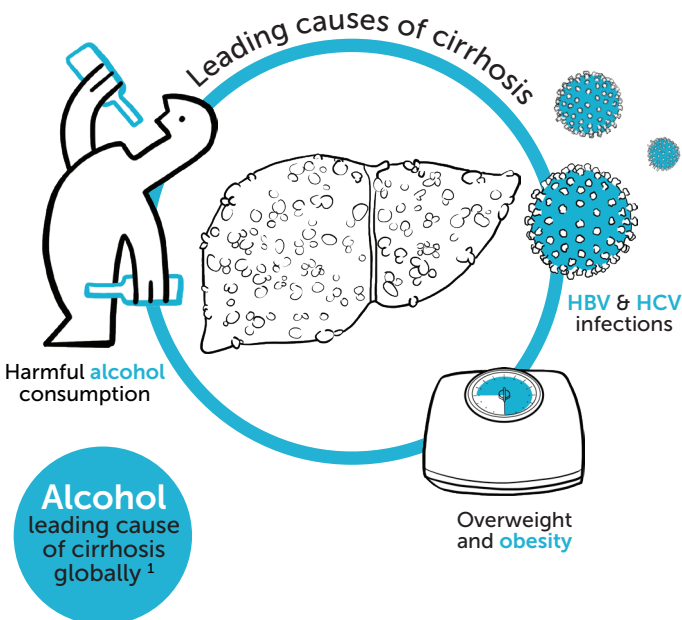
Liver disease accounts for

2,*,*

deaths worldwide

● Cirrhosis ● Viral hepatitis ● Liver cancer

11th leading cause of deaths worldwide

Liver disease is responsible for **1 out of 25 deaths** worldwide [1]

<€200 to >€3000 per patient a month [2]

Cirrhosis is 15th leading cause of DALY [1]

DALY: Disability-adjusted life years.

Leading causes of cirrhosis

Harmful **alcohol** consumption

HBV & **HCV** infections

Alcohol leading cause of cirrhosis globally [1]

Overweight and **obesity**

HBV: Hepatitis B virus, HCV: Hepatis C virus.

Because cirrhosis is a progressive disease, efficient treatment and management of patients with chronic liver disease are essential to improve patients' survival rates and reduce the socioeconomic impact of the disease.

It is remarkable to note that there have been no new, disease-modifying approaches to the treatment of chronic liver failure. Liver transplantation is the one treatment that has shown promise in improving patient survival by restoring essential functions where no alternative treatment of comparable effectiveness exists even for patients with severe acute-on-chronic liver failure. System for organ allocation that ensures equitable distribution continues to be an unmet medical need for patients with cirrhosis, and particularly those who progress into acute-on-chronic liver failure. Importantly, precipitating events associated with short-term mortality among patients with acute-on-chronic liver failure are not reflected in the conventional prognostic models for organ allocation falling short in prioritizing most severe patients with decompensated cirrhosis for liver transplantation.

The alarming increase in obesity rates, alcohol consumption, and an aging population mean that liver disease will become an even greater global health concern over the next decade. Experts agree that the major causes of liver disease (i.e., alcohol-related liver disease, non-alcoholic fatty liver disease, and viral hepatitis) are amenable to prevention and treatment providing an opportunity to reduce the burden of liver disease and save lives. There is an urgent need to engage with policymakers and health authorities to invest in preventive actions and surveillance as regards chronic liver disease.

The Foundation is actively working to change the status quo and is focused on supporting and engaging with all types of stakeholders whether they are working to advance fundamental knowledge, improve treatment, develop new technologies or contribute to draft protocols and guidelines for better health of patients with chronic liver disease.

OUR JOURNEY

Our motivation is the driving force of our journey of learning. We have challenged standards and conventions to advance knowledge and improve clinical practice in the diagnosis and treatment of cirrhosis and its complications.

The European Foundation for the Study of Chronic Liver Failure is a private non-profit organization connecting biomedical researchers and healthcare professionals with each other, with patients and patient associations, and with society.

The Foundation is a self-governing fellowship of distinguished researchers, medical doctors, and professionals from a variety of disciplines within the biomedical sciences.

The Foundation has made pioneering efforts in conducting a series of large, international prospective studies that have been instrumental in reclassifying the trajectory of patients with chronic liver disease and led to the clinical, prognostic and pathophysiological definition of the syndrome referred to as "acute-on-chronic liver failure" characterized by acute decompensation of cirrhosis, severe systemic inflammation, organ failures, and high short-term mortality. We are inspiring best clinical practices for the management of patients with chronic liver disease and promoting a more sustainable and equitable healthcare system.

2006 — OUR FOUNDATIONS

Our current strategy builds on the will of a group of hepatologists to support research in the field of chronic liver disease. Back in 2006, standard medical treatment for patients with cirrhosis lacked any integrative approach to understand and manage the disease. The CLIF Consortium was then established as the major collaborative research effort that have ever existed in Europe aimed at understanding the mechanisms that lead to chronic liver failure.

2008/09 — Endorsement by the European Association for the Study of the Liver

In 2008, the CLIF Consortium presented a formal proposal to the governing board of the European Association for the Study of the Liver (EASL) in seeking its support. In January 2009, 19 active members of EASL signed a petition for EASL to provide academic support to the CLIF Consortium to pursuit its purpose. One month later, EASL endorsed the consortium with the official name "EASL-CLIF Consortium".

Today, 117 centers in Europe are members of the EASL-CLIF Consortium.

2009 — Provision of legal and financial support

In 2009, representatives of Fundació Clínic per a la Recerca Biomèdica and Grifols together with the Chair of the EASL-CLIF Consortium Steering Committee, signed an agreement by which Fundació Clínic per a la Recerca Biomèdica would provide legal support to the EASL-CLIF Consortium and Grifols would grant an unrestricted fund of €3.5 M for a period of 5 years.

2011/13 — First multicenter investigation of the EASL-CLIF Consortium: The CANONIC study

The CANONIC study, a prospective observational study in 1349 patients with decompensated cirrhosis admitted to 29 European hospitals, aimed to characterize a syndrome that later would be referred to as acute-on-chronic liver failure (ACLF). The first patient was included in January 2011 and data collection completed in less than one year. Main results from the CANONIC study were published in *Gastroenterology* in 2013.

The CANONIC study has allowed for a comprehensive assessment of the epidemiology, natural history, diagnostic criteria, clinical course, prognosis, prevention and treatment of ACLF, and represents a solid base for future investigations.

2015

Establishment of the European Foundation for the Study of Chronic Liver Failure

In 2015, the European Foundation for the Study of Chronic Liver Failure (EF CLIF) is established as a non-profit, independent legal entity and registered under no. 2908 in the Register of Foundations of the Government of Catalonia.

From this moment on, the Foundation provides the legal and institutional framework for the clinical research activities conducted by the EASL-CLIF Consortium under the umbrella of the EASL Chair, and supports the newly constituted Grifols Chair in the promotion of translational research in chronic liver disease with Grifols increasing unrestricted funding to €1.5 M per year.

2017 /18

The PREDICT study

In March 2017, EF CLIF started the PREDICT study, a new observational study conducted in 44 European centers that looked at 1273 patients hospitalized with acute decompensation of cirrhosis in the critical period prior to ACLF development aimed to identify the precipitating events of ACLF and further understand the mechanisms of ACLF progression.

2015 /20

A new paradigm of acute decompensation of cirrhosis

Over the last five years, pioneering studies conducted by EF CLIF have paved the way to better understanding the clinical course of acute decompensation of cirrhosis. Results from the PREDICT study have allowed to identify four patterns of acute decompensation of cirrhosis in hospitalized patients with cirrhosis (i.e., stable decompensated cirrhosis, unstable decompensated cirrhosis, pre-ACLF and ACLF) and further defining ACLF based on the number of organ/system failures. Collaborative research efforts have led to the hypothesis that systemic inflammation is the principal mechanism of acute decompensation of cirrhosis and ACLF.

2018 /20

The ACLARA study

The ACLARA study is the first investigation developed by EF CLIF in Latin America with the aim to gain a broader global perspective on ACLF epidemiology and pathophysiology. This effort has been facilitated greatly through the establishment of the ACLARA Consortium, which includes a network of 51 hospitals in 7 countries.

2018 /21

Albumin as a drug

In the recent years, EF CLIF has contributed to provide evidence of the benefits of long-term administration of albumin to patients with cirrhosis in preventing its complications and increasing survival. Ongoing and future studies conducted under the umbrella of the Grifols Chair will shed light on the mechanisms of action of albumin and its therapeutic potential, promisingly implicating its use for precision medicine.

2019

MICROB-PREDICT

With the EU-funded MICROB-PREDICT project, we are investigating the interplay between gut and liver to enable accurate stratification of patients with chronic liver disease and pave the way for personalize therapies.

2020

DECISION
With the EU-funded DECISION project, we are exploring the potential of novel combinatorial therapies to prevent the high mortality rate associated with chronic liver disease.

2020

The CHANCE study
We launch the CHANCE study to assess the benefit of liver transplantation for patients with ACLF grade 2 or 3.

2021

A Special Issue of *Journal of Hepatology* discusses current and future directions for the management of chronic liver disease
Experts in the field including several researchers of the EASL-CLIF Consortium review current knowledge of cirrhosis and its complications and discuss the implications for the development of novel biomarkers, devices and drugs to improve treatment for patients with acute decompensation of cirrhosis and ACLF.

2021

A-TANGO
With the EU-funded A-TANGO project, we aim to evaluate the safety and effectiveness of a novel combinatorial treatment with the potential to improve the clinical outcomes of patients with alcohol-related liver disease.

2021

The COBALT study
We launch the COBALT study to find out if SARS-CoV-2 vaccines have a protective effect in chronic liver disease and after liver transplantation. Three centers, AAST Papa Giovanni XXIII Hospital (Italy), Hannover Medical School (Germany), and Hôpitaux Universitaires de Genève (Switzerland) run the study in a pediatric population.

2021

The DISCOVERY study
We launch the DISCOVERY study to assess the effect of human albumin on B cell function in acute decompensated cirrhosis.

2022

Read about our progress in page 18.

OUR NETWORK

Through collaboration, the European Foundation for the Study of Chronic Liver Failure's network provides the framework to carry out research that impacts the care and management of patients with chronic liver disease around the world.

EASL-CLIF Consortium

Since its foundation in 2009, the European Association for the Study of the Liver (EASL) Chair supports research activities through the EASL-CLIF Consortium across Europe. Our network is composed of 117 tertiary care and university hospitals with a strong background in liver disease offering hepatology clinic service where patients can be seen and treated.

The research activities of the network of hospitals organized in the setting of the EASL Chair are carried out under the direction of the EASL-CLIF Consortium Steering Committee. Through the large-scale observational studies we fund, these centers contribute to help drafting clinical practice guidelines that improve healtcare and patients' outcomes. The EASL-CLIF Consortium also provides the framework to initiate new research ideas and programs, and offers the next generation of scientists and research leaders unique opportunities to drive future research in the area of liver disease.

Improving care for patients with chronic liver disease through research

Professor Paolo Angeli, who acts as Chair of the EASL-CLIF Consortium Steering Committee, reflects on the importance of EF CLIF and shares his insights on the future contributions of the Foundation to the field.

"I think that the EASL-CLIF Consortium is a fundamental institution for high-quality research in the field of chronic liver disease and acute-on-chronic liver failure. I think it is the first example of a research network which is operating in this field with great results."

"We should improve, through research, care for patients with liver disease, particularly with advance chronic liver disease.

The role of the EASL-CLIF Consortium is crucial, we should develop a new strategy for treatment, but overall a new strategy for the prevention of the major complications of chronic liver disease. In this setting, it is crucial to find out some options to prevent and to treat acute decompensation of cirrhosis and acute-on-chronic liver failure."

"My main aim is to involve young researchers and to give them a very important role within the EASL-CLIF Consortium. Because I think that the future is in their hands."
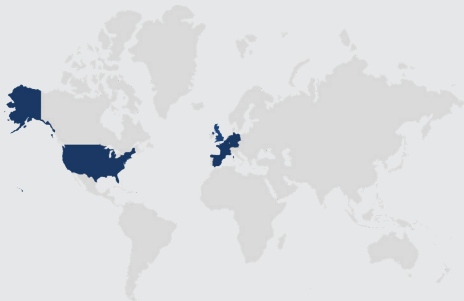
Our growing network of research laboratories, tertiary care and university hospitals

EASL-CLIF Consortium

117 centers in 28 countries

European Network for Translational Research

21 centers in 7 countries

Global Projects

96 centers in 22 countries

Austria
01. Klinikum Klagenfurt am Wörthersee
02. Medical University of Graz
03. Medical University of Vienna
04. Tirol Kliniken GmbH

Belgium
01. CUB Hôpital Erasme
02. Ghent University Hospital
03. University Hospital Antwerp
04. UZ Leuven

Croatia
01. University Hospital Dubrava
02. Zagreb University Hospital

Czech Republic
01. Institute for Clinical and Experimental Medicine

Denmark
01. Aarhus University Hospital
02. Copenhagen University Hospital Hvidovre
03. Nykoebing Falster Hospital
04. Odense University Hospital
05. Rigshospitalet−University Hospital Copenhagen

Estonia
01. West Tallinn Central Hospital

France
01. CHU Amiens−Picardie
02. CHU Angers
03. CHU Rennes−Hôpital De Pontchaillou
04. CHU Toulouse−Hôpital Purpan
05. CHRU Tours−Trousseau Hospital *
06. Hôpital Beaujon
07. Hôpital Claude Huriez
08. Hôpital Henri-Mondor
09. Hôpital Jean-Verdier
10. Hôpital Paul-Brousse
11. Hôpital Pitié-Salpêtrière
12. Hôpital Tenon
13. Jean Minjoz University Hospital

Georgia
01. Georgian National Hepatobiliary Center

* Newly elected member in 2022.

Germany
01. Bonn University Hospital
02. Charité–Universitätsmedizin Berlin
03. Düsseldorf University Hospital
04. Goethe University Frankfurt
05. Hannover Medical School
06. Jena University Hospital
07. University Medical Center Mainz
08. Saarland University Medical Center
09. University Halle-Wittenberg
10. University Hospital Aachen
11. University Hospital Essen
12. University Hospital Freiburg
13. University Hospital Heidelberg
14. University Hospital Leipzig
15. University Hospital Münster
16. University Hospital of Magdeburg
17. University Hospital of Munich
18. University Hospital Würzburg
19. University Medical Center Hamburg-Eppendorf

Greece
01. Laiko General Hospital of Athens

Hungary
01. University of Debrecen

Iceland
01. Landspitali University Hospital

Ireland
01. St. Vincent's University Hospital

Italy
01. ASST Grande Ospedale Metropolitano Niguarda
02. Città della Salute e della Scienza di Torino - Presidio Molinette
03. Internal Medicine ASL Brindisi
04. IRCCS Policlinico San Donato
05. Messina University Hospital
06. Policlinico di Palermo
07. Sapienza University of Rome
08. University of Bologna
09. University of Firenze
10. University of Padova
11. University of Udine
12. University of Verona

Latvia
01. Riga East University Hospital

Lithuania
01. Hospital of Lithuanian University of Health Sciences
02. Siauliai Hospital

Luxembourg
01. Centre Hospitalier de Luxembourg

Norway
01. Oslo University Hospital

Poland
01. Medical University of Warsaw
02. Pomeranian Medical University

Portugal
01. Centro Hospitalar de Trás-Os-Montes e Alto Douro
02. Centro Hospitalar e Universitário de Coimbra
03. Centro Hospitalar Uiversitário Lisboa Norte
04. Centro Hospitalar Universitário do Porto
05. Hospital Curry Cabral
06. Hospital de Santa Luzia de Viana do Castelo

Slovakia
01. F.D. Roosevelt University Hospital,
02. Pavol Jozef Šafárik University

Spain
01. Clínica Universitaria de Navarra
02. Hospital Clínic de Barcelona
03. Hospital de la Santa Creu i Sant Pau
04. Hospital General Universitario Gregorio Marañón
05. Hospital Germans Trias i Pujol
06. Hospital Marqués de Valdecilla
07. Hospital Universitari de Bellvitge
08. Hospital Universitari Vall d'Hebron
09. Hospital Universitario Ramón y Cajal
10. Hospital Universitario Reina Sofía
11. Hospital Universitario Virgen del Rocío

Sweden
01. Linköpin University Hospital
02. Sahlgrenska University Hospital

Switzerland
01. Centre Hospitalier Universitaire Vaudois–University of Lausanne
02. Ente Ospedaliero Cantonale–Università della Svizzera Italiana
03. Geneva University Hospitals
04. St. Gall Cantonal Hospital
05. University Hospital Basel
06. University Hospital of Bern
07. Zürich University Hospital

The Netherlands
01. Erasmus Medical Center
02. Leiden University Medical Centre

Turkey
01. Ankara University School of Medicine
02. Karadeniz Teknik Universitesi Tip Fakultesi
03. Marmara University Medical School
04. Sakarya University School of Medicine

Ukraine
01. Ivano-Frankivsk National Medical University

United Kingdom
01. Glasgow Royal Infirmary
02. Imperial College London
03. King's College Hospita
04. Leeds Teaching Hospitals
05. Nottingham Biomedical Research Centre
06. Queen Alexandra Hospital in Portsmouth
07. Queen Elizabeth Hospital Birmingham
08. Royal Free Hospital
09. University Hospitals Plymouth

Making progress towards personalized medicine approaches to chronic liver disease

Dr. Joan Clària, who acts as Director of the Grifols Chair, shares his insights about the role of the European Network for Translational Research (ENTR) within EF CLIF and how the analysis of multiomics data can provide complementary information to clinical data to develop models for the prognosis of liver disease and, particularly, acute-on-chronic liver failure.

"The ENTR is integrated by research laboratories focused on translational research on liver disease. It complements the research activities by the EASL-CLIF Consortium which is mainly focused on clinical research. The ENTR is the perfect fit for EF CLIF as it brings expertise to process large datasets from high-throughput techniques, apply modeling methods and identify novel biomarkers to better understand disease progression and response to treatment."

The integration of multiomics data offers many opportunities to liver disease research, with great potential to improve the clinical management of patients with chronic liver disease and contribute to the implementation of personalized medicine.

"The vision of the Grifols Chair is to understand, first and foremost, what are the medical needs for patients to benefit from faster diagnosis and better treatment options. Taking advantage of the experiments we can carry out on cells and animal models, we are able to test potential new therapeutic approaches to further our understanding of liver disease and assess efficacy of treatment before new drugs or drug combinations can translate into clinical practice."

European Network for Translational Research

The Grifols Chair promotes translational studies in centers across Europe and North America within the framework of the European Network for Translational Research (ENTR). The research activities of the 21 centers within our network are performed under the direction of the Director and Honorary Director of the Grifols Chair.

Belgium
01. CUB Hôpital Erasme–Université Libre de Bruxelles

France
01. French Alternative Energies and Atomic Energy Commission
02. French Institute of Health and Medical Research
03. GenoSplice
04. Hôpital Beaujon
05. Vaiomer

Germany
01. Lipidomix
02. Tübingen University

Spain
01. Bioscience Research Group, Grifols
02. Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas
03. Centro Nacional de Análisis Genómico
04. CICbioGUNE
05. Hospital Clínic de Barcelona
06. Hospital Germans Trias i Pujol
07. Navarrabiomed
08. Owl Metabolomics
09. Universitat Rovira i Vigili

The Netherlands
01. Erasmus Medical Center

United Kingdom
01. Foundation for Liver Research
02. University College London

United States of America
01. Massachussets General Hospital

Global Projects

The Global Projects chapter offers the framework to promote research in cirrhosis around the world and brings the opportunity to strengthen connections between healthcare professionals and researchers across geographical borders. Over the last five years, the Foundation has successfully expanded its geographical scope providing the context to support transcontinental collaborative research projects.

Argentina
01. Hospital Alemán de Buenos Aires
02. Hospital Británico de Buenos Aires
03. Hospital de Infecciosas F. J. Muñiz
04. Hospital Italiano de Buenos Aires
05. Hospital Nacional Prof. Alejandro Posadas
06. Hospital Provincial del Centenario
07. Hospital Universitario Austral

Australia
01. Austin Hospital
02. Sir Charles Gairdner Hospital
03. Royal Prince Alfred Hospital

Brazil
01. Botucatu Medical School
02. Escola Paulista de Medicina
03. Faculdade de Ciências Médicas da Universidade Estadual de Campinas
04. Faculdade Regional de Medicina de São José do Rio Preto
05. Hospital das Clínicas da Universidade de São Paulo
06. Hospital das Clinicas da Universidade Federal de Minas Gerais
07. Hospital das Clínicas de Ribeirão Preto
08. Hospital de Base do Distrito Federal
09. Hospital de Clínicas de Porto Alegre
10. Hospital Federal de Bonsucesso
11. Hospital Português de Salvador Bahia
12. Hospital São Rafael
13. Hospital Universitário Cassiano Antonio Moraes
14. Hospital Universitário Clementino Fraga Filho
15. Hospital Universitário Pedro Ernesto
16. Hospital Universitário Professor Edgard Santos
17. Hospital Universitário Walter Cantídio
18. Instituto do Fígado e Transplantes de Pernambuco
19. Irmandade Santa Casa de Misericórdia de Porto Alegre
20. Universidade Federal de Goiás

Canada
01. University of Alberta
02. University of Toronto

Chile
01. Clínica Las Condes
02. Clinica Universidad de los Andes
03. Hospital Clínico San Borja Arriarán
04. Hospital Clínico Universidad de Chile
05. Pontificia Universidad Católica de Chile
06. Universidad Austral de Chile–Hospital Base Valdivia

China
01. Queen Mary Hospital Hong Kong

Colombia
01. Clínica General del Norte
02. Hospital Pablo Tobón Uribe
03. La Cardio

France
01. CHU Montepellier–Hôpital Saint Éloi
02. CHU Strasbourg–Hôpital Hautepierre
03. Hôpital de la Croix-Rousse

Germany
01. University Hospital Tübingen
02. University Medical Center Mainz

India
01. Amrita Institute of Medical Sciences
02. Dr. Rela Institute & Medical Centre
03. Fortis Memorial Research Institute
04. Global Hospital–Super Speciality & Transplant Centre
05. Max Super Speciality Hospital
06. Medanta
07. Yashoda Hospitals

Italy
01. Azienda Ospedaliero Universitaria Pisana
02. Ca' Granda–Policlinico Milano
03. Ospedale Papa Giovanni XXIII-Bergamo

Japan
01. Hiroshima University Hospital
02. Kyushu University Hospital
03. Nagasaki University Hospital
04. University of Tokyo Hospital

Korea
01. Samsung Medical Center

Mexico
01. Centro Médico Issemym
02. Fundación Clínica Médica Sur
03. Hospital de Especialidades Centro Médico Nacional La Raza
04. Hospital General de México Dr. Eduardo Liceaga
05. Hospital General Juárez
06. Hospital San José Tec de Monterrey
07. Instituto de Salud Digestiva y Hepática
08. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán
09. Star Médica
10. Universidad Veracruzana

Paraguay
01. Hospital de la Universidad Nacional de Asunción

Peru
01. Hospital EsSalud-Arequipa
02. Hospital Nacional Arzobispo Loayza
03. Hospital Nacional Daniel Alcides Carrión
04. Hospital Nacional Edgardo Rebagliati Martins
05. Hospital Nacional Guillermo Almenara

Spain
01. Hospital Universitari i Politècnic La Fe
02. Hospital Universitario 12 de Octubre
03. Hospital Universitario La Paz

Sweden
01. Karolinska Institutet

Taiwan
01. Kaohsiung Chang Gung Memorial Hospital

Turkey
01. İnönü University

United Kingdom
01. Royal Infirmary of Edinburgh

United States of America
01. Baylor St. Luke's Medical Center
02. Baylor University Medical Center
03. Cedars-Sinai Medical Center
04. Cleveland Clinic
05. Ichan School of Medicine at Mount Sinai
06. Michael E. DeBakey Veterans Affairs Medical Center
07. Tampa General Hospital
08. The University of Chicago Medicine
09. University of Colorado
10. University of Maryland School of Medicine
11. University of Utah Health
12. Weill Cornell Medicine, New York–Presbiterian Hospital

STATEMENT FROM OUR DIRECTOR

Without any doubt, 2023 will be the year of the ACLARA study. The effort of hundreds of Latin American colleagues, nurses, and other staff developing this observational prospective investigation in 1286 patients with acutely decompensated cirrhosis, will be rapidly transformed into scientific material, improving our understanding on the mechanisms and treatment of this disease.

The first article derived from the ACLARA study, performed in 45 university hospitals from México, Colombia, Perú, Chile, Brazil, Paraguay, and Argentina, will be available soon. We wanted to publish the study in a clinical journal, and *Gastroenterology* was a most appropriated candidate.

The study presented robust data indicating that the magnitude of systemic inflammation in patients hospitalized by acutely decompensated cirrhosis correlates with genetic ancestry, being patients with higher proportion of Native American ancestry the most predisposed population to develop ACLF, severe ACLF and early death than patients with higher proportion of African American ancestry, or European American ancestry.

This work opens an extensive area of research and has evident clinical consequences. The question on the mechanism leading to higher systemic inflammatory response to pro-inflammatory precipitants in the Native American population with cirrhosis, raises the important question of whether this also occur in other conditions associated with systemic inflammation, such as, for example, severe sepsis and septic shock. The ACLARA study also suggests that patients with cirrhosis and Native American genetic ancestry, which correlates closely with the external phenotype, should be prioritized for rapid liver transplant over other genetic ancestries not only at the Central and South American regions, but also in the United States and Canada, where there are 65 million of Latin Americans, 45 million in California, or in Europe where there are almost 7 million, 3.5 million in Spain.

Following this paper, several studies based on the ACLARA study will be published soon in European and American journals. Some of them are specific projects from the EF CLIF, but many will be the result of a fruitful collaboration with our partners in projects we coordinate within the European Unions's Horizon 2020 Research and Innovation Program.

Professors Trebicka (Germany), Ratou (France) and Jalan (UK), leading the MICROB-PREDICT, DECISION and A-TANGO consortia, respectively, will join clinical and omics data from more than 4500 patients included in the CANONIC, PREDICT and ACLARA studies into one of the largest prospective efforts of modern research of cirrhosis. We all should be proud of leading this adventure.
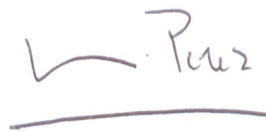
In 2023, we will continue being immersed into serious difficulties. The invasion of Ukraine by the Russian army represents a terrible humanitarian disaster in the core of Europe, that affects deeply the sensitivity of Europeans, Americans, and many other populations all over the world. However, the war also impacts essential logistic and economic activities and, of course, this also impact the activities of the Foundation. In this context, I want to express my gratitude to all investigators and staff members of the Foundation for their enthusiasm. Complex projects, such as the CHANCE study, continue being developed with normality. Up to date, we have enrolled more than 700 patients from Europe, Asia, America, and Oceania in this study, which aims to assess liver transplantation in the management of patients with ACLF. Interestingly, Latin American transplant programs in Brazil and Argentina are leading the CHANCE study, a feature that clearly reflects the positive impact of the ACLARA study on the research of cirrhosis in this continent.

During 2022, two important new activities have been developed by the Foundation. First, with the intention to incorporate young investigators into the activities of the Foundation, we have established the Inspiring and Writing Group under the leadership of Thierry Gustot. The aim of this initiative is to import new ideas from young European investigators into studies using data and biobank samples from the Foundation. We are still in the early development of this initiative which, if successful, will be extended to other geographical areas. The second new activity relates to the development of a spin off company, Albimmune S.L., to investigate the potential role of albumin treatment on the innate immune cell function in cirrhosis and other diseases associated with systemic inflammation.

This company was born in the setting of a joint venture between the Foundation and Grifols S.A. The first study is almost finished, and soon we will start a proof-of-concept randomized clinical trial in several hospitals in Barcelona and Madrid assessing the potential effect of albumin treatment on systemic inflammation in non-cirrhotic patients with sepsis and septic shock.

Bearing these considerations in mind, I believe 2023 is the start of a promising period. Of course, we will need to continue working as we did in previous years. However, 2023 will be the year in which all efforts previously undertaken by the EASL-CLIF Consortium, the ACLARA Consortium, and the MICROB-PREDICT, DECISION and A-TANGO Consortia will begin to bear fruit.

Every year, whenever I start writing this statement for the EF CLIF Annual Report, I remember Joan Córdoba, one of the youngest and more promising investigators from the Consortium. Joan passed away in 2014, shortly after finishing the CANONIC study. Last year, we mourned the loss of Ignacio Calero, the legal advisor of the Foundation and member of the Board of Trustees. He was a young lawyer, who contributed to the creation of the Foundation and advised us from its beginnings. With them we lost not only scientific or legal expertise, but also common sense, enthusiasm, and friendship.

Professor Vicente Arroyo
Director

STATEMENT FROM OUR GENERAL MANAGER

It has been another year of progress in many fronts, with the significant success of our ongoing research activities and consolidation of our expanded network.

Progress towards our vision of improving survival and the quality of life of patients with chronic liver disease The COVID-19 pandemic opened a new front for liver disease research in unexpected ways. In 2021, we launched COBALT, a new short-term project to assess the protective effect of two- and three-dose of the vaccine in patients with chronic liver disease or liver transplant recipients. Our findings will help to inform policy makers on vaccination strategies and the use of booster doses, and identify individuals at high risk of infection within this vulnerable group of patients.

This year, our researchers have contributed to a series of studies comparing data from different European countries showing significant differences in how patients with ACLF are selected for liver transplantation. Improving outcomes for patients with chronic liver disease very much relies on access to liver transplantation and the attitude of healthcare professionals. CHANCE investigators across the world are contributing to make liver transplantation available to patients with ACLF grades 2 and 3. Preliminary data are already showing the benefits of liver transplantation in these very sick patients. We also aim to identify predictors of futility in recipients where expected outcomes would be too poor to justify transplantation. This will allow us to develop strategies to optimize allocation of organs. We have passed our milestone of 500 patients recruited and aim to complete recruitment this year. The results from the CHANCE study should change the way patients are treated.

Access to personalized treatment is a vital step to improve survival and the quality of life of patients with acute decompensation of cirrhosis and ACLF. The projects we coordinate within the EU funding program for research and innovation want to make treatment available for patients with chronic liver disease faster. Novel drug combinatorial approaches will soon reach patients participating in our clinical trials within MICROB-PREDICT, DECISION and A-TANGO thanks to the efforts of our partners across consortia.

This year, we have seen the many developments and achievements by our network of collaborators. I am proud to report that we are setting up three independent clinical trials for success. Our research focuses on the safety and effectiveness of combinations of established medicines with new uses that have been proven to be promising in the preclinical stage of these studies and are now going to be tested in a clinical setting.

Facing challenging times

We are planning on completing many ongoing projects and ensuring sustainable growth and development. We still face the aftershocks of the COVID-19 pandemic that together with the impacts of the raising costs of living at the local and international level are slowing us down.

Staff turnover increased in the past year and continued in post-pandemic. To address this challenge, we have implemented a new flexible working policy and continue engaging with our employees to build a stimulating working environment. Attracting and retaining the right talent is one of our top priorities. I am so glad to count with a team of highly dedicated and talented professionals. They are essential for the success of the research activities we promote and support. In the following year, we will invest in expanding the capacity of the Data Management Center and continue supporting our researchers in making sense of data.

Supporting the next generation of liver research leaders

With the establishment of the Inspiring and Writing Group, we are providing unique opportunities to researchers in our network to tackle the biggest unmet needs of patients with chronic liver disease. Through this initiative, we bring together international teams of multidisciplinary researchers to address unanswered questions in liver disease research.

I am amazed and inspired by members of the Inspiring and Writing Group for their response to our call for proposals. By facilitating resources and fostering exchange of knowledge, we hope they will contribute to ongoing studies from conceptualization and idea generation to carrying out research and writing of scientific articles too.
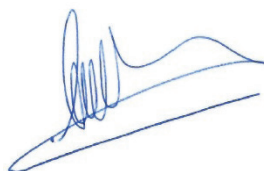
Ensuring integrity and transparency

We have established the first Scientific Advisory Board to provide independent oversight of the EASL-CLIF Consortium, ENTR and Global Projects network, ensuring transparency regarding our clinical and translational operations, and providing input and recommendations on our research strategy. The Scientific Advisory Board discussed our previous research strategy and plans for the next year with a focus on budgetary issues. Their feedback has helped us define a new scientific direction to ensure we meet the high targets we set ourselves and identify new funding opportunities.

Working with patient representatives

Over the years, we have created the research environment that allows us to translate laboratory discoveries and clinical observations into better care for patients with chronic liver disease. But only if we actively collaborate with them, we will fully understand the many barriers people affected with chronic liver disease are facing and their actual needs. Through our EU-funded projects, we work closely with the European Liver Patients' Association (ELPA) in all matters related to communication, dissemination, and exploitation of results. By providing accurate and easy to understand information on project progress, we are engaging with the broader liver community. We are committed to continue developing campaigns in collaboration of patients and patient representatives locally to raise awareness of chronic liver disease and inform about how public funds are spent to ultimately influence policy.

It has been an exciting year, and I want to thank all our staff, collaborators and partners for their amazing work and continued support.

Dr Anna Bosch
General Manager

2022 HIGHLIGHTS

Registration of Albimmune S.L.
We partnered with Grifols to further expand our research on albumin for therapeutic applications.

CHANCE study
recruited more than 500 patients giving patients with ACLF grade 2 or 3 the opportunity to receive a liver transplant.

See page 29.

COBALT study
recruited more than 1100 patients.

See page 32.

EF CLIF researchers contributed to an updated **EASL position paper** reviewing liver-specific effects of COVID-19 and providing guidance on the treatment of chronic liver disease and care of adult liver transplant patients.

Study by the ELITA-EF CLIF Working Group revealed **inequity of access to liver transplantation** for patients with ACLF in Europe.
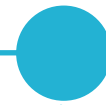
Researchers at EF CLIF and the Institute for Health Science Research Germans Trias i Pujol found a link between **innate immunity and lipid homeostasis** in patients with ACLF.

A population-based study analyzed the **course of cirrhosis and its complications** in Germany for over a decade.

Inspiring and Writing Group
was established to facilitate the exchange of knowledge between a multi-disciplinary group of experts with an interest in chronic liver disease.

Scientific Advisory Board
was first established as a consultancy body to convey its opinions on matters related to the development of EF CLIF.
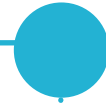
CHRU Tours–Hôpital Trousseau
in France joined the EASL-CLIF Consortium.

Study identified **albumin lipid composition** changes in acute decompensation of cirrhosis.

Researchers at EF CLIF and Hospital Clínic de Barcelona revealed new insights into the pharmacokinetics of **tigecycline**, a broad-spectrum antibiotic, in critically ill patients with cirrhosis.
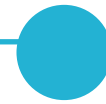
A large surveillance study showed differences in the **pattern of multi-drug resistant bacteria** in patients with cirrhosis that require critical care.

MESSAGE FROM OUR SCIENTIFIC DIRECTOR

Despite the ravages of the COVID-19 pandemic and the disturbances caused by it, 2022 has been a year of further consolidation for EF CLIF continuing its path from organic growth towards strategic progression. One major emphasis is on consolidating existing partnerships and building wider networks and broader collaborations.

The completion and the publication of the first hugely important manuscript arising from the ACLARA study consolidates the relationship with Latin American investigators. The progress and the massive support from over 50 liver transplant units has contributed hugely to extending EF CLIF studies beyond Europe and Latin America to North America, India, Japan and Australia as part of the CHANCE study. This study has also been pivotal in engaging investigators well beyond the hepatology community to surgeons, intensivists and anesthesiologists.

CHANCE has also allowed consolidation of partnerships with ILTS and ELITA, the International and European societies focussing on liver transplantation. The COBALT Consortium brought in experts in immunology and infectious diseases from many new collaborating centres to extend the EF CLIF partnership to better understand COVID-19 immunizations in patients with cirrhosis. The CANONIC and PREDICT study investigators have continued to participate in collaborative publications, which continue to grow.

The European grants led by EF CLIF, namely, MICROB-PREDICT and DECISION are starting to exploit the knowledge built by them through initiation of crucial clinical trials using biomarkers for better selection of patients. As a results of these investigations, the EF CLIF partnerships with basic scientists and translational research experts including industry have blossomed. The A-TANGO grant progresses one of the stated aims of EF CLIF of finding novel therapies. The clinical trial of two novel drugs for patients with acute on chronic liver failure is due to start in the first half of 2023.

The results of clinical trials based on two previous EU grants, ALIVER and CARBALIVE, in which EF CLIF was participant, have been completed yielding exciting new results, which are due to be published soon and will enter the next phase of clinical trials.

These EU-sponsored Consortia have been the backbone of the scientific growth of EF CLIF and are starting to have substantial impact.

Finally, the partnership with EASL has been further strengthened through several discussions during the year and a plan for how the two organizations collaborate has been developed. One of the important achievements of this partnership is further development of the plan to organize an international 'Cirrhosis Summit' in collaboration with all the other major stakeholders working in the field of advanced liver disease. In addition to the progress EF CLIF has made in better understanding decompensated cirrhosis, the greatest clinical impact is the recognition by the liver transplant regulators that patients with acute-on-chronic liver failure, a condition that EF CLIF has played a pivotal role in characterizing, will have priority on the transplant waiting list in some countries.

In conclusion, I am delighted to see the progress EF CLIF has made as we continue along our stated aim of strategic progression and building wider collaboration recognizing the huge negative impact cirrhosis is having on patient's lives.

Professor Rajiv Jalan
Scientific Director

SPOTLIGHT
A CHANCE to access liver transplantation for patients with chronic liver disease

Providing access to liver transplantation can help increase survival for patients with decompensated cirrhosis that develop acute-on-chronic liver failure (ACLF). The results from the CHANCE study will allow for better defining allocation criteria and waitlist prioritization for patients with ACLF grade 2 or 3.

Dr. Thierry Gustot, Clinical Director of the Liver Transplant Unit at the CUB Hôpital Erasme and Principal Investigator of the CHANCE study, explains how this project could benefit these patients in the future and allow harmonization across the world.

"Due to prospective and global design of the CHANCE study, we plan to answer to several uncertainties: waiting list outcomes and organ allocation for patients with severe ACLF; objective limits for liver transplantation in patients with severe ACLF to define futility; the ideal timing of liver transplantation for severe ACLF patients to improve the liver transplant results, the characteristics of donor organs impacting the liver transplantation outcomes for patients with severe ACLF; the post-liver transplantation outcomes, potential complications and quality of life of patients with severe ACLF; the resources utilization for liver transplantation in case of patients with severe ACLF;

exploration of new biomarkers to predict the prognosis on the waiting list and after liver transplantation for patients with severe ACLF; and the mechanisms of liver and extrahepatic organ recovery after liver transplantation."

"CHANCE is a prospective non-interventional observational study with a detailed follow-up of three subgroups of patients: patients listed for liver transplantation with ACLF 2 or 3 at the time of listing or developing on waiting list, patients listed for liver transplantation with decompensated cirrhosis without ACLF 2 or 3 and poor liver function, and patients with ACLF 2 or 3 not listed for liver transplantation. We collect extensive clinical data on the waiting list, during the liver transplantation procedure and after liver transplantation until one year. Moreover, we collect multiples samples (serum, plasma, DNA, RNA, urine, saliva, peripheral blood mononuclear cells, liver biopsy) at several time points."

CHANCE offers a unique opportunity to explore the impact of liver transplantation on patients with severe ACLF. Regarding to study design, the novelty of CHANCE relies on the prospective nature of the study and its global scope. Gustot adds: "CHANCE is the first prospective study assessing liver transplantation in patients with severe ACLF. All previous publications described retrospective data preventing an intention-to-treat analysis. Moreover, the global scope of the CHANCE study will allow us to analyze the heterogeneity in the management of these patients, organ allocation systems and surgical techniques."

New findings derived from the CHANCE study are expected to translate into clinical practice and help to overcome the many barriers to access liver transplantation. Gustot continues: "Liver transplantation remains the only treatment with drastic survival benefit for patients with severe ACLF. We wish to define the modalities to adequately and rapidly select the candidates for liver transplantation, to ensure them a fair access to this treatment and to define the specificities of management to improve at most their prognosis."

Our bold ambition builds on the intensive and collaborative research effort of the many people involved in the study who combine leadership and technical expertise. Gustot says: "The CHANCE study involves the commitment of many people around the world. The executive group composed of Professor Rajiv Jalan as Scientific Coordinator, myself as Principal Investigator, and Javier Fernández and William Bernal as co-Principal Investigators work closely with the EF CLIF General Manager Anna Bosch and the Head of the Data Management Center Cristina Sánchez-Garrido who are responsible for logistics and scientific issues related to the study. The International Liver Transplant Society (ILTS), the European Liver and Intestine Transplant Association (ELITA) and EF CLIF bring together experts in decompensated cirrhosis and liver transplantation. In addition, the executive group relies on 15 Regional Coordinators managing a group of participating centers. A total of 92 centers from 27 countries are contributing to the study. This project would be impossible without the involvement of all investigators contributing actively to the large CHANCE Consortium."

In reflecting on the motivations to lead this project, Gustot concludes: "Patients with ACLF 2 or 3 have a mortality that exceeds 50% at 3 months despite current therapeutic advances. Through the accumulation of data collected, we have learned that liver transplantation is feasible for ACLF 2 or 3 patients. Nevertheless, according to an observational study carried out in Europe, only 9% of ACLF patients reach liver transplantation. Generating objective data to ultimately improve access to liver transplantation is a priority for me. The CHANCE study has brought together experts in chronic liver disease, intensive care management and liver transplantation from different continents with diverse medical cultures. Being part of this multidisciplinary research environment offers me professional and human enrichment."

ONGOING STUDIES

GLOBAL PROJECTS

Sponsored by EF CLIF
ACLARA
See page 28.

CHANCE
See page 29.

EASL CHAIR ACTIVITIES

Sponsored by EF CLIF
COBALT
See page 32.

EU-funded projects
A-TANGO
See page 33.

DECISION
See page 33.

MICROB-PREDICT
See page 34.

Ancillary studies
A possible role for FXR polymorphisms in the etiopathogenesis of acute decompensation of cirrhosis and ACLF
See page 36.

Biomarkers of renal tubular damage in predicting response to terlipressin and albumin in patients with hepatorenal syndrome
See page 36.

Glycomics-based biomarkers for diagnosis and prognosis in ACLF
See page 37.

Molecular markers to predict chronic liver failure and to explore its mechanistic pathways in decompensated cirrhosis
See page 37.

GRIFOLS CHAIR ACTIVITIES

Sponsored by EF CLIF
DISCOVERY
See page 40.

Autophagy as a mediator of HSA anti-inflammatory
See page 41.

Definition of the utility of immune checkpoint receptors as therapeutic targets in ACLF
See page 41.

Effects of albumin on human neutrophil function in patients suffering from acute decompensation and ACLF
See page 42.

Extracellular vesicles as biomarkers in patients with acute decompensation of cirrhosis
See page 42.

Genome-wide association study in patients with acute decompensation of cirrhosis
See page 43.

Identification of albumin receptors and characterization of albumin intracellular trafficking in human peripheral blood mononuclear cells
See page 43.

Influence of gender on albumin response in samples from the ATTIRE cohort
See page 44.

INDUSTRY-SPONSORED RESEARCH

Sponsored by Grifols
ALADDIN
See page 46.

APACHE
See page 46.

PRECIOSA
See page 48.

Sponsored by Cellaïon
DHELIVER/HEP102
See page 47.

Sponsored by Versantis—GENFIT
Liposomal peritoneal dialysis for the management of hepatic encephalopathy
See page 47.

OTHER COLLABORATIVE PROJECTS

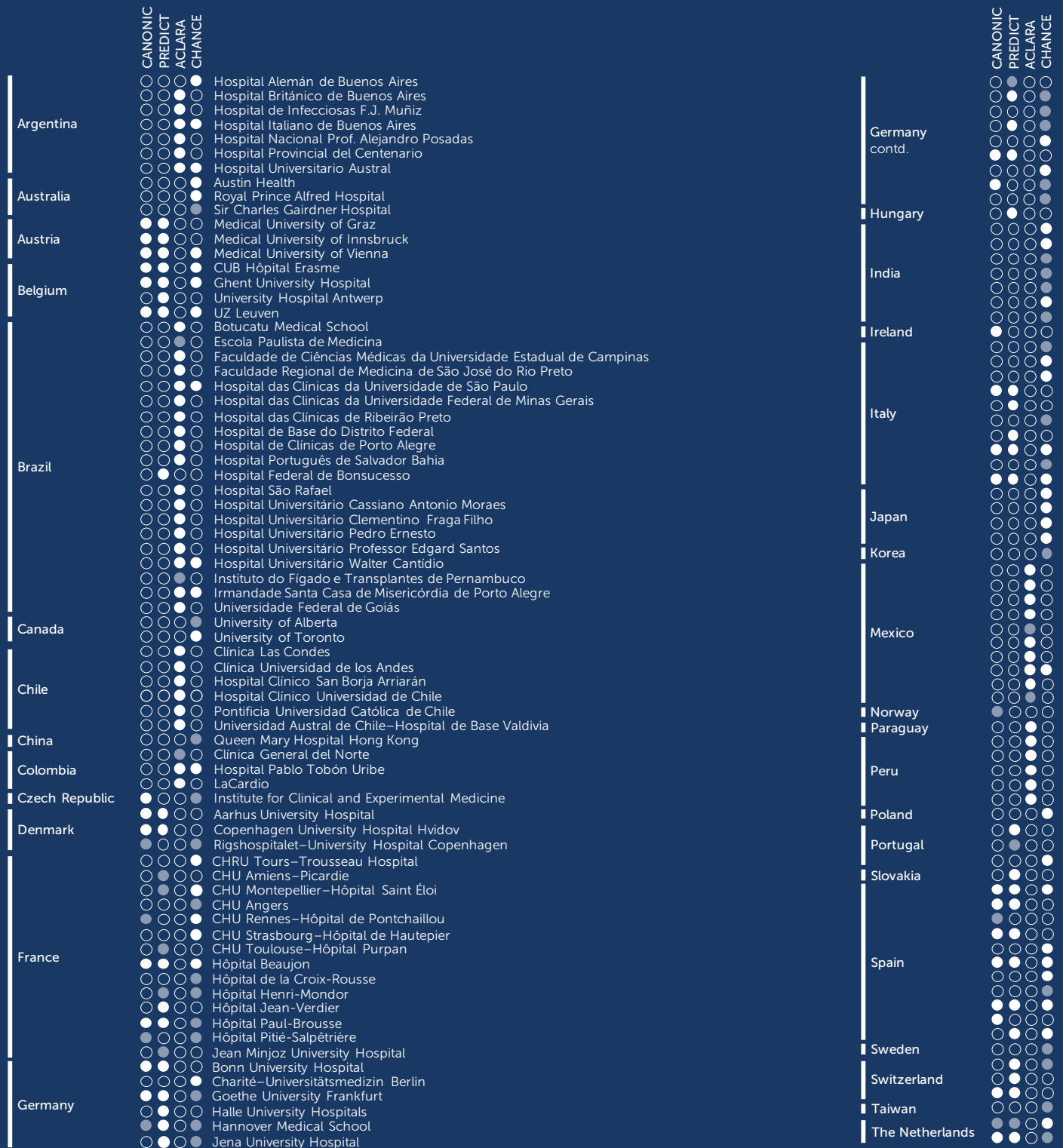### EU-funded, multidisciplinary collaborative projects
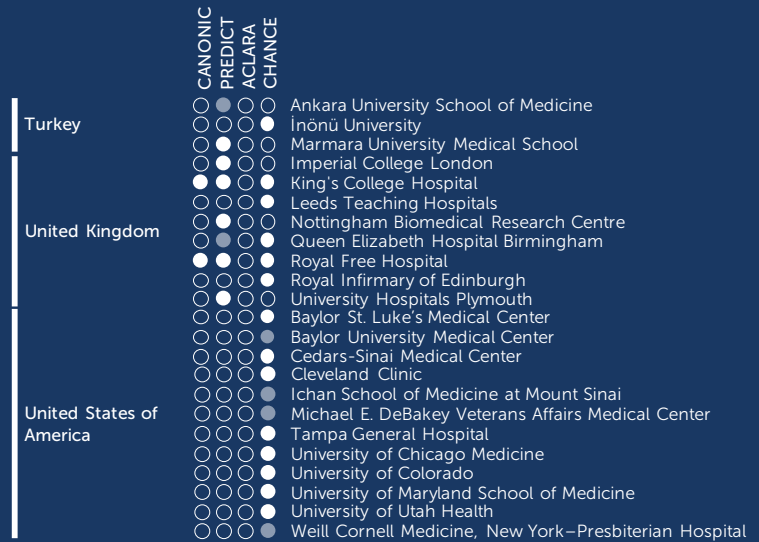IHMCSA
See page 50.

LIVERHOPE
See page 50.

Our worldwide research network

Columns: CANONIC · PREDICT · ACLARA · CHANCE

Argentina
- Hospital Alemán de Buenos Aires
- Hospital Británico de Buenos Aires
- Hospital de Infecciosas F.J. Muñiz
- Hospital Italiano de Buenos Aires
- Hospital Nacional Prof. Alejandro Posadas
- Hospital Provincial del Centenario
- Hospital Universitario Austral

Australia
- Austin Health
- Royal Prince Alfred Hospital
- Sir Charles Gairdner Hospital

Austria
- Medical University of Graz
- Medical University of Innsbruck
- Medical University of Vienna

Belgium
- CUB Hôpital Erasme
- Ghent University Hospital
- University Hospital Antwerp
- UZ Leuven

Brazil
- Botucatu Medical School
- Escola Paulista de Medicina
- Faculdade de Ciências Médicas da Universidade Estadual de Campinas
- Faculdade Regional de Medicina de São José do Rio Preto
- Hospital das Clínicas da Universidade de São Paulo
- Hospital das Clínicas da Universidade Federal de Minas Gerais
- Hospital das Clínicas de Ribeirão Preto
- Hospital de Base do Distrito Federal
- Hospital de Clínicas de Porto Alegre
- Hospital Português de Salvador Bahia
- Hospital Federal de Bonsucesso
- Hospital São Rafael
- Hospital Universitário Cassiano Antonio Moraes
- Hospital Universitário Clementino Fraga Filho
- Hospital Universitário Pedro Ernesto
- Hospital Universitário Professor Edgard Santos
- Hospital Universitário Walter Cantídio
- Instituto do Fígado e Transplantes de Pernambuco
- Irmandade Santa Casa de Misericórdia de Porto Alegre
- Universidade Federal de Goiás

Canada
- University of Alberta
- University of Toronto

Chile
- Clínica Las Condes
- Clínica Universidad de los Andes
- Hospital Clínico San Borja Arriarán
- Hospital Clínico Universidad de Chile
- Pontificia Universidad Católica de Chile
- Universidad Austral de Chile–Hospital de Base Valdivia

China
- Queen Mary Hospital Hong Kong

Colombia
- Clínica General del Norte
- Hospital Pablo Tobón Uribe
- LaCardio

Czech Republic
- Institute for Clinical and Experimental Medicine

Denmark
- Aarhus University Hospital
- Copenhagen University Hospital Hvidov
- Rigshospitalet–University Hospital Copenhagen

France
- CHRU Tours–Trousseau Hospital
- CHU Amiens–Picardie
- CHU Montepellier–Hôpital Saint Éloi
- CHU Angers
- CHU Rennes–Hôpital de Pontchaillou
- CHU Strasbourg–Hôpital de Hautepier
- CHU Toulouse–Hôpital Purpan
- Hôpital Beaujon
- Hôpital de la Croix-Rousse
- Hôpital Henri-Mondor
- Hôpital Jean-Verdier
- Hôpital Paul-Brousse
- Hôpital Pitié-Salpêtrière
- Jean Minjoz University Hospital

Germany
- Bonn University Hospital
- Charité–Universitätsmedizin Berlin
- Goethe University Frankfurt
- Halle University Hospitals
- Hannover Medical School
- Jena University Hospital

Columns: CANONIC · PREDICT · ACLARA · CHANCE

Germany contd.

Hungary

India

Ireland

Italy

Japan

Korea

Mexico

Norway

Paraguay

Peru

Poland

Portugal

Slovakia

Spain

Sweden

Switzerland

Taiwan

The Netherlands

● Not yet recruiting / Withdrawn | ○ Recruiting center

Mainz University Medical Center
University Hospital Aachen
University Hospital Heidelberg
University Hospital Leipzig
University Hospital Münster
University Hospital of Munich
University Hospital Tübingen
University Medical Center Hamburg-Eppendorf
University Medical Center Mainz
University of Debrecen
Amrita Institute of Medical Sciences
Dr. Rela Institute & Medical Centre
Fortis Memorial Research Institute
Global Hospital–Super Specialty & Transplant Centre
Max Super Speciality Hospital
Medanta
Yashoda Hospitals
St. Vincent's University Hospital
Azienda Ospedaliero Universitaria Pisana
ASST Grande Ospedale Metropolitano Niguarda
Ca' Granda–Policlinico Milano
Città della Salute e della Scienza di Torino-Presidio Molinette
Internal Medicine ASL Brindisi
Ospedale Papa Giovanni XXIII-Bergamo
Sapienza University of Rome
University of Bologna
University of Firenze
University of Padova
Hiroshima University Hospital
Kyushu University Hospital
Nagasaki University Hospital
University of Tokyo Hospital
Samsung Medical Center
Centro Médico Issemym
Fundación Clínica Médica Sur
Hospital de Especialidades Centro Médico Nacional La Raza
Hospital General de México Dr. Eduardo Liceaga
Hospital General Juárez
Hospital San José Tec de Monterrey
Instituto de Salud Digestiva y Hepática
Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán
Star Médica
Universidad Veracruzana
Oslo University Hospital
Hospital de la Universidad Nacional de Asunción
Hospital EsSalud-Arequipa
Hospital Nacional Arzobispo Loayza
Hospital Nacional Daniel Alcides Carrión
Hospital Nacional Edgardo Rebagliati Martins
Hospital Nacional Guillermo Almenara
Medical University of Warsaw
Centro Hospitalar de Trás-Os-Montes e Alto Douro
Centro Hospitalar Universitário do Porto
Hospital Curry Cabral
Pavol Jozef Šafárik University
Hospital Clínic de Barcelona
Hospital de la Santa Creu i Sant Pau
Hospital General Universitario de Alicante Doctor Balmis
Hospital General Universitario Gregorio Marañón
Hospital Universitari i Politècnic La Fe
Hospital Universitari Vall d'Hebron
Hospital Universitario 12 de Octubre
Hospital Universitario La Paz
Hospital Universitario Ramón y Cajal
Hospital Universitario Reina Sofía
Hospital Universitario Virgen del Rocío
Karolinska Institutet
Geneva University Hospitals
St. Gall Cantonal Hospital
University Hospital of Bern
Kaohsiung Chang Gung Memorial Hospital
Erasmus Medical Center
Leiden University Medical Centre

Country	CANONIC	PREDICT	ACLARA	CHANCE	Institution
Turkey	○	◐	○	○	Ankara University School of Medicine
	○	○	○	●	İnönü University
	○	●	○	○	Marmara University Medical School
United Kingdom	○	●	○	○	Imperial College London
	●	●	○	○	King's College Hospital
	○	○	○	●	Leeds Teaching Hospitals
	○	●	○	○	Nottingham Biomedical Research Centre
	○	◐	○	●	Queen Elizabeth Hospital Birmingham
	●	●	○	○	Royal Free Hospital
	○	○	○	●	Royal Infirmary of Edinburgh
	○	●	○	○	University Hospitals Plymouth
United States of America	○	○	○	●	Baylor St. Luke's Medical Center
	○	○	○	◐	Baylor University Medical Center
	○	○	○	●	Cedars-Sinai Medical Center
	○	○	○	●	Cleveland Clinic
	○	○	○	◐	Ichan School of Medicine at Mount Sinai
	○	○	○	◐	Michael E. DeBakey Veterans Affairs Medical Center
	○	○	○	●	Tampa General Hospital
	○	○	○	●	University of Chicago Medicine
	○	○	○	●	University of Colorado
	○	○	○	●	University of Maryland School of Medicine
	○	○	○	●	University of Utah Health
	○	○	○	◐	Weill Cornell Medicine, New York–Presbyterian Hospital

Throught design and delivery of large-scale observational studies, we bring together international researchers and healthcare professionals to accelerate progress on practice-changing management and treatment that benefits patients with chronic liver disease worldwide.

GLOBAL PROJECTS

Fostering collaboration beyond geographical borders to develop strategies to promote health equity

The Global Projects chapter connects healthcare professionals and experts over the world to further our understanding of the epidemiology and pathophysiology of acute-on-chronic liver failure. Through collaborative research, the Global Projects also aims to identify novel biomarkers and therapeutic targets in cirrhosis and develop guidelines that will contribute to minimize regulatory barriers and facilitate better outcomes and quality of life for patients with chronic liver disease worldwide.

ACLARA

Flair José Carrilho
Principal Investigator, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brazil

Richard Moreau
Principal Investigator, European Foundation for the Study of Chronic Liver Failure, Spain

Sponsor: EF CLIF, Spain

ACLARA: Prevalence, epidemiology, characterization and mechanisms of acute-on-chronic liver failure in Latin America. Comparison with data from other regional studies (Europe and Asia)
Observational study

ACLARA is a prospective observational study conducted in 1274 patients with acute decompensation of cirrhosis in 46 centers across 7 Latin American countries with the aim to assess the prevalence of acute-on-chronic liver failure (ACLF) at enrollment and short-term death (i.e., death within 28 days after enrollment). Clinical, laboratory and demographic data was recorded at enrollment and one-year clinical course data was also collected. Results from this study suggest the existence of race differences in the prevalence and clinical course of ACLF.

The ACLARA study was conducted in Latin America because different races, including European Americans, African Americans, Native Americans and mixed races, are living in this continent. The ACLARA study was unique because it collected a comprehensive set of data. Indeed, not only the patients' race was reported but also DNA was collected to assess the individual distribution of each of the three major genetic ancestries (i.e., European, African, and Native American). In addition, the ACLARA study collected sociodemographic characteristics, comorbidities, information on treatments administered before enrollment, and prior history of cirrhosis; clinical and laboratory data at enrollment; and outcomes within 28 days (including liver transplantation and death among non-transplanted patients). Therefore, the data obtained in the ACLARA study enabled us to construct multivariable models with the objective to assess whether differences in genetic ancestry or race are associated with ACLF at enrollment and short-term death among patients non-electively admitted to the hospital for acutely decompensated cirrhosis.

Helping to change the way we manage and treat chronic liver disease

"The most striking novel finding of this study was that Native American genetic ancestry or Native American race (vs. European American race) were independently associated with ACLF at presentation, finding that indicate differences in genetic ancestry or race contribute to outcome disparities in cirrhosis", says Richard Moreau.

"The association of Native American genetic ancestry and Native American race with ACLF indicate that Native American patients with cirrhosis should be included in programs of tight surveillance in order to benefit from urgent treatment of triggers of acute decompensation of liver disease. This could be a first step towards personalized medicine, which is an unmet medical need in the field of decompensated cirrhosis. In addition, the discovery that differences in genetic ancestry and race are associated with differences in outcomes among patients with acutely decompensated cirrhosis, may change the policy of prioritization and allocation of liver transplants in these patients", adds Moreau.

CHANCE

CHANCE: Liver transplantation in patients with cirrhosis and severe acute-on-chronic liver failure – Indications and outcomes
Observational study

Thierry Gustot
Principal Investigator, CUB Hôpital Erasme, Belgium

William Bernal
Co-Principal Investigator, King's College Hospital, UK

Javier Fernández
Co-Principal Investigator, Liver Intensive Care Unit, Hospital Clínic de Barcelona-IDIBAPS, Spain
European Foundation for the Study of Chronic Liver Failure, Spain

Rajiv Jalan
Scientific Coordinator, European Foundation for the Study of Chronic Liver Failure, Spain

Sponsor: EF CLIF, Spain

CHANCE is a multicenter, global, observational study designed to assess the benefit of liver transplantation in patients with acute-on-chronic liver failure (ACLF) grade 2 or 3. This study counts with the support of the International Liver Transplantation Society (ILTS) and the European Liver and Intestine Transplant Association (ELITA) to recruit 2000 patients in 92 centers in 27 countries around the world.

The primary objective of the CHANCE study is to compare one-year graft and patient survival rates after liver transplantation in patients with ACLF grade 2 or 3 at the time of liver transplantation with patients with decompensation of cirrhosis without ACLF grade 2 or 3 and transplant-free survival of patients with ACLF grade 2 or 3 not listed for liver transplantation. The international nature of this study will allow for deep assessments of the potential impact of different precipitating factors of ACLF, different types of liver transplantation (deceased donor vs. living donor liver transplantation) and different regional and national allocation systems on transplant outcomes.

Acute-on-chronic liver failure is a life-threatening condition without evidence-based treatment. The role of liver transplantation is still incompletely understood. A few retrospective studies suggest that it is associated with a substantial survival benefit. We do not currently know the criteria for selecting candidates, the risk factors for post-transplant mortality and the most appropriate way to position these patients on the waiting list. Some studies also suggest that liver transplantation of patients with ACLF 2 or 3 is associated with significant resource mobilization, longer hospitalizations and more frequent complications. In a context of organ shortage, we must ensure equitable distribution of livers to recipients to ensure adequate overall outcomes.

## Moving beyond a one-size-fits-all approach to chronic liver disease

"The CHANCE study will be the first prospective study analyzing intention-to-treat liver transplantation for patients with ACLF 2 or 3. The description of the clinical trajectories on the waiting list could allow us to define potentially new rules for organ allocation. Demonstrating the risk factors for post-transplant mortality could be the basis for defining transplant limits. These results will be essential to select the optimal candidates for transplantation and to define which procedure and which organ (deceased donor and living donor, extended donor criteria) are acceptable in this specific situation", says Thierry Gustot.

EASL CHAIR ACTIVITIES

Advancing knowledge and contributing to standards development to improve treatment and management of chronic liver disease

The EASL Chair promotes research in liver disease in Europe through a collaborative effort aimed at furthering our knowledge and understanding of the mechanisms underlying cirrhosis and its complications. The EASL-CLIF Consortium provides the framework to carry out ancillary studies and clinical trials that will lead to evaluate new therapies in cirrhosis, establish diagnostic criteria, and identify predictors for the design of new prognostic scores for chronic liver disease and acute-on-chronic liver failure— to improve the quality of life and survival of current and future patients with cirrhosis.
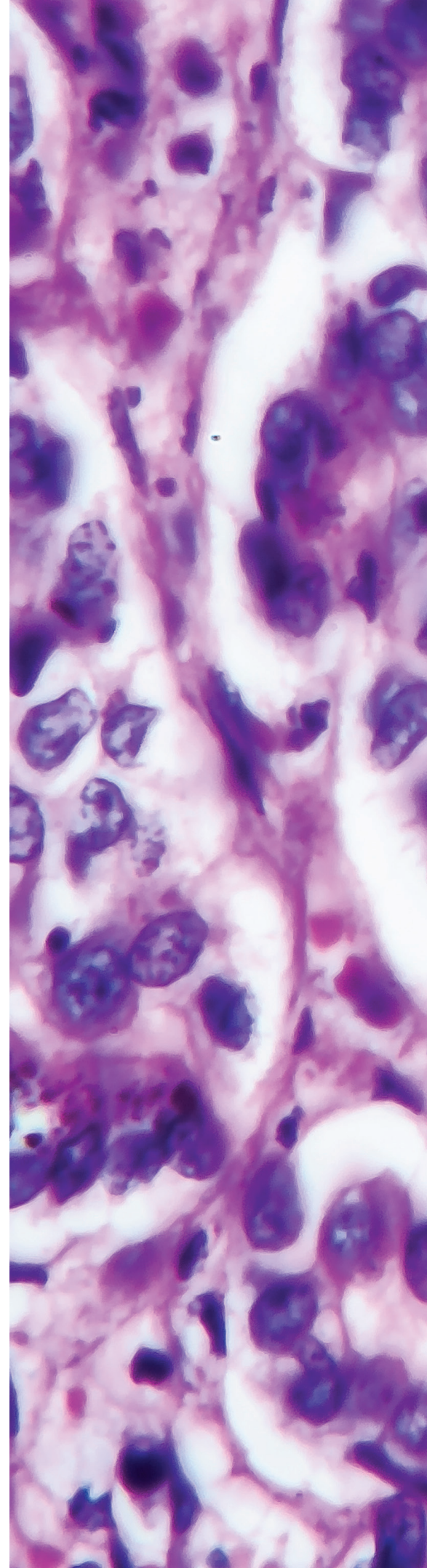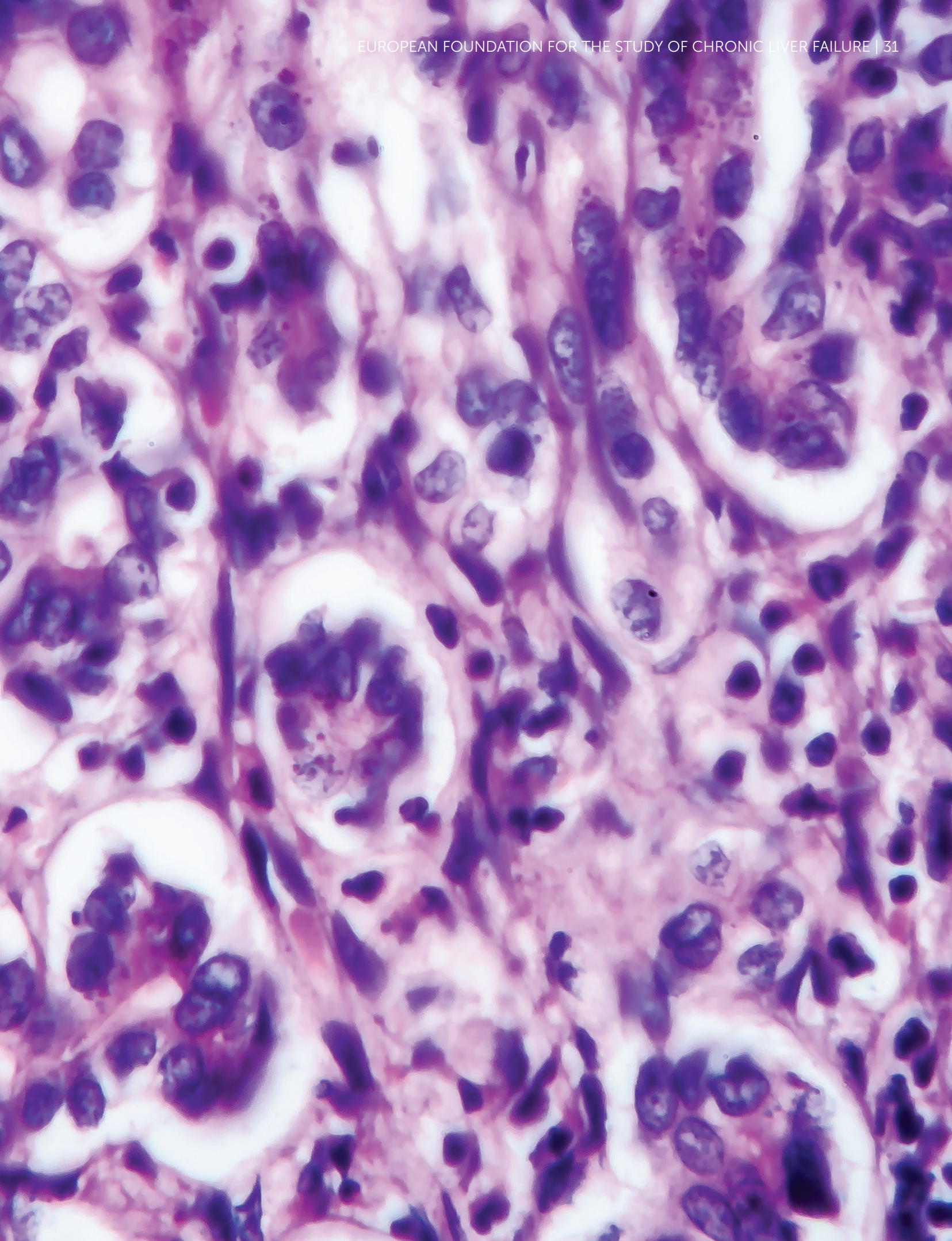
cobalt

COBALT: COVID-19 vaccination and biomarkers in cirrhosis and post-liver transplantation
Observational study

Gautam Mehta
Principal Investigator, University College London, UK

Rajiv Jalan
Principal Investigator, Royal Free Hospital−University College London, UK
European Foundation for the Study of Chronic Liver Failure, Spain

Sponsor: EF CLIF, Spain

The aim of the COBALT study is to determine the protective effect of COVID-19 vaccination in liver disease.

Patients with cirrhosis, acute-on-chronic liver failure (ACLF), and hepatocellular carcinoma appear to be at high risk of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection and progress to most severe forms of COVID-19 with at least 5-fold increased risk of death. Patients with cirrhosis have been shown to have markedly worse outcomes from COVID-19. Moreover, there is very little data on the effectiveness of SARS-CoV-2 vaccines in cirrhosis or liver transplant patients since they were not included in initial clinical trials.

We will compare responses after a 2-dose and 3-dose of the vaccine with healthy controls, to look at the level of antibody response. We will also investigate the durability of response and degree of protection against COVID-19.

Currently, AAST Papa Giovanni XXIII Hospital (Italy), Hannover Medical School (Germany), and Hôpitaux Universitaires de Genève (Switzerland) are actively recruiting participants and running a sub-study of COBALT in a pediatric population.

Guiding effective clinical management and vaccination strategies for patients with chronic liver disease

"This project is pivotal for vulnerable liver patients, who remain concerned about COVID-19 during this Winter season", says Gautam Mehta.

"There remains a degree of vaccine hesitancy amongst the general public, including liver patients. High-quality data are required to reassure our patients, and to identify individuals at risk of poor vaccine response and breakthrough infection. COVID-19 remains a major problem in many parts of the world, such as China and Africa. These data will inform policy for booster vaccines, and also help guide the use of novel antivirals as they become available", adds Mehta.

A-TANGO: Novel treatment of acute-on-chronic liver failure using synergistic action of G-CSF and TAK-242

Rajiv Jalan
Coordinator, Royal Free Hospital–University College London, UK
European Foundation for the Study of Chronic Liver Failure, Spain

Cornelius Engelmann
Clinical Trial Coordinator, Charité–Universitätsmedizin Berlin, Germany

Find out more online at **a-tango.eu**

The EU-funded A-TANGO project aims to bring a novel treatment (G-TAK) that combines a drug known to targets inflammation and granulocyte colony-stimulating factor (G-CSF) which improves hepatocyte proliferation. Alongside the identification of novel biomarkers for patient selection and prognosis, G-TAK is expected to improve the clinical outcome of patients with alcohol-reated liver disease who are at high risk to develop acute-on-chronic liver failure (ACLF). The A-TANGO Consortium will perform a phase II randomized controlled trial to evaluate the safety and effectiveness of this novel treatment.

More than 10 million people worldwide suffer from decompensated cirrhosis, often as a result of severe alcoholic hepatitis (sAH) or other chronic liver diseases. In its final stages, decompensated cirrhosis leads to ACLF. Effective treatment of ACLF is an urgent and unmet need.

"Treatment of ACLF is an unmet need. The combinatorial approach of G-CSF and a toll-like 4 receptor antagonist (TAK-242) offers the dual benefit of inhibiting systemic inflammation and allowing liver regeneration, which could impact positively on the outcomes of patients with ACLF. The results could dramatically impact the survival of patients with ACLF, a patient population which is responsible for the mortality of over 1 million people world-wide. The trial is being performed in about 20 European Hepatology centers linked with EF CLIF and aims to recruit its first patients by mid-2023", says Rajiv Jalan.

DECISION: Decompensated cirrhosis – Identification of new combinatorial therapies based on systems approaches

Pierre-Emmanuel Rautou
Coordinator, Hôpital Beaujon, France

Paolo Caraceni
Clinical Trial Coordinator, University of Bologna, Italy

Find out more online at **decision-for-liver.eu**

The EU-funded DECISION project aims to understand the pathophysiology of decompensation of cirrhosis leading to ACLF by means of combining integrated multiomic profiling and clinical data from patient cohorts within CANONIC – Chronic liver failure acute-on-chronic liver failure, PREDICT – Predicting acute-on-chronic liver failure in cirrhosis, and ACLARA – Prevalence, epidemiology, characterization and mechanisms of acute-on-chronic liver failure in Latin America. DECISION will help to identify novel combinatorial therapies to prevent high mortality for patients with decompensation of cirrhosis.

The DECISION Consortium will optimize most promising combinatorial therapies in animal models during the pre-clinical stage of the study prior to conducting a phase IIb randomized controlled trial of the best combination in patients at high-risk to develop ACLF.

While most cirrhosis patients initially do not show symptoms, acute decompensation of cirrhosis, defined as the body's inability to cope with the progressing dysfunctionality of the liver, leads to drastic symptoms.

"The DECISION project will identify a combination of existing drugs able to improve outcome of patients with acute decompensation of cirrhosis and decrease mortality at 3 months", says Pierre-Emmanuel Rautou.

MICROB-PREDICT

MICROB-PREDICT: Microbiome-based biomarkers to predict decompensation of liver cirrhosis and treatment response

Jonel Trebicka
Coordinator, University Hospital Münster, Germany
European Foundation for the Study of Chronic Liver Failure, Spain

Aleksander Krag
Clinical Trial Coordinator, Odense University Hospital, Denmark

Sponsor: EU's H2020 research and innovation programme under grant agreement no. 825694
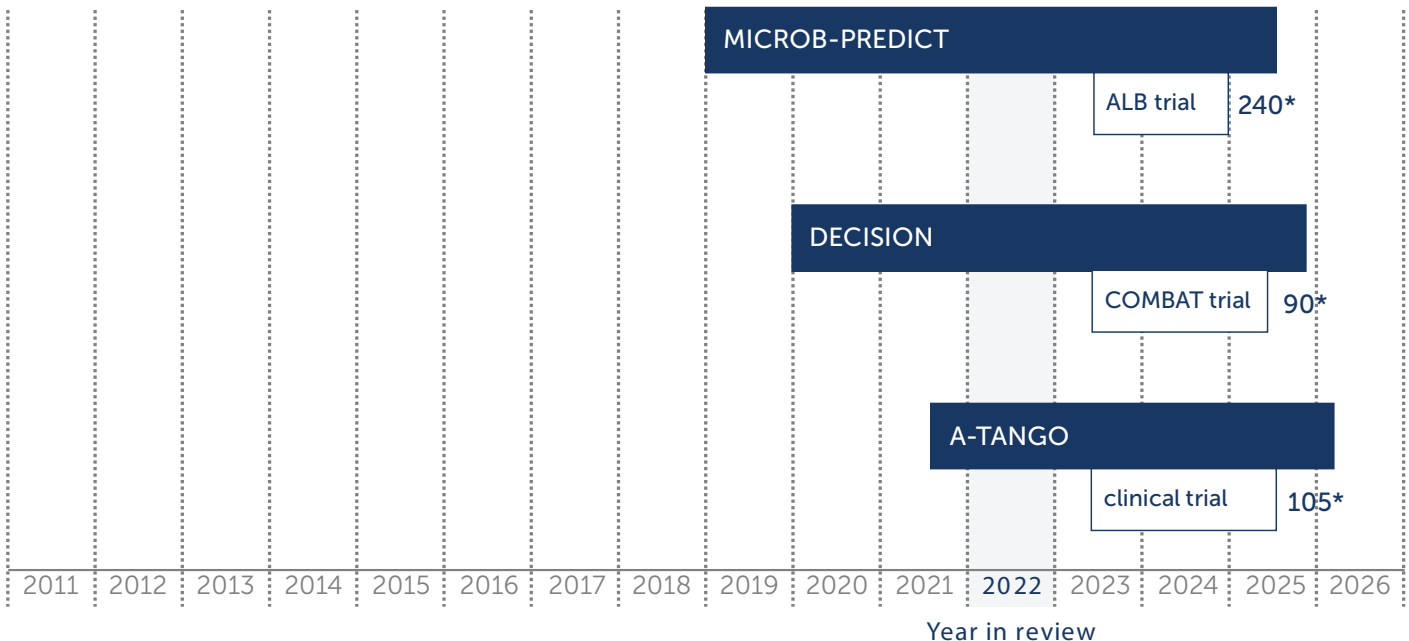
Find out more online at
microb-predict.eu

The EU-funded MICROB-PREDICT project aims to investigate the interplay between gut and liver. The MICROB-PREDICT Consortium will identify microbiome-based biomarkers associated with chronic liver disease and generate data from large patient cohorts. Collectively, this information will enable accurate patient stratification and pave the way for new personalized therapies.

End-stage liver disease is a major cause of morbidity and mortality, and has a large socioeconomic impact because of high health care costs and the patients' inability to work or seek employment. It is crucial to develop novel treatments for patients with cirrhosis and acute-on-chronic liver failure (ACLF).

"The project has already a variety of biomarkers to predict ACLF development and response to different drugs and currently we are at the validation phase of these findings. The validated findings will then be translated into point-of-care tests, which will be available for physicians and help patients' stratification. These tools have the potential to revolutionize the field of hepatology, by faster decision for monitoring, intensive care unit admission and choice of therapies", says Jonel Trebicka.

Overview of EU-funded projects we coordinate

* Number of patients to be recruited in planned interventional studies within these projects.

| | MICROB-PREDICT | | | | | |
| ALB trial | 240* |
| DECISION |
| COMBAT trial | 90* |
| A-TANGO |
| clinical trial | 105* |

2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 **2022** 2023 2024 2025 2026

Year in review

● Publication of the **Checklist for participants to assure informed consent/other mechanisms for those unable to give a written consent** within MICROB-PREDICT and DECISION

● Publication of the **infographics** based on the Guidelines for reviewing health research and innovation projects that use emergent technologies and personal data within MICROB-PREDICT and DECISION

Our partners across consortia

Country	Partner	MICROB-PREDICT	DECISION	A-TANGO
Belgium	European Liver Patients Association	●	●	●
Belgium	KU Leven	●	○	○
Denmark	Nordic Bioscence A/S	○	●	○
Denmark	Region Syddanmark	●	○	○
Denmark	University of Copenhagen	●	○	○
France	French Alternative Energies and Atomic Energy Commission	●	●	○
France	French Institute of Health and Medical Research	○	●	○
France	French Research Institute for Agriculture, Food and Environment	●	○	○
France	Hôpital Pitié-Salpêtrière	○	●	●
France	University of Paris	○	●	○
France	Vaiomer	●	○	○
Germany	Biobyte Solutions GmbH	●	○	○
Germany	Charité−Universitätsmedizin Berlin	○	○	●
Germany	Concentris GmbH	●	●	●
Germany	European Molecular Biology Laboratory	●	○	○
Germany	Goethe University Frankfurt	●	●	○
Germany	Max Plank Society for the Advancement of Science E.V.	●	○	●
Germany	University Hospital Aachen	○	●	○
Germany	University of Leipzig	○	○	●
Hungary	University of Debrecen	●	○	○
Ireland	Crowdhelix Ltd.	○	○	●
Italy	Azienda Ospedaliera Sant'Orsola Malpighi	○	●	○
Italy	Città della Salute e della Scienza di Torino-Presidio Molinette	○	●	○
Italy	University of Padova	○	●	○
Italy	University of Turin	○	●	○
Norway	University of Oslo	●	○	○
Spain	Alpha Bioresearch SL	○	○	●
Spain	Fundació Clínic per a la Recerca Biomèdica	●	●	○
Spain	Fundación Pública Miguel Servet	○	●	○
Spain	Hospital Clínic de Barcelona	●	●	○
Spain	Institut Català de la Salut	○	●	○
Spain	Institut Català de Nanociència i Nanotecnologia	●	○	○
Spain	Servicio Madrileño de Salud	○	●	○
Spain	University of Barcelona	●	●	○
Sweden	YouHealth AB	○	●	○
Switzerland	European Association for the Study of the Liver	●	●	●
Switzerland	International Market Access Consulting GmbH	○	○	●
The Netherlands	Erasmus MC	○	●	○
The Netherlands	Leiden University Medical Centre	●	○	●
United Kingdom	Hepix Ltd.	○	○	●
United Kingdom	King's College Hospital	●	○	○
United Kingdom	University College London	●	○	●
United Kingdom	Yaqrit Ltd.	○	○	●

● Member

A possible role for FXR polymorphisms in the etiopathogenesis of acute decomposition of cirrhosis and acute-on-chronic liver failure
Ancillary study

Wim Laleman
Principal Investigator, Department of Gastroenterology and Hepatology, University Hospitals Leuven, KU Leuven, Belgium

Jonel Trebicka
Principal Investigator, University Hospital Münster, Germany
European Foundation for the Study of Chronic Liver Failure, Spain

Sponsor: UZ Leuven, Belgium

Infections are the most common precipitants of acute-on-chronic liver failure (ACLF), but in more than 40% of patients, no precipitating event is identified. Numerous observations have substantiated a pivotal role for dysregulated systemic inflammation as the pacemaker in (multi-)organ failure and a dysfunctional gut–liver axis as a major instigator. The underlying molecular backbone remains largely unknown.

Recent translational and clinical research has suggested a central role for defective farnesoid X receptor (FXR) signaling in protracted hepatic inflammation and intestinal bacterial translocation, factors which are known to shape ACLF. The FRX is a bile acid activated nuclear receptor that regulates key genes in the metabolic process of bile acid synthesis and involved in the metabolism of carbohydrates and lipids

representing a promising therapeutic target for bile acid-related liver diseases. This study will explore FXR polymorphisms in the development of acute decompensation of cirrhosis and ACLF within the CANONIC and PREDICT study cohorts.

"The genetic risk of patients to decompensate has not been determined so far. Since FXR seems to play a role in development of cirrhosis and also its modulation may prevent complications, its genetic variants may also play a role. If the association is clear, then this helps to stratify care in the patients and probably with different monitoring and survellaince strategies in different genotypes. In addition, FXR-agonists may be then a strategy to treat these patients. Therefore, this project may open novel horizons in the care of patients", says Jonel Trebicka.

Biomarkers of renal tubular damage in predicting response to terlipressin and albumin in patients with hepatorenal syndrome
Ancillary study

Salvatore Piano
Principal Investigator, University of Padova, Italy

Paolo Angeli
Principal Investigator, University of Padova, Italy

Sponsor: University of Padova, Italy

The combination of vasoconstrictors and albumin is the treatment of choice in patients with hepatorenal syndrome–acute kidney injury (HRS–AKI). Predictors of response to vasoconstrictors and albumin may be useful in clinical practice, because can anticipate the clinical course of the disease and may mitigate the risk of side effects. So far, clinical predictors have been identified, such as baseline serum creatinine, serum bilirubin, acute-on-chronic liver failure (ACLF) grade and changes in mean arterial pressure. The association of a higher ACLF grade with a lower response to terlipressin and albumin is of particular interest, because may suggest a role for severe inflammation affecting renal tubular function.

The aim of this study is to identify whether urinary biomarkers of tubular damage can predict response to treatment with terlipressin and albumin in patients with HRS–AKI within PREDICT and ACLARA.

We will assess the ability of investigated biomarkers to predict the reversal of HRS–AKI and in-hospital mortality, 28-day mortality and 90-day mortality, in patients with HRS–AKI.

"The project wants to identify novel predictors of response to vasoconstrictors and albumin in patients with HRS–AKI using urinary biomarkers/ metabolites.The use of vasoconstrictors and albumin can cause relevant side effects and the identification of predictors of response to those treatment can help to personalize the therapeutic approach and to avoid the use of a futile and potentially dangerous treatment in patients that are unlikely to have a benefit. Moreover, the analysis of urinary metabolites can unveil novel pathways involved in the pathogenesis of the syndrome and can pave the way for the development of new treatments for those patients less likely to benefit from vasoconstrictors and albumin", says Salvatore Piano.

Glycomics-based biomarkers for diagnosis and prognosis in acute-on-chronic liver failure
Ancillary study

Xavier Verhelst
Principal Investigator, Department of Gastroenterology and Hepatology, Ghent University Hospital, Belgium

Hans van Vlierberghe
Principal Investigator, Department of Gastroenterology and Hepatology, Ghent University Hospital, Belgium

Sponsor: Ghent University Hospital, Belgium

In the development of precision medicine, efficient biomarkers are needed that can be used for the diagnosis, prognostication and monitoring of disease evolution. Based on a large experience in the study of protein glycosylation in liver disease, our team aims at developing glycomics-based biomarker in liver disease. The goal of this project is to study changes in serum protein glycosylation in patients with acute-on-chronic liver failure (ACLF) in order to describe different phenotypes in ACLF based on the serum glycomics profile, related to diagnosis, outcome and disease evolution.

This project aims at exploring alterations of the serum glycome during the development of ACLF and correlating these changes to the diagnosis of ACLF and the outcome upon ACLF development.

"Glycomic changes in the blood of our patients are mirroring changes inside the liver cells. This should give us precious information on what is going wrong in patients with ACLF, leading to better care for these patients. New non-invasive tools to monitor patients with ACLF will help clinicians to improve decision-making in the treatment of ACLF", says Xavier Verhelst.

Molecular markers to predict chronic liver failure and to explore its mechanistic pathways in decompensated cirrhosis
Ancillary study

Cornelius Engelmann
Principal Investigator, Charité–Universitätsmedizin Berlin, Germany

Sponsor: Charité–Universitätsmedizin Berlin, Germany

Acute-on-chronic liver failure (ACLF) is a syndrome with dismal prognosis and lack of effective treatment options. Liver transplantation is the only curative therapy, however, only available to a minority of patient due to contraindications and shortage of donor organs. Moreover, having validated predictors and biomarkers would help to select patient for individual treatment strategies.

This project aims to understand the role of bacterial translocation and immune cell-derived microparticles in mediating the progression of cirrhosis to decompensation and ACLF in patients within PREDICT – Predicting acute-on-chronic liver failure in cirrhosis.

"Establishing new biomarkers is the basis to stratify patients with respect to prognosis as well as diagnostic and therapeutic strategies", says Cornelius Engelmann.

GRIFOLS CHAIR ACTIVITIES

Translating scientific discovery into the clinic to improve care for patients with cirrhosis

The Grifols Chair promotes research aimed at characterizing the mechanisms underlying the presence of systemic inflammation in patients with decompensation of cirrhosis and its role in the development of acute-on-chronic liver failure.

SERIAL No. KD056.54846025

DISCOVERY: Assessing the effects of human albumin on B cells in acutely decompensated cirrhosis
Translational research

Richard Moreau
Principal Investigator, European Foundation for the Study of Chronic Liver Failure, Spain

Joan Clària
Principal Investigator, Hospital Clínic de Barcelona-IDIBAPS, Spain
European Foundation for the Study of Chronic Liver Failure, Spain

Joan José Lozano
Principal Investigator, CIBERehd, Spain

Sponsor: EF CLIF, Spain

Patients with acute-on-chronic liver failure (ACLF) exhibit systemic inflammation, immunosuppression, and a high prevalence of infections leading patients to hospital and also during hospital stay (secondary infections), which are deadly complications. Genome-wide analysis of RNA expression in blood from patients with ACLF have shown a marked reduction in RNA signatures related to CD4 T cells, CD8 T cells, natural killer cells and B cells, findings that suggest blood lymphocyte depletion and therefore immunosuppression.

To date, there are no therapies against immunosuppression in ACLF. Albumin is commonly used in patients with cirrhosis, including patients treated by large-volume paracentesis, and patients with spontaneous bacterial peritonitis, or type 1 hepatorenal syndrome. Recent translational studies, suggest that albumin may decrease the intensity of systemic inflammation and mitigate immunosuppression in decompensated cirrhosis. Moreover, the ANSWER trial conducted in patients with decompensated cirrhosis has shown that a significant reduction in the number of episodes of bacterial infection likely contributed to the increase in the probability of survival observed in patients assigned to long-term albumin administration.

To assess if albumin mitigates immunosuppression in decompensated cirrhosis, we investigated the different populations of circulating immune cells, using their respective RNA signatures identified by whole-blood RNA sequencing in patients hospitalized with acutely decompensated cirrhosis who had or had not received albumin. Additional patients with acutely decompensated cirrhosis were assigned to experiments investigating either the *ex vivo* effects of albumin or the *in vivo* effect of albumin before and after albumin administration.

Tackling unmet medical needs in chronic liver disease

"Our study revealed that albumin administration was able to activate B cells and their differentiation to antibody-producing plasma cells and revigorate antimicrobial function of neutrophils. B cells and neutrophils are major players in immune responses against pathogens. Together, these findings strongly suggest that albumin mitigates, at least in part, immunosuppression by stimulating two subsets of cells involved in host immunity. The "immune-stimulating" effect of albumin may have contributed to the decrease in the number bacterial infections observed in the ANSWER study among patients who had been assigned to receive long-term albumin administration. Therefore, albumin administration may become an important component of strategies aiming to restore appropriate host immune responses to pathogens in patients with decompensated cirrhosis", says Richard Moreau.

Autophagy as a mediator of human serum albumin anti-inflammatory effects
Translational research

Sophie Lotersztajn
Principal Investigator, Center for
Inflammation Research, UMR1149
Inserm, France

Sponsor: EF CLIF, Spain

Prior studies have demonstrated that LC3-associated phagocytosis, a non-canonical form of autophagy, is an anti-inflammatory pathway during chronic liver disease and limits fibrosis progression leading us to hypothesized that albumin functions as an activator of LC3-associated phagocytosis and that its anti-inflammatory properties rely on LC3-associated phagocytosis activation. Pilot studies have demonstrated that human serum albumin enhances selective pathways of autophagy in specific blood cell sub-types from both healthy subjects and patients with cirrhosis. Validation of these preliminary observation is being performed in a larger cohort of cirrhotic patients and exploring the early signaling pathways leading to autophagy activation upon human serum albumin treatment.

Definition of the utility of immune checkpoint receptors as therapeutic targets in acute-on-chronic liver failure
Translational research

Shilpa Chokshi
Principal Investigator, Roger Williams
Institute of Hepatology, Foundation for
Liver Research, UK

Sponsor: EF CLIF, Spain

We have measured levels of several immune checkpoints in both the CANONIC cohort and a smaller longitudinal cohort. Several immune checkpoints are elevated with increasing acute-on-chronic- liver failure (ACLF) grade, and we have found higher levels of some of these factors can discriminate clinical outcomes. Results from our study have also demonstrated that ACLF grade increases markers of gut translocation, suggesting this contributes to the pathological state; different patterns of soluble immune checkpoints associate with different predisposition and injury in ACLF; levels of some galectins, important immune checkpoints, are elevated in ACLF liver tissue at the transcriptional level and are also produced by stressed liver tissue in an explant model; levels of immune checkpoints are dynamic in ACLF; and further experiments from this longitudinal cohort have shown that blockade of some factors can affect the immune response *in vitro*.

"Measurements of systemic soluble checkpoint receptors are useful both as potential diagnostic/prognostic biomarker but also to expose mechanisms underlying immunopathogenesis of disease. The defining contribution of soluble checkpoint receptors in ACLF remains unclear and was the aim of this investigation. Understanding the role of soluble checkpoint receptors in the immunoparesis observed in ACLF could potentially represent innovative immune-based therapeutic approaches to rescue antibacterial defences in these patients", says Shilpa Chokshi.

Effects of albumin on human neutrophil function in patients suffering from acute decompensation and acute-on-chronic liver failure
Translational research

Daniel Irimia
Principal Investigator, Massachussets General Hospital, MA, USA

Sponsor: EF CLIF, Spain

In patients with cirrhosis neutrophil dysfunction is associated with higher risk of infection. This study aims to assess whether albumin levels could affect neutrophil function and thus contribute to restore the natural defenses against microbes to prevent organ failures and increase survival in patients with acute decompensation and acute-on-chronic liver failure (ACLF). Neutrophil swarming, an essential process of the innate immune response, was tested *in vitro*. Results have shown that the antimicrobial activity of neutrophils from patients with cirrhosis is impaired in a neutrophil swarming assay. Further investigations are needed to assess whether administration of albumin has a positive effect in restoring neutrophil function in patients with chronic liver disease.

Extracellular vesicles as biomarkers in patients with acute decompensation of cirrhosis
Translational research

Pierre-Emmanuel Rautou
Principal Investigator, Hôpital Beaujon, France

Sponsor: EF CLIF, Spain | EU's H2020 research and innovation programme under grant agreement no. 847949

Scoring and prediction systems such as the MELD, MELD-Na, and Child–Pugh scores have a poor prognostic value in patients with acute decompensation of cirrhosis. A robust prognostic score focusing on patients with acute decompensation is therefore urgently needed.

Extracellular vesicles are vesicles released outside the cells by all cell types and can be found in all biological fluids such as blood. The composition of extracellular vesicles reflects the type of activation or stress their mother cell was exposed to. Therefore, extracellular vesicles content holds great potential for predicting the disease trajectory. In cirrhosis, detrimental changes occur not only in the liver, but also in many other organs and systems including vessels, immune cells, gut, muscles, and kidneys.

Plasma extracellular vesicles exhibit a remarkable potential to capture multiorgan involvement associated with cirrhosis.

The objective of this project is to characterize plasma large extracellular vesicles profiles associated with the outcome of patients with acute decompensation of cirrhosis by re-analyzing standardized biobank samples from patients included in the PREDICT and ACLARA cohorts. This study is embedded in the EU-funded DECISION project.

"We have measured plasma extracellular vesicles concentrations in the blood of over 1300 patients with cirrhosis and found a signature able to improve prediction of patients' outcome", says Pierre-Emmanuel Rautou.

Genome-wide association study in patients with acute decompensation of cirrhosis
Translational research

Eric Trépo
Principal Investigator, CUB Hôpital Erasme–Université Libre de Bruxelles, Belgium

Sponsor: EF CLIF, Spain

Patients with decompensated cirrhosis are particularly prone to organ dysfunction, which drives patients' prognosis. Several clinical factors have been associated with organ dysfunction (e.g., older age, male gender, ancestry). However, many patients with decompensated cirrhosis with these clinical risk factors never develop organ dysfunctions, suggesting a genetic susceptibility. Genome-wide association studies have provided significant insight into the genetic architecture and the pathogenesis of liver disease. However, no data are currently available in decompensated cirrhosis.

This study aims to perform a genome-wide association study to identify genetic variations associated with decompensated cirrhosis and its related complications. This project relies notably on three observational cohorts of patients with acute decompensation of cirrhosis including CANONIC, PREDICT, and ACLARA for which genome-wide data have been generated with a single nucleotide polymorphism array.

The identification of genetic variation associated with features of decompensation of cirrhosis may lead to novel insight in the pathophysiology of this disease.

"The project aims to identify common genetic variants that are associated with features of decompensated cirrhosis such as acute-on-chronic liver failure, infection, and renal dysfunction. Finding some susceptibility genes that modulate the risk of these life-threatening complications has the potential to provide a better comprehension of the underlying biological mechanisms driving these complications. These findings may advance our understanding of the pathogenesis of decompensated cirrhosis and guide the development of novel drug targets", says Eric Trépo.

Identification of albumin receptors and characterization of albumin intracellular trafficking in human peripheral blood mononuclear cells
Translational research

Loredana Saveanu
Principal Investigator, INSERM U1013, Université Paris Descartes, Sorbonne Paris Cité, France

Sponsor: EF CLIF, Spain

Several studies showed a correlation between serum albumin concentration and the severity of hepatic and septic disease severity and mortality rates, leading to the indication of parenteral albumin therapy in the case of decompensated liver diseases and septic shock. The exact mechanisms by which albumin supplementation may improve the clinical outcome are not known. However, several laboratories have demonstrated immunomodulatory and anti-inflammatory effects of albumin therapy in complication of cirrhosis.

In this context, we proposed to identify the main cellular population in the blood that internalizes albumin, the receptors leading to albumin intracellular storage and the endocytic mechanisms by which albumin enters in the cells.

This project addresses three different objectives related with the trafficking of the albumin molecule in peripheral immune cells: Identify the peripheral human blood cells that most efficiently internalize the albumin molecule; identify the albumin receptor(s) in this process; and investigate the intracellular trafficking pathway of albumin after binding to its receptor(s) following their internalization.

"We found that classical monocytes, the most abundant cell population in blood, are the most efficient cells in albumin up-take. Expression levels of proteins involved in the process of albumin internalization and the number of classical monocytes could be useful for predicting the patient response to albumin infusions", says Loredana Saveanu.

Influence of gender on albumin response in samples from the ATTIRE cohort
Translational research

Alastair O'Brien
Principal Investigator, Institute for Liver and Digestive Health–University College London, UK

Sponsor: EF CLIF, Spain

Acute decompensation and acute-on-chronic liver failure (ACLF) are characterized by increased systemic inflammation and immunosuppression. There are data supporting gender differences in the inflammatory response in health and differences in outcomes between genders in acute decompensation of cirrhosis/ACLF. Post-hoc subgroup analyses of the neutral ATTIRE trial – Albumin to prevent infection in chronic liver failure – suggested a differential effect of targeted albumin infusions according to gender and so we are investigating this in greater detail.

Investigating data from the ATTIRE trial significantly higher interleukin-8 (IL-8) levels in women were found irrespective of treatment group, suggesting a difference in the inflammatory response, although infection rates and overall outcomes were similar and targeted albumin had no discernible effect on IL-8, one of the major mediators of the inflammatory response. The improved renal function in albumin-treated women without evidence of increased adverse events may relate to their increased rate of serum albumin increment. Plasma sample analyses from the targeted albumin patients suggest a reduction in plasma renin activity and an improvement in albumin function in females but not males.

"These data suggest sex differences in response to fluid resuscitation, that we will investigate further", says Alastair O'Brien.

INDUSTRY-SPONSORED RESEARCH

Turning global challenges in cirrhosis into opportunities to save patients' lives

We partner with industry to address unmet medical needs in cirrhosis and generate insights to drive innovative therapeutic solutions that can transform and revolutionize patient care.

ALADDIN: Pathogenesis of acute-on-chronic liver failure and mechanisms of action of plasma exchange with human serum albumin 5% in decompensated cirrhotic subjects with systemic inflammation and acute-on-chronic liver failure
Translational research

Joan Clària
Principal Investigator, Hospital Clínic de Barcelona-IDIBAPS, Spain
European Foundation for the Study of Chronic Liver Failure, Spain

Sponsor: Grifols S.A., Spain

Several studies indicate that systemic inflammation plays a causal role in the development of acute-on-chronic liver failure (ACLF). In parallel, important progress has been made in the characterization of albumin pleiotropic properties (i.e. oncotic, antioxidative, anti-inflammatory) to propose that albumin can ameliorate systemic inflammation in patients with high risk of developing ACLF.

The ALADDIN study is a translational research project currently being performed in European centers participating in the APACHE trial, a phase III, multicenter, randomized, open-label trial involving intensive care units with expertise in the management of critically ill cirrhotic patients. The ALADDIN study is an agnostic investigation aimed to assess the mechanisms of systemic inflammation and ACLF in a large series of patients with and without ACLF. Protein expression, kinomic and genotyping will be determined using high-throughput molecular biology techniques in patients with ACLF from the APACHE study. Since patients included in the APACHE study will be investigated before, during and after treatment, the study will also assess the mechanism of action of plasma exchange and predictors of response in patients with ACLF.

"The ALADDIN study is a unique investigation that could prove for the first time that plasma exchange using human serum albumin as the main replacement fluid can be effective and safe in the treatment of patients with decompensated cirrhosis with systemic inflammation and ACLF", says Joan Clària.

APACHE: Short-term survival of subjects with acute-on-chronic liver failure after plasma exchange with human serum albumin 5%
Interventional study

Javier Fernández
Principal Investigator, Liver Intensive Care Unit, Hospital Clínic de Barcelona-IDIBAPS, Spain
European Foundation for the Study of Chronic Liver Failure, Spain

Fin Stolze Larsen
Principal Investigator, Rigshospitalet–University Hospital Copenhagen, Denmark

Sponsor: Grifols S.A., Spain

ClinicalTrials.gov Identifier: NCT03702920

Patients with acute-on-chronic liver failure (ACLF) are at high risk of short-term mortality. The higher the number of organ failure, the lower the survival. Liver support systems were developed in the past to improve liver function allowing either the compensation of the patient or bridging them to liver transplantation. Bioartificial systems are no longer available and studies on albumin dialysis have not demonstrated that these systems improve survival in ACLF. On the contrary, high-volume plasma exchange improves transplant-free survival in patients with acute liver failure. A pilot study performed in the Hospital Clínic de Barcelona demonstrated that this treatment is safe in patients with ACLF.

The APACHE study is a phase III, multicenter, randomized, open-label trial in 380 patients with ACLF grade 1b, 2 or 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 treatment. The study is being performed in 31 centers across Europe and North America.

"The APACHE study is the largest randomized clinical trial evaluating a liver support system ever performed in patients with ACLF and is aimed to demonstrate that plasma exchange is able to improve 90-day transplant-free survival in patient with 1 to 3 organ failures. If the APACHE study is positive, we would have, for the first time, a liver support system capable to improve survival in these sick patients", says Javier Fernández.

DELHIVER/HEP102: Randomized, placebo-controlled, double blind, multicenter phase IIb study to evaluate the efficacy and safety of HepaStem® in patients with acute-on-chronic liver failure
Interventional study

Frederik Nevens
Principal Investigator, UZ Leuven, Belgium

Sponsor: Cellaïon, Belgium

ClinicalTrials.gov Identifier: NCT04229901

The DHELIVER/HEP102 study is a multicenter, interventional, double-blind, randomized, placebo-controlled trial designed to assess the efficacy of HepaStem® in 100 patients with acute-on-chronic liver failure (ACLF) grade 1 or 2. Patients with ACLF grade 1 or 2 will be eligible to screen for participation in the trial and will be randomized across two treatment arms: patients receiving two weekly intravenous infusions of HepaStem® and patients receiving placebo. The primary outcome measure is overall survival at 90 days post-first infusion. Secondary outcome measures include transplant-free survival at 90 days post-first infusion, at day 90 while free of ACLF, at day 90 with MELD-Na score < 15, and assessment of hepatic function parameters and prognostic scores.

Liposomal peritoneal dialysis for the management of hepatic encephalopathy
Interventional study

Jonel Trebicka
Principal Investigator, University Hospital Münster, Germany
European Foundation for the Study of Chronic Liver Failure, Spain

Sponsor: Versantis–GENFIT, France

This single-center, open-label, single ascending and repeated doses, phase Ib clinical trial is designed to assess the safety, efficacy, and pharmacokinetics of VS-01 in patients with decompensated liver cirrhosis. VS-01 is a potentially lifesaving, multi-organ support therapy with the potential to timely reverse acute-on-chronic liver failure (ACLF) by enhancing the clearance of ammonia and other toxins following paracentesis. Results have shown that single and repeated intraperitoneal administrations of VS-01 are safe and well tolerated in patients with decompensated cirrhosis. VS-01 has been found to markedly improve the psychometric test results and efficiently clear ammonia and ACLF-associated metabolites from blood supporting future development of VS-01 in patients with overt hepatic encephalopathy and ACLF.

preciosa

PRECIOSA: Effects of long-term administration of human albumin in subjects with decompensated cirrhosis and ascites
Interventional study

Javier Fernández
Principal Investigator, Liver Intensive Care Unit, Hospital Clínic de Barcelona-IDIBAPS, Spain
European Foundation for the Study of Chronic Liver Failure, Spain

Paolo Angeli
Principal Investigator, University of Padova, Italy

Sponsor: Grifols S.A., Spain

ClinicalTrials.gov Identifier:
NCT03451292

Current clinical guidelines recommend the administration of short-term albumin in patients with spontaneous bacterial peritonitis, large volume paracentesis or hepatorenal syndrome–acute kidney injury. The ANSWER study suggested that long-term albumin administration (for 18 months) improves survival in cirrhotic patients with ascites requiring moderate doses of diuretics. However, this strategy is poorly applied in clinical practice mainly due to logistical problems given the high amount of candidates and a survival benefit of "only" 11%.

The PRECIOSA study is a phase III, multicenter, randomized, open-label trial that will include 410 patients with decompensated liver cirrhosis with ascites at high risk of acute-on-chronic liver failure (ACLF) and short-term mortality (CLIF-C AD score > 49) aimed to determine whether long-term albumin administration (1.5 g/kg body weight every 10 days for 12 months) improves one-year transplant-free survival in comparison with standard medical treatment. The study is being performed in 35 centers across Europe and North America.

"If the results of this study are positive, two large randomized clinical trials would provide evidence that periodic albumin administration improves survival in a specific subset of cirrhotic patients with ascites, establishing the rationale for the implementation of this treatment in clinical practice", says Javier Fernández.

OTHER COLLABORATIVE PROJECTS

Strengthening connections with academia and industry for a sustainable future

Within the framework of the European Union's Horizon 2020 program, we have continued expanding our network of collaborators to foster mobility, contribute to the further development of a borderless market for research and innovation, and deliver impactful results for the benefit of the broader research community and society.

Human Microbiome Action

Jöel Doré
Coordinator, French Research Institute for Agriculture, Food and Environment, France

Sponsor: EU's H2020 research and innovation programme under grant agreement no. 946590

Find out more online at
humanmicrobiomeaction.eu

IHMCSA: International human microbiome coordination and support action

Human−microbes interplay has proven essential for the maintenance of health and wellbeing and profiling of microbiomes will become an essential feature of the personalized preventive nutrition and medicine of tomorrow. Europe has gained a leading position in microbiome science and yet to fulfill societal expectations, an international consensus will be essential on key aspects. These include clinical trial design as well as analytical standards.

The IHMCSA project will tackle all necessary steps to open the perspective of managing nutrition and health of the human microbiome. Involving key stakeholders representing the multiplicity of actors concerned, including citizens, IHMCSA will map existing material, delineate necessary steps and pathways for innovation and build consensus on priorities and means for the future of microbiome science and its translation.

"To date, the interpretation and generalization of microbiome-based diagnostic and therapeutic approaches has been severely hampered by the lack of comparability of study designs, different target populations and common confounding factors in microbiome analysis. The microbiome crucially contributes to the progression of chronic liver disease, especially through the gut−liver axis. Minimum standards in clinical trial design and analytical standards will boost future microbiome science and will lead to reliable diagnostic and therapeutic microbiome-based approaches more quickly", says Jonel Trebicka.

LIVERH♥PE

Pere Ginès
Coordinator, Hospital Clínic de Barcelona-IDIBAPS, Spain

Sponsor: EU's H2020 research and innovation programme under grant agreement no. 731875

Find out more online at
liverhope-h2020.eu

ClinicalTrials.gov Identifier:
NCT03150459

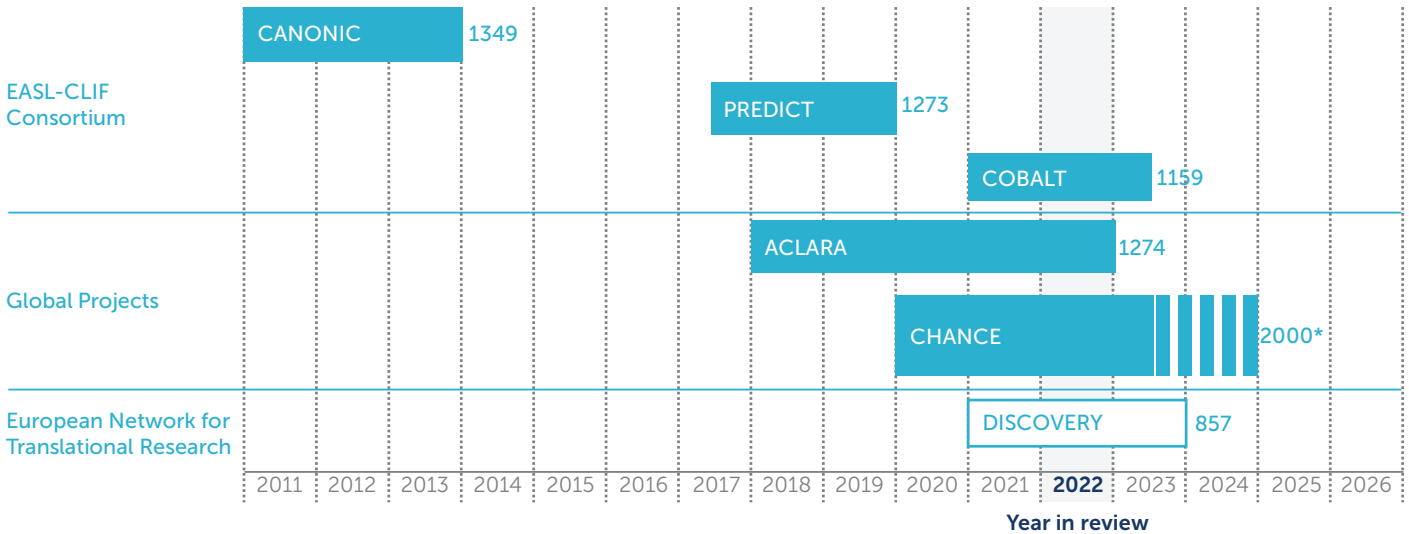### LIVERHOPE: Simvastatin and rifaximin as new therapy for patients with decompensated cirrhosis

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. This dual therapeutic approach is supported by preclinical data. Two randomized double-blind trials are being conducted to investigate safety, tolerability, and efficacy of combination of simvastatin plus rifaximin in patients with decompensated cirrhosis in five European countries. The expected impact is to stop progression to acute-on-chronic liver failure (ACLF), the main cause of death, to decrease complications of the disease, reduce hospital readmissions, and improve cost-effectiveness of therapy.
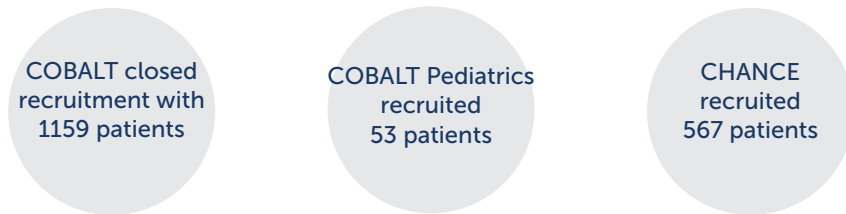
2022 BY THE NUMBERS

Overview of our flagship projects progress

Number of patients participating in each of our flagship projects from 2011 to 2023. * Expected.

EASL-CLIF Consortium		
CANONIC	1349	
PREDICT	1273	
COBALT	1159	

Global Projects

ACLARA 1274

CHANCE 2000*

European Network for Translational Research

DISCOVERY 857

2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 **2022** 2023 2024 2025 2026

Year in review

Patient recruitment

COBALT closed recruitment with 1159 patients

COBALT Pediatrics recruited 53 patients

CHANCE recruited 567 patients

Training

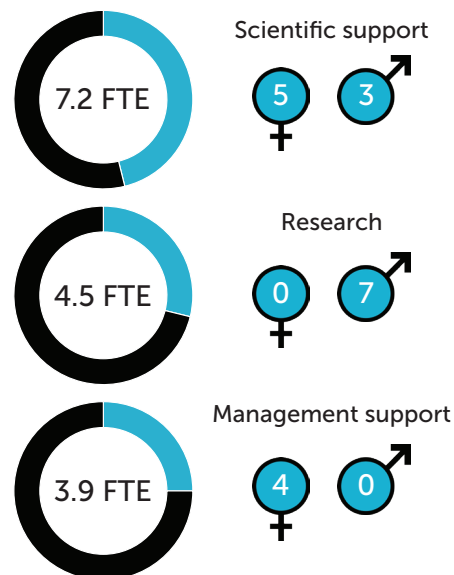**224 users** from 44 centers trained

129 h of training delivered

Collaborators in ongoing studies are trained by staff at the Data Management Center before the start of patient enrollment.

EF CLIF staff

7.2 FTE — Scientific support: 5 ♀ / 3 ♂

4.5 FTE — Research: 0 ♀ / 7 ♂

3.9 FTE — Management support: 4 ♀ / 0 ♂

EF CLIF collaborators

367 Principal Investigators — Include laboratory-based principal investigators, consultant physicians, intensivists, and surgeons

764 Investigators — Include PhD candidates, postdoctoral researchers, research nurses, and pathologists
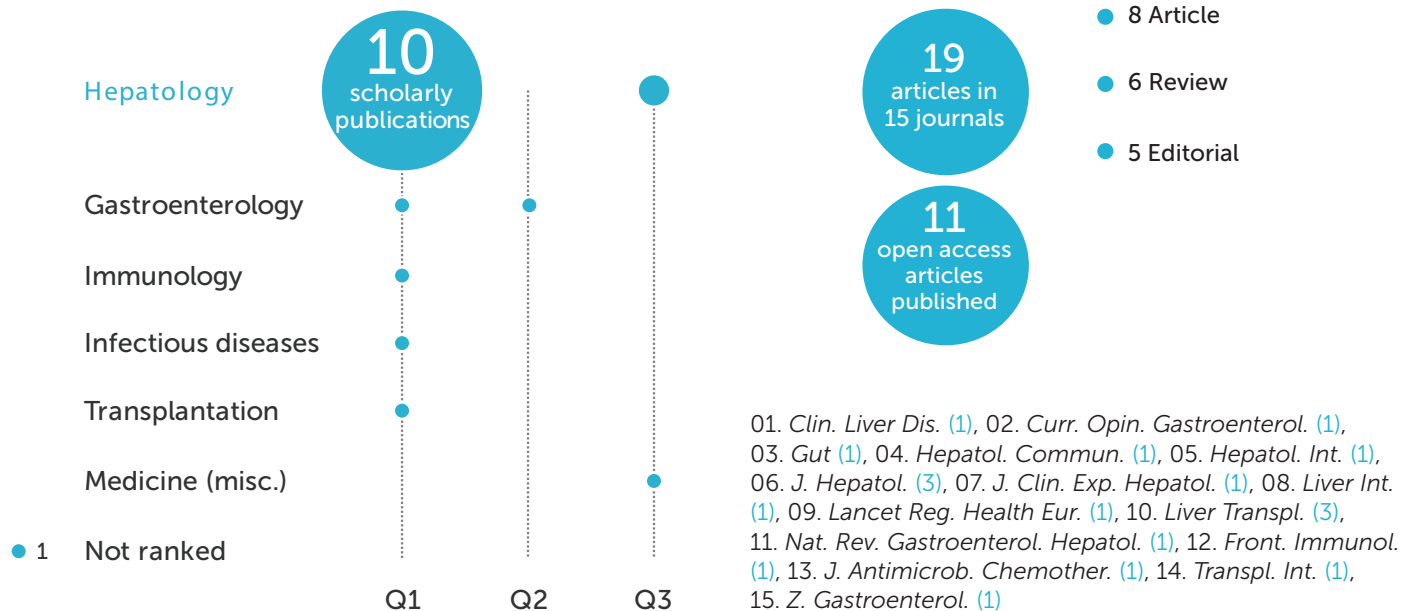
Media appearances

#

Liver transplantation for ACLF: Opportunities, challenges and pitfalls
EASL Studio Season 3, Episode 2
14 September 2022

EASL Studio on EASL–Home of Hepatology website, EASL Campus, YouTube

EASL Studio Podcast on Spotify, Apple Podcast, TuneIn, Podcastera

Scientific publications

SJR best quartile *

Hepatology — **10** scholarly publications

Gastroenterology

Immunology

Infectious diseases

Transplantation

Medicine (misc.)

1 — Not ranked

Q1   Q2   Q3

19 articles in 15 journals

- 8 Article
- 6 Review
- 5 Editorial

11 open access articles published

01. *Clin. Liver Dis.* (1), 02. *Curr. Opin. Gastroenterol.* (1), 03. *Gut* (1), 04. *Hepatol. Commun.* (1), 05. *Hepatol. Int.* (1), 06. *J. Hepatol.* (3), 07. *J. Clin. Exp. Hepatol.* (1), 08. *Liver Int.* (1), 09. *Lancet Reg. Health Eur.* (1), 10. *Liver Transpl.* (3), 11. *Nat. Rev. Gastroenterol. Hepatol.* (1), 12. *Front. Immunol.* (1), 13. *J. Antimicrob. Chemother.* (1), 14. *Transpl. Int.* (1), 15. *Z. Gastroenterol.* (1)

* 2021 SCImago Journal Ranking based on 2020 Scopus® data.
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Scientific presentations

7 oral presentations at 7 events

01. 1º Curso: Tópicos selectos en Hepatología (Hepatología Selecta, online) (1), 02. The Liver Meeting 2022 (AASLD, Washington D.C., USA) (1), 03. International Liver Congress 2022 (EASL, London, UK) (1), Symposium 227 (Falk Foundation, online) (1), 04. Journées de Gastroentérologie et d'Hépatologie, EPU de l'Université de Paris Cité (Paris, France) (1), 05. Annual Meeting of the Hungarian Association of Gastroenterology (MGT, Siofok, Hungary) (1), 06. XXVII Congreso de la Asociación Latinoamericana para el Estudio del Hígado (ALEH, Buenos Aires, Argentina) (1)

8 poster presentations at 4 events

01. International Liver Congress 2022 (EASL, London, UK) (1), 02. The Liver Meeting 2022 (AASLD, Washington D.C., USA) (3), 03. XXXI Congrés de la Societat Catalana de Digestologia (Societat Catalana de Digestologia, Girona, Spain) (2), 04. 47º Congreso anual de la Asociación Española para el Estudio del Hígado (AEEH, Madrid, Spain) (2)

RESEARCH OUTPUT

List of scientific publications

Cirrhosis-associated immune dysfunction
Albillos A, Martin-Mateos R, Van der Merwe S, Wiest R, Jalan R, Álvarez-Mon M. *Nat Rev Gastroenterol Hepatol*. 2022 Feb;19(2):112-134. DOI: 10.1038/s41575-021-00520-7. Epub 2021 Oct 26.

Causes of variability in listing and access to liver transplantation for critically ill patients with cirrhosis: Acknowledging the elephant in the room
Artzner T, Belli L, Faitot F, Jalan R. *Liver Transpl*. 2022 Dec;28(12):1953-1954. DOI: 10.1002/lt.26559. Epub 2022 Sep 5.

Location and allocation: Inequity of access to liver transplantation for patients with severe acute-on-chronic liver failure in Europe
Artzner T, Bernal W, Belli LS, Conti S, Cortesi PA, Sacleux SC, Pageaux GP, Radenne S, Trebicka J, Fernandez J, Perricone G, Piano S, Nadalin S, Morelli MC, Martini S, Polak WG, Zieniewicz K, Toso C, Berenguer M, Iegri C, Invernizzi F, Volpes R, Karam V, Adam R, Faitot F, Rabinowich L, Saliba F, Meunier L, Lesurtel M, Uschner FE, Michard B, Coilly A, Meszaros M, Poinsot D, Besch C, Schnitzbauer A, De Carlis LG, Fumagalli R, Angeli P, Arroyo V, Fondevila C, Duvoux C, Jalan R; ELITA/EF-CLIF Working Group. *Liver Transpl*. 2022 Sep;28(9):1429-1440. DOI: 10.1002/lt.26499. Epub 2022 Jun 16.

Alcohol and acute-on-chronic liver failure
Open Access
Ballester MP, Sittner R, Jalan R. *J Clin Exp Hepatol*. 2022 Sep-Oct;12(5):1360-1370. DOI: 10.1016/j.jceh.2021.12.010. Epub 2021 Dec 22.

Tigecycline population pharmacokinetics in critically ill patients with decompensated cirrhosis and severe infections
Bastida C, Hernández-Tejero M, Cariqueo M, Aziz F, Fortuna V, Sanz M, Brunet M, Fernández J, Soy D. *J Antimicrob Chemother*. 2022 Apr 27;77(5):1365-1371. DOI: 10.1093/jac/dkac036.

Albumin lipidomics reveals meaningful compositional changes in advanced cirrhosis and its potential to promote inflammation resolution
Open Access
Casulleras M, Flores-Costa R, Duran-Güell M, Zhang IW, López-Vicario C, Curto A, Fernández J, Arroyo V, Clària J. *Hepatol Commun*. 2022 Jun;6(6):1443-1456. DOI: 10.1002/hep4.1893. Epub 2022 Feb 18

Trends and the course of liver cirrhosis and its complications in Germany: Nationwide population-based study (2005 to 2018)
Open Access
Gu W, Hortlik H, Erasmus HP, Schaaf L, Zeleke Y, Uschner FE, Ferstl P, Schulz M, Peiffer KH, Queck A, Sauerbruch T, Brol MJ, Rohde G, Sanchez C, Moreau R, Arroyo V, Zeuzem S, Welsch C, Trebicka J. *Lancet Reg Health Eur*. 2021 Nov 4;12:100240. DOI: 10.1016/j.lanepe.2021.100240. eCollection 2022 Jan.

Impact of COVID-19 on the liver and on the care of patients with chronic liver disease, hepatobiliary cancer, and liver transplantation: An updated EASL position paper
Marjot T, Eberhardt CS, Boettler T, Belli LS, Berenguer M, Buti M, Jalan R, Mondelli MU, Moreau R, Shouval D, Berg T, Cornberg M. *J Hepatol*. 2022 Oct;77(4):1161-1197. DOI: 10.1016/j.jhep.2022.07.008. Epub 2022 Jul 20.

Rectal colonization by resistant bacteria increases the risk of infection by the colonizing strain in critically ill patients with cirrhosis
Open Access
Prado V, Hernández-Tejero M, Mücke MM, Marco F, Gu W, Amoros A, Toapanta D, Reverter E, Peña-Ramirez C, Altenpeter L, Bassegoda O, Mezzano G, Aziz F, Juanola A, Rodríguez-Tajes S, Chamorro V, López D, Reyes M, Hogardt M, Kempf VAJ, Ferstl PG, Zeuzem S, Martínez JA, Vila J, Arroyo V, Trebicka J, Fernandez J. *J Hepatol*. 2022 May;76(5):1079-1089. DOI: 10.1016/j.jhep.2021.12.042. Epub 2022 Jan 22.

Liver transplantation in acute-on-chronic liver failure grade 3: Fifty shades of gray
Putignano A, Gustot T. *Liver Transpl*. 2022 Jun;28(6):933-935. DOI: 10.1002/lt.26440. Epub 2022 Mar 13.

Transplantation in acute-on-chronic liver failure: Feasibility and futility
Open Access
Queck A, Weiler N, Trebicka J. *Clin Liver Dis* (Hoboken). 2022 May 20;19(5):191-193. DOI: 10.1002/cld.1195. eCollection 2022 May.

Reduced plasma extracellular vesicle CD5L content in patients with acute-on-chronic liver failure: Interplay with specialized pro-resolving lipid mediators
Open Access
Sánchez-Rodríguez MB, Téllez É, Casulleras M, Borràs FE, Arroyo V, Clària J, Sarrias MR. *Front Immunol*. 2022 Mar 7;13:842996. DOI: 10.3389/fimmu.2022.842996. eCollection 2022.

Liver transplantation as a cornerstone treatment for acute-on-chronic liver failure
Open Access
Schulz MS, Gu W, Schnitzbauer AA, Trebicka J. *Transpl Int*. 2022 Mar 17;35:10108. DOI: 10.3389/ti.2022.10108. eCollection 2022.

Acute-on-chronic liver failure: A global disease
Open Access
Schulz M, Trebicka J. *Gut*. 2022 Jan;71(1):5-6. DOI: 10.1136/gutjnl-2020-323973. Epub 2021 Feb 25.

Impact of compensated cirrhosis on survival in patients with acute-on-chronic liver failure
Open Access

Thanapirom K, Teerasarntipan T, Treeprasertsuk S, Choudhury A, Sahu MK, Maiwall R, Pamecha V, Moreau R, Al Mahtab M, Chawla YK, Devarbhavi H, Yu C, Ning Q, Amarapurkar D, Eapen CE, Hamid SS, Butt AS, Kim DJ, Lee GH, Sood A, Lesmana LA, Abbas Z, Shiha G, Payawal DA, Yuen MF, Chan A, Lau G, Jia J, Rahman S, Sharma BC, Yokosuka O, Sarin SK; APASL ACLF Working Party. *Hepatol Int*. 2022 Feb;16(1):171-182. DOI: 10.1007/s12072-021-10266-8. Epub 2021 Nov 25.

Using machine learning for predicting outcomes in ACLF
Open Access

Tonon M, Moreau R. *Liver Int*. 2022 Nov;42(11):2354-2355. DOI: 10.1111/liv.15399.

Role of albumin in the treatment of decompensated liver cirrhosis

Trebicka J. *Curr Opin Gastroenterol*. 2022 May 1;38(3):200-205. DOI: 10.1097/MOG.0000000000000838. Epub 2022 Mar 11.

Severe alcoholic hepatitis as precipitant for organ failure and ACLF

Trebicka J, Louvet A, Arroyo V, Jalan R, Shah VH, Moreau R. Z *Gastroenterol*. 2022 Jan;60(1):67-76. DOI: 10.1055/a-1713-3796. Epub 2022 Jan 18.

Mitochondrial dysfunction governs immunometabolism in leukocytes of patients with acute-on-chronic liver failure
Open Access

Zhang IW, Curto A, López-Vicario C, Casulleras M, Duran-Güell M, Flores-Costa R, Colsch B, Aguilar F, Aransay AM, Lozano JJ, Hernández-Tejero M, Toapanta D, Fernández J, Arroyo V, Clària J. *J Hepatol*. 2022 Jan;76(1):93-106. DOI: 10.1016/j.jhep.2021.08.009. Epub 2021 Aug 25.

List of scientific presentations

Tratamiento del ACLF: Terapia base y posible focos terapéuticos
Webinar

Arroyo, V. 1º Curso: Topicos selectos en Hepatología. Hepatología Selecta. 27 October 2022, this event was held online.

El análisis lipidómico de la molécula de albumina de pacientes con cirrosis hepática identifica importantes alteraciones en su composición lipídica y una menor abundancia de mediadores pro-resolutivos
Poster

Casulleras M, Flores-Costa R, Duran-Güell M, Zhang IW, López-Vicario C, Curto A, Fernández J, Arroyo V, Clària J. In Book of Abstracts: *47º Congreso Anual de la Asociación Española para el Estudio del Hígado (AEEH)*, 25–27 May 2022, Madrid, Spain.

Targeted lipidomics identifies a characteristic lipid mediator signature in patients with acutely decompensated cirrhosis
Poster

Contreras B, López-Vicario C, Casulleras M, Duran-Güell M, Flores-Costa R, Sanchéz-Rodríguez MB, Zhang IW, Clària J. In Book of Abstracts: *XXXI Congrés de la Societat Catalana de Digestologia*, 2–4 June 2022, Girona, Spain.

Albumin preserves hepatocyte mitochondria from cytokine-induced damage through the common stress responsive transcription factor ATF3
Poster

Duran-Güell M, Garrabou G, Flores-Costa R, Casulleras M, López-Vicario C, Zhang IW, Sánchez B, Contreras BJ, Romero-Grimaldo B, Horrillo R, Costa M, Arroyo V, Clària J. In Book of Abstracts: *The Liver Meeting 2022*, 4–8 November 2022, Washington D.C., USA.

Management of sepsis in ACLF
Lecture

Fernández, J. In Book of Abstracts: *The Liver Meeting 2022*, 4 November 2022, Washington D.C., USA.

La inducción de peritonitis polimicrobiana en modelos murinos de cirrosis descompensada reproduce los fallos orgánicos extrahepáticos que definen el desarrollo de ACLF
Poster

Flores-Costa R, Contreras BJ, Salvatella A, Duran-Güell M, Casulleras M, Kraus N, Klein S, López-Vicario C, Zhang IW, Díaz A, Rautou PE, Fernández J, Trebicka J, Arroyo V, Clària J. In Book of Abstracts: *47º Congreso Anual de la Asociación Española para el Estudio del Hígado (AEEH)*, 25–27 May 2022, Madrid, Spain.

Albumin glyco-oxidation is increased in patients with decompensated cirrhosis and ascites
Poster

Horrillo R, Mestre A, Pérez A, Alcaraz E, Torres M, Arroyo V, Fernández J, Clària J, Costa M. In Book of Abstracts: *The Liver Meeting 2022*, 4–8 November 2022, Washington D.C., USA.

Plasma exchange with albumin increases effective albumin levels in patients with acute-on-chronic liver failure
Oral communication

Horrillo R, Mestre A, Pérez A, Vidal J, Alcaraz E, Torres M, Arroyo V, Fernández J, Clària J, Costa M. In Book of Abstracts: *XXVII Congreso de la Asociación Latinoamericana para el Estudio del Hígado (ALEH)*, 6–9 September 2022, Buenos Aires, Argentina.

Essential lipid autacoids rewire mitochondrial energy efficiency in metabolic dysfunction-associated fatty liver disease
Poster

López-Vicario C. In Book of Abstracts: *The Liver Meeting 2022*, 4–8 November 2022, Washington D.C., USA.

Systemic (mis)communication in severe alcoholic hepatitis
Lecture

Moreau, R. Symposium 227: Pathophysiology and Clinical Management of Alcoholic Hepatitis, Falk Foundation, 21 January 2022, this event was held online.

OUR APPROACH

Les études qui ont marqué 2020 et 2021
Lecture
Moreau, R. Journées de Gastroentérologie et d'Hépatologie, EPU de l'Université de Paris Cité, 30 April 2022, Paris, France.

Novel clinical and pathophysiological prospects defining the trajectory of cirrhosis
Lecture
Moreua, R. In Book of Abstracts: *Annual Meeting of the Hungarian Association of Gastroenterology (MGT)*, UEG-based session, 13 June 2022, Siofok, Hungary.

Clinical scenarios: Influence of underlying liver disease and precipitating events
Lecture
Moreau, R. In Book of Abstracts: *International Liver Congress 2022*, 25 June 2022, London, UK.

Reduced plasma extracellular vesicle CD5L content in patients with acute on-chronic liver failure: Interplay with specialized pro-resolving lípid mediators
Poster
Sánchez-Rodríguez MB, Téllez E, Casulleras M, Borràs FE, Arroyo V, Clària F, Sarrias MR. In Book of Abstracts: *XXXI Congrés de la Societat Catalana de Digestologia*, 2–4 June 2022, Girona, Spain.

Reduced plasma extracellular vesicle CD5L content in patients with acute-on-chronic liver failure: Interplay with specialized pro-resolving lipid mediators
Poster
Sánchez-Rodríguez MB, Téllez E, Casulleras M, Borras F, Arroyo V, Clària J, Sarrias MR. In Book of Abstracts: *International Liver Congress 2022*, 22–26 June 2022, London, UK.

Research environment

Inspiring and Writing Group

The Inspiring and Writing Group works across disciplines and brings together expertise in end-stage liver disease, liver transplantation, critical care, gut microbiome, hepatic vascular disorders, hepatic encephalopathy, acute kidney injury, and liver regeneration. Members of this working group contribute to the analysis of clinical and omics data from former EF CLIF studies and the conceptualization of new hypothesis that may lead to novel breakthrough discoveries.

Appointed members of the Inspiring and Writing Group:

Tony Bruns
University Hospital Aachen, Germany

Paolo Caraceli
University of Bologna, Italy

Andrea De Gottardi
Ente Ospedaliero Cantonale– Università della Svizzera Italiana, Switzerland

Cornelius Engelmann
Charité–Universitätsmedizin Berlin, Germany

Virginia Hernández-Gea
Hospital Clinic Barcelona, Spain

Wim Laleman
UZ Leuven, Belgium

Alexandre Louvet
Hôpital Claude Huriez, France

Mattias Mandorfer
Medical University of Vienna, Austria

Rosa Martín Mateos
Hospital Universitario Ramón y Cajal, Spain

Sara Montagnese
University of Padova, Italy

Raj Mookerjee
University College London, Royal Free Hospital, UK

Alastair O'Brien
University College London, Royal Free Hospital, UK

Pierre-Emmanuel Rautou
APHP Hôpital Beaujon, France

Debbie L. Shawcross
Institute of Liver Studies, Kings College Hospital, UK

Vanessa Stadlbauer
Medical University of Graz, Austria

Dominique Thabut
Hôpital Pitié-Salpêtrière, France

Eric Trépo
CUB Hôpital Erasme–Université Libre de Bruxelles, Belgium

Thierry Gustot
Chair
CUB Hôpital Erasme, Belgium

Salvatore Piano
Secretary
University of Padova, Italy

Regional Coordinators

Our growing network of regionally based research coordinators is helping us to conduct large, global-scale investigations to further our understanding of the epidemiology and pathophysiology of chronic liver disease. Our Global Projects chapter is better supporting our collaborators across different geographical regions and improving communication within each of the regions. With the launch of the CHANCE study, we have been able to continue expanding our global research network. To support research activities within CHANCE, we have appointed 15 Regional Coordinators each of which oversee activities within their region.

Regional Coordinators in North America, Latin America, Europe, Asia and Oceania, help us to engage and provide support to the teams across their area. Overseeing ethical and legal approval processes and patient recruitment, Regional Coordinators are able to ensure effective coordination and communication of all relevant research activities and events related to the CHANCE study.

Appointed Regional Coordinators:

Luca Belli
Italy

Marina Berenguer
Spain

Susumu Eguchi
Japan

Laure Elkrief
France

Constantino Fondevila
Spain

Adrian Gadano
Argentina

Thierry Gustot
Belgium

Ruben Hernaez
United States of America

Constantine Karvellas
Canada

Geoffrey McCaughan
Australia

Silvio Nadalin
Germany

Wojciech Polak
The Netherlands

Mohamed Rela
India

KS Suh
Korea

Yaman Tokat
Turkey

Christian Toso
Switzerland

Rachel Westbrook
United Kingdom

Research infrastructure

Score calculators

We have developed evidence-based medical calculators for the diagnosis and prognosis of chronic liver disease.

CLIF-C AD score

The Chronic Liver Failure Consortium acute decompensation (CLIF-C AD) score predicts mortality at 1, 3, 6 and 12 months in hospitalized cirrhotic patients with acute decompensation without ACLF.

CLIF-C ACLF score

The Chronic Liver Failure Consortium acute-on-chronic liver failure (CLIF-C ACLF) score predicts mortality at 1, 3, 6 and 12 months in hospitalized cirrhotic patients with ACLF.

Data platforms

We make use of computing resources such as relational databases and cloud-based services to develop data collection and management systems to record, store and analyze clinical trial data. We are compliant with the General Data Protection Regulation (GDPR) and implement the highest standards to ensure data integrity across the clinical studies we sponsor and research projects we support.

Omics data

Since 2017, we have generated 15 Tb of transcriptomic data and 123 Gb of genomic data from more than 3100 patients and healthy subjects.

Clinical data

Through our electronic case report forms, we collect patient clinically relevant data including computed tomography scan images. Clinical data complements genomic data providing in-depth information about patients' management and disease progression.

Quality of life data

EQ-5D assessess self-reported health status of participants in our studies considering mobility, self-care, usual activities, pain/disconfort and anxiety/depression.

Electronic case report forms

Our custom-built electronic case report form (eCRF) platform provides a secure and private workspace for clinical researchers to capture and manage demographic and clinical data including laboratory reports, medications and adverse events during the course of ongoing patient care or as part of a clinical trial.

Data Hub

The EF CLIF Data Hub is a web-based environment where researchers can access omics and clinical data securely. When patients give consent to having blood and other tissue samples collected, processed, and analyzed as part of any of our large observational studies, genomic, transcriptomic, proteomic and/or metabolomic data is pseudoanonymized and stored along with any other data in our servers accessible through the EF CLIF Data Hub. Researchers who are granted access to the EF CLIF Data Hub can use the data we store to generate further knowledge that can lead to improve diagnosis, prognosis, and treatment of chronic liver disease.

Biobank

Biological samples including blood, urine and saliva, and solid tissue from liver biopsy are routinely collected throughout our observational studies and biobanked for a variety of omics applications.

We are users of the Biomat Biorepository and the Biobank at Hospital Clínic de Barcelona–Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) to store large prospective collections of biological specimens within our clinical trials. This scheme offers unique opportunities for researchers to use collected samples to answer specific research questions when funding is available to them to conduct further analyses. We facilitate validation of biomarkers to aid the development of therapeutics and clinical trial end points for chronic liver disease for the benefit of current and future patients.

Quality matters

RNA-sequencing (RNA-seq) is a high-sensitive method used for gene expression analysis. It allows for high-throuput screening of thousands to millions of biological samples to identify known and novel transcript features in a single assay. RNA-seq is a very powerful tool for transcriptome profiling in complex diseases such as chronic liver disease. Transcriptome analysis not only offers the possibility to better understand disease pathobiology, but also has the potential to improve clinical diagnosis, and when integrated with other types of molecular data, predict clinical outcomes and guide therapeutic decisions.

To ensure a successful RNA-seq experiment, RNA should be of sufficient quality to prepare a sequencing library. The quality of the initial samples is by far the most important factor for all subsequent steps in whole blood RNA-seq,

from template preparation to sequencing. The quality and stability of the RNA in blood samples is greatly influenced by the collection technique employed, sample storage conditions and processing. We at EF CLIF use Tempus™ blood collection tubes for stabilization and isolation of total RNA for whole blood gene expression analysis.

Patricia Sierra, one of our Data Managers, explains "The development and set up of the biobank logistics is key to retrieve human specimens with the required quality to carry out future research and guarantee that the data resulting from the analysis of these samples is comparable. The proper identification of biological samples ensures their treaceability from its collection and processing, to its storage and final use. A double registry system helps us capture all sample information – samples are physically registered on paper and

through the designated electronic case report form.

As data managers, we design protocols considering all and every specific aspects of the biobank logistics for each of our large, observational studies. Protocols on sample collection, processing, and storage are a valuable resource for investigators participating in these studies. The processing of Tempus™ blood collection tubes is simple but very efficient, so we are confident that the majority of these samples are comparable to one another."

Training is an integral part of the activities carried out by our staff at the Data Management Center. Investigators that collaborate in our large observational studies and agree to contribute with both clinical data and samples are required to complete training to learn how to collect, temporarily store and process samples according to our protocols.

Patricia adds: "We work to ensure that biological samples are collected, processed and stored under the same conditions in all participating centers. Cooperation is an essential requirement to achieve quality samples in any of our multicenter studies. I am very grateful to all the people at the participating centers involved in this process for their dedication, since biological samples provide an enormous added value to the clinical data although their importance is not always recognized."

The execution of large, global studies such as CHANCE comes with many additional challenges. Providing a continued supply of products to collaborating centers and ensuring a safe and secure transport of samples upon collection is critical for the success of the study, as Patricia explains: "Setting up the logistics for the CHANCE biobank has been a personal challenge due to the large number of biological samples to be collected, large number of participating centers and their geographical location. We had to solve all sorts of issues, such as material stoppages at customs or stock breaks from our suppliers. Thanks to the cooperation between our staff at the Data Management Center and the participating centers, we have been able to successfully overcome these unforseen circumstances. This highlights the vital importance of good communication and teamwork in this type of study."

Patricia concludes: "I want to stress how critical all this process is given the hard work of all the people involved in the life cycle of a biological sample, including handling and ultimate analysis. We all contribute our part to biomedical research."

OUR STAFF

RESEARCHERS

Vicente Arroyo
Director and Principal Investigator

Rajiv Jalan
Principal Investigator

Joan Clària
Principal Investigator

Richard Moreau
Principal Investigator

Javier Fernández
Principal Investigator

Jonel Trebicka
Principal Investigator

Juan Manuel Díaz
EF CLIF Research Scholar

DATA MANAGEMENT CENTER

Cristina Sánchez-Garrido
Head of the Data Management Center

Pedro Izquierdo-Bueno
CIO/CTO

Ferran Aguilar
Bioinformatician

Anna Curto Vilalta
Bioinformatician

Montserrat Pujadas
Data Manager

Patricia Sierra
Data Manager

Carlos de la Peña
Statistician

Eva Usón
Statistician

ADMINISTRATION

Anna Bosch
General Manager

Cecilia Ducco
Administrative Assistant

Lidia Garcia-Campmany
Scientific Communications Manager

Yolanda Godoy
Scientific Assistant

STRUCTURE & MANAGEMENT

Corporate governance

The Foundation has a public duty to conduct its affairs in a transparent manner and to meet the regulatory requirements of relevant authority bodies. The Foundation's Statements require the existence of three separate bodies: Board of Trustees, Executive Scientific Committee, and the Scientific Advisory Board, each with clearly defined functions and responsibilities, to oversee and manage the Foundation's activities.

Board of Trustees
In accordance with the Foundation's Statements, the Board of Trustees exerts its roles of governance and management as a representative body of the Foundation. The Board of Trustees is responsible for ensuring that the Foundation's goals are fulfilled, and for duly administrating the goods and rights that are drawn by of the Foundation to guarantee the maintenance of the Foundations' resources and their use. The Board of Trustees is required to approve an audited financial statement for each financial year.

Vicente Arroyo
President of the Board of Trustees
Director of EF CLIF, Spain

Mauro Bernardi
Emeritus Professor of Internal Medicine at University of Bologna, Italy

Antonio Páez
Vice-President of Scientific and Medical Affairs, Scientific Innovations Office at Grifols, Spain

Ignasi Bruguer
Lawyer at Osborne Clarke, Spain, joined in January 2023

Changes to Board of Trustees in this financial year:
Ignacio Calero, Lawyer at Osborne Clarke, Spain, passed away in October 2022

Trustee biographies are available at **efclif.com**

Executive Scientific Committee
The Executive Scientific Committee is composed by the Chair and the Vice-Chair of the EASL-CLIF Consortium Steering Committee, the Chair of the Scientific Advisory Board, the Director of the Grifols Chair, the Head of Clinical Operations, the General Manager of EF CLIF, the Scientific Director of EF CLIF, and the EF CLIF Director. The Executive Scientific Committee liaises with the Scientific Advisory Board to discuss any matters concerning the annual research program, publication policy, and strategic planning. The Executive Scientific Committee reports to the Board of Trustees on annual basis.

Scientific Advisory Board
The Scientific Advisory Board is a consultancy body whose main mission is to convey its opinion about the operational activities of the Foundation, its annual research plan, the publication policy and other strategic issues regarding the Foundation's development to the Executive Scientific Committee.

Jean-Charles Nault
Hôpital Avicenne, France
Cordeliers Research Center, University of Paris, INSERM UMR 1138, France

Luca Valenti
University of Milan, Italy

Frank Tacke
Charité−Universitätsmedizin Berlin, Germany

Sophie Lotersztain
Center for Research in Inflammation, University of Paris, INSERM U1149, France

Eric Trépo
CUB Hôpital Erasme−Université Libre de Bruxelles, Belgium

Paolo Caraceni
University of Bologna, Italy

Mala K. Maini
University College London, UK

José María Mato
CICbioGUNE, Spain

Tom Hemming Karlsen
University of Oslo, Norway

Helena Cortez-Pinto
University of Lisbon, Portugal

Jessica Zucman-Rossi
Cordeliers Research Center, University of Paris, INSERM UMR 1138, France

Guliana Magri
Hospital del Mar Research Institute, Spain

Richard Moreau
Chair
European Foundation for the Study of Chronic Liver Failure, Spain

Jonel Trebicka
Secretary
European Foundation for the Study of Chronic Liver Failure, Spain

Chair and Secretary biographies are available at **efclif.com**

Management Committees

Executive Team
The Executive Team is responsible for the overall management of the Foundation and for the leadership of its staff and partners. It works to deliver on the strategic plan for ongoing studies and projects and is responsible for the financial sustainability of the Foundation.

Vicente Arroyo
Director

Anna Bosch
General Manager

Rajiv Jalan
Scientific Director

Joan Clària
Director of the Grifols Chair and Head of Translational Operations

Javier Fernández
Head of Clinical Operations

Cristina Sánchez-Garrido
Head of the Data Management Center

Executive Team biographies are available at **efclif.com**

Sample and Data Usage Committee

The Sample and Data Usage Committee reviews newly submitted project proposals in order to analyze its alignment with the aim of the project which originated the sample or data collection requested, its technical/ethical viability, and its potential scientific impact. The Sample and Data Usage Committee is composed by the Head of Translational Operations, the Head of Clinical Operations, the Head of the Data Management Center, the Scientific Director of EF CLIF, the General Manager of EF CLIF and the EF CLIF Director. The Principal Investigator(s) of the project(s) samples and data are requested from also contribute to the evaluation and decision making process of granting access to samples and datasets of interest available in the EF CLIF databases.

EASL-CLIF Consortium Steering Committee

The EASL-CLIF Consortium Steering Committee oversees the research activities carried out by the EAS-CLIF Consortium.

Paolo Angeli
Chair
University of Padova, Italy

Thierry Gustot
Vice-Chair
CUB Hôpital Erasme, Belgium

Agustin Albillos
Hospital Universitario Ramón y Cajal, Spain

Carlo Alessandria
Città della Salute e della Scienza di Torino−Presidio Molinette, Italy

William Bernal
King's College Hospital, UK

Paolo Caraceni
University of Bologna, Italy

Christophe Duvoux
Hôpital Henri-Mondor, France

Javier Fernández
Hospital Clínic de Barcelona, Spain

Wim Laleman
UZ Leuven, Belgium

Lise Lotte Gluud
Copenhagen University Hospital Hvidovre, Denmark

Raj Mookerjee
Royal Free Hospital, UK

Mária Papp
University of Debrecen, Hungary

Pierre-Emmanuel Rautou
Hôpital Beaujon, France

Thomas Reiberger
Medical University of Vienna, Austria

Cristina Sánchez-Garrido
European Foundation for the Study of Chronic Liver Failure, Spain

Christian Trautwein
University Hospital Aachen, Germany

Jonel Trebicka
University Hospital Münster, Germany

Chair and Vice-Chair biographies are available at **efclif.com**

Grifols Chair Directorate

The Grifols Chair Directorate oversees the research activities carried out by the European Network for Translational Research.

Richard Moreau
Honorary Director
European Foundation for the Study of Chronic Liver Failure, Spain

Joan Clària
Director
Hospital Clínic de Barcelona-IDIBAPS, Spain
European Foundation for the Study of Chronic Liver Failure, Spain

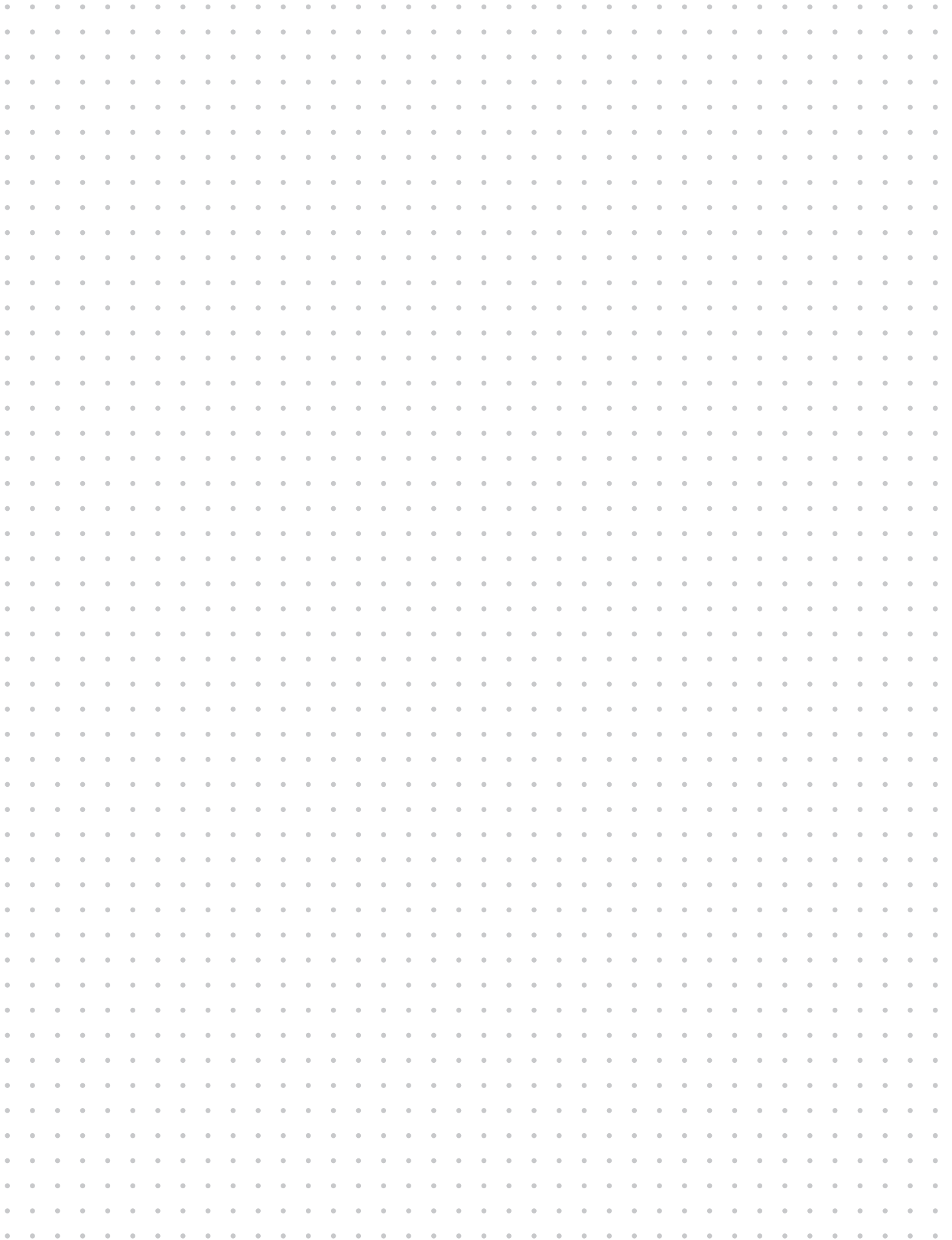Grifols Chair Directorate biographies are available at **efclif.com**

EF CLIF

EUROPEAN FOUNDATION
FOR THE STUDY OF
CHRONIC LIVER FAILURE

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