EF Clif

EUROPEAN
FOUNDATION
FOR THE STUDY
OF CHRONIC
LIVER FAILURE

SUMMARY OF ACTIVITIES

2019

EF Clif

EUROPEAN
FOUNDATION
FOR THE STUDY
OF CHRONIC
LIVER FAILURE

EF Clif

EUROPEAN
FOUNDATION
FOR THE STUDY
OF CHRONIC
LIVER FAILURE

Published by

EF Clif
Travessera de Gràcia, 11, 7th floor
08021 Barcelona (Spain)

Art Direction
marcmontala.com

SUMMARY OF ACTIVITIES

2019

CONTENTS

Letter of the Chairman

1 The burden of cirrhosis in healthcare worldwide

2 Mission, vision and values

3 Our organisation

4 Board of trustees

5 Research at the EF Clif

5.1. The EASL Chair

5.1.1. The EASL-Clif Consortium hospital network and associated investigators.

5.1.2. Consortium projects.

5.2. The Grifols Chair

5.2.1. The European Network of Translational Research and associated investigators.

5.3. Global projects

5.3.1. The Latin American Clif Consortium and associated investigators.

6 Our staff

7 Facts and figures

7.1. Patient cohorts in the EF Clif studies

8 2019 in images

9 Progress report

10 Scientific publications

LETTER OF THE CHAIRMAN

In addition to the publication of excellent articles derived from its regular scientific production, the EF Clif has been very active during 2019 in other relevant aspects.

The database of the Predict study, the second large-scale observational investigation supported by the EF Clif, was completed. This is a complex process consisting in deep revision of the database by the medical staff, biostatisticians and data managers, thousands of queries to the investigators, and revision and re-revisions of hundreds of clinical reports by the participating hospitals. Completion of the data base permitted European investigators to start the 6-year EU Horizon 2020 "Microb-Predict" project, led by Jonel Trebicka (Frankfort) and by the EF Clif as coordinator centre, assessing the role of microbiota on the pathogenesis and prognosis of acute decompensation and ACLF, and to start also the design of the second EU Horizon 2020 EU "Decision" project of the EF Clif led by Pierre Emmanuel Ratou (Paris).

The Aclara study, which is being performed in 48 Latin American hospitals, is almost finished. The aim of this study is to ascertain the prevalence of ACLF in this continent and its potential relationship with ethnicity. At present, there are more than 1200 patients enrolled. Enrolment was completed in Brazil in November 2019 and will finalize in Argentina, Chile, Paraguay, Peru, Colombia and Mexico in June 2020.

In 2019 we also initiated a new and exciting project. In collaboration with the European Liver and Intestine Transplant Association (ELITA) and the International Liver Transplantation Society (ILTS), we started the design of an ambitious large-scale observational study on liver transplantation in patients with ACLF.

Members of these two prestigious scientific societies and of the EASL-CLIF Consortium are currently elaborating the project and selecting centres from Europe, Asia and North- and South America. We expect to enrol the first patient within the last trimester of 2020 and finish the study in 2023.

The experience of the EF Clif in the designing and conducting large-scale international observational studies, in the handling of biological samples and in the elaboration of complex articles using big data, has rose the interest of young investigators and other research personnel to get experience in these aspects. With the collaboration of Cellex Foundation (Barcelona), we therefore initiated a program to support this activity three years ago. Currently, three research fellows from Bologna, Paris and Buenos Aires are working in Barcelona on projects derived from the Predict and Aclara studies. We are most grateful to Cellex Fundation for its support.

In September 2019, the Second Scientific Meeting of the EF Clif was developed in Venice under the Presidency of Prof. Paolo Angeli. More than 100 investigators attended the meeting, and they gave proofs to form a cohesive group of researchers, aware of being involved in a transcendent adventure.

Finally, the EF Clif has recently published a call for the position of Scientific Director. His (her) mission is to lead the EF Clif Scientific Committee and, together with the Chairman of the EASL-CLIF Consortium, the Director of the Grifols Chair and the General Manager of EF Clif, to elaborate and control the development of its annual Research Program. This call is the result of the continuous consolidation process of the Foundation.

Vicente Arroyo

1

THE BURDEN OF CIRRHOSIS IN HEALTHCARE WORLDWIDE

According to the latest data, published in January 2020, liver disease accounts for approximately 2 million deaths per year worldwide. From these, more than 1.3 million are due to cirrhosis decompensation, i.e. development of ascites, hepatic encephalopathy and/or gastrointestinal haemorrhage, and its progression to Acute on Chronic Liver Failure (ACLF), and the rest are due to viral hepatitis and hepatocellular carcinoma. Cirrhosis is currently the 11th most common cause of death globally and liver cancer is the 16th leading cause of death; combined, they account for 3.5% of all deaths worldwide.

The high short-term mortality of patients with acute decompensation of cirrhosis, despite the numerous therapies they currently receive as standard of care, is caused by the incomplete understanding of the pathophysiology of this disease and the fact that patients' heterogeneity is not taken into account for individual patient management.

Thus, a strong Research Program focused on cirrhosis and its complications and treatment is crucial to improve the quality of life of patients affected by this disease and to reduce its associated mortality.

Studies led by the Grifols Chair and the EASL-CLIF Consortium already completed and published or in the process of being published have revealed new mechanisms that help to understand the pathophysiology of acute decompensation of cirrhosis and the development of the ACLF syndrome, the therapeutic effects of albumin, and some of the pathophysiological processes that are ameliorated by this molecule.

2

MISSION, VISION AND VALUES

MISSION

The EF Clif is intended to support high quality research and education on Acute-on-Chronic Liver Failure (ACLF), in order to improve the quality of life and to increase the survival of patients with liver cirrhosis.

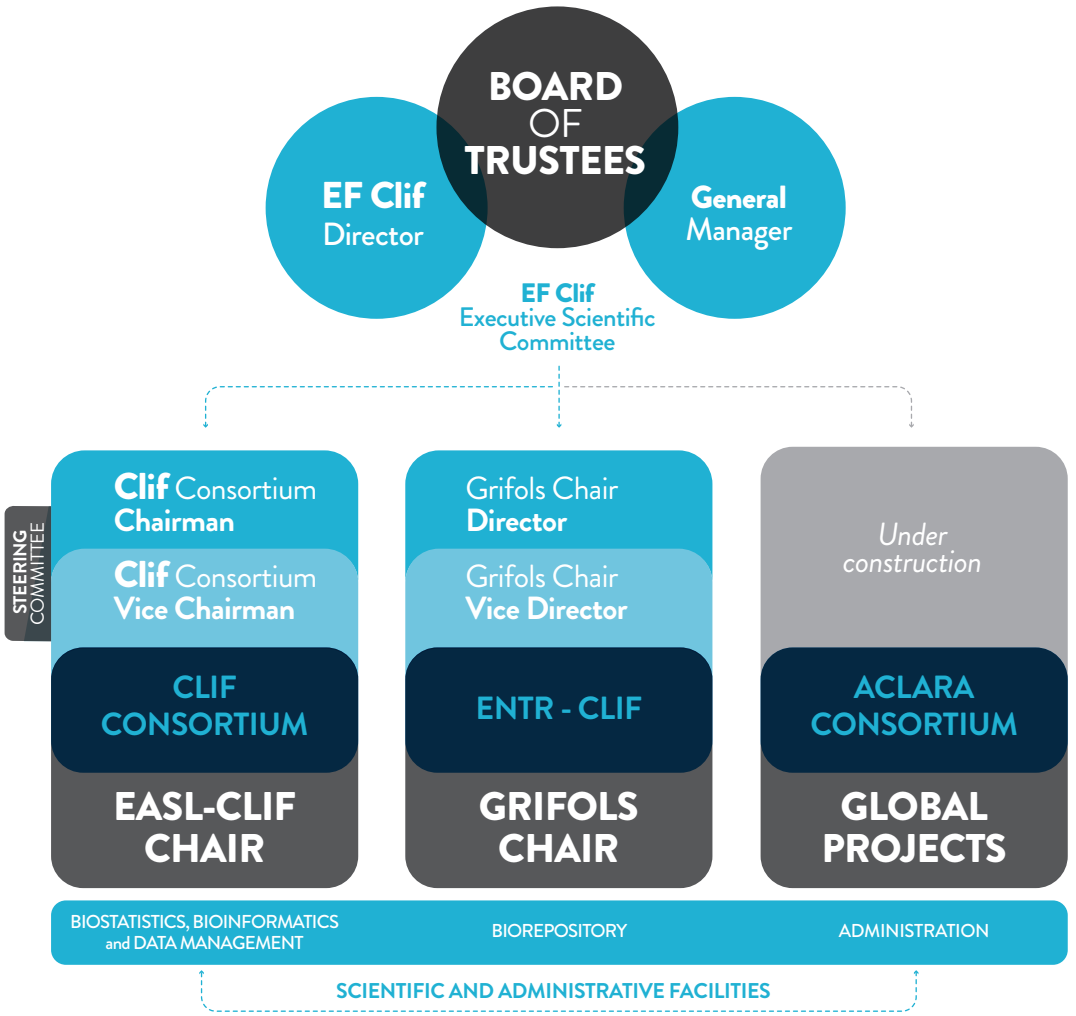
VISION

Our aim is helping investigators to achieve their objectives and being a referent in ACLF research, in order to increase survival of patients with liver cirrhosis and improve their quality of life.

SERVICE	EDUCATION	WELFARE
INNOVATION	COMPROMISE	DYNAMISM
HEALTH	QUALITY OF LIFE	TRANSPARENCY
RESEARCH	DEDICATION	COMMITMENT
UNITY	ACCURACY	INDEPENDENCE

3

OUR **ORGANISATION**



4

BOARD OF TRUSTEES

VICENTE **ARROYO**
M.D.

- Emeritus Professor of Medicine, University of Barcelona Medical School, Spain.
- Director of the EF Clif.
- Recognition Award. European Association for the Study of the Liver.

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

MAURO **BERNARDI**
M.D.

- Professor of Internal Medicine at Bologna University, Italy.
- Director, Postgraduate School in Internal Medicine.
- Distinguished Service Award, Italian Association for the Study of the Liver.

Main research interest
Cirrhosis and related complications, hepatocellular carcicoma, chronic viral hepatitis, liver transplantation clinical aspects and treatment of alcoholism.

ANTONI **PÁEZ**
M.D. B. Sc.

- Director, Medical & Technical Department. Grifols Bioscience Industrial Group.
- Graduated in Medicine and Surgery from the Autonomous University of Barcelona.
- Graduated in Physical Science. Open University (United Kingdom).

Main research interest
New functions of plasma proteins.

IGNACIO **CALERO**
Lawyer

- Lawyer at Osborne Clarke.
- Graduated in Law from the Autonomous University of Madrid.
- Master's Degree in Corporate Legal Advice from the Instituto de Empresa Business School (Madrid, 2003).

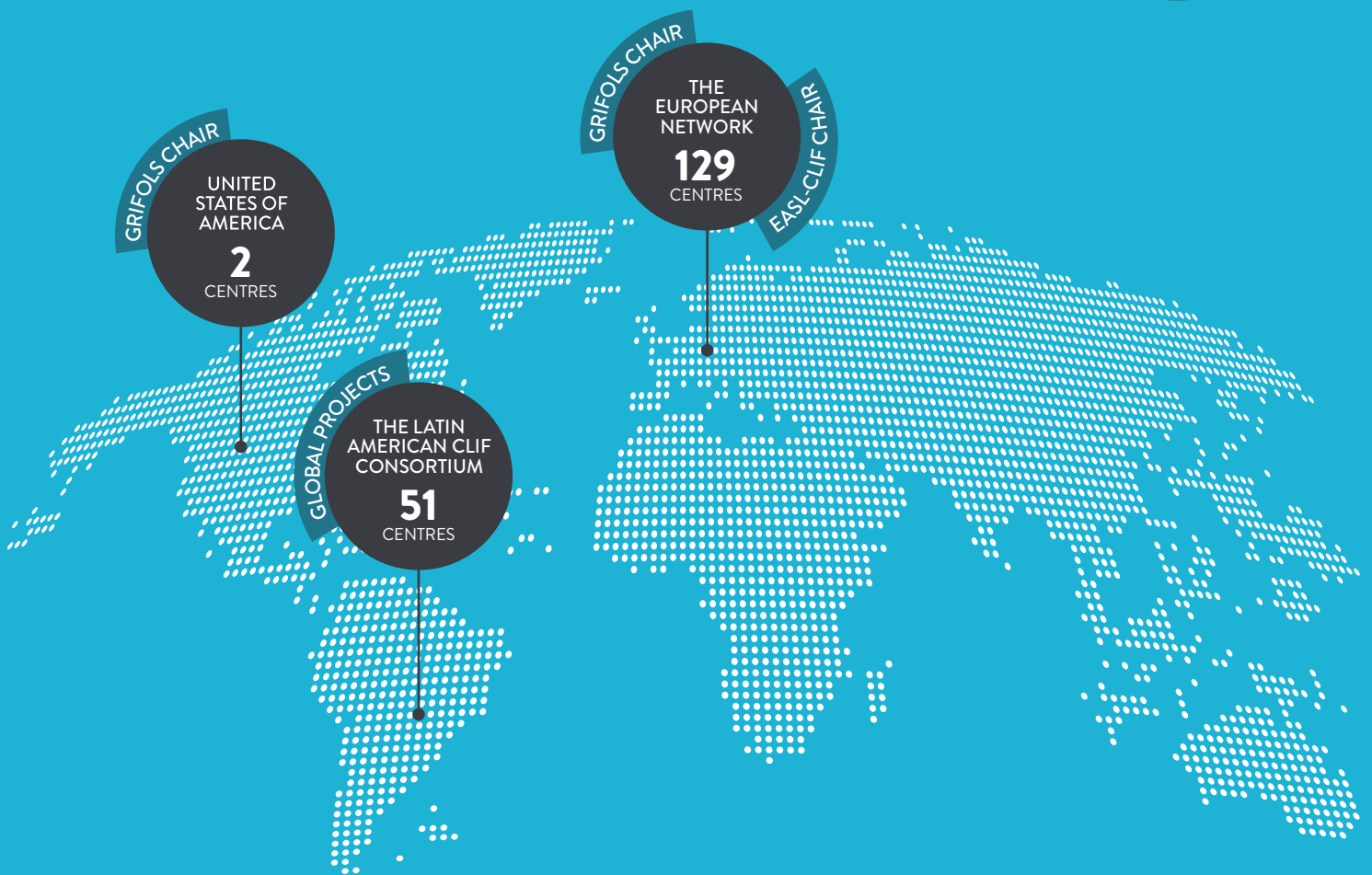
Main interests
He is focused in Company Law, Competition and Industrial Property.

5

RESEARCH **AT THE EF Clif**

The **EF Clif Research Program** is successfully performed, due to the excellent network of collaborators located around the world.

182 CENTRES



106

THE EASL-CLIF CHAIR

THE EASL-CLIF CONSORTIUM HOSPITAL NETWORK

(see page 15)

- 4 AUSTRIA
- 4 BELGIUM
- 1 CROATIA
- 1 CZECH REPUBLIC
- 5 DENMARK
- 1 ESTONIA
- 13 FRANCE
- 1 GEORGIA
- 18 GERMANY
- 1 HUNGARY
- 1 ICELAND
- 1 IRELAND
- 10 ITALY
- 1 LATVIA
- 2 LITHUANIA
- 2 THE NETHERLANDS
- 1 NORWAY
- 2 POLAND
- 4 PORTUGAL
- 2 SLOVAK REPUBLIC
- 10 SPAIN
- 2 SWEDEN
- 6 SWITZERLAND
- 3 TURKEY
- 1 UKRAINE
- 9 UNITED KINGDOM

25

THE GRIFOLS CHAIR

THE EUROPEAN NETWORK OF TRANSLATIONAL RESEARCH

(see page 25)

- 6 FRANCE
- 2 GERMANY
- 11 SPAIN
- 1 SWEDEN
- 1 THE NETHERLANDS
- 2 UNITED KINGDOM
- 2 USA

51

GLOBAL PROJECTS

THE LATIN AMERICAN CLIF CONSORTIUM

(see page 26)

- 6 ARGENTINA
- 18 BRAZIL
- 7 CHILE
- 3 COLOMBIA
- 11 MEXICO
- 1 PANAMA
- 1 PARAGUAY
- 5 PERU

5.1

THE EASL-CLIF CHAIR

The scientific activities of the network of hospitals organized in the setting of the EASL-CLIF Chair are performed under the direction of a Chairman and a Vice-Chairman and of a Clif Consortium Steering Committee of 17 additional members. During the **EASL International Liver Congress** held in April 2019 in Vienna, the EASL-CLIF Clif Consortium Steering Committee met to renew itself with **17 members**.

Name	Site	City	Country
Agustin Albillos	Hospital Universitario Ramon y Cajal	Madrid	Spain
Carlo Alessandria	San Giovanni Battista Hospital-University of Turin	Torino	Italy
Paolo Angeli	University of Padova	Padova	Italy
William Bernal	King's College Hospital	London	United Kingdom
Paolo Caraceni	Policlinico S Orsola-Malpighi	Bologna	Italy
Christophe Duvoux	Henri Mondor University Hospital	Créteil	France
Javier Fernández	Hospital Clínic	Barcelona	Spain
Thierry Gustot	Erasme University Hospital	Bruxelles	Belgium
Wim Laleman	Gasthuisberg University Hospital	Leuven	Belgium
Lise Lotte Gluud	Copenhagen University Hospital Hvidovre	Copenhagen	Denmark
Raj Mookerjee	Royal Free Hospital	London	United Kingdom
Mária Papp	University of Debrecen	Debrecen	Hungary
Marco Pavesi	EF Clif	Barcelona	Spain
Pierre Emmanuel Rautou	Hôpital Beaujon	Clichy	France
Thomas Reinberger	AKH University Hospital	Wien	Austria
Christian Trautwein	Aachen University Hospital	Aachen	Germany
Jonel Trebicka	JW Goethe University Hospital	Frankfurt	Germany

5.1.1

THE **EASL-CLIF CONSORTIUM HOSPITAL NETWORK** AND ASSOCIATED INVESTIGATORS

CENTRES BY **COUNTRY**

01. AUSTRIA

MEDICAL UNIVERSITY OF GRAZ
Rudolf Stauber
Vanesa Stadlbauer
Karl Oettl

TIROL KLINIKEN, ACAD. TEACHING HOSPITAL HALLINTERNAL MEDICINE
Heinz Zoller
Klemens Zotter
Markus Niederreiter
Maria Effengerger

KLAGENFURT AM WÖRTHESEE HOSPITAL
Markus Peck Radosavljevic
Simona Bota
Florian Hucke

MEDICAL UNIVERSITY OF VIENNA
Thomas Reiberger
Mattias Mandorfer

02. BELGIUM

C.U.B. HÔPITAL ERASME
Thierry Gustot
Christophe Moreno
Françoise Smits

UNIVERSITY HOSPITAL ANTWERP
Sven Francque
Luisa Vonghia
Thomas Vanwolleghem

GHENT UNIVERSITY HOSPITAL
Hans Van Vlierberghe
Helena Degroote
Anja Geerts
Xavier Verhelst

UZ LEUVEN
Frederik Nevens
Wim Laleman
Schalk van de Merwe
Hannelie Korf
Rita Furtado Feio

03. CROATIA

ZAGREB UNIVERSITY HOSPITAL
Irena Hrstic

04. CZECH REPUBLIC

INSTITUTE FOR CLINICAL AND EXPERIMENTAL MEDICINE
Jan Sperl
Sona Frankova
Jana Rauvolfova

05. DENMARK

AARHUS UNIVERSITY HOSPITAL
Henning Groenbaek
Hendrik Vilstrup
Niels Kristian AAgaard
Marianne Vonsild
Karen Louise Thomsen

RIGSHOSPITALET
Fin Stolze Larsen
Christian Mortensen

HVIDOVRE UNIVERSITY HOSPITAL
Flemming Bendtsen
Lise Lotte Gluud
Troels MalkeBusk
Soren Møller

NYKOEBING FALSTER HOSPITAL
Stig Bondesen

ODENSE UNIVERSITY HOSPITAL
Aleksander Krag

06. ESTONIA

WEST TALLIN CENTRAL HOSPITAL
Vadim Brjalin
Külliki Suurmaa

07. FRANCE

CHU AMIENS –PICARDIE
Nguyen-Khac

CHU ANGERS
Frédéric Oberti

HÔPITAL MINJOZ
Thierry Thevenot
Delphine Weil-Verhoeven
Jean Paul Cervoni

HÔPITAL AVICENNE BOBIGNY
Dominique Roulot

HÔPITAL JEAN VERDIER
Pierre Nahon

HÔPITAL BEAUJON
Claire Francoz
François Durand
Richard Moreau
Pierre-Emmanuel Rautou
Dominique Valla
Catherine Paugam-Burtz

HÔPITAL HENRI MONDOR
Christophe Duvoux
Jean Philippe Richardet

HÔPITAL CLAUDE HURIEZ
Philippe Mathurin
Alexandre Louvet
Guillaume Lassailly
Sébastien Dharancy
Valérie Canva

HÔPITAL TENON- PARIS
Jean Didier Grange

HÔPITAL PITIÉ SALPÊTRIÈRE - PARIS
Dominique Thabut
Marika Rudler

RENNES UNIVERSITY HOSPITAL
Edouard Bardou-Jacquet
Ludvine Legros

CHU TOULOUSE
Christophe Bureau
Marie Angèle Robic

HÔPITAL PAUL BROUSSE
Faouzi Saliba
Didier Samuel
Audrey Coilly
Sophie Caroline Sacleux

08. GEORGIA

GEORGIAN NATIONAL HEPATOBILIARY CENTER
V Katsarava
Gocha Barbakadze

09. GERMANY

AACHEN UNIVERSITY HOSPITAL
Christian Trautwein
Pavel Strnad
Tony Bruns

UNIVERSITY OF BONN
Christian Jansen
Michael Praktiknjo

DUSSELDORF UNIVERSITY HOSPITAL
Dieter Häussinger

UNIVERSITY HOSPITAL OF ESSEN
Christian Lange
Heiner Wedemeyer

J W GOETHE UNIVERSITY HOSPITAL-FRANKFURT
Stefan Zeuzem
Jonel Trebicka
Frank Uschner
Robert Shierwagen
Sabine Klein

UNIVERSITY HOSPITAL OF FREIBURG
Robert Thimme
Dominik Bettinger

UNIVERSITY HOSPITAL HALLE-WITTENBERG
Alexander Zipprich
Cristina Ripoll

HAMBURG-EPPENDORF UNIVERSITY HOSPITAL
Ansgar Lohse
Johannes Kluwe
Thomas Horvatits

HANNOVER MEDICAL SCHOOL
Thomas von Hahn
Michael Manns

UNIVERSITY HOSPITAL OF HEIDELBERG
Christian Rupp
Uta Merle

SAARLAND UNIVERSITY MEDICAL CENTER
Frank Lammert
Matthias Reichert

JENA UNIVERSITY HOSPITAL
Sven Reuken

UNIVERSITY HOSPITAL LEIPZIG
Thomas Berg

UNIVERSITY OF MAINZ HOSPITAL
Peter R. Galle
Marcus-A. Wörns
Michael Nagel
Christian Labenz

MUNICH UNIVERSITY HOSPITAL
Alexander Gerbes

MÜNSTER UNIVERSITY HOSPITAL
Hartmut Schmidt

UNIVERSITY HOSPITAL OF MAGDEBURG
Ali Canbay

UNIVERSITY HOSPITAL WÜRZBURG
Andreas Geier
Oliver Göetze

10. HUNGARY

UNIVERSITY OF DEBRECEN
Mária Papp
Zsusanna Vitalis
István Tornaí
Tamas Tornai
Boglçarka Balogh

11. ICELAND

LANDSPITALI UNIVERSITY HOSPITAL
Sigurdur Olafsson

12. IRELAND

ST VINCENT'S UNIVERSITY HOSPITAL
Aiden McCormick
Jun Liong Chin

13. ITALY

ALMA MATER STUDIORUM. UNIV. DI BOLOGNA
Mauro Bernardi
Paolo Caraceni
Marco Domenicali
Maurizio Baldassarre
Giacomo Zaccherini
Manuel Tufoni

ASL BRINDISI
Pietro Gatti
Vincenzo Bocaccio
Emanuela Ciracì
Rosaria Martina
Roberto Italia
Valeria Rollo
Vincenzo Valiani

OSPEDALE NIGUARDA, MILAN
Luca Saverio Belli
Chiara Mazzarelli

POLICLINICO SAN DONATO. UNIVERSITY OF MILAN
Francesco Salerno

AZIENDA OSPEDALIERA DI PADOVA
Paolo Angeli
Alessandra Brocca
Marco Di Pascoli
Chiara Formentin
Carmine Gambino
Andrea Martini
Sara Montagnese
Salvatore Piano
Antonella Romano
Antonietta Sticca
Marta Tonon

POLICLINICO OF PALERMO
Vito di Marco
Vicenza Cavalruso

UNIVERSITY HOSPITAL OF MESSINA
Giovanni Raimondo
Irene Cacciola
Roberto Filomia
Gaia Gaccamo
Sergio Maimone
Carlo Saitta

UNIVERSITY OF ROME
Manuela Merli

AZIENDA OSPEDALIERA CITTÀ DELLA SALUTE E DELLA SCIENZA DI TORINO
Carlo Alessandria
Daniela Campion

INTERNAL MEDICINE. UNIVERSITY OF UDINE
Pierluigi Toniutto
Davide Bitetto
Ezio Fornasiere
Elisa Fumolo

14. LATVIA

RIGA EAST UNIVERSITY HOSPITAL
Ieva Tolmane

15. LITHUANIA

HOSPITAL OF LITHUANIAN UNIVERSITY OF KAUNAS
Limas Kupcinskas

SIAULIAI HOSPITAL
Gitana Acute

16. NETHERLANDS

LEIDEN UNIVERSITY MEDICAL CENTER
Minneke J Coenraad
Jelte Schaapman

ERASMUS UNIVERSITY MEDICAL CENTER ROTTERDAM
Rob de Man
Caroline den Hoed
Wojtek Polak

17. NORWAY

OSLO UNIVERSITY HOSPITAL
Zbigniew Konopski
John Willy Haukeland
Vikas Kumar Sarna
Håvard Midgard

18. POLAND

MEDICAL UNIVERSITY OF WARSAW
Marcin Krawczyk
Piotr Milkiewicz

POMERIAN MEDICAL UNIVERSITY
Anna Boron Kaczmarska

19. PORTUGAL

CENTRO HOSPITALAR LISBOA NORTE
Rui Marinho
Rui Palma
Paula Guerreiro

CENTRO HOSPITALAR UNIVERSITÁRIO DO PORTO
Filipe Nery
Alexandre Pinto
Miguel Ricardo
Diana Valadares

CHTMAD VILA REAL
José A Presa Ramos
Joanna Calvâo
Monica Mesquita

CURRY CABRAL HOSPITAL
Filipe S. Cardoso
Luis Bagulho
Nuno Germano
Rui Pereira

20. SLOVAK REPUBLIC

PAVOL JOZEF SAFARIK UNIVERSITY IN KOSICE
Peter Jarcuska
Martin Janicko
Jakub Gazda

ROOSEVELT UNIVERSITY HOSPITAL BANSKA BYSTRICA
Lubomir Skladany
Svetlana Adamcova Selcanova
Daniela Jancekova
Pavol Molčan
Ján Strachan

21. SPAIN

HOSPITAL UNIVERSITARI GERMANS TRIAS I PUJOL
Rosa Mª Morillas
Alba Ardèvol
Helena Masnou

HOSPITAL CLINIC BARCELONA
Pere Ginès
Javier Fernández
Elsa Solà
Elisa Pose
Manuel Morales Ruiz
Constantino Fondevila

HOSPITAL DE LA SANTA CREU I SANT PAU
Germán Soriano
Concepción Mª del Mar
Maria Poca Sans

HOSPITAL UNIVERSITARI VALL D'HEBRON.
Víctor Vargas
Joan Genescà
Macarena Simón-Talero

HOSPITAL UNIVERSITARIO REINA SOFÍA
Manuel de la Mata
Patricia Aguilar Melero
José Luis Montero Álvarez

HOSPITAL UNIVERSITARI BELLVITGE
José Castellote
Alberto Navarrete

HOSPITAL UNIVERSITARIO RAMÓN Y CAJAL
Agustín Albillos
Miguel Rodríguez-Gandía

HOSPITAL GENERAL UNIVERSIDAD GREGORIO MARAÑÓN
Rafael Bañares
María Vega Catalina
Luís Ibáñez
Ana Clemente
Diego Rincón

CLINICA UNIVERSITARIA NAVARRA
Jorge Quiroga

HOSPITAL VIRGEN DEL ROCÍO
Manuel Romero Gómez
Javier Ampuero

22. SWEDEN

LINKÖPIN UNIVERSITY HOSPITAL
Stergios Kechagias

SAHLGRENSKA UNIVERSITY HOSPITAL
Maria Antonella Burza
Anna Cederbog

23. SWITZERLAND

INSELSPITAL BERNE
Jean François Dufour
Annalisa Berzigotti

UNIVERSITY HOSPITAL OF GENEVE
Laurent Spahr
Giulia Magini

LAUSANNE UNIVERSITY HOSPITAL
Pierre Deltenre
Artru Florent

ST GALL CANTONAL HOSPITAL
David Semela

UNIVERSITY HOSPITAL BASEL
Christine Bernsmeier

ZÜRICH UNIVERSITY HOSPITAL
Beat Mühlhaupt

24. TURKEY

ANKARA UNIVERSITY FACULTY OF MEDICINE
Ramazan Idilman
Zeynep Melekoglu Ellik

MARMARA UNIVERSITY SCHOOL OF MEDICINE
Osman Ozdogan
Coşkun Demirtaş
Ilkay Ergenç
Caglayan Keklikkiran

KARADENIZ SCHOOL OF MEDICINE
Mehmet Arslan

25. UKRAINE

IVANO-FRANKIVSK NATIONAL MEDICAL UNIVERSITY
Virstyk Nataliya
Oleg Virstyuk

26. UNITED KINGDOM

UNIVERSITY HOSPITALS BIRMINGHAM
Ahmed Elsharkawy
Neil Rajoriya

GLASGOW ROYAL INFIRMARY
Ewan Forrest

IMPERIAL COLLEGE
Mark Thursz
Nikhil Vergis

KING'S COLLEGE HOSPITAL
William Bernal
George Auzinger
Mark McPhail
Vishal Patel
Debbie Shawcross

LEEDS TEACHING HOSPITAL
Joanna Moore
Richard Parker

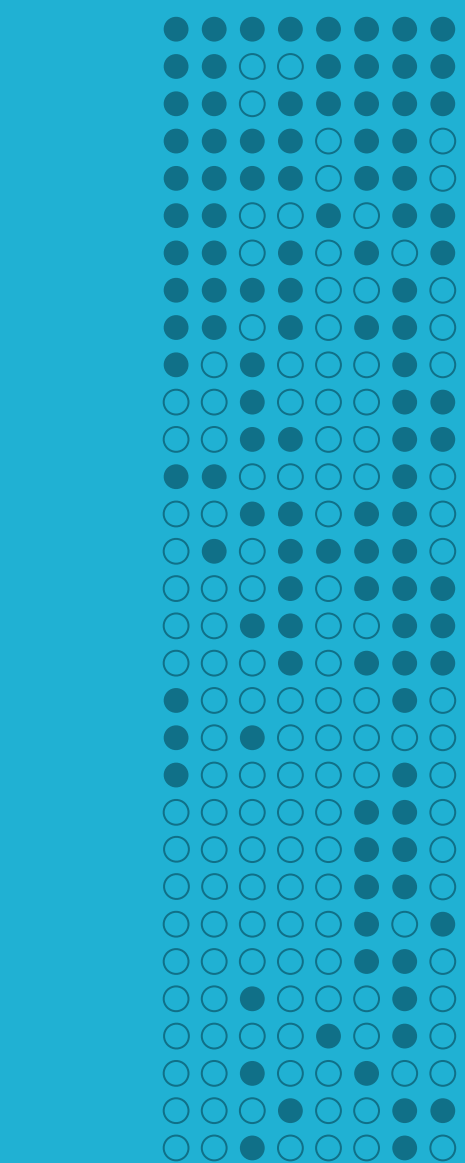
ROYAL FREE HOSPITAL
Rajiv Jalan
Raj Mookerjee
Gautam Mehta
Jane Macnaughtan

UNIVERSITY HOSPITALS NOTTINGHAM
Stephen Ryder
Guru Aithal
Aloysious Aravinthan
Peter Eddowes
Neil Guha
Martin James
Suresh Venkatchalapathy
Emilie Wilkes

PLYMOUTH HOSPITAL TRUST
Juan Acevedo
Matthew Cramp

QUEEN ALEXANDRA HOSPITAL. PORTSMOUTH
Richard Aspinall
Joanna Dowman
Andrew Fowell

EF Clif
STUDIES



152

CENTRES BY PROJECT

Gasthuisberg University Hospital, Leuven
Hospital Clínic Universitari, Barcelona
Royal Free London, London
Erasme University Hospital, Bruxelles
University of Padova, Padova
King's College Hospital, London
Rigshospitalet, Univesity Hospital of Copenhagen
Hôpital Beaujon, Clichy
Hôpital Paul Brousse, Villejuif
Graz University Hospital, Graz
Ghent University Hospital, Gent
Aarhus University Hospital, Aarhus
Munich University Hospital, München
JW Goethe University Hospital, Frankfurt
Universitaetsklinikum, Bonn
Hospital General Univ. Gregorio Marañón, Madrid
Hospital Universitario Ramon y Cajal, Madrid
Hospital Universitario Vall d'Hebron, Barcelona
Innsbruck University Hospital, Innsbruck
Klagenfurt am Wörthersee Hospital-KABEG, Klagenfurt
AKH University Hospital, Wien
Antwerp University Hospital, Edegem
Hvidovre Hospital, Hvidovre
Jena University Hospital, Jena
Hamburg-Eppendorf University Hospital, Hamburg
University Medical Center Mainz, Mainz
Hannover Medical School, Hannover
University of Debrecen, Debrecen
Ospedale Niguarda, Milano
San Giovanni Battista Hospital, Torino
Sapienza University of Rome, Roma

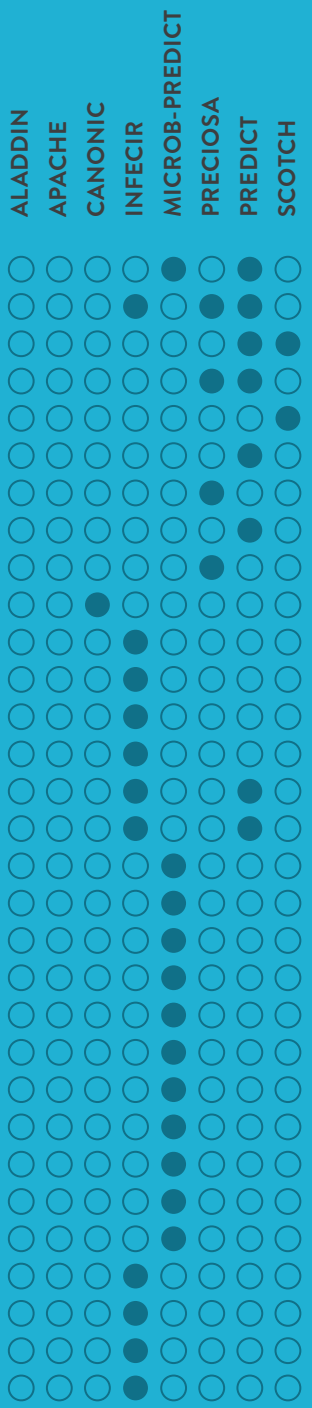
9,2%
14
ALADDIN

9,2%
14
CANONIC

4,6%
7
MICROB-PREDICT

9,2%
14
PREDICT

EF Clif STUDIES



CENTRES BY PROJECT

Leiden University Medical Centre, Leiden
Hospital Universitari Sant Pau, Barcelona
Plymouth Hospitals, Plymouth
Queen Elizabeth Hospital, Birmingham
Institute for Clinical and Experimental Medicine, Praha
Centre Hospitalier Universitaire, Angers
Hôpital Henri Mondor, Créteil
Hôpital Jean Verdier, Bondy
University Hospital Jean Minjoz. Besançon
Georgian National Hepatobiliary Center, Tbilisi
Leipzig University Hospital, Leipzig
Martin Luther University Hospital, Halle-Wittenberg
Münster University Hospital, Münster
Aachen University Hospital, Aachen
Policlinico S Orsola-Malpighi, Bologna
Internal Medicine PO Ostuni, Brindisi
Erasmus Medical Centre, Rotterdam
Centro Hospitalar Tras os Montes e Alto Douro, Vila Real
Pavol Jozef Safarik University,Košice
Hospital Universitario Virgen del Rocío, Sevilla
University Hospital, Basel
Univ. Clinic of Visceral Surgery and Medicine-Inselspital, Berne
Hôpitaux Universitaires, Genève
St Gall Cantonal Hospital, Saint Gallen
Marmara Universty School of Medicine, Istanbul
Ankara University School of Medicine, Ankara
Nottingham University Hospitals, Nottingham
St Vincent's University Hospital, Dublin
Policlinico San Donato - University of Milan, Milano
Oslo University Hospital, Ullevål-Oslo
Hospital Universitario Reina Sofía, Córdoba

7,2%
11
APACHE

13,8%
21
INFECIR

13,8%
21
PRECIOSA

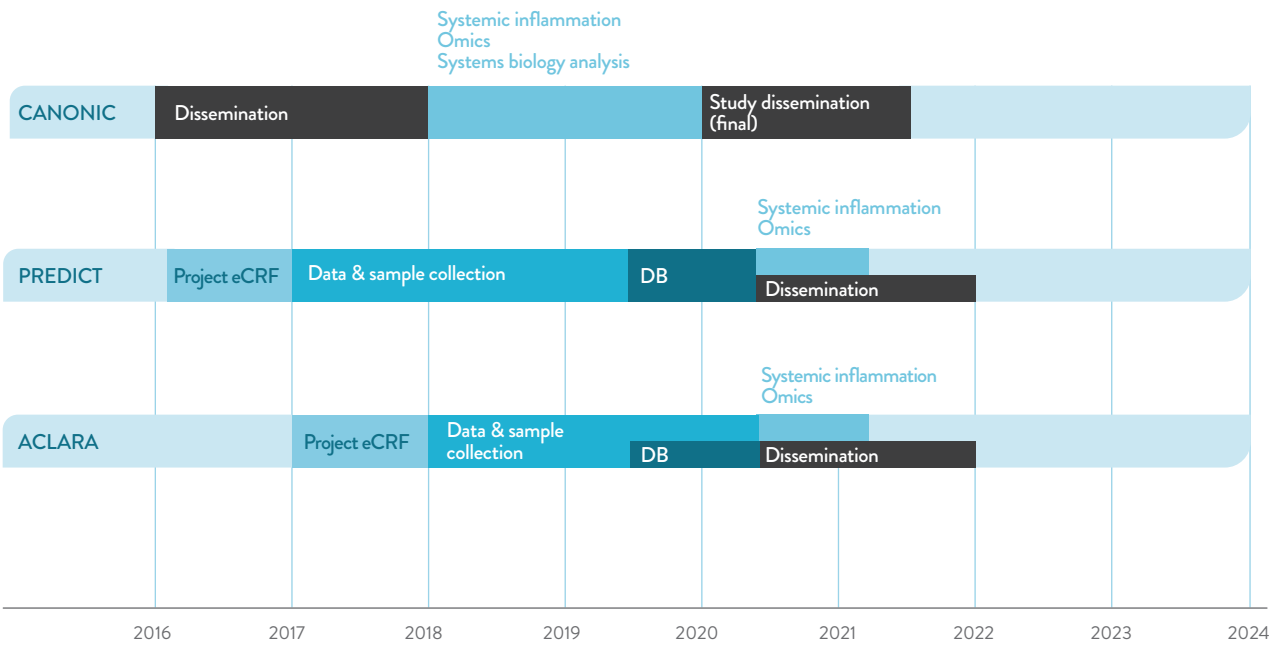
32,8%
50
SCOTCH

5.1.2

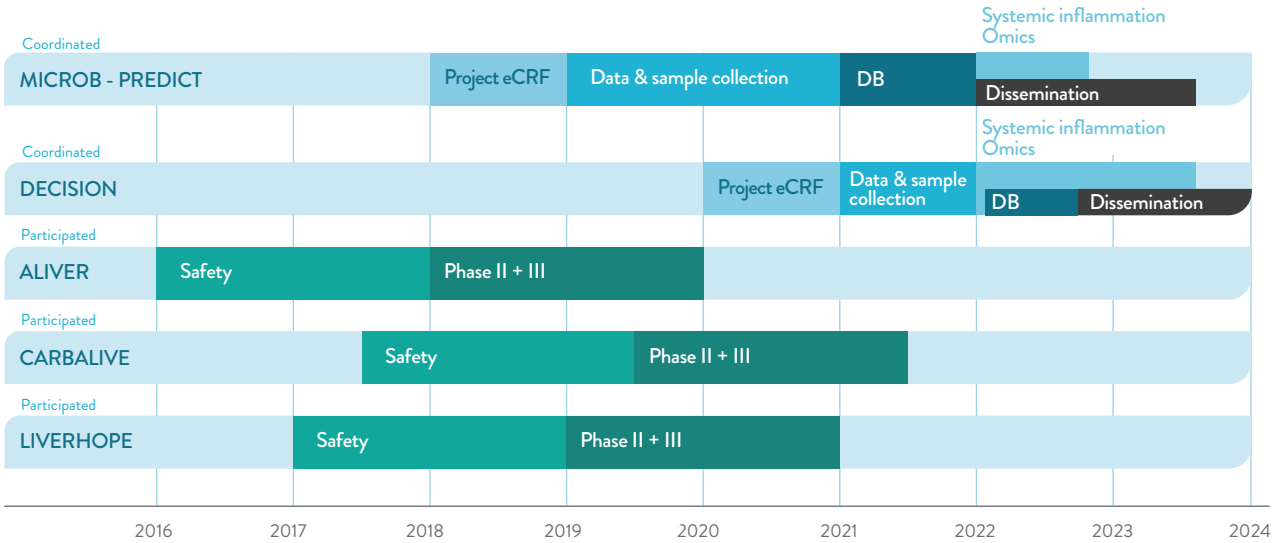
CONSORTIUM **PROJECTS**

EASL-Clif CHAIR **STUDIES** CALENDAR

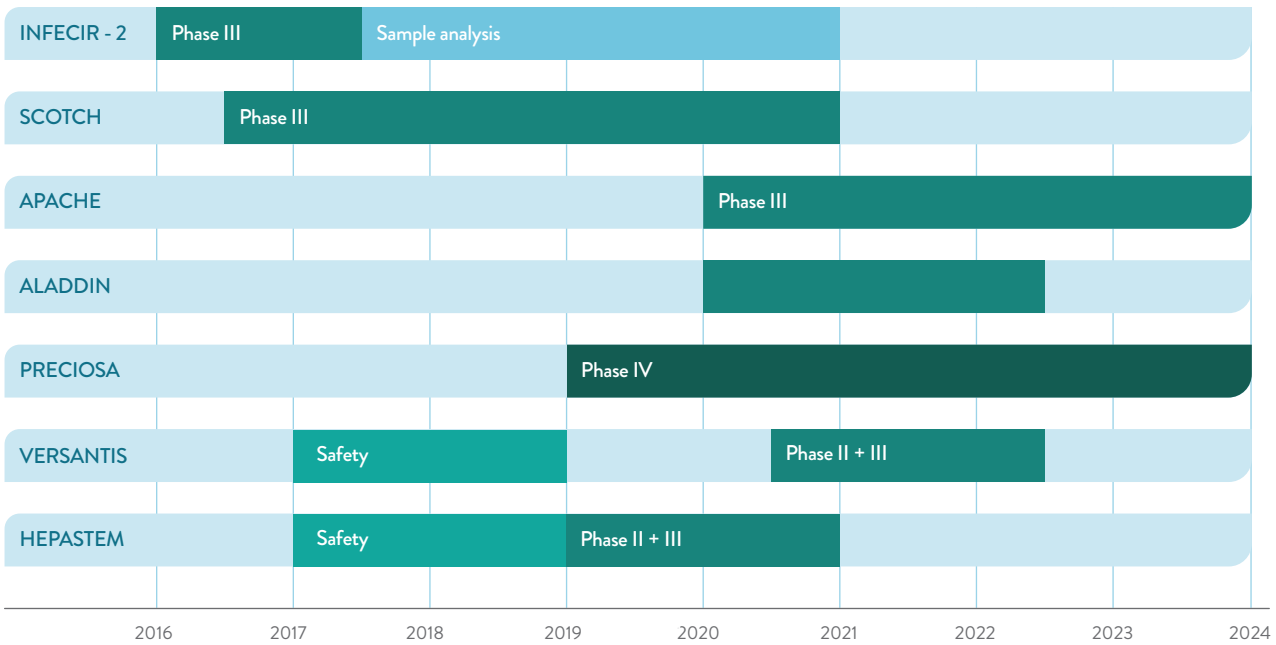
EF Clif FUNDED



EUROPEAN H2020 FUNDED



OTHER FUNDING



5.2

THE GRIFOLS CHAIR

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

The main objective of the **Grifols Chair** for Translational Research is to foster and promote research studies aimed at characterizing the mechanisms underlying the presence of systemic inflammation in patients with decompensated cirrhosis and its role in the development of ACLF.

Director
Vicente Arroyo
EF Clif, Barcelona

Deputy Director
Richard Moreau
Hôpital Beaujon, Clichy

Secretary
Joan Clària
Hospital Clínic, Barcelona

5.2.1

THE EUROPEAN NETWORK OF TRANSLATIONAL RESEARCH AND ASSOCIATED INVESTIGATORS

FRANCE

HÔPITAL BEAUJON, CLICHY
Pierre-Emmanuel Rautou

COMMISSARIAT À L'ÉNERGIE ATOMIQUE ET AUX ÉNERGIES ALTERNATIVES (CEA)
Christophe Junot
François Fenaille

AMBIOTIS
Marc Dubordeau

VAIOMER
Benjamin Lelouvier

GENOSPLICE TECHNOLOGY
Pierre de la Grange

INSTITUT NATIONAL DE LA SANTÉ ET DE LA RECHERCHE MÉDICALE (INSERM)
Richard Moreau
Loredana Saveanu

GERMANY

LIPIDOMIX
Michael Rothe

TÜBINGEN UNIVERSITY
Markus Templin

SPAIN

BIOBANCO VASCO
Lucía Iglesias

CIBERISCIII
Juanjo Lozano Salvatella

CIC BIOGUNE
Ana Aransay

CNAG
Holger Heyn

EF Clif
Joan Clària
Ferran Aguilar

GERMANS TRIAS I PUJOL HOSPITAL
Rosa Mª Sarrias

BIOSCIENCE RESEARCH GROUP, GRIFOLS
Montse Costa Coll
Raquel Horrillo

HOSPITAL CLÍNIC DE BARCELONA
Joan Clària
Wladimiro Jiménez
Mireia Casulleras
Marta Duran Güell
Ingrid Zhang
José Alcaraz-Quiles
Roger Flores-Costa
Cristina López Vicario
Guillermo Fernández-Varo

NAVARRABIOMED
David Gomez-Cabrero
Núria Planell Picola
Arantxa Urdangarin Iztueta

OWL METABOLOMICS
Marta Iruarrizaga

UNIVERSITAT ROVIRA I VIGILI
Oscar Yanes
Maria Vinaixa

SWEDEN

KAROLINSKA INSTITUTET
Craig Wheelock

THE NETHERLANDS

ERASMUS MEDICAL CENTER
Joyce van Meurs

UNITED KINGDOM

FOUNDATION FOR LIVER RESEARCH
Shilpa Chokshi
Roger Williams

UNIVERSITY COLLEGE LONDON AND ROYAL FREE HOSPITAL
Derek W Gilroy
Alistair O'Brien

USA

MASSACHUSETTS INSTITUTE OF TECHNOLOGY (MIT)
Daniel Irimia

UNIVERSITY OF CALIFORNIA, LOS ANGELES (UCLA)
Rita Cantor
Aldons Lusis

5.3

GLOBAL PROJECTS

It is well known that significant breakthroughs in the knowledge of pathophysiology will be only possible through transcontinental collaborations.
This is the main reason why, one of the main objectives that was established at the constitution of the EF Clif was to become a global foundation to promote research in cirrhosis on the five continents. In this regard, EF Clif will become a key player in fostering global collaborations. The participation of the American Association for the Study of Liver Diseases (AASLD) and the Asian Pacific Association for the Study of Liver (APASL) will be crucial for the success of the venture.
By the end of 2017, the EF Clif initiated the first extra European study, the ACLARA study, in Latin America. By 2020 a new global, ambitious, large-scale, prospective observational study in Europe, America, Asia and Australia, will be developed, which is aimed at understanding the role of liver transplantation in patients with severe ACLF. Given the increasing importance of global projects in the portfolio of the Foundation activity, it has been decided to establish a new area entirely dedicated to the promotion of transcontinental projects, the Global Projects Area.

5.3.1

THE LATIN AMERICAN CLIF CONSORTIUM AND ASSOCIATED INVESTIGATORS

ARGENTINA

HOSPITAL UNIVERSITARIO AUSTRAL
Manuel Mendizábal
Marcelo Silva

HOSPITAL BRITÁNICO DE BUENOS AIRES
Luis Colombato
Nora Fernández
Javier Benavides
Silvina Paz
Mercedes Rodríguez Gazzari

HOSPITAL NACIONAL PROFESOR ALEJANDRO POSADAS
Eduardo Fassio

HOSPITAL ITALIANO DE BUENOS AIRES
Adrian Gadano
Sebastián Marciano
Juan Manuel Díaz

HOSPITAL DE INFECCIOSAS F. J. MUÑIZ
Hugo Fainboim

HOSPITAL PROVINCIAL DEL CENTENARIO
Fernando Bessone

BRAZIL

HOSPITAL DAS CLINICAS DA UNIVERSIDADE FEDERAL DE MINAS GERAIS
Claudia Alves Couto

UNIVERSIDADE ESTADUAL PAULISTA
Giovanni Faria Silva

HOSPITAL DE BASE
DO DISTRITO FEDERAL
Liliana Sampaio Costa Mendes

UNIVERSIDADE ESTADUAL
DE CAMPINAS
Daniel Ferraz de Campos Mazo

UNIVERSIDADE FEDERAL
DA PARAÍBA
José Eymard Medeiros Neto

HOSPITAL UNIVERSITÁRIO
WALTER CANTÍDIO
Tarsicio Daniel dos Santos da Rocha
Cyntia Viana

HOSPITAL DAS CLÍNICAS DA
UNIVERSIDADE FEDERAL DE GOIÁS
Rafael Oliveira Ximenes

HOSPITAL DE CLINICAS
DE PORTO ALEGRE
Mario Reis Alvares-da-Silva

IRMANDADE SANTA CASA DE
MISERICÓRDIA DE PORTO ALEGRE
Ângelo Zambam de Mattos

INSTITUTO DO FÍGADO E
TRANSPLANTES DE PERNAMBUCO
Leila Maria Moreira Beltrão Pereira

HOSPITAL DAS CLINICAS DE
MEDICINA DE RIBEIRÃO PRETO
Fernanda Fernandes Souza

HOSPITAL UNIVERSITÁRIO
PEDRO ERNESTO
Carlos Terra

HOSPITAL FEDERAL
DE BONSUCESSO
Gustavo Henrique Santos Pereira
Flávia Ferreira Fernándes

HOSPITAL UNIVERSITÁRIO
CLEMENTINO FRAGA FILHO
Renata de Mello Peres

HU PROFESSOR
EDGARD SANTOS
André Castro Lyra
Lourianne Cavalcante

HOSPITAL PORTUGUÊS
DE SALVADOR BAHIA
Paulo Lisboa Bittencourt
Liana Codes

HOSPITAL DE BASE DA FACULDADE DE
MEDICINA DE SÃO JOSÉ DO RIO PRETO
Rita de Cássia Martins Alves da Silva

HOSPITAL DAS CLÍNICAS DA
UNIVERSIDADE DE SÃO PAULO
Flair Carilho
Alberto Queiroz Farias

ESCOLA PAULISTA DE MEDICINA
Roberto José de Carvalho-Filho
Letícia Yasuda Carreira
Ana Cristina de Castro Amaral

HU CASSIANO ANTONIO MORAES
Luciana Lofêgo Gonçalves

CHILE

PONTIFICIA UNIVERSIDAD
CATÓLICA DE CHILE
Marco Arrese
Carlos Esteban Benítez Fajardo

HOSPITAL CLÍNICO
UNIVERSIDAD DE CHILE
Jaime Poniachik
Juan Pablo Roblero Roblero

HOSPITAL CLÍNICO
SAN BORJA ARRIARÁN
Edmundo Aravena

CLÍNICA UNIVERSIDAD
DE LOS ANDES
Gabriel Mezzano Puentes

CLÍNICA LAS CONDES
Leyla Nazal Ortiz

CLÍNICA ALEMANA DE SANTIAGO
Jorge Contreras

UNIVERSIDAD AUSTRAL DE CHILE.
HOSPITAL DE VALDIVIA
Claudio L. Toledo
Jorge Flandez Rodríguez

COLOMBIA

CLÍNICA GENERAL DEL NORTE
Rolando José Ortega Quiroz

FUNDACIÓN CARDIOINFANTIL
Óscar Beltrán
Carolina Salinas

HOSPITAL PABLO TOBÓN URIBE
Juan Ignacio Marín Zuluaga
Juan Carlos Restrepo Gutiérrez

MEXICO

FUNDACIÓN CLÍNICA MÉDICA SUR
Misael Uribe
Norberto Chávez Tapia

INSTITUTO NACIONAL DE CIENCIAS
MÉDICAS Y NUTRICIÓN SALVADOR
ZUBIRÁN
Aldo Torre Delgadillo

HOSPITAL GENERAL
DE MÉXICO DR. EDUARDO LICEAGA
José Luis Pérez Hernández
Fátima Higuera de la Tijera

HOSPITAL DE ESPECIALIDADES
CENTRO MÉDICO NACIONAL
LA RAZA
Mauricio Castillo Barradas

HOSPITAL GENERAL JUÁREZ
Scherezada Mejía Loja
Raúl Uvaldo Aguilar Moreno

HOSPITAL CENTRAL MILITAR
Eira Cerda Reyes

INSTITUTO DE SALUD DIGESTIVA Y HEPÁTICA
René Malé Velázquez

STAR MÉDICA
Iarah Montalvo
Luis Alberto Chi

CENTRO MÉDICO INSSEMYN
María Sarai González Huezo

HOSPITAL SAN JOSÉ TEC DE MONTERREY
Francisco Bosques
Rocío García de la Garza

UNIVERSIDAD VERACRUZANA
José María Remes Troche

PANAMA

HOSPITAL SANTO TOMÁS
Enrique Aurelio Adames Almengor

PARAGUAY

HOSPITAL DE CLÍNICAS DE LA UNIVERSIDAD NACIONAL DE ASUNCIÓN
Marcos Girala
Karin Vicek

PERU

HOSPITAL NACIONAL EDGARDO REBAGLIATI MARTINS
Milagros Dávalos Moscol
Javier Díaz Ferrer

HOSPITAL NACIONAL GUILLERMO ALMENARA
Pedro Martín Padilla Machaca
Bertha Cardenas Ramírez

HOSPITAL NACIONAL ARZOBISPO LOAYZA
Adelina Zarela Lozano Miranda

HOSPITAL NACIONAL DANIEL A. CARRIÓN
Pedro Montes Teves

HOSPITAL ESSALUD
Raúl Castro

6

OUR **STAFF**

MANAGEMENT

GENERAL MANAGER
Anna Bosch

ADMINISTRATIVE ASSISTANT
Cecilia Ducco

SCIENTIFIC ASSISTANT
Yolanda Godoy

DATA MANAGEMENT CENTRE

HEAD
Marco Pavesi

BIOINFORMATICIANS
Ferran Aguilar
Anna Curto

DATA MANAGERS
Anna Curto
Esaú Moreno
Cristina Sánchez

STATISTICIANS
Àlex Amorós
Elisabet García
Carla Pitarch

RESEARCH ASSOCIATES

DIRECTOR
Vicente Arroyo

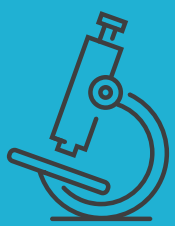
TRANSLATIONAL RESEARCH COORDINATORS
Joan Clària
Richard Moreau

CLINICAL RESEARCH
Javier Fernández
Jonel Trebicka

VISITING CLINICAL RESEARCHERS
Emmanuel Weiss
Giacomo Zaccherini

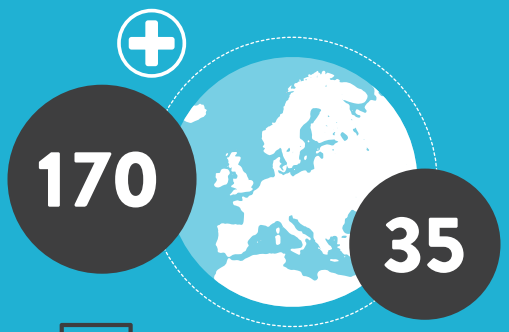
7

FACTS AND FIGURES

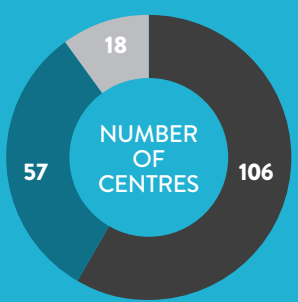


MORE THAN **800 INVESTIGATORS** WORKING ON **EF Clif** SPONSORED SCIENTIFIC PROJECTS, FUNDED WITH MORE THAN

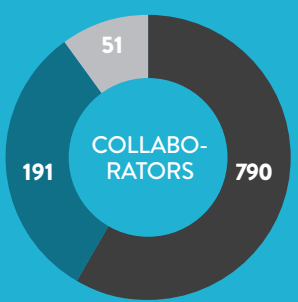
7,000,000 € / year



170 CENTRES DISTRIBUTED IN **3 INTERNATIONAL NETWORKS** IN **35 COUNTRIES** ACROSS THE WORLD.



EASL-CLIF
ACLARA
ENTR



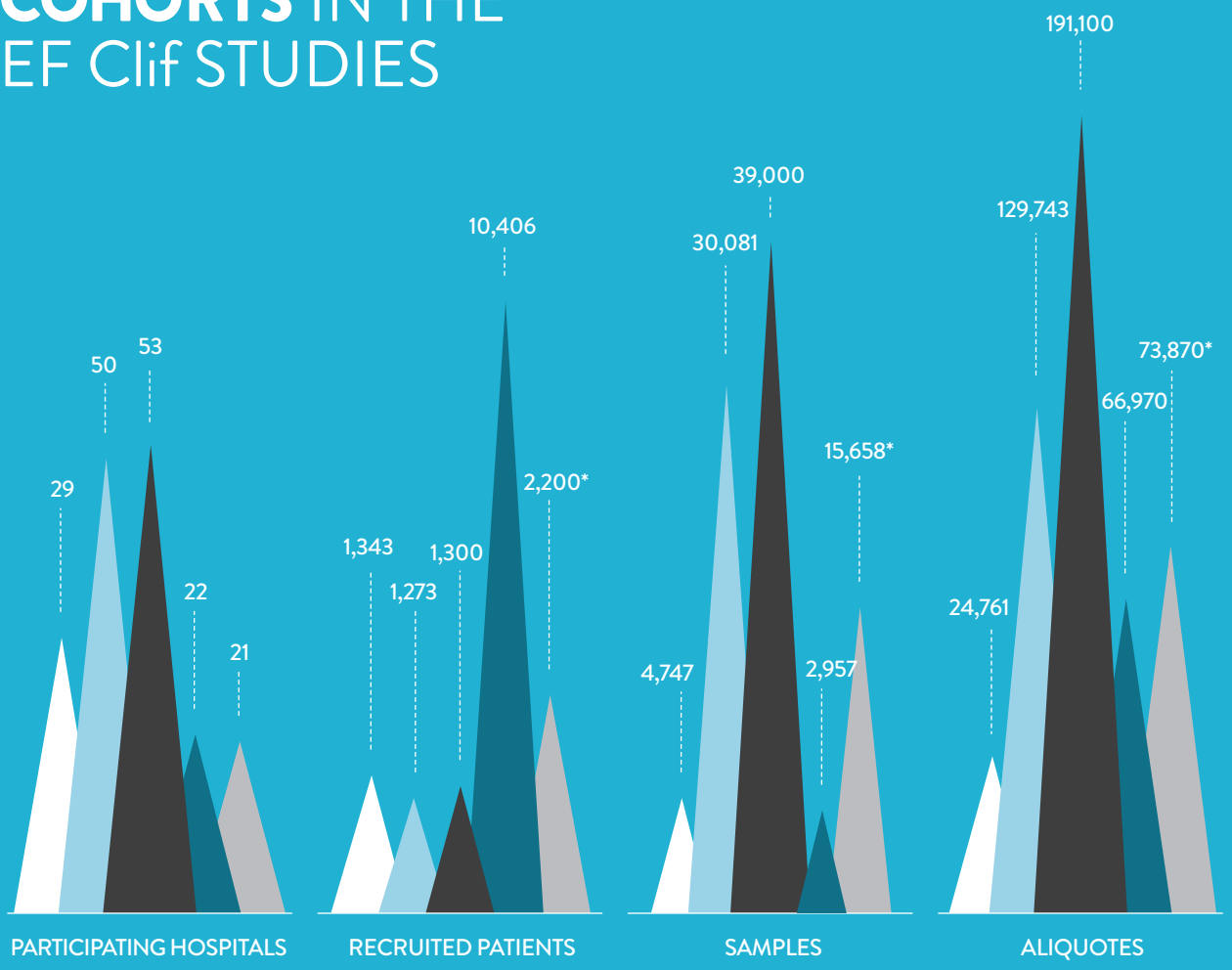
EASL-CLIF
ACLARA
ENTR

48% EASL-CLIF **54%** ACLARA **45%** ENTR

52% EASL-CLIF **46%** ACLARA **55%** ENTR

7.1

PATIENTS COHORTS IN THE EF Clif STUDIES



*Expected

8

2019 IN **IMAGES**

THE MICROB-PREDICT PROJECT IS ALREADY RUNNING!

The kick-off meeting gathered all the researchers who participate in the **MICROB-PREDICT Project** for three days in a nice venue, with astonishing sea views. This meeting was crucial to organize the milestones and deliverables planned for 2019.

JANUARY

APRIL

THE EF Clif PARTICIPATED IN THE INTERNATIONAL LIVER CONGRESS 2019

The ILC took place from 10 to 14 April, 2019. in Vienna with the attendance of around 10,000 delegates from more than 121 countries. During the meeting, the **EASL-CLIF Consortium** celebrated its General Assembly and the 1st meeting of the renovated Steering Committee.

EF Clif RETREAT

The **EF Clif Staff** spent two days in Torroella de Montgrí for a scientific retreat. The EF Clif professionals shared their impressions on the research activities of the EF Clif and discussed about the new projects and the future of the Foundation.

THE ACLARA STUDY HAS REACHED MORE THAN HALF OF THE EXPECTED INCLUSIONS

In only 8 months, the participant centres in the **ACLARA Study** had reached 745 inclusions, from 38 centres in 5 different countries. There were five active centres in Argentina, 21 in Brazil, five in Chile, eight in Mexico and five in Peru. By the end of the year, the patients in the study were more than 1,000, including centres from Colombia and Paraguay, in addition to the previously mentioned ones.

ACLARA

MAY JUNE JULY

THE CLIF-CONSORTIUM CELEBRATES ITS 10TH ANIVERSARY

The **EF Clif** organized an academic event at the central headquarters of the Foundation, followed by a dinner at the Grifols Museum, in order to celebrate the 10th anniversary of the first and largest research activity of the EF Clif, the EASL-Clif Consortium.

THE EF Clif HAS RECEIVED A HORIZON 2020 GRANT FOR THE DECISION PROJECT

The **DECISION** project has as a main objective to enhance the understanding of the pathophysiology of decompensation of cirrhosis, by integrating results of multiomic profiles together with comprehensive clinical data and biological samples of more than 2,200 patients. The project will start in 2020 and will last for 6 years.

DECISION

DR EMMANUEL WEISS JOINS THE EF Clif THANKS TO THE CELLEX PROGRAM FOR YOUNG RESEARCHERS

The Cellex grant has given **Dr Weiss** the opportunity to stay in Barcelona as a Visiting Professor during a year, developing his research activity on single cell transcriptomics.

AUGUST SEPTEMBER OCTOBER

THE 1ST EF Clif VENICE MEETING ON ACLF WAS A GREAT SUCCESS, GATHERING TOP SCIENTISTS FROM ALL OVER THE WORLD

In the premises of the Fondazione Cini, the most active members of the **Clif Consortium and other outstanding researchers** from around the world attended a two-day Symposium entitled "The Acute-on-Chronic Liver Failure syndrome in cirrhosis".
The attendants were invited to a formal dinner on Friday 18 and enjoyed an evening together, while sharing their impressions on the advances leaning to a best understanding of ACLF.

DR GIACOMO ZACCHERINI, NEW VISITING FELLOW AT THE EF Clif

Dr Zaccherini is a Research Fellow in hepatology of the University of Bologna and carries out his clinical activity at the S.Orsola-Malpighi University Hospital. He will stay for six months in our headquarters in Barcelona, working on the characteristics of different organ failures in patients with acutely decompensated cirrhosis, using the metabolomics data from the CANONIC Study cohort.

NOVEMBER DECEMBER

THE EF Clif WAS PRESENT AT THE ASSLD IN BOSTON, WHERE IT CELEBRATED THE ACLARA INVESTIGATORS' MEETING

A group of **ACLARA** investigators met during the ASSLD in Boston to share their impressions to the study. Researchers from Latin America and Spain had the opportunity to discuss about the advances of the project and to plan the next steps of it.

9

PROGRESS REPORT

EASL-CLIF CONSORTIUM PROJECTS

1. PREDICT STUDY

PI: Jonel Trebicka
(University of Bonn, Germany)
Promoter: EF Clif

The recruitment for the **PREDICT Study** was closed on the 31 of July 2018 and the last patient and last visit was on the 30 of October 2018. Finally, 47 centres included at least one patient. In total, 1,308 patients were recruited, 1,071 of which were admitted for the treatment of an episode of mere-AD and 227 were recruited with ACLF at inclusion. After the cleaning of the database, the first two papers have been prepared in 2019.

The first paper describes the trajectory of acute decompensation of liver cirrhosis and distinguishes three different phenotypes. Three groups of patients were identified: Pre-ACLF patients (n=218), who developed ACLF and had 3-month and 1-year mortality rates of 53.7% and 67.4%, respectively. Unstable decompensated cirrhosis (UDC) patients (n = 233) required ≥1 readmission not developing ACLF and had 21.0% and 35.6% mortality rates. Stable decompensated cirrhosis (SDC) patients (n = 620) who were neither readmitted, nor developed ACLF and showed a 1-year mortality of only 9.5%. The three groups differed significantly in the grade and course of systemic inflammation (high-grade at enrollment with aggravation during follow-up in pre-ACLF; low-grade at enrollment with subsequent steady-course in UDC; and low-grade at enrollment with subsequent improvement in the SDC) and prevalence of surrogates of severe portal hypertension throughout the study (high in UDC versus low in pre-ACLF and SDC). Mere AD is a heterogeneous condition with three different clinical trajectories and two major pathophysiological mechanisms: systemic inflammation and portal hypertension.

The second study describes the role of precipitating events (PE) in the development of ACLF. A clinical event that precipitates the development of ACLF needs to have two properties. On the one hand, ACLF development should be in close chronological relationship with the PE, meaning that the diagnosis of the PE should be done before or at the time of ACLF onset, and ACLF onset should occur during the duration of the PE-effect. On the other hand, the PE should be characterized by a sufficient severity to induce organ dysfunction and/or failure. The most important PE seems to be bacterial infections (BI). BI were considered a potential PE for ACLF if they were diagnosed prior ACLF onset but resolved within the 48 hours timeframe before diagnosis of the syndrome or were detected at ACLF onset. BI occurring between day 1 and day 10 after the diagnosis of ACLF were considered as complications of ACLF and BI that resolved more than 48 hours before the onset of ACLF were considered unrelated to ACLF. Similarly, the criteria for acute alcoholic liver injury, gastrointestinal bleeding and other PEs were defined. The analysis is still work in progress.

Overall, **PREDICT Study** was another example of successful collaboration within the European Academic centers and underlines the importance of the disease. It is believed that this study will uncover major parts of currently unknown pathogenesis of development of ACLF and deliver important insight in potential therapeutic approaches of this disease.

2. INFECIR 2 STUDY

PI: Javier Fernández
(Hospital Clínic, Barcelona, Spain).
Funder/Promoter: Fundació Clínic

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

This was a phase IV, open-label, multicentre European RCT aimed at evaluating if albumin administration impacts survival in patients with advanced cirrhosis and non-SBP infections. From April 2014 to December 2016, 776 patients were screened and 119 patients (15.3%) were included in the study. Hospital Clinic of Barcelona (n=33), University of Padova (n=9), Sapienza University in Rome (n=9), University Hospital in Bonn (n=9), San Giovanni Battista Hospital, Turin (n=7) and Erasme Hospital, Brussels and Aarhus University Hospital (n=6 each) were the centres with the highest inclusion rates. The study was stopped in December 2016 due to low recruitment rate and lower than expected hospital mortality.
The results of the study have been recently published in two manuscripts: 1) Fernández J, Angeli P, Trebicka J, et al. Efficacy of albumin treatment for patients with cirrhosis and infections unrelated to spontaneous bacterial peritonitis. *Clin Gastroenterol Hepatol* 2019 Aug 5. pii: S1542-3565 (19)30844-4; 2) Fernández J, Clària J, Amorós A, et al. Effects of albumin treatment on systemic and portal hemodynamics and systemic inflammation in patients with decompensated cirrhosis. *Gastroenterology* 2019 Jul;157(1):149-162.

3. SCOTCH TRIAL

PI: Alexander Wilmer
(University Hospital, UZ Leuven, Belgium)
Sponsor: University Hospitals Leuven

Study designed to assess the clinical impact and safety of low dose steroids in the treatment of hypotensive cirrhotic patients with suspicion of sepsis (Supplemental Corticosteroids in Cirrhotic Hypotensive Patients with Suspicion of Sepsis. The SCOTCH – trial).

This is a phase IV, double-blind, randomized, placebo-controlled, multicentres trial, in cirrhotic patients with septic shock aimed to assessing if stress dose steroids treatment improves 28-day mortality in cirrhotic patients with septic shock (n=356).
Ten centres are currently active to recruit: Spain (n=4), Belgium (n=2), United Kingdom (n=2) and Italy and Czech Republic (n=1, each). However, only four centres have recruited patients: Barcelona, Leuven, Plymouth and Prague. Until now, 316 patients have been screened and 86 (27%) have been included. We estimate that the inclusion will finish at the end of 2022. An interim analysis has been scheduled after the inclusion of the first 100 patients.

4. APACHE TRIAL

PI: Javier Fernández
(Hospital Clínic, Barcelona, Spain) and Fin Stolze Larsen (Rigshospitalet, Copenhagen, Denmark)
Sponsor: Instituto Grifols, S.A.

The **APACHE Trial** is aimed at studying the effects of plasma exchange on short-term survival in patients with ACLF and high risk of mortality (Effects of Plasma Exchange with Human Serum Albumin 5% on Short-term Survival in Patients with Acute-On-Chronic Liver failure at High Risk of Hospital Mortality).

This is a phase III, multicentre, randomized, open-label trial in 380 patients with ACLF-1b, ACLF grade 2 or ACLF-3a aimed at determining whether plasma exchange with 5% albumin (from 4 to 9 plasma exchange sessions) improves 90-day survival in comparison with standard medical therapy.
The first centre was activated in April 2019, and the first patient was included in June 2019. Twenty seven centres were active to recruit at the end of 2019, 18 in Europe and 9 in USA. Twelve more (nine in Europe and three in USA) will be activated in the next few months. Until now, 18 patients have been screened and 17 patients have been included. The estimated duration of the study is 48 months.

5. ALADDIN STUDY

PI: Joan Clària
(Hospital Clínic, Barcelona, Spain), Richard Moreau (Hôpital Beaujon, Clichy, France), and Ramon Bataller (University of Pittsburgh, USA)
Sponsor: Instituto Grifols, S.A.

The **ALADDIN Study** is a complementary study to the APACHE Trial, aimed at assessing the mechanisms of systemic inflammation and ACLF in patients with and without ACLF.

This translational research project is coupled to the APACHE Trial. It is performed in blood and plasma samples and monocytes and neutrophils, obtained from patients with ACLF included in the APACHE Trial (n=150) and from an additional group of 100 patients with acute decompensated cirrhosis but without ACLF, which serve as a control group. Patients of the control group will be enrolled in the Hospital Clinic in Barcelona.
The **ALADDIN Study** is performed in selected European Centres participating in the APACHE Trial. The submission process (CA and EC) has been completed and until date, two centres have been activated (Frankfurt and Hospital Clinic in Barcelona). Eight additional hospitals will be activated in the next few months.

6. PRECIOSA TRIAL

PI: Javier Fernández
(Hospital Clínic, Barcelona, Spain)
and Paolo Angeli (Padova, Italy).
Sponsor: Instituto Grifols, S.A.

The **PRECIOSA Trial** is focused on exploring the effects on survival of long-term albumin administration in patients with decompensated cirrhosis.

This is a phase IV, European and American, multicentre, randomized open-label trial in 410 patients with decompensated liver cirrhosis with ascites, aimed at determining whether long-term albumin administration (1.5 g/kg body weight every 10 days for 12 months) improves 1-year transplant-free survival, in comparison with standard medical therapy.
The first centre was activated in April 18, and the first patient was included in July 2018. Forty three centres were active to recruit at the end of 2019, 31 in Europe and 12 in USA. Two additional North American centres will be activated in the next months. Until now, 58 patients have been screened and 43 patients have been included. The estimated duration of the study is 48-72 months. A new amendment to the protocol (version number 5) containing changes aimed at improving the recruitment rate and the selection of patients with poor prognosis, will be submitted shortly for approval to the CA and EC in USA and Europe.

7. MICROB-PREDICT

MICROBiome-based biomarkers to PREDICT decompensation of liver cirrhosis and treatment response.

SC1-BHC-03-2018
Exploiting research outcomes and application potential of the human microbiome for personalized prediction and prevention of disease.

PI: Jonel Trebicka
(University of Frankfurt, Germany)
Promoter: European Commission H2020

As coordinator, the EF Clif presented the project entitled "MICROBiome-based biomarkers to PREDICT decompensation of liver cirrhosis and treatment response (**MICROB-PREDICT**)". Briefly, microbiome is causally involved in cirrhosis progression and it is often the first barrier for drugs, on their way into the patient. Thereby, microbiome metabolizes the drugs, shapes their effects and, possibly, determines the host response to drugs. A better understanding of the underlying processes is necessary for more personalized risk stratification, and consequently, it is crucial to have more informed, clinical decision-making, with regard to patient health care and treatment.
The aims of **MICROB-PREDICT** are 1) to better understand the role of microbiome and the gut-liver-axis interactome with respect to microbiome functionalities, 2) to identify microbiome-based biomarkers and signatures for personalized prediction of decompensation and ACLF, and response to treatment, 3) to design three new tests as easy-to-use tools and point-of-care, smartphone-connected nano-biosensors, and 4) to validate them in a randomized controlled trial.
To achieve these aims, **MICROB-PREDICT** has a structured program in 11 workpackages, which will assemble existing data and samples from major microbiome initiatives in hepatology (12 international studies, >10,000 patients),

and enrich them with holistic and in-depth analysis, using cutting-edge multi-omics technologies of host and microbiome from different body sites in samples of >1,000 patients, collected in a longitudinal manner with sequential visits and controlling for confounders.
This project was accepted for funding and the project started successfully on January 1st 2019. The involvement of world-leading microbiome and omics specialists, technology leaders and clinical experts makes this a program of scientific excellence. Indeed, in 2019 a challenge was announced in the kick-off meeting in Barcelona. Within WP2 and WP3, dealing with multi-omics could finish several deliverables already one year before the planed timeline and promising for the future work.
The resonance of the kick-off meeting in the media was expansive, thanks to the press releases, the press conference and further, with the presentation of the project in the community hub in the EASL. This was ensured by the involvement of patient organizations (ELPA) and the European Association for the study of the Liver (EASL) and also in the future EF Clif will channel our results into a powerful dissemination, communication, training and exploitation program.

MICROB-PREDICT

8. DECISION

Decompensated cirrhosis: identification of new combinatorial therapies based on system approaches.

SC1-BHC-02-2019
Systems approaches for the discovery of combinatorial therapies for complex disorders.

PI: Pierre-Emmanuel Rautou
(INSERM and Hepatology Department at Beaujon Hospital, Clichy, France)
Promoter: European Commission H2020

Cirrhosis mortality is mainly associated with cirrhosis decompensation (development of ascites, hepatic encephalopathy, gastrointestinal haemorrhage and progression to Acute on Chronic Liver Failure (ACLF). Despite multiple treatments, mortality in patients with decompensation of cirrhosis remains high. The EU-funded **DECISION** project aims to understand the pathophysiology of decompensation of cirrhosis leading to ACLF or death, and to decrease patient mortality. The project will study the pathophysiology of decompensation of cirrhosis by integrating results of high-throughput multi-omic profiling with comprehensive clinical data from 2,200 fully characterised patients with available standardised biological samples.
DECISION will help to identify novel combinatorial therapies to prevent high mortality for patients with decompensation of cirrhosis. Finally, researchers will optimise these therapies in new animal models and then test the best combination in high-risk patients in a Phase II clinical trial.The DECISION project will gather the expertise from 22 different European partners (hospitals, research foundations and institutes, patient and physician associations, and small and medium-sized enterprises, SMEs) and will officially start on April 1st, 2020.

DECISION

CLIF **GLOBAL** PROJECTS

1. ACLARA STUDY

PI: Flair Carrilho
(Hospital das Clínicas, Sao Paulo, Brasil)
Promoter: EF Clif

The **ACLF-ACLARA Study** is a prospective follow-up observational investigation in 1,300 patients with cirrhosis hospitalized for AD with and without ACLF at 56 hospitals, designed to assess the characteristics of the ACLF syndrome in Latin America.

Latin America is one of the regions where epidemiological studies of diseases promoted by systemic inflammation, such as ACLF, are of special interest. First, the prevalence and severity of ACLF has been reported to be very high in young individuals with cirrhosis and active alcoholism, a common subset of patients in Latin American countries. Secondly, the role of ethnicity on the severity and mortality of diseases, associated with systemic inflammation (i.e., sepsis) is a well-recognized feature in multiracial countries such the United States. Mortality is significantly higher in African Americans, followed by Amerindians, Caucasians and Oriental.
Finally, there are very few data on ACLF in Latin America, and three performed studies show that the mortality rate of patients with is double than in Europe (60% vs 32%). Therefore, it is very likely that ACLF could represent a major health care problem in the whole Latin American continent, and particularly in those countries with high percentage of African Americans (Brazil, Panama and Colombia), and Amerindians (Mexico, Colombia and Peru), as compared with countries with high proportion of Caucasians (Argentina and Chile).
The **ACLARA Study** is a joined project between the EF Clif, the European CLIF Consortium, and the Latin American CLIF Consortium. It will consist of a prospective follow-up observational investigation in 1,300 consecutive patients with cirrhosis hospitalized for AD with and without ACLF.
Clinical and standard laboratory data and samples for measuring circulating levels of inflammatory inducers and mediators, biomarkers of systemic circulatory dysfunction and oxidative stress, innate immune cell function and cell death, and genotyping (only assessed at enrolment), transcriptomics and metabolomics will be obtained at admission, eight days after admission and at hospital discharge. The one-year clinical course (survival, liver transplantation and causes of death) will also be recorded.
During the year 2019 there were 47 active centres in Argentina, Brazil, Colombia, Chile, which included 1,197 patients. Recruitment is expected to go on until May 2020.

ACLARA

THE GRIFOLS CHAIR STUDIES

1. THE IMMUNOMODULATION EFFECTS OF ALBUMIN

PI: Joan Clària
(Hospital Clínic, Barcelona, Spain)
Promoter: EF Clif

Study 1
In vitro studies in immune cells.

Human serum albumin (HSA) is an emerging treatment for preventing excessive systemic inflammation and organ failure(s) in patients with acutely decompensated (AD) cirrhosis. In this project, we investigated the molecular mechanisms underlying the immunomodulatory properties of HSA.

Similar to that observed during the administration of HSA to infected patients with AD cirrhosis who have elevated circulating bacterial DNA rich in CpG motifs (CpG-DNA), in isolated leukocytes HSA abolished CpG-DNA-induced cytokine expression. The reduction in cytokine levels was independent of HSA oncotic and scavenging properties. Similar anti-inflammatory effects were observed with recombinant human albumin. Moreover, HSA exerted widespread changes on the immune cell transcriptome, specifically in genes related to the endosomal compartment involved in cytosolic DNA sensing and type I interferon responses.

Using flow cytometry and confocal microscopy analyses, we demonstrated that HSA was taken up by leukocytes and internalized in vesicles positively stained with EEA1, a marker of early endosomes. Indeed, HSA and CpG-DNA colocalized in endosomes, the compartment where CpG-DNA binds to TLR9, its cognate receptor. Furthermore, HSA also inhibited poly(I:C)- and LPS-induced IRF3 phosphorylation and TRIF-mediated responses, which are exclusive of endosomal TLR3 and TLR4 signaling, respectively. Importantly, the immunomodulatory actions of HSA did not compromise leukocyte defensive mechanisms such as phagocytosis, efferocytosis and intracellular ROS production.

Finally, the in vitro immunomodulatory effects of HSA in isolated leukocytes were confirmed in vivo in analbuminemic humanized FcRn transgenic mice.

In conclusion, these findings indicate that HSA internalizes in immune cells and modulates their responses through interaction with endosomal TLR signaling, thus providing a mechanism for the benefits of HSA infusions in patients with cirrhosis.

These studies are accepted for publication in *Science Translational Journal*. In addition, the intracellular pathways of HSA signaling are currently further elucidated in a collaboration with Loredana Saveanu from INSERM (Paris). In this collaboration, we explore the intracellular fate of internalized albumin and identify the endocytic pathways by which albumin is internalized using specific shRNA constructs for specific inactivation of each endocytic route.

Study 2
Ex vivo studies in precision-cut liver and renal tissue slices.

Albumin infusions reduce the circulating levels of pro-inflammatory cytokines and improve the outcome of patients with acutely decompensated (AD) cirrhosis at risk of developing organ failure(s). In this study, we investigated whether in addition to reducing cytokine levels, albumin was able to protect tissues from the damaging actions of these inflammatory mediators. We circumscribed our investigation to TNFα, which represents a paradigmatic example of the connection between immunity and tissue injury.

Our findings indicate that incubation of hepatocytes with albumin in vitro significantly reduced TNFα-induced apoptosis by mechanisms related to inhibition of the lysosomal release of the cysteine protease cathepsin B accompanied by reductions in the cytosolic levels of pro-apoptotic signals Bid and Bax and cytochrome c released from the mitochon-

dria, resulting in decreased caspase-3 activity. The anti-apoptotic actions of human albumin were reproduced by recombinant human albumin expressed in Oryza sativa and were confirmed ex vivo in precision-cut liver slices challenged with TNFα.

We also performed in vivo experiments in mice with pre-existing cirrhosis and expressing the human genes for albumin and neonatal Fc receptor (hAlb+/+/hFcRn+/+), which further confirmed the ability of albumin to protect against lipopolysaccharide/D-galactosamine-induced TNFalpha- mediated liver injury.

We finally translated these findings to the clinical setting and demonstrated that the hepatic apoptotic index, calculated by the plasma levels of caspase-cleaved keratin 18 to the keratin 18 ratio was significantly lower in patients with AD cirrhosis receiving human serum albumin therapy.

In conclusion, these findings uncover novel mechanisms by which albumin protects organs from cytokine-induced tissue injury, providing new avenues for understanding why albumin infusions are an effective therapy in the management of patients with AD cirrhosis.

The results of this study have been submitted to the journal *Hepatology* and is currently under review.

Study 3

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

We investigated the effect of albumin treatment (20% solution) on hypoalbuminemia, cardiocirculatory dysfunction, portal hypertension, and systemic inflammation in patients with decompensated cirrhosis with and without infections.

First, we assessed the effects of long-term (12 weeks) treatment with low- and high-albumin dosages (LAlbD, and HAlbD, respectively) on serum albumin, plasma renin, cardiocirculatory function, portal pressure and a large panel of cytokines in 18 non-infected patients (Pilot-PRECIOSA study). We also assessed the effect of short-term (one week) treatment with antibiotics alone versus antibiotics plus albumin on plasma cytokines in biobanking samples from 78 patients with bacterial infections included in a RCT (INFECIR-2 study).

Circulatory dysfunction and systemic inflammation were extremely unstable in many patients included in the pilot-PRECIOSA study. Long-term treatment with HAlbD but not with LAlbD was associated with normalization of serum albumin, improvement in circulation stability and left ventricular function, and suppression of keystone cytokines, without significant changes in portal pressure. The immunomodulatory effect of albumin observed in the Pilot-PRECIOSA study was confirmed in the INFECIR-2 study patients treated with albumin.

In summary, albumin treatment improves systemic inflammation and cardiocirculatory dysfunction in patients with decompensated cirrhosis. These effects may underlie the beneficial effects of albumin therapy on clinical outcomes in decompensated cirrhosis.

This study has been published in *Gastroenterology* during 2019.

Additional studies have been initiated with samples from the INFECIR-2 study to further characterize the effects of albumin on immune metabolism. For this, a collaboration has been initiated with the Metabolomics platform of the University Rovira i Virgili of Reus (URV-IISPV-CIBERDEM). This platform has access to state-of-the-art technology in nuclear magnetic resonance (NMR) and mass spectrometry (MS) and will implement untargeted metabolomics in samples collected at baseline (time 0) and at 3 and 7 days after HSA therapy. In addition, in these samples we are currently performing “albuminomics” to identify free and albumin-bound bioactive lipids in patients with decompensated cirrhosis before and after receiving albumin in patients from INFECIR-2.

Study 4

Immune checkpoint receptors in cirrhotic patients with acute decompensation with and without ACLF.

PI: Shilpa Chokshi
(Institute of Hepatology, Foundation for Liver Research, London, UK)
Promoter: EF Clif

Checkpoint receptors are inhibitory receptors that physiologically regulate the balance between protective anti-pathogen/tumour immunity and immune-mediated tissue damage. Both chronic antigeneamia and systemic inflammation can drive hyper-expression of these receptors on immune cells, particularly T-cells, in order to switch off injurious immune responses but inadvertently promote pathogen persistence due to immune exhaustion and paralysis. We have previously shown that these receptors play a crucial role in the deranged immunity seen in Alcoholic Hepatitis (Markwick et al, Gastroenterology 2015). This dysregulated host immune response is also characteristic of patients with ACLF who present clinically with a profound immunodeficiency alongside a whole-body inflammatory response. The dynamics and expression of checkpoint receptors in ALCF is unknown.

ACLF represents an immunological paradox. Patients exhibit a hyperinflammatory state at the clinical and molecular level that exists in parallel with a profound immunoparesis and increased susceptibility to bacterial infection. We have recently demonstrated for the first time a relationship between increased gut permeability and several stimulatory and inhibitory soluble checkpoint receptors in the CANONIC cohort. Specifically, we quantified 17 soluble immune checkpoints by ELISA in the serum of 511 patients with decompensated cirrhosis included in the CANONIC Study; 334 with acute decompensation and 177 with ACLF at inclusion. We found that the soluble immune activatory checkpoints CD40 ($p < 0.001$), CD137 ($p = 0.009$) and CD27 ($p = 0.003$) increased significantly with increasing ACLF grade. The soluble immunosuppressive checkpoint BTLA (B and T-cell Lymphocyte-As sociated) increased significantly with increasing ACLF grade ($p = 0.004$). Soluble CD80, which can be both inhibitory and stimulatory, also increased with ACLF grade ($p = 0.002$). Galectin 9 and Galectin 1, which have numerous immunomodulatory roles, also increased with ACLF progression ($p < 0.0001$). Transplant-free survival at 28 days (CD40: $p < 0.001$, CD137: $p < 0.001$, CD80: $p = 0.035$, BTLA: $p = 0.035$, Galectin 9: $p = 0.027$, Galectin 1: $p = 0.027$) and 1 year (CD40: $p = 0.043$, CD137: $p < 0.001$, BTLA: $p < 0.001$, Galectin 9: $p < 0.001$, Galectin 1: $p < 0.001$) was also significantly associated with lower serum levels of immune checkpoints at presentation. Plotting the data as a heatmap demonstrates that levels of several checkpoint receptors increase in parallel in individual patients and this pattern is associated with increasing ACLF grade.

These findings demonstrate an association of increased levels of several stimulatory and inhibitory immune checkpoints with increasing ACLF grade. In addition, levels of certain soluble immune checkpoints can predict clinical outcome and further suggest that this activatory/inhibitory milieu is important in generating and maintaining the pathological hyperinflammatory hypoimmune state that is seen in patients with ACLF. These intriguing findings raises several mechanistic questions, which we are currently aiming to address with in vitro experiments investigating the effect of blocking these soluble checkpoint receptors on the functionality of peripheral immune cells collected longitudinally from patients with ALCF. The blockade of these receptors may reconstitute a functional immune state in ACLF and with many of these molecules being in clinical development, they may represent a tangible therapeutic opportunity for ACLF, which are severely lacking currently.

2. METABOLOMICS UNCOVERS A UNIQUE BLOOD METABOLITE FINGERPRINT OF PATHOPHYSIOLOGICAL RELEVANCE IN PATIENTS WITH ACLF

PI: Richard Moreau

Promoter: EF Clif

ACLF, which develops in patients with acutely decompensated (AD) cirrhosis, is characterized by intense systemic inflammation and organ failure(s). Because systemic inflammation is energetically expensive, its metabolic costs may result in organ dysfunction/failure. In this study, we aimed to analyze blood metabolome in patients with cirrhosis, with and without ACLF.

The investigation employed untargeted metabolomics using liquid chromatography coupled to high-resolution mass spectrometry in serum from 650 patients with AD (acute decompensation of cirrhosis, without ACLF), 181 with ACLF, 43 with compensated cirrhosis, and 29 healthy subjects. This investigation identified 137 annotated metabolites, of which 100 were increased in patients with ACLF of any grade, relative to those with AD, and 38 composed a distinctive blood metabolite fingerprint for ACLF. These 38 metabolites had a very close relationship with the ACLF syndrome and allow to discriminate patients with AD cirrhosis and ACLF from those with mere AD.

Moreover, in patients with ACLF, the intensity of the fingerprint increased across ACLF grades, and was similar in patients with kidney failure and in those without, indicating that the fingerprint reflected not only decreased kidney excretion but also altered cell metabolism. In addition, the fingerprint was closely associated with inflammatory markers such as tumor necrosis factor α, soluble CD206, and soluble CD163.

In general terms, ACLF was characterized by intense proteolysis and lipolysis; amino acid catabolism; extra-mitochondrial glucose metabolism through glycolysis, pentose phosphate, and D-glucuronate pathways; depressed mitochondrial ATP-producing fatty acid β-oxidation; and extra-mitochondrial amino acid metabolism giving rise to metabolites which are metabotoxins.

In conclusion, patients with ACLF have blood metabolite accumulation witnessing profound alterations in major metabolic pathways. The metabolites identified in this study would allow to determine the clinical status of each patient, the degree of severity of the liver disease and a greater precision in its diagnosis. In this regard, this study opens the door to the discovery of prognosis markers that would allow an early diagnosis and may contribute to the design of new therapies to prevent the multiorgan failure characteristic of ACLF, which usually causes the patient's death.

These results have already been accepted for publication in *Journal of Hepatology*.

3. GENOME-WIDE ASSOCIATION ANALYSES (GWAS) IDENTIFY NOVEL GENETIC VARIANTS ASSOCIATED WITH THE ACLF SYNDROME

PI: Joan Clària
Promoter: EF Clif

We genotyped 829 patients with AD cirrhosis recruited in the CANONIC study using the Infinium® Global Screening Array (Illumina, San Diego, CA). This array has a very rich up-to-date content, includes 692,368 SNPs and is suitable for GWAS including rare variants, while also containing clinically relevant content. Prior to association analysis, a validation of the data was performed. All Caucasian patients, according to the database, were selected and the remaining patients were analysed by IBD with HAPMAP data. The genotypes with a MAF of less than a 1% were excluded from the sample. SNPs with a Hardy-Weinberg analysis p-value of less than 0.001 were also excluded. Some markers with locus missingness were also excluded. Finally, we checked the sex concordance with the database.

The final database available for GWAS analysis included 806 individuals and 500,953 SNPs. The association between each single nucleotide polymorphism (SNP) and traits relevant to the ACLF syndrome was tested using linear regression, adjusted for age, gender and ethnicity. The traits included in the analysis were ACLF, organ dysfunction or organ failure, mortality (28-day, 90-day and 6-month), markers of systemic inflammation (cytokines, CRP and WBC count), oxidative stress (HNA2, irreversible oxidized albumin) and macrophage activation (sCD206 and sCD163). The association analysis was performed using PLINK software.

Continuous variables were normalized if needed. Additional permutation tests were performed to confirm associations and to avoid false positives. The SNPs were considered significantly associated when the Bonferroni adjusted p-value was less than 5.0x10-8. In addition, we performed a replication study in 559 samples of patients with AD cirrhosis (316 samples came from (Bologna collection) and 243 samples came from (Hungary collection).

The GWAS analysis identified 17 candidate SNPs strongly associated with clinical and laboratory features of the ACLF syndrome. Two SNPs were significantly associated with the sCD206 levels (marker of macrophage activation). One SNP (rs71497223) was located within the MRC1 gene (association p-value of 1.97E-18) and was protective: it was associated with lower systemic inflammation, better prognostic scores, lower bacterial infections prevalence and lower mortality.

COLLABORATIVE **PROJECTS**

The **EF Clif** participates as a partner or advisor in a wide variety of external research projects, either funded by the **European H2020 program** or by **private companies**:

1. ALIVER

PI: Rajiv Jalan
(University College, London, UK)
Funder/Promoter: European Commission H2020

This is a European multicentre, two phase project on the role of a new artificial liver support system (DIALIVE) in patients with ACLF. The first phase consists in a randomized controlled study, to evaluate the safety and performance of The DIALIVE Liver Dialysis Device in patients with ACLF versus standard of care. This trial is currently ongoing.
After successful completion of the DIALIVE Safety & Performance study, a second phase is planned, consisting of a randomized controlled trial of 100 patients, to assess the efficacy of the DIALIVE versus standard medical therapy in ACLF patients. The main aim-point is 3-month survival.

ALIVER

2. CARBALIVE

PI: Rajiv Jalan
(University College, London, UK)
Funder/Promoter: European Commission H2020

The aim of the **CARBALIVE** project is to further develop and validate a novel nanoporous carbon adsorbent (Yaq-001), capable of removing bacterial endotoxin and other metabolic toxins relevant to the progression of bacterial translocation and endotoxemia, in patients with cirrhosis and ACLF and those with non-alcoholic fatty liver disease. A first randomized controlled trial to assess treatment Safety is scheduled to start in January 2019.

CARBALIVE

3. LIVERHOPE

PI: Pere Ginès
(Hospital Clínic, Barcelona, Spain)
Funder: European Commission H2020

The objective of **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.
It includes two clinical trials. The first one is a small comparative study (still ongoing) to assess safety. In a second phase, a double-blind randomized clinical trial will compare the explored treatment versus placebo and efficacy in preventing ACLF development and improvement survival in patients with decompensated cirrhosis.

LIVERHOPE

4. HEPASTEM

PI: Frederik Nevens
(UZ Gasthuisberg, Leuven, Belgium)
Promoter: PROMETHERA

Promethera Biosciences is a start-up pharmaceutical company from Leuven that develops innovative therapies for the treatment of liver diseases. The **HEPASTEM** study is a phase-two clinical trial, aimed at assessing the safety and efficacy of heterologous human adult liver-derived progenitor cells in the management of patients with ACLF.

5. LIPOSOMAL PERITONEAL DIALYSIS FOR THE MANAGEMENT OF HEPATIC ENCEPHALOPATHY

PI: Jonel Trebicka
(University of Bonn, Germany)
Funder/Promoter: Versantis

Versantis is a start-up pharmaceutical company from Zurich that develops innovative therapies based on lipid microvesicles. This study consists of a two-phase clinical investigation, aimed at assessing the safety and efficacy of ammonia scavenging microvesicles (liposomes) administered intraperitoneally in the management of patients with cirrhosis and hepatic encephalopathy.
The first-in-man phase I trial started in 2019 and already included three patients, which were successfully treated. The treatment was very well tolerated and first data seem very promising and we look forward to the next cohorts of this study.

10

SCIENTIFIC **PUBLICATIONS**

01. ACUTE-ON-CHRONIC LIVER FAILURE IN PATIENTS WITH ALCOHOL-RELATED LIVER DISEASE. Gustot T, Jalan R. 2019. Journal of Hepatology. 70; 319-327

02. SARCOPENIA IS ASSOCIATED WITH DEVELOPMENT OF ACUTE-ON-CHRONIC LIVER FAILURE IN DECOMPENSATED LIVER CIRRHOSIS RECEIVING TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT. Praktiknjo M, Clees C, Pigliacelli A, Fischer S, Jansen C, Lehmann J, Pohlmann A, Lattanzi B, Krabe V, Strassburg C, Arroyo V, Merli M, Meyer C, Trebicka J. 2019. Clinical and Translational Gastroenterology. 10; 1-8

03. ACUTE-ON-CHRONIC LIVER FAILURE IN CIRRHOSIS REQUIRES EXPEDITED DECISION FOR LIVER TRANSPLANTATION. Arroyo V. 2019. Gastroenterology. 156; 1248-1249

04. ADDRESSING PROFILES OF SYSTEMIC INFLAMATION ACROSS THE DIFFERENT CLINICAL PHENOTYPES OF ACUTELY DECOMPENSATED CIRRHOSIS. Trebicka J, Amorós A, Pitarch C, Titos E, Alcaraz-Quiles J, Schierwagen R, Deulofeu C, Fernández-Gómez J, Piano S, Caraceni P, Oettl K, Sola E, Laleman W, McNaughtan J, Mookerjee R, Coenraad M, Welzel T, Steib Ch, García R, Gustot T, Rodríguez Gandía M, Bañares R, Albillos A, Zeuzem S, Vargas V, Saliba F, Nevens F, Alessandria C, De Gottardi A, Zoller H, Ginès P, Sauerbruch T, Gerbes A, Stauber R, Bernardi M, Angeli P, Pavesi M, Moreau R, Clària J, Jalan R, Arroyo V. 2019. Frontiers in Immunology. Volum 10

05. EFFECTS OF ALBUMIN TREATMENT ON SYSTEMIC AND PORTAL HEMODYNAMICS AND SYSTEMIC INFLAMMATION IN PATIENTS WITH DECOMPENSATED CIRRHOSIS. Fernández J, Clària J, Amorós A, Aguilar F, Castro M, Casulleras M, Acevedo J, Duran-Güell M, Nuñez L, Costa M, Torres M, Horrillo R, Ruiz-del-Arbol L, Villanueva C, Prado V, Arteaga M, Trebicka J, Angeli P, Merli M, Alessandria C, Aagsrd N, Soriano G, Durand F, Gerbes A, Gustot T, Welzel T, Salerno F, Bañares R, Vargas V, Albillos A, Silva A, Morales-Ruiz M, Pavesi M, Jalan R, Bernardi M, Moreau R, Páez A, Arroyo V.. 2019. Gastroenterology. 157; 149-162

06. EASL INTERNATIONAL RECOGNITION AWARD RECIPIENT 2019: PROF. FLAIR JOSE CARRILHO. Arroyo V. 2019. Journal of Hepatology. 70; 826-827

07. REVIEW OF DEFECTIVE NADPH OXIDASE ACTIVITY AND MYELOPEROXIDASE RELEASE IN NEUTROPHILS FROM PATIENTS WITH CIRRHOSIS. Moreau R, Perianin A, Arroyo V. 2019. Frontiers in Immunology. 10; artic. 1044 1-7

08. ORCHESTRATION OF TRYPTOPHAN-KYNURENINE PATHWAY ACUTE DECOMPENSATION AND ACUTE-ON-CHRONIC LIVER FAILURE IN CIRRHOSIS. Clària J, Moreau R, Fenaille F, Amorós A, Junot Ch, Gronbaek H, Coenraad M, Pruvost A, Ghettas A, Chu-Van E, Lopez-Vicario C, Oettls K, Caraceni P, Alessandria C, Trebicka J, Pavesi M, Deulofeu C, Albillos A, Gustot T, Welzel T, Fernandez J, Strauber R, Saliba F, Butin N, Colsch B, Moreno Ch, Durand F, Nevens F, Bañares R, Benten D, Ginès P, Gerbes A, Jalan R, Angeli P, Bernardi M, Arroyo V.. 2019. Hepatology. 69; 1686-1701

09. BLOOD METABOLOMICS UNCOVERS INFLAMMATION-ASSOCIATED MITOCHONDRIAL DYSFUNCTION AS A POTENTIAL MECHANISM UNDERLYING ACLF. Moreau R, Clària J, Aguilar F, Fenaille F, Lozano J, Junot Ch, Colsch B, Caraceni P, Trebicka J, Pavesi M, Alessandria C, Nevens F, Saliba F, Welzel T, Albillos A, Gustot T, Fernández J, Moreno Ch, Baldassare M, Zaccherini G, Piano S, Montagnese S, Vargas V, Genescà J, Solà E, Bernal W, Butin N, Hautbergue T, Cholet S,

Castelli F, Jansen Ch, Campion D, Mookerjee R, Rodríguez-Gandía M, Soriano G, Durand F, Benten D, Bañares R, Stauber R, Gronbaek H, Coenraad M, Ginès P, Gerbes A, Jalan R, Bernardi M, Arroyo V, Angeli P. 2019. Journal of Hepatology. In press

10. LIVER TRANSPLANTATION FOR NON-ALCOHOLIC STEATOHEPATITIS IN EUROPE: WHERE DO WE STAND? Durand F, Pavesi M, Cheung R. 2019. Journal of Hepatology. 71; 240-242

11. EFFICACY OF ALBUMIN TREATMENT FOR PATIENTS WITH CIRRHOSIS AND INFECTIONS UNRELATED TO SPONTANEOUS BACTERIAL PERITONITIS. Fernández J, Angeli P, Trebicka J, Merli M, Gustot T, Alessandria C, Aagaard N.K, Gottardi A, Welzel T, Gerbes A, Vargas V, Albillos A, Salerno F, Durand F, Bañares R, Stauber R, Prado V, Ateaga M, Hernández Tejero M, Aziz F, Morando F, Jansen C, Lattanzi B, Moreno C, Campion D, Gronbaek H, García R, Sánchez C, García E, Amorós A, Pavesi M, Clària J, Moreau R, Arroyo V. 2019. Clinical Gastroenterology and Hepatology. In press

12. META ANALYSIS OF INDIVIDUAL-PATIENT DATA OF ALBUMIN DIALYSIS IN ACLF: FOCUS ON TREATMENT INTENSITY. Bañares R, Ibáñez-Samaniego L, Torner J, Pavesi M, Olmedo C, Catalina M, Albillos A, Larsen s, Nevens F, Hassanein T, Schmidt H, Heeman U, Jalan R, Moreau R, Arroyo V. 2019. Therapeutic Advances in Gastroenterology. 12:1-12

13. THE DEVELOPMENT AND OUTCOME OF ACLF AFTER SURGICAL INTERVENTIONS. Klein L, Chang J, Gu W, Manekeller S, Jansen Ch, Lingohr P, Pratiknjo M, Kalf J, Schulz M, Spengler U, Strassburg Ch, Cárdenas A, Arroyo V, Trebicka J. 2019. Liver Transplantation. 26; 227-237

14. COMPARTMENTALIZATION OF IMMUNE RESPONSE AND MICROBIAL TRANSLOCATION IN DECOMPENSATED CIRRHOSIS. Alvarez-Silva C, Schierwagen R, Pohlmann A, Magdaleno F, Uschner F, Ryan P, Vehreschild M, Clària J, Latz E, Lelouvier B, Arumugam M, Trebicka J. 2019. Frontiers in Immunology. vol 10 artic. 69

15. PATHOPHYSIOLOGICAL ROLE OF PROSTANOIDS IN COAGULATION OF THE PORTAL VENOUS SYSTEM IN LIVER CIRRHOSIS. Queck A, Thomas D, Jansen Ch, Schreiber Y, Rüschenbaum S, Praktiknjo M, Schwarzkopf K, Mücke M, Schierwagen R, Uschner F, Meyer C, Clària J, Zeuzem S, Geisslinger G, Trebicka J, Lange Ch. 2019. PLOS One. 14(10):e0222840

15
SCIENTIFIC ARTICLES

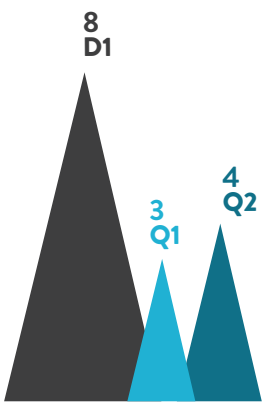
10 ORIGINAL RESEARCH ARTICLES

2 REVIEW ARTICLES

3 EDITORIALS

MEAN IF **10,61**

TOTAL IF **159,19**



15 ARTICLES PUBLISHED

8 articles **D1**

3 articles **Q1**

4 articles **Q2**

9 ARTICLES ARE SIGNED by authors from **5 or more EASL-Clif** Consortium Members

5 ARTICLES ARE SIGNED by authors from **15 or more EASL-Clif** Consortium Members

EF Clif

EUROPEAN
FOUNDATION
FOR THE STUDY
OF CHRONIC
LIVER FAILURE

EF Clif

EUROPEAN
FOUNDATION
FOR THE STUDY
OF CHRONIC
LIVER FAILURE

Travessera de Gràcia, 11, 7th floor
08021 Barcelona (Spain)
+34 932 271 400

efclif@efclif.com
www.efclif.com