EF Clif

EUROPEAN
FOUNDATION
FOR THE STUDY
OF CHRONIC
LIVER FAILURE

2020 **SUMMARY** OF **ACTIVITIES**

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SUMMARY OF ACTIVITIES

2020

CONTENTS

LETTER OF THE PRESIDENT

2020 has been a terrible year for the Humanity because of the Covid2019 Pandemic. This introductory letter describing the activities of EFClif within this year, however, is a clear exponent of the human ability to adapt to extreme circumstances. Working remotely, outside the EFClif headquarters, we have been able to finalise the **ACLARA** study, which included 1,245 patients hospitalized with acute decompensation of cirrhosis hospitalized in more than 40 hospitals from seven Latin-American countries (Mexico, Colombia, Perú, Brazil, Argentina, Paraguay, and Chile).

We revised hundreds of thousands of clinical and standard laboratory data, closing the final clinical database, and successfully initiated the complex process of importing several thousands of biological samples that will help to understand the behaviour of the acute-on-chronic Liver failure (ACLF) in the Central and South Latin-American Area. The **ACLARA** study is also important because it will also introduce the first concepts on the role of ethnicity in the prevalence and severity of the syndrome. I am extremely grateful to the hundreds of researchers (nurses and physicians) from the Latin-American CLIF Consortium participating in the study and to the components of the **ACLARA** study office in the Hospital das Clinicals in Sao Paulo for their excellent work.

2020 has been also the year of launching the organization the **CHANCE** study, which is aimed to assess the role of liver transplantation in the management of ACLF. The study is a joint venture of EFClif, the European Liver and Intestine Transplant Association (ELITA) and the International Liver Transplant Society (ILTS). The **CHANCE** study will represent a major challenge for EFClif, since it plans to include 3000 patients that will be transplanted in 95 hospitals from Europe, North and South America, Asia, and Oceania. After the initial study recently accepted for publication by EFClif reporting excellent survival rates in **CANONIC** study patients with ACLF 2 and 3 treated by liver transplantation, an increasing number prospective and retrospective studies from Europe and USA have confirmed our observation.

However, the indication of Liver transplantation is still extremely heterogeneous among different transplant units, with many of them considering patients with ACLF as being too ill for such a complex surgical procedure. It is, therefore, time to develop a definitive prospective study that stablish clear indications and futility criteria of liver transplantation in these patients. The **CHANCE** study will start including patients in May 2021, with only 4 months delay over the expected time.

Finally, 2020 has been a fruitful year for the scientific production of EFClif. Eighteen articles, including nine original research articles, were published. We are still publishing studies derived from the **CANONIC** study, our first large-scale multicentre investigation initiated in 2009. However, in 2020 we already published our first two articles derived from the **PREDICT** study, ensuring a second wave of important publications.

All these scientific activities, within a context of extremely severe emotional and logistic difficulties, would have been impossible without the enthusiasm of our investigators from the European and Latin-American CLIF Consortiums and the staff of EFClif in Barcelona. I am proud of them.

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 CLIF Consortium already completed and published or in the process of being published have revealed new mechanisms that help understanding 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, in order to improve the quality of life and to increase the survival of patients with liver cirrhosis.

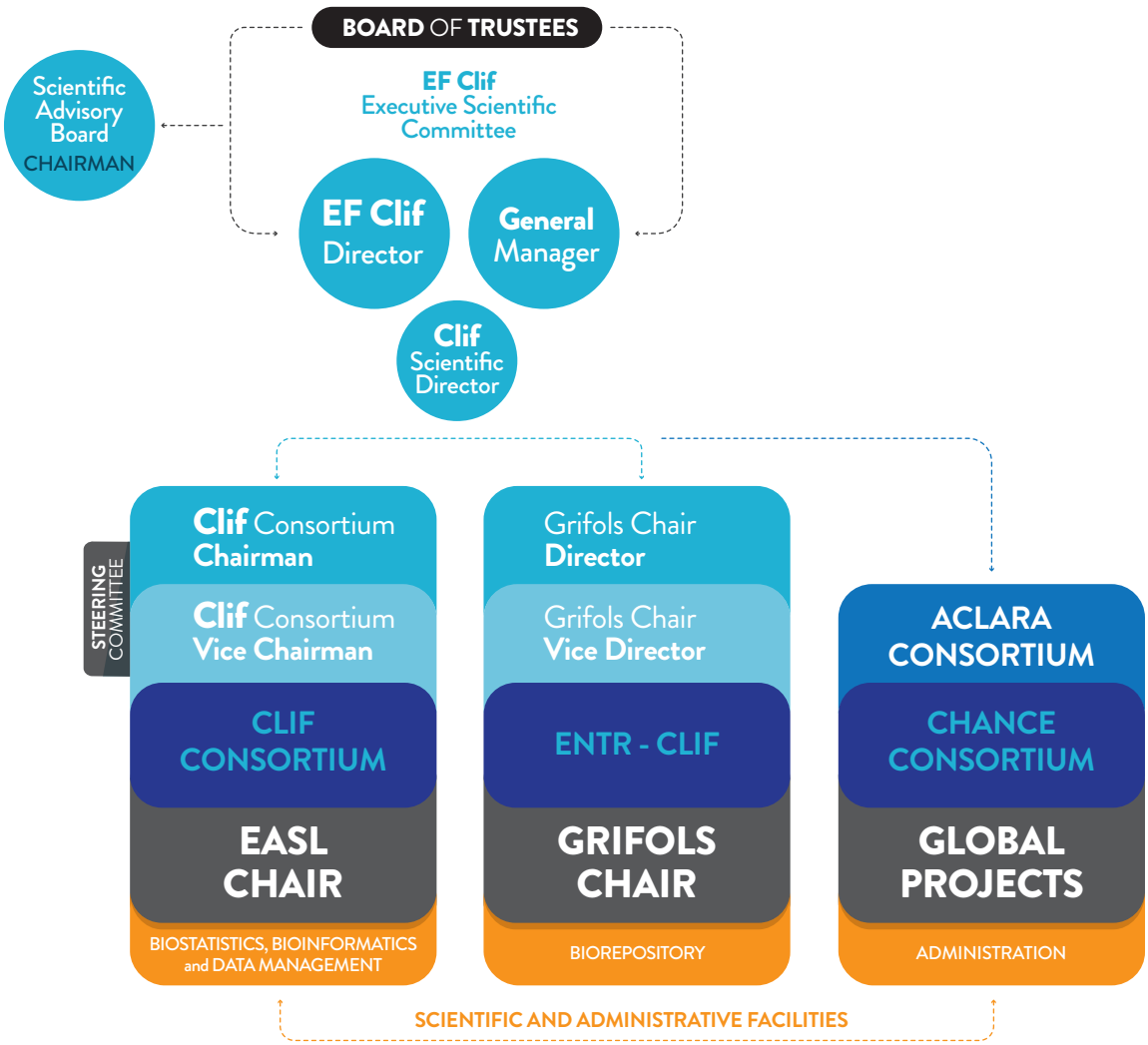
VISION

Our aim is helping investigators to achieve their objectives and being a referent in Acute on Chronic Liver Failure 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

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ARROYO
M.D.

- Emeritus Professor of Medicine, University of Barcelona Medical School, Spain.
- Director of the EF Clif.
- President of the Board of Trustees.
- 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).

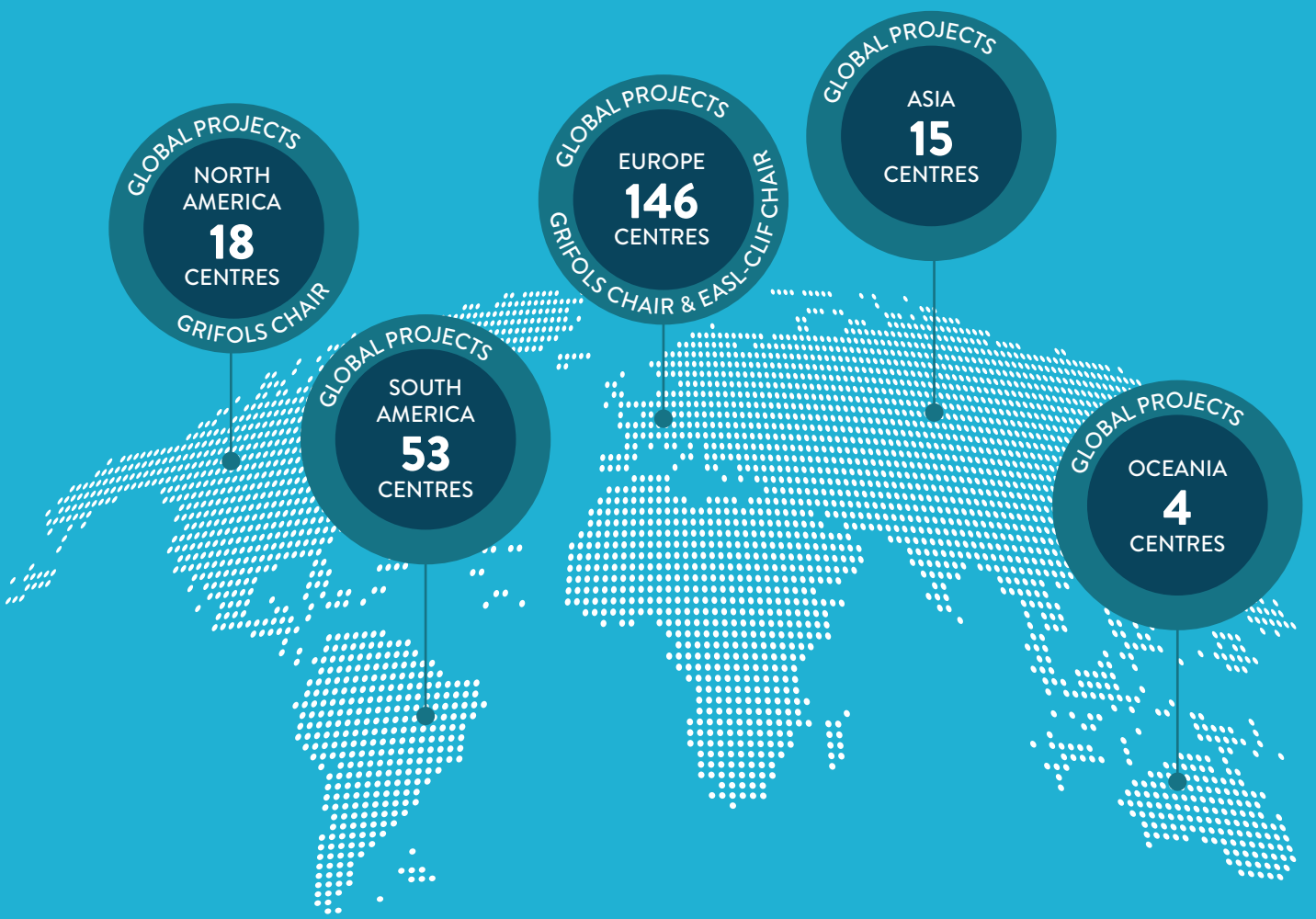
Main interests
He specializes in Company Law, Competition and Industrial Property.

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.

236 CENTRES



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28 COUNTRIES

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- 2 CROATIA
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- 19 GERMANY
- 1 GREECE
- 1 HUNGARY
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- 11 ITALY
- 1 IRELAND
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- 2 SLOVAK REPUBLIC
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- 1 THE NETHERLANDS
- 2 UNITED KINGDOM
- 2 USA

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- 7 ARGENTINA
- 3 AUSTRALIA
- 20 BRAZIL
- 2 CANADA
- 3 COLOMBIA
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- 1 THE NETHERLANDS
- 1 TAIWAN
- 3 TURKEY
- 1 UNITED KINGDOM
- 14 USA

5.1

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5.1.1

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

CENTRES BY PROJECT

EF Clif STUDIES

ACLARA · ALADDIN · ALIVER · CANONIC · CARBALIVE · CHANCE · COVID · DECISION · INFECIR · LIVERHOPE · MICROB-PREDICT · PRECIOSA · PREDICT · SCOTCH

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CZECH REPUBLIC
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Nykoebing Falster Hospital
Odense University Hospital

ESTONIA
West Tallin Central Hospital

FRANCE
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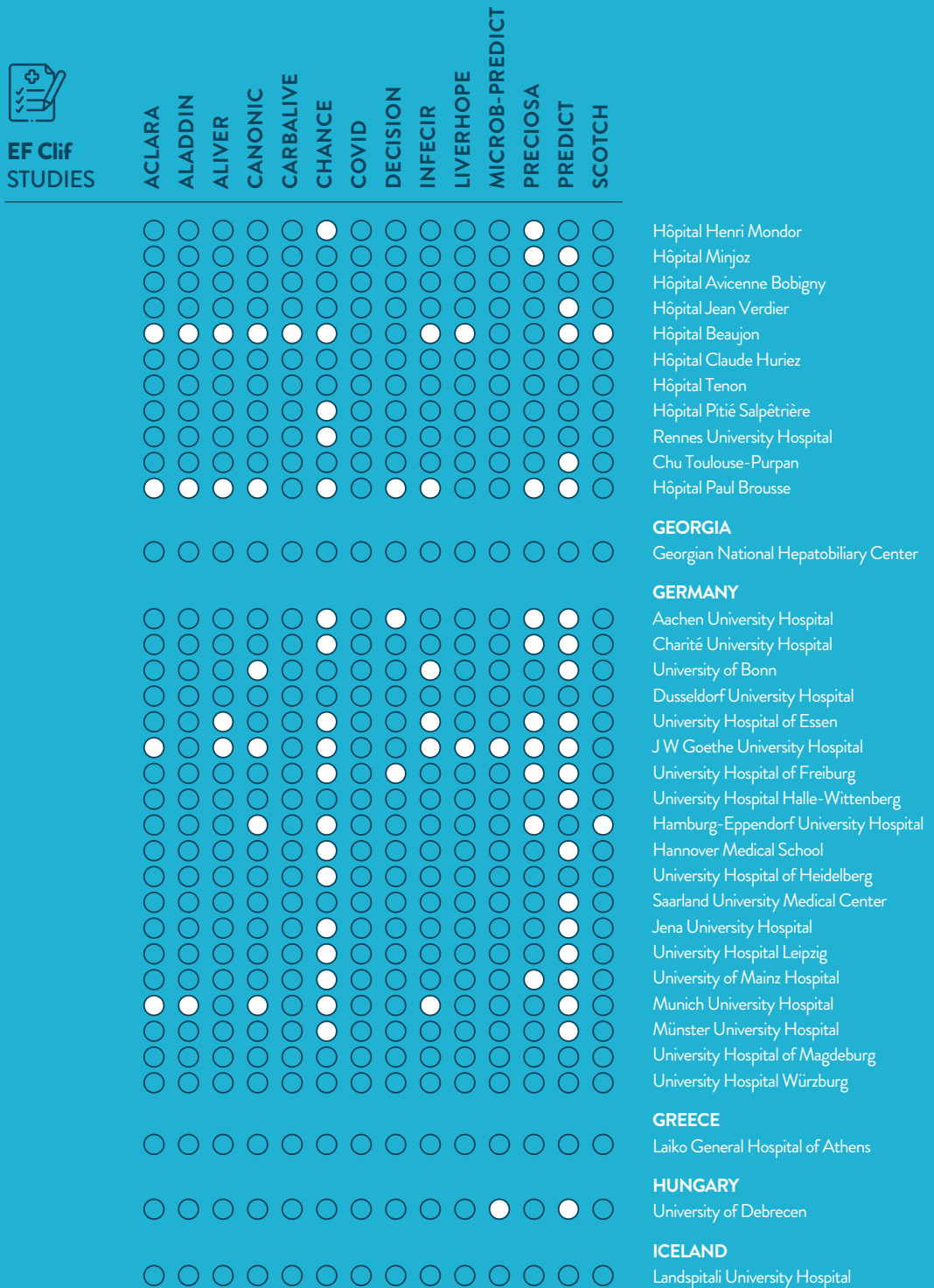
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STUDIES
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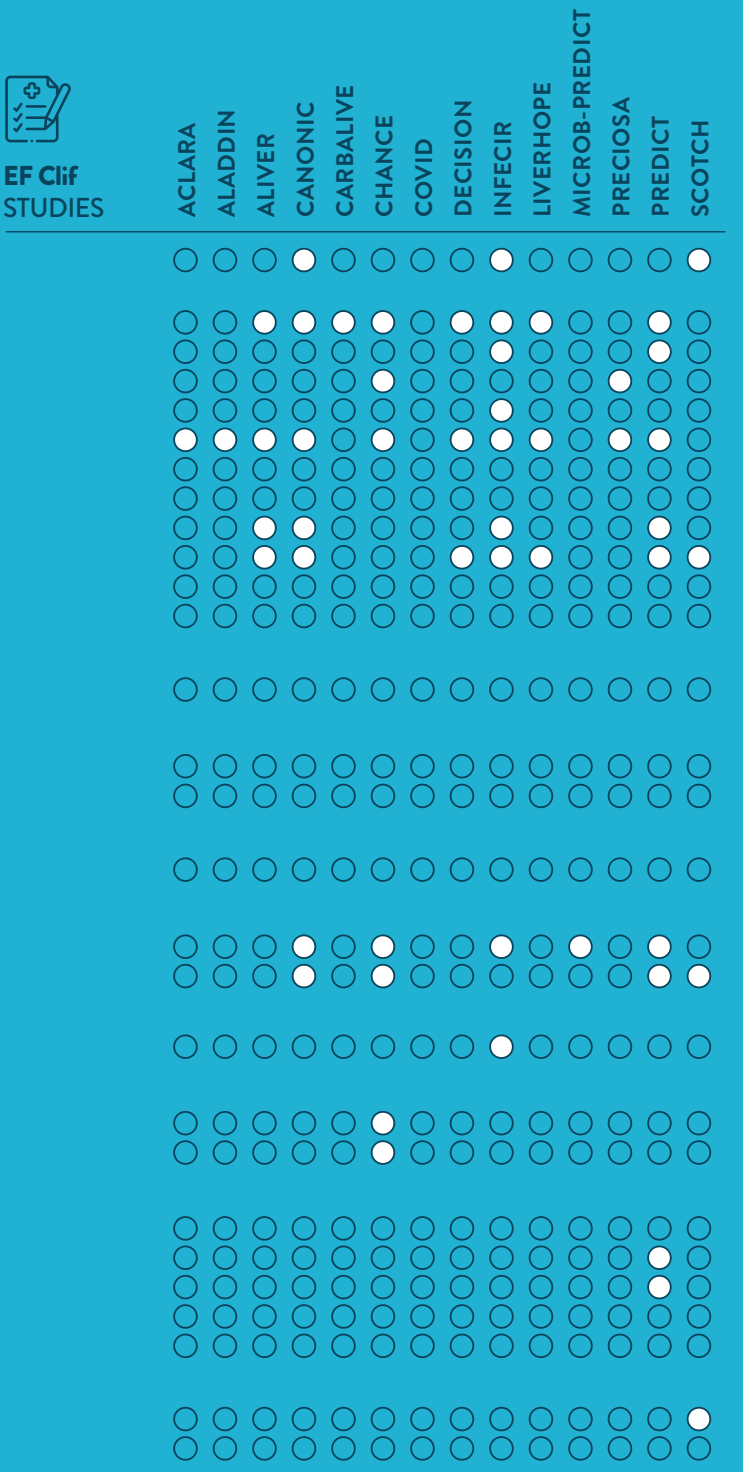

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Depart. of Medical and Surgical Sciences, University of Bologna
Asl Brindisi
Ospedale Niguarda
Policlinico San Donato. University of Milan
Azienda Ospedaliera di Padova
Policlinico of Palermo
University Hospital of Messina
University of Rome
Azienda Ospedaliera Città della Salute e della Scienza di Torino
Internal Medicine. University of Udine
University of Verona. Liver Unit

LATVIA
Riga East University Hospital

LITHUANIA
Hospital of Lithuanian University of Kaunas
Siauliai Hospital

LUXEMBOURG
Centre Hospitalier de Luxembourg

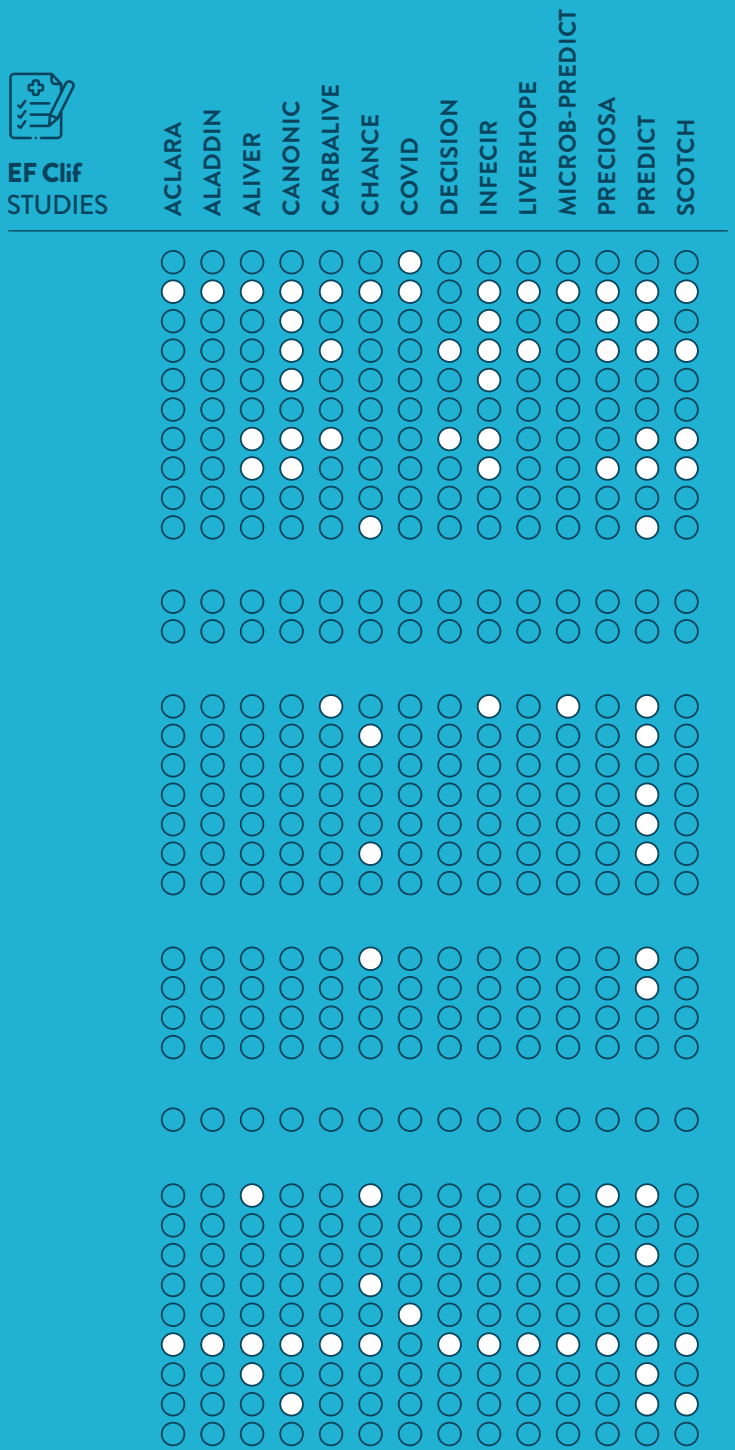
THE NETHERLANDS
Leiden University Medical Center
Erasmus University Medical Center Rotterdam

NORWAY
Oslo University Hospital

POLAND
Medical University of Warsaw
Pomerian Medical University

PORTUGAL
Centro Hospitalar Lisboa Norte
Centro Hospitalar Universitário do Porto
Chtmad Vila Real
Curry Cabral Hospital
Hospital Santa Luzia

SLOVAK REPUBLIC
Pavol Jozef Safarik University in Kosice
Roosevelt University Hospital Banska Bystrica



SPAIN
- Hospital Universitari Germans Trias i Pujol
- Hospital Clinic Universitari de Barcelona
- Hospital de la Santa Creu i Sant Pau
- Hospital Universitari Vall d'Hebron
- Hospital Universitario Reina Sofía
- Hospital Universitari Bellvitge
- Hospital Universitario Ramón y Cajal
- Hospital General Universitario Gregorio Marañón
- Clinica Universitaria Navarra
- Hospital Virgen del Rocío

SWEDEN
- Linköpin University Hospital
- Sahlgrenska University Hospital

SWITZERLAND
- Inselspital Berne
- University Hospital of Geneve
- Lausanne University Hospital
- St Gall Cantonal Hospital
- University Hospital Basel
- Zürich University Hospital
- Università della Svizzera Italiana

TURKEY
- Ankara University Faculty of Medicine
- Marmara University School of Medicine
- Karadeniz School of Medicine
- Sarkaya University School of Medicine

UKRAINE
- Ivano-Frankivsk National Medical University

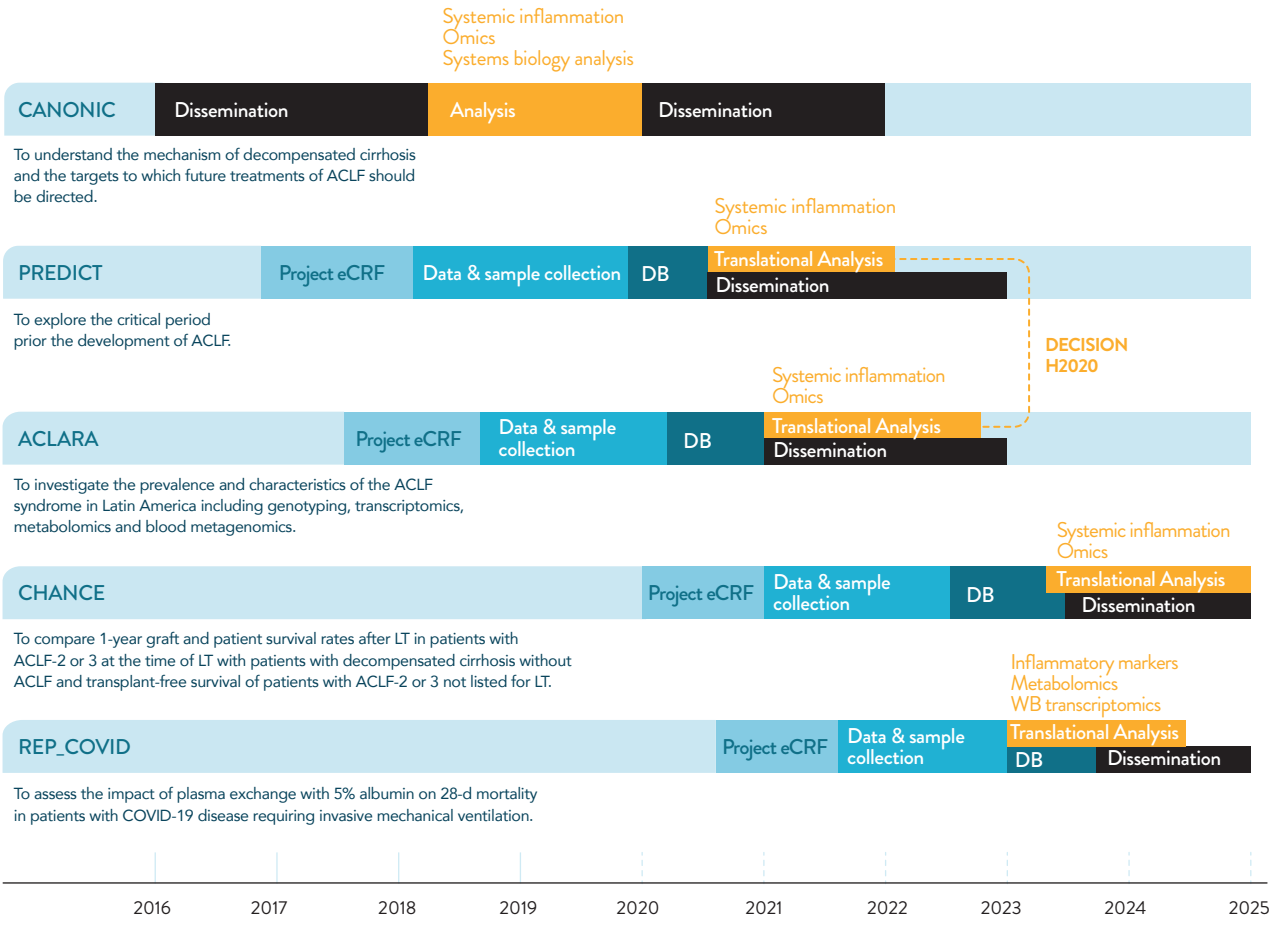
UNITED KINGDOM
- University Hospitals Birmingham
- Glasgow Royal Infirmary
- Imperial College
- King's College Hospital
- Leeds Teaching Hospital
- University College London and Royal Free Hospital
- University Hospitals Nottingham
- Plymouth Hospital Trust
- Queen Alexandra Hospital Portsmouth

STUDIES BY CENTRES

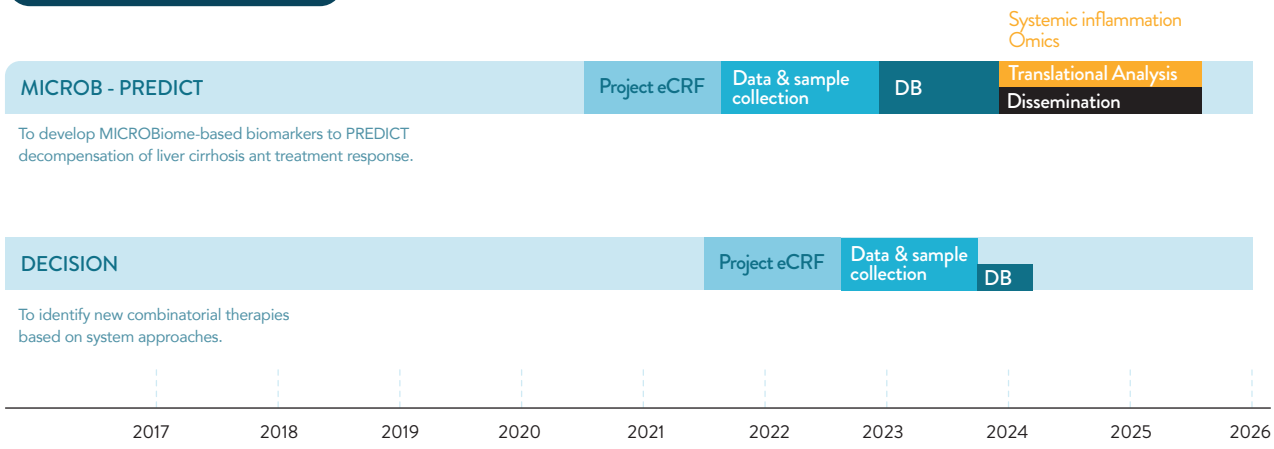
5.1.3

CONSORTIUM PROJECTS
EASL-Clif CHAIR STUDIES CALENDAR

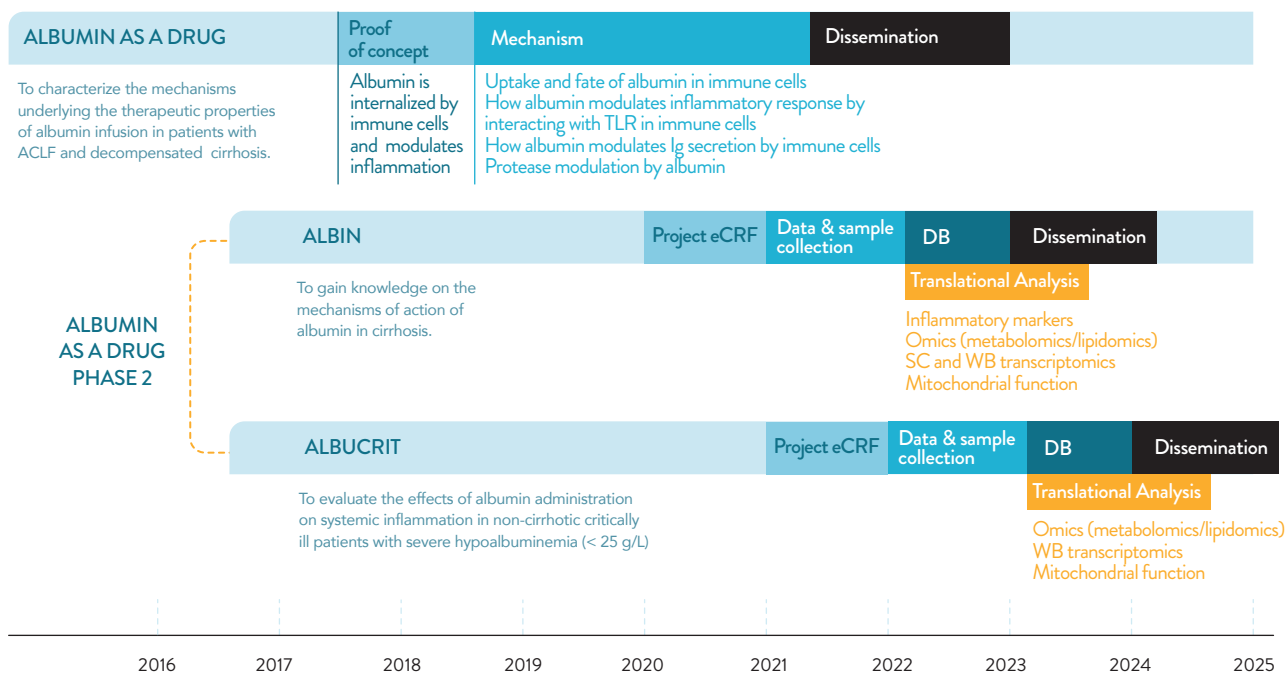
CLINICAL PROJECTS



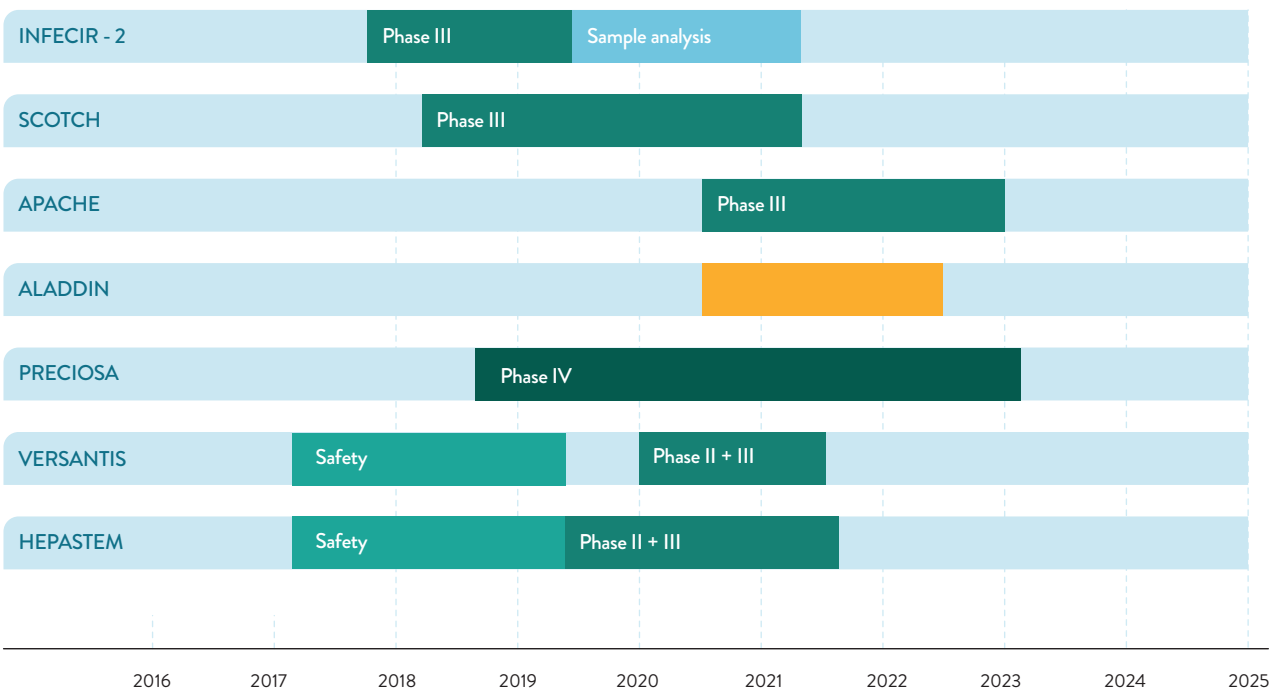
H2020



TRANSLATIONAL PROJECTS



CLINICAL TRIALS



5.2

THE GRIFOLS CHAIR

The scientific activities of the **European Network of Translational Research (ENTR)** centers, 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

THE EUROPEAN NETWORK OF TRANSLATIONAL RESEARCH AND ASSOCIATED INVESTIGATORS

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AMBIOTIS
Marc Dubordeau

HÔPITAL BEAUJON
Pierre-Emmanuel Rautou

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

GENOSPLICE TECHNOLOGY
Pierre De La Grange

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BIOBANCO VASCO
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Mireia Casulleras
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Ingrid Zhang
Roger Flores-Costa
Cristina López Vicario
Wladimiro Jiménez
Guillermo Fernández-Varo

NAVARRABIOMED
David Gomez-Cabrero
Núria Planell Picola
Arantxa Urdangarin Iztueta

OWL METABOLOMICS
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FOUNDATION FOR LIVER RESEARCH
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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 in the 5 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.

ARGENTINA

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Margarita Anders
Federico Orozco

HOSPITAL ITALIANO DE BUENOS AIRES
Adrián Gadano
Sebastián Marciano
Juan Manuel Diaz

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 DE INFECCIOSAS F. J. MUÑIZ
Hugo Fainboim

HOSPITAL PROVINCIAL DEL CENTENARIO
Fernando Bessone
Gabriela Juaristi

AUSTRALIA

AUSTIN HEALTH
Marie Sinclair

SIR CHARLES GAIRDNER HOSPITAL
Gary Jeffrey

ROYAL PRINCE ALFRED HOSPITAL
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Avik Majumdar

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UNIVERSIDADE ESTADUAL PAULISTA
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HOSPITAL DE BASE DO DISTRITO FEDERAL
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UNIVERSIDADE ESTADUAL DE CAMPINAS
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UNIVERSIDADE FEDERAL DA PARAÍBA
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HÔPITAL TROUSSEAU
Laure Elkrief

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Silvia Wagner

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Ashwin Ramonah

FORTIS HOSPITAL GROUP
Vivek Vij

MEDANTA MEDICITY
Avi Soin

AMRITA INSTITUTE OF MEDICAL SCIENCES
S.Sudhindran

GLOBAL HOSPITAL. SUPER SPECIALITY & TRANSPLANT CENTRE
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MAX SAKET HOSPITAL
Subhash Gupta

YASHODA HOSPITALS
Dharmesh Kapoor

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CA' GRANDA. POLICLINICO MILANO
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Paolo de Simone

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Masahiro Ohira

KYOTO UNIVERSITY HOSPITAL
Shintaro Yagi

KYUSHU UNIVERSITY HOSPITAL
Tomoharu Yoshizumi

NAGASAKI UNIVERSITY HOSPITAL
Susumu Eguchi
Takanobu Hara

TOKYO UNIVERSITY HOSPITAL
Nobuhisa Akamatsu

KOREA

SAMSUNG MEDICAL CENTER
Jong Man Kim

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Norberto Chávez Tapia

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Graciela Castro Narro
Ernesto Márquez

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

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Mauricio Castillo Barradas

HOSPITAL GENERAL JUÁREZ
Scherezada Mejía Loja
Raúl Uvaldo Aguilar Moreno

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Lilian Torres Made

STAR MÉDICA
Iarah Montalvo
Luis Alberto Chi

CENTRO MÉDICO INSSEMYN
María Sarai González Huezo

HOSPITAL SAN JOSÉ TEC DE MONTERREY
Francisco Bosques
Emilio Sandoval González

UNIVERSIDAD VERACRUZANA
José María Remes Troche

THE NETHERLANDS

UNIVERSITY MEDICAL CENTER GRONINGEN (UMCG)
Robert Porte
Aad van den Berg

NEW ZEALAND

AUCKLAND CITY HOSPITAL
Dominic Ray-Chaudhuri

PARAGUAY

HOSPITAL DE CLÍNICAS DE LA UNIVERSIDAD NACIONAL DE ASUNCIÓN
Marcos Girala
Cecilia Insfram

PERÚ

HOSPITAL NACIONAL EDGARDO REBAGLIATI MARTINS
Milagros Dávalos Moscol
Javier Díaz Ferrer

HOSPITAL NACIONAL GUILLERMO ALMENARA
Pedro Martín Padilla
Alfonso Solar
Bertha Cardenas Ramírez

HOSPITAL NACIONAL ARZOBISPO LOAYZA
Adelina Zarela Lozano Miranda
Jorge Garavito

HOSPITAL NACIONAL DANIEL A. CARRIÓN
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Jaime Fustamante
Briny Rodríguez

HOSPITAL ESSALUD-AREQUIPA
Raúl Castro
Katherine Zevallos

SPAIN

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Carmen Vinaixa
Marina Carmen Berenguer Haym

TAIWAN

KAOHSIUNG CHANG GUNG MEMORIAL HOSPITAL
Chee Chien Yong

TURKEY

ACIBADEM ATAKENT HOSPITAL
Remzi Emiroğlu

ISTANBUL MEMORIAL BAHCELIEVLER HOSPITAL
Kamil Polat

INONU UNIVERSITY, LIVER TRANSPLANTATION INSTITUTE
Sezai Yılmaz

UNITED KINGDOM

SCOTTISH LIVER TRANSPLANT UNIT, ROYAL INFIRMARY
Kenneth Simpson

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Lance Stein
Natasha Morris

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Kirti Shetty
John LaMattina

THE UNIVERSITY OF CHICAGO MEDICINE
Helen Te
Diego DiSabato

BAYLOR COLLEGE OF MEDICINE
Robert Rahimi
Amar Gupta

BAYLOR ST. LUKE'S MEDICAL CENTRE
Jalal Prasun

HOUSTON METHODIST HOSPITAL
Akshay Shetty
Robert McMillan

MICHAEL E DEBAKEY VA MEDICAL CENTER
Rubén Hernáez
Ronald Timothy Cotton

CEDARS-SINAI COMPREHENSIVE TRANSPLANT CENTER
Vinay Sundaram
Nicholas Nissen

COLUMBIA UNIVERSITY
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Elizabeth Verna

ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI
Ghideon Ezaz
Chiara Rocha

WEILL CORNELL MEDICINE
Brett Fortune
Ben Samstein

UNIVERSITY OF PENNSYLVANIA
Nadim Mahmud

UNIVERSITY OF UTAH HEALTH
Juan F. Gallegos-Orozco

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
Tanja Gasic
Esaú Moreno
Cristina Sánchez
Patricia Sierra

STATISTICIANS
Àlex Amorós
Elisabet García

CTO/CIO
Pedro Izquierdo-Bueno

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DIRECTOR
Vicente Arroyo

SCIENTIFIC DIRECTOR
Rajiv Jalan

TRANSLATIONAL RESEARCH COORDINATORS
Joan Clària
Richard Moreau

CLINICAL RESEARCH
Javier Fernández
Jonel Trebicka

VISITING CLINICAL RESEARCHERS
Juan Manuel Díaz
Emmanuel Weiss
Giacomo Zaccherini

7

FACTS AND FIGURES

1,000

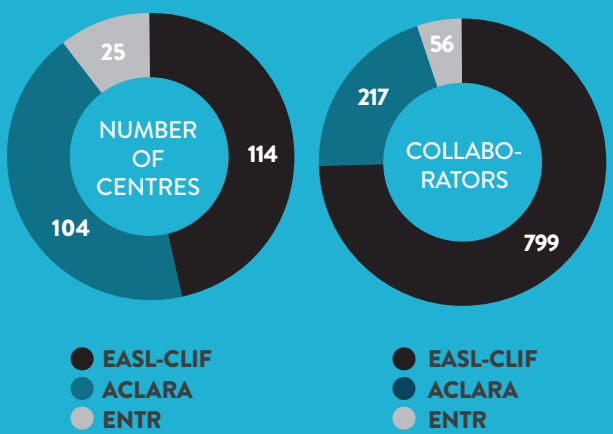
MORE THAN **1,000 INVESTIGATORS** WORKING ON **EF Clif** SPONSORED SCIENTIFIC PROJECTS, FUNDED WITH MORE THAN

7,000,000 € / year

236 CENTRES

44 COUNTRIES

COLLABORATORS IN EUROPE, NORTH AMERICA, SOUTH AMERICA, ASIA AND OCEANIA **236 CENTRES DISTRIBUTED IN 3 INTERNATIONAL NETWORKS, IN 44 COUNTRIES AROUND THE WORLD**.



42% EASL-CLIF **44%** ACLARA **45%** ENTR

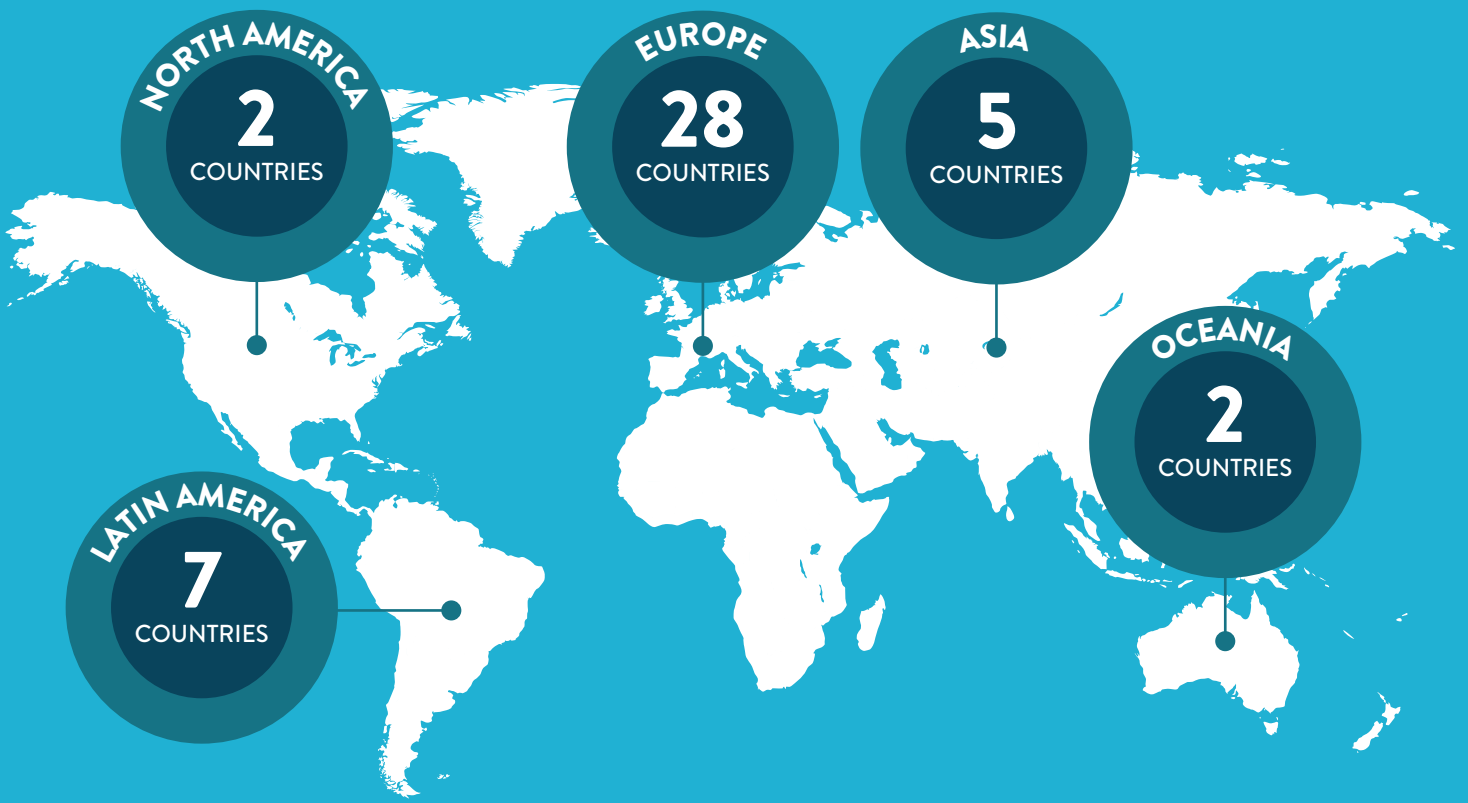
58% EASL-CLIF **56%** ACLARA **55%** ENTR

7.1

INTERNATIONAL NETWORKS

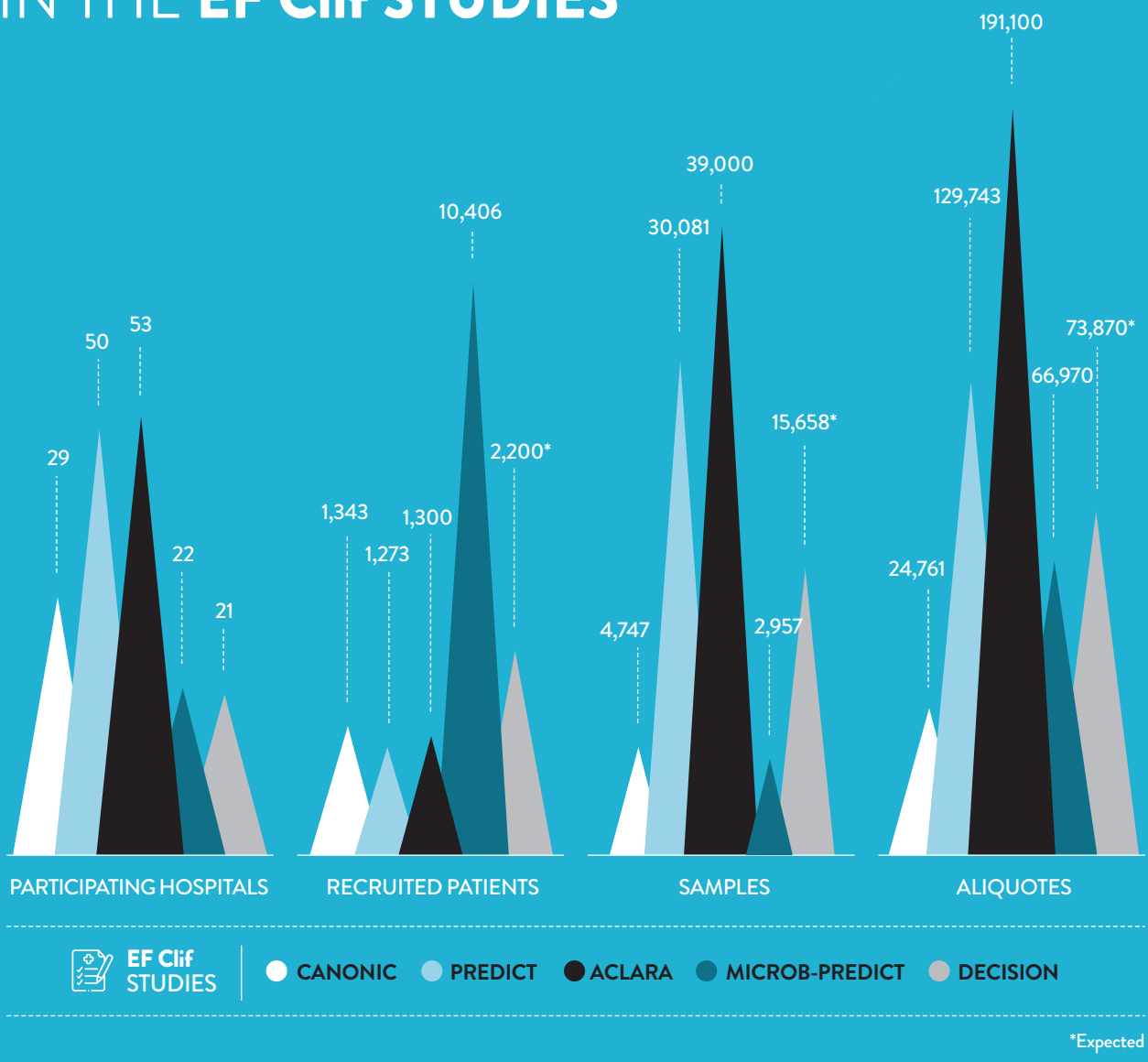
44 COUNTRIES

- EASL-CLIF CONSORTIUM: **EUROPE**
- ENTR-EUROPEAN NETWORK FOR TRANSLATIONAL RESEARCH: **EUROPE AND NORTH AMERICA**
- GLOBAL PROJECTS: **ASIA, EUROPE, NORTH AMERICA, LATIN AMERICA AND OCEANIA**



7.2

PATIENTS COHORTS IN THE **EF Clif STUDIES**



*Expected

8

2020 **MILESTONES**

FEBRUARY 13th

Prof Rajiv Jalan was named as the Scientific Director of the EF Clif

Prof Jalan's extensive experience in Hepatology research and his relevant and consolidated track record of publications worldwide make him an ideal candidate for this new position.

He has vast expertise in leading collaborative international projects such as the EU H2020 ALIVER and CARBALIVE. Together with Prof. Vicente Arroyo, Director of the EF Clif, they have led the Strategic Research Program of the Foundation.

Rajiv Jalan (MBBS, MD, PhD, FRCP, FRCPE, FAASLD) is currently Professor of Hepatology at the Institute for Liver and Digestive Health, UCL Medical School and Hon. Consultant at the Royal Free Hospital. He was the former Editor in Chief of Journal of Hepatology and is a Founder member of the EASL Clif Consortium.

His work intends to provide leadership to investigate the clinical, pathophysiological and novel therapeutics for patients with cirrhosis, in order to significantly diminish the number of deaths within the next 10 years.

He plans to achieve it by consolidating the huge influence EF Clif has had in leading, re-defining, performing and disseminating studies in the field.

MARCH 24th

ACLARA. Stop of Recruitment

Inclusion was planned to be closed in the 3rd quarter of 2020. However as on that date, 1291 patients were included, out of the foreseen 1300, it was decided to suspend patients' recruitment to focus the effort to fight the COVID-19 pandemic.

ACLARA

APRIL 16th

The EF Clif leads the DECISION Project

The DECISION project is a Horizon 2020 funded research, whose overall aim is to prevent ACLF and drastically reduce mortality rates in patients with decompensated cirrhosis.

For 5.5 years, Prof Pierre-Emmanuel Rautou will coordinate 21 relevant European institutions to analyse and integrate data and biological samples from 2,000 patients, validate the results in animal models and test the most promising resultant therapy in a phase II clinical trial.

The patients participating in the DECISION research will take advantage of these treatments, while future patients will benefit of the novel combinatorial therapies and improved guidelines derived from the project.

MAY 05th

The EF Clif leads the REP-COVID Study

The trial is endorsed by the EF Clif and has engaged four hospitals in the area of Barcelona: Hospital Clinic, Hospital de Bellvitge, Hospital del Mar and Hospital Germans Trias i Pujol.

The REP COVID study is led by two investigators of the EF Clif, Dr Javier Fernández, in the clinical setting and Dr Joan Clària, in the management of biological samples. Grifols supports it by supplying the investigational products: 5% albumin and intravenous immunoglobulin. The EF Clif data management centre designed the eCRF and will perform the data analysis.

MAY 18th

Review article in the New England Journal of Medicine

Acute-on-Chronic Liver failure is signed by the Prof Vicente Arroyo, Prof Rajiv Jalan and Prof. Richard Moreau, all members of the EF Clif.

The publication of this article represented a recognition of the excellent work performed by many European investigators from the EASL-CLIF Consortium and Grifols Chair over the years.

JULY 07th

The EASL Clif Consortium raised its partners to 114

During the annual meeting of the Steering Committee, 8 hospitals from Croatia, Germany, Greece, Italy, Luxembourg, Portugal, Switzerland and Turkey were chosen to be part of the EASL Clif Consortium University Hospital Dubrava, led by Ivica Grgurevic; Charité University Hospital in Berlin, by Cornelius Engelmann; Laiko General Hospital of Athens, by George Papatheodoridis; Liver Unit.

University of Verona, by Davide Sacerdoti; Centre Hospitalier de Luxembourg, by Verónica Prado; Hospital de Santa Luzia in Viana do Castelo, by Rogerio Corga; Università della Svizzera Italiana, by Roberto di Donato and Sakarya University School of Medicine, by Aydin Seref Köksal are the new members.

NOVEMBER

The CHANCE Study, a new challenge for the EF Clif

Together with the International Liver Transplantation Society (ILTS) and the European Liver and Intestine Transplant Association (ELITA), the EF Clif has developped this Study. More than 70 hospitals in Europe, North and South America and the Asian-Pacific Region will participate in it. Inclusion is foreseen to start in the second quarter of 2021.

The CHANCE Study will compare survival rates after liver transplantation in patients with ACLF and transplant-free survival of patients the same group of patients. It will have a duration of 2 years and intends to include 3,000 patients worldwide.

9

PROGRESS REPORT

PROJECTS DERIVED FROM THE CANONIC STUDY

Metabolomic score in patients from the CANONIC Study. Validation in patients from the PREDICT Study

Translational research

Richard Moreau (EF Clif. Barcelona, Spain)

Christophe Junot (CEA. Saclay, France)

Promoter: EF Clif

Start date: 01/01/2020

End date: 31/12/2020

Untargeted blood metabolomics performed in 831 patients with acutely decompensated (including 181 with ACLF) revealed a 38-metabolite signature that was distinctive of ACLF versus no ACLF (J Hepatol 2020;72:688-701). The objective of the study was to validate the 38-metabolite signature previously found in the CANONIC Study among 800 patients with acutely decompensated cirrhosis enrolled in the PREDICT study.

Within 2020, the analysis of blood metabolomics was completed. The results show that 36 of the 38 metabolites has a discriminative accuracy for distinguishing patients with poor outcomes (development of ACLF, death) from those with better outcomes. A report of the results is under preparation.

Addressing the role of amino acids in systemic inflammatory responses and organ failures in patients with ACLF

Translational research

Richard Moreau (EF Clif. Barcelona, Spain)
Vicente Arroyo (EF Clif. Barcelona, Spain)
Giacomo Zaccherini (University of Bologna. Bologna, Italy;
EF Clif (visiting fellow). Barcelona, Spain

Promoter: EF Clif
Start date: 1/01/2020
End date: 23/11/2020

The objective of the study was to reanalyse the metabolome data set obtained, in patients with acutely decompensated cirrhosis enrolled in the CANONIC study, in order to assess the relative contribution of main organ system failures to changes in blood metabolic in samples collected. The results showed that blood metabolites were mainly composed of amino acids and distributed across 9 distinct modules. ACLF was characterized by increases in the 9 metabolite modules. Increases in a large proportion of metabolites were independently associated with kidney failure; the same true for liver failure. Lesser proportions of metabolites were independently associated with the grade of hepatic encephalopathy. The results have been reported in an original article published in Journal of Hepatology (2021; in press).

GWAS analysis in the CANONIC patients. Validation in patients from the PREDICT Study. Association with metabolomics and with inflammatory markers

Translational research

Joan Clària (Hospital Clínic Barcelona-IDIBAPS; EF Clif. Barcelona, Spain)
Eric Trepo (Hôpital Erasme, Université Libre de Bruxelles. Brussels, Belgium)

Promoter: EF Clif
Start date: 01/01/2019
End date: 30/06/2021

The aim of this study was the identification of genetic variants associated with the progression to ACLF in patients with acutely decompensated cirrhosis. Additionally, this study aimed at identifying

genetic variants that might influence the clinical course and severity of advanced liver disease.
The study was initially performed in 829 patients with decompensated cirrhosis recruited in the CANONIC study (a multicentre observational investigation involving 1343 hospitalized patients with cirrhosis from February to September 2011 in 29 liver units within 8 European countries), which were genotyped using the Infinium® Global Screening Array (Illumina, San Diego, CA).

To gain power, the study was expanded to include 778 patients with decompensated cirrhosis from the PREDICT study and more than 1000 patients from the ACLARA study, both multicentre observational investigations within European and Latin American countries, respectively. The genotyping for these two additional cohorts is currently ongoing.

PROJECTS DERIVED FROM THE PREDICT STUDY

The clinical course of cirrhosis is characterized by recurrent episodes of acute decompensation separated by more or less long periods in which the disease remains compensated under medical treatment. The PREDICT study (1335 patients with acute decompensation not associated with ACLF, 175,000 biological samples) is the second large observational study conducted by the CLIF Consortium. It was designed in 2016, started in 2017 and completed in June 2018, and its data revised and cleaned until March 2019.

The objective of the study is to characterize the episodes of acute decompensation and, most importantly, to develop prognostic tools to PREDICT and stratify the type of patients at risk of developing ACLF and die. The final goal is to provide physio-pathological and clinical bases that justify the paradigm change in the therapeutic guidelines of decompensated liver cirrhosis. This feature is simultaneously being pursued by the PRECIOSA study (prevention of episodes of acute decompensation).

The initial results indicate that acute decompensation in cirrhosis and the ACLF syndrome are part of the same disorder: systemic inflammation crisis and secondary metabolic dysregulation. The ACLF syndrome would be the most extreme clinical condition of acute decompensation and its main cause of death. The first findings of the PREDICT Study have been published in 2020 in two different articles in The Journal of Hepatology, the main journal in the field.

Detailed agnostic assessment of precipitating events for acute decompensation (AD) and ACLF: Prevalence, association with AD at enrolment and importance in clinical course severity

Observational study

Jonel Trebicka (Goethe University Frankfurt. Frankfurt, Germany; EF Clif. Barcelona, Spain)
Javier Fernández (Hospital Clínic Barcelona-IDIBAPS; EF Clif. Barcelona, Spain)

Promoter: EF Clif
Start date: 01/03/2017
End date: 31/01/2020

This multicentre, prospective, observational PREDICT study analyses and characterized the precipitants leading to AD. The PREDICT study included 1,273 patients with AD and focused on the characteristics of precipitants, specifically induction of organ dysfunction/failure and/or systemic inflammation, chronology, intensity, and relationship to outcome in both AD phenotypes (No-ACLF and ACLF). In particular, in proven bacterial infections and severe alcoholic hepatitis, either alone or in combination, accounted for almost all (96-97%) acute decompensation and ACLF. Whilst type of the precipitants was not associated with mortality, the number was. This study identified precipitants that are significantly associated with a distinct clinical course and prognosis of patients with AD. Specific preventative and therapeutic strategies targeting these events may improve outcome in decompensated cirrhosis.

The Natural History of AD in cirrhosis: phenotypes, pathophysiology and development of a specific clinical score to PREDICT ACLF development and stable decompensated cirrhosis

Observational study

Jonel Trebicka (Goethe University Frankfurt. Frankfurt, Germany; EF Clif. Barcelona, Spain)
Javier Fernández (Hospital Clínic Barcelona-IDIBAPS; EF Clif. Barcelona, Spain)

Promoter: EF Clif
Start date: 01/03/2017
End date: 30/09/2020

The present study described for the first time three different clinical courses of patients with AD after hospital admission. The first clinical course (pre-ACLF) included patients who develop ACLF and has high probability of death. These patients are characterized by high-grade systemic inflammation.

The second clinical course (unstable decompensated cirrhosis) included patients requiring frequent hospitalizations unrelated with ACLF, show low-grade systemic inflammation, but suffer characteristically from complications related to severe portal hypertension. They present lower risk of mortality than patients with pre-ACLF.

Finally, the third clinical course (stable decompensated cirrhosis), included two-third of all patients admitted hospital with AD. They do not present severe systemic inflammation or frequent complications related with portal hypertension, rarely require hospital admission and present an extremely low 1-year mortality risk.

Chronological relationship between the clinical course of AD and the changes in systemic inflammation, metabolic dysregulation, transcriptomics, lipidomics and markers of mitochondrial dysfunction

Translational research

Richard Moreau (EF Clif. Barcelona, Spain)
Joan Clària (Hospital Clínic Barcelona-IDIBAPS; EF Clif. Barcelona, Spain)
Emmanuel Weiss (INSERM. Paris, France)

Promoter: EF Clif
Start date: 01/01/2019
End date: 31/12/2020

The objective of this study was to profile by Omics approaches the chronological relationship between the clinical course of decompensated cirrhosis and the changes in systemic inflammation, metabolic dysregulation, transcriptomics, lipidomics and markers of mitochondrial dysfunction.

The initial results indicate that acute decompensation in cirrhosis and the ACLF syndrome are part of the same disorder driven by systemic inflammation that leads to secondary mitochondrial dysfunction and metabolic dysregulation. The inflammatory markers of the entire PREDICT cohort have been measured (including all the time points of the study). The metabolomics and lipidomics data are already available from all patients at inclusion. The transcriptomic analysis of the patients is also well advanced.

Microbiome-based biomarkers to PREDICT decompensation of liver cirrhosis, ACLF and treatment response

Observational study

Jonel Trebicka (Goethe University Frankfurt. Frankfurt, Germany; EF Clif. Barcelona, Spain)

Promoter: H2020-EU.3.1.2- 825694
Start date: 01/01/2019
End date: 31/03/2025

The aims of the study are to better understand the role of microbiome and the gut-liver-axis interactome;) to identify and validate microbiome-based biomarkers and signatures for personalized prediction of decompensation and ACLF, and response to treatment; to design three new tests as easy-to-use tools and point-of-care, smartphone-connected nano-biosensors; and to validate them in a RCT.

So far, the foundations for the completion of the first objective were laid: In the MUCOSA-PREDICT cohort, we analysed the microbiome and the host using many omics techniques. The data are currently being analysed. The second objective is dependent on the final results of analysis ongoing. Still, important progress could be made during this funding period. Regarding the third objective, we use extensive cohorts and cover large parts of the world and many geographic regions of Europe, and we control for this important confounder. To reach the last objective, the protocol of the ALB-TRIAL is close to finalization, with a design to test the biomarker(s) that specifically predict treatment response to albumin.

Glycomics-based biomarkers for diagnosis and prognosis in Acute-on-Chronic Liver Failure

Observational study

Xavier Verhelst (Ghent University Hospital. Ghent, Belgium)
Hans Van Vlierberghe (Ghent University Hospital. Ghent, Belgium)

Promoter: EF Clif
Start date: 01/01/2020
End date: 30/06/2021

Changes in serum protein glycosylation occur in several liver diseases and have been the basis for the development of diagnostic and prognostic biomarkers. The goal of this work was to

assess if there is an association between changes in protein glycosylation and the severity of ACLF. A second goal was to study if these changes relate to outcome in patients with ACLF.

A pilot study has been started. The serum N-glycomic profile is analysed of specific subsets of patients with different degrees of ACLF and different outcomes. At this day, the glycomic profiles have been analysed. The interpretation of the data and statistical analysis is ongoing.

THE ACLARA STUDY

Prevalence, Epidemiology, Characterization and Mechanisms of Acute-on-Chronic Liver Failure (ACLF) in LAtin AmeRicA. Comparison with data from other regional studies (Europe and Asia) (ACLARA Study)

Observational study

Flair Carrilho (University of São Paulo School of Medicine. São Paulo, Brazil)
Richard Moreau (EF Clif. Barcelona, Spain)
Alberto Queiroz Farias (University of São Paulo School of Medicine. São Paulo, Brazil)

Promoter: EF Clif
Start date: 18/05/2020
End date: 30/12/2021

The ACLARA Study is a prospective follow-up observational investigation in 1,300 cirrhotic patients, hospitalized for AD with and without ACLF at 56 hospitals, aimed to assess the characteristics of the ACLF in Latin America. Standard laboratory data and one-year clinical course were recorded to measure mediators, biomarkers, genotyping and make transcriptomics and metabolomics analysis.

Recruitment was planned to be closed in the 3rd quarter of 2020. But due to the COVID-19 pandemic, it was stopped in March 2020. Patients were screened and enrolled from June 2018 to March 2020. A total of 1,285 were eventually enrolled. Demographic and general characteristics, data related to the past medical history, clinical data at enrolment and standard laboratory

analysis -including biomarkers of systemic inflammation, measurements estimating organ function and severity scores- were collected. After the cleaning of the database, the first paper has been prepared. It describes the prevalence and survival of ACLF from a Latin American cohort. Additionally, it characterizes ACLF in these populations, including clinical course severity and relationship between ethnicity distribution, lifestyle and other features related to geographic and environmental variations.

THE LIVER TRANSPLANT PROJECT

Liver Transplantation in patients with CirrHosis and severe ACLF: iNdications and outComE (CHANCE), a global study in Europe, Latin America, North America, China, India, Taiwan, Japan and Korea

Non-observational study without drugs

Thierry Gustot (HUB Erasme. Brussels, Belgium)
Javier Fernández (Hospital Clínic Barcelona-IDIBAPS; EF Clif. Barcelona, Spain)
William Bernal (King's College. London, United Kingdom)

Promoter: EF Clif
Start date: 01/10/2020
End date: 31/12/2025

CHANCE is a multicentre, international, observational study, designed to assess the results of liver transplantation in patients with Acute-on-Chronic Liver Failure grade 2 or 3. It will recruit 3,000 patients around the world. The final version of the protocol was validated by the Scientific board in December 2020.

The participating centres (95) were selected by a feasibility questionnaire on clinical data and sample collection, around the world. The electronic CRF will be finalized ad the beginning of 2021. The first approval by ethical committee was obtained in February 2021 in Hospital Clinic, Barcelona. The recruitment will start in the second quarter 2021 for three countries: Spain, India and United Kingdom.

ALBUMIN AS A DRUG

Pilot study on the relationship between albumin administration and changes in the transcriptomic profile. An investigation in patients from the PREDICT Study receiving albumin as treatment for several complications during clinical course

Observational study

Richard Moreau (EF Clif. Paris, France)
Joan Clària (Hospital Clínic Barcelona-IDIBAPS; EF Clif. Barcelona, Spain)
Emmanuel Weiss (INSERM. Paris, France)

Promoter: EF Clif
Start date: 01/01/2020
End date: 30/04/2021

The objective of the study is to use whole-blood RNA sequencing (RNA-seq) data obtained in patients of the PREDICT study, to investigate the effects of intravenous albumin on circulating immune cells from patients with severe forms of acutely decompensated cirrhosis.

Thirty-seven patients without shock have been investigated using whole-blood RNA sequencing (RNA-seq), that was performed twice in 18 patients (before and after albumin administration), and once in 19 patients not receiving albumin. Whole-blood RNA-seq data were obtained once in 10 healthy subjects. We uncovered that those patients who had not received albumin had a generalized decrease in RNA signatures of lymphoid cells and that albumin electively abrogated the decline in RNA signatures of B cells.

These findings prompted us to perform additional studies in 31 new patients with acutely decompensated assigned to either whole-blood RNA-seq (to explore the effects of albumin in patients with septic shock), bulk RNA-seq in peripheral blood mononuclear cells (PBMCs), blood flow cytometry, or single-cell RNA-seq (scRNA-seq) in PBMCs). Results have been used to write a first report that has been submitted for publication.

ALBIN. Mechanisms of action of ALbumin in patients with cirrhosis and Bacterial INfections

Prospective cohort study

Javier Fernández (Hospital Clínic Barcelona-IDIBAPS; EF Clif. Barcelona, Spain)

Promoter: EF Clif
Start date: 01/07/2020
End date: 31/07/2022

Prospective cohort multicentre study, aimed at gaining knowledge of the mechanisms of action of albumin in cirrhosis. Fifty patients will be included: 25 with SBP receiving albumin and 25 with non-SBP infections, but sepsis who will not receive albumin. Inflammatory markers, blood metabolomics and lipidomics, whole-blood and single-cell transcriptomics and mitochondrial function will be evaluated. The study is currently active in two centres, Hospital Clinic and Hospital del Mar. Until date, only 3 patients have been included, all three in the non-albumin group.

Identification of albumin receptors and albumin endocytic trafficking in human monocytes

Basic translational research

Loredana Saveanu (INSERM. Paris, France)
Joan Clària (Hospital Clínic Barcelona-IDIBAPS; EF Clif. Barcelona, Spain)
Sophie Lotersztajn (INSERM. Paris, France)

Promoter: EF Clif
Start date: 01/06/2019
End date: 31/12/2020

Human albumin (HSA) is currently used in the treatment of chronic liver diseases, where, as recently demonstrated, it promotes an anti-inflammatory response. By combining cellular biology and immunology methods, we aim to identify the cell population that up-take the most efficiently the HSA in human blood, the HSA receptors and their intracellular trafficking and signalling.

By performing multiparametric flow cytometry experiments on peripheral mononuclear blood cells, we identified a cell population that is, by far, the most efficient in HSA internalization. After feeding these cells with HSA, we immunoprecipitated the HSA and by quantitative mass-spectrometry we identified an HSA receptor protein candidate.

We are currently validating these data and we have set-up, in human primary cells, the depletion of HSA receptor candidate by lentivirus-coded specific shRNA. In parallel, using cell lines "similar" to HSA receptive primary cells, we identified the endocytosis mechanisms involved in HSA up-take. These results remain to be validated in primary cells, from healthy people and, if possible, from chronic liver disease patients.

Definition of the utility of immune checkpoint receptors as therapeutic targets in ACLF

Translational research

Shilpa Chokshi (Foundation for Liver Research. London, United Kingdom)

Promoter: EF Clif
Start date: 01/09/2018
End date: 31/10/2021

Acute on Chronic Liver Failure (ACLF) is an immunological paradox. It is a hyperinflammatory state at with coexisting profound immunoparesis. Immune checkpoints and their soluble forms have been shown in many contexts, to modulate autoimmunity and responses to infection or malignancy. We, therefore, aimed to explore their role in initiation and propagation of the pathological immune response in ACLF.

We have measured levels of several immune checkpoints in the CANONIC cohort and, also in a smaller longitudinal cohort. Several are elevated with increasing ACLF grade, and we show higher levels of some of these factors can discriminate clinical outcomes. We also demonstrate that ACLF grade increases markers of gut translocation, suggesting that this contributes to the pathological state that different patterns of soluble immune checkpoints associate with different predisposition and injury in ACLF. We also state that 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 mode and that levels of immune checkpoints are dynamic in ACLF.

Coincubation and FACS experiments from this longitudinal cohort have shown that blockade of some factors can affect the immune response in vitro. The laboratory experiments are complete, and analysis of this exciting data is being finalized and a publication prepared.

Albuminomics: identification of metabolites and lipids bound to albumin in patients with decompensated cirrhosis, patients with ACLF and healthy subjects

Basic research

Joan Clària (Hospital Clínic Barcelona-IDIBAPS; EF Clif. Barcelona, Spain)
Michael Rothe (Lipidomix. Berlin, Germany)
Óscar Yanes (Universitat Rovira i Virgili. Reus, Spain)

Promoter: EF Clif
Start date: 01/01/2020
End date: 31/12/2020

The goal of this project was to identify which metabolites and bioactive lipid mediators circulate free or bound to albumin, in the vascular bed of patients with acutely decompensated cirrhosis. To achieve this goal, plasma samples were processed suing immunoaffinity columns, able to separate the albumin-enriched fraction from the albumin-depleted fraction.

The metabolomic and lipidomic profiles of the albumin-enriched and albumin-depleted fractions were obtained by LC-MS/MS. Metabolomic analysis still needs further tuning but the lipidomic analysis have revealed a specific signature of lipids not bound by albumin. Within this signature, we have identified a small set of bioactive lipid mediators, which have the ability to modulate the immune system in the systemic circulation.

Effects of albumin on human neutrophil function in patients suffering from AD and ACLF

Translational study

Daniel Irimia (Massachusetts General Hospital. Boston, USA)

Promoter: EF Clif
Start date: 01/04/2020
End date: 31/03/2021

Albumin levels are low in patients with chronic liver failure. Here, we are testing the hypothesis that albumin levels affect neutrophil function, the key white blood cells that protect against infections. If this is true, increasing the levels of albumin in chronic liver failure patients may help restore the natural defences against microbes.

We started working on the project with a 4 months-delay due to the pandemic. On the four tasks of the project, we completed the first two, representing approx. 66% of the proposed work. For these tasks, we performed a through characterization of the effect of albumin on the neutrophil antimicrobial functions, using neutrophils from healthy donors, with and without stimulation. For this purpose, we employed a recently reported assay, named neutrophil swarming.

In parallel work, we determined using the same swarming assay that the neutrophils from patients with cirrhosis are impaired in their antimicrobial activities. The remaining work will leverage these two streams of knowledge and determine with high precision if albumin has an effect on patients' neutrophils, in the context of chronic liver failure.

Autophagy as a mediator of HSA anti-inflammatory effects

Basic translational study

Sophie Lotersztajn (INSERM. Paris, France)
Loredana Saveanu (INSERM. Paris, France)
Joan Clària (Hospital Clínic Barcelona-IDIBAPS; EF Clif. Barcelona, Spain)

Promoter: EF Clif
Start date: 22/07/2020
End date: 31/12/2021

Autophagy is a major player in the regulation of anti-inflammatory response. Based on our preliminary data, this project will investigate whether human serum albumin (HSA) triggers autophagy in blood cells at different stages of chronic liver diseases, and whether the anti-inflammatory properties of HSA rely on autophagy activation and explore the underling molecular mechanisms.

Our pilot studies demonstrate that HSA enhances particular pathways of autophagy in specific blood cell sub-types from both, healthy subjects and patients with cirrhosis. We are further validating these data in a larger cohort, and explore the early signalling pathways, leading to autophagy activation upon HSA treatment. Current studies also combine pharmacological and lentivirus-coded specific shRNA approaches, to identify the molecular mechanisms leading to autophagy activation by HAS. These concern the identification of cellular receptors and the intracellular trafficking mechanisms that -upon HSA treatment- are able to trigger autophagy in peripheral blood cells from both, healthy and cirrhotic patients.

Effects of albumin in a human model of dermal inflammation

Experimental medicine

Allastair O'Bryen (UCL, Royal Free Hospital. London, United Kingdom)

Promoter: EF Clif
Start date: 31/12/2020
End date: 31/08/2021

Chronic liver disease is associated with profound immunological changes that leave patients highly susceptible to infection. Albumin, the large circulating plasma protein, has been shown to have anti-inflammatory effects and we shall investigate this, using a human blister model of inflammation. As England is in lockdown, recruiting healthy volunteers for the blister models is not currently possible. We have, therefore, investigated possible lipid mediators that may be modified by albumin infusions by performing analyses on existing plasma and blister samples from patients with decompensated cirrhosis and correlating this with albumin treatment and measured circulating levels.

Protein and lipid inflammatory signatures in circulating exosomes in patients with ACLF

Basic translational research

Maria Rosa Sarrias (Germans Trias i Pujol Research Institute (IGTP). Badalona, Spain)

Promoter: EF Clif
Start date: 15/07/2019
End date: 30/06/2021

The objective of this study is to compare the lipid mediator signature and the content of immune-resolving proteins in exosomes from ACLF patients with full-blown systemic inflammation, with that of exosomes from patients with mere acute decompensation, compensated cirrhosis and healthy subjects.

Extracellular vesicles (EVs) were isolated from plasma by Size-Exclusion Chromatography (SEC). The EV were defined as positive for EV markers CD9 and CD5L, and their size, amount and morphology characterized by NTA and cryo-EM, respectively. Then, EVs were analysed by LC-MS/MS to characterize the profile of pro-resolving lipids. The results suggest a loss of pro-resolving lipids and CD5L protein content in EVs from ACLF vs decompensated cirrhotic patients. Moreover, in vitro analyses on macrophage activity showed that CD5L signalling affects lipid mediator content, and viceversa, providing for the first time, a link between this anti-inflammatory protein and pro-resolving lipid signalling in liver pathology.

COLLABORATIVE PROJECTS AND CLINICAL TRIALS

The EFClif 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:

Development of DIALIVE, A novel LIVER Dialysis Device for the treatment of patients with Acute on Chronic Liver Failure (ACLF). ALIVER

Randomised controlled clinical trial

Rajiv Jalan (UCL, Royal Free Hospital. London, United Kingdom)

Funder: H2020-EU.3.1.2- 7733057
Start date: 01/01/2017
End date: 30/09/2020

The ALIVER programme was designed to evaluate a novel approach to treating patients with acute-on chronic liver failure (ACLF) using a novel dialysis device, DIALIVE™. Its design is based on the understanding that albumin is destroyed, in patients with liver failure and allows removal and replacement of albumin and removal of DAMPs and PAMPS.

During 2020 the randomised controlled clinical trial of Dialive™ in adult patients with ACLF was completed and data analysis started. All indicates that Dialive™ treated patients experience an improvement of biomarkers, thought to be associated with the cytokine storm and organ failure in ACLF. If confirmed, it will mean that patients on Dialive™ show statistically significant benefits, compared to the control arm, ten days after the start of the treatment protocol of three to five sessions of eight to 12 hours each.

Yaqrit Discovery Ltd., a spin off company from University College London, where DIALIVE was discovered will perform the next phase of clinical trials so that, the device can start to save lives of ACLF patients. www.aliver.info

CARBALIVE

Randomised controlled clinical trial

Rajiv Jalan (UCL, Royal Free Hospital. London, United Kingdom)

Funder: H2020-EU.3.1.2- 634579
Start date: 01/05/2015
End date: 31/01/2021

Carbalive™ is a product for the treatment of patients with decompensated cirrhosis, specifically designed to remove harmful bacterial toxins from the gut, reduce gut inflammation and its permeability, preventing them from leaking into the rest of the body. This research was led by the members of the Liver Failure Group at University College London.

Data from the trial also showed trends in the improvements of a wide range of biomarkers of systemic inflammation, which is especially notable because Carbalive™ is not systemically absorbed. Measures of gut-specific health also improved in Carbalive™ patients compared to those on the placebo arm. These improvements were associated with trends towards reduction in the markers of gut inflammation, and less translocation (leakiness) of the gut wall; characteristic problems associated with cirrhosis and its complications. Yaqrit Discovery Ltd., will perform the next phase of clinical trials before it becomes available for use to treat patients with decompensated cirrhosis. www.carbalive.eu

LIVERHOPE

Randomised controlled clinical trial

Pere Ginès (Hospital Clínic-IDIBBAPS. Barcelona, Spain)

Funder: H2020-EU.3.1.2- 731875
Start date: 01/01/2017
End date: 31/06/2022

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 gutliver axis and the persistent hepatic and systemic inflammatory response. The LiverHope project is unique in that it represents the first approach to develop a new combination therapy, able to prevent the progression of the disease.

If the results are positive this may represent a treatment to stabilize the disease and prevent it from progressing. This will have a huge impact in the natural history of the disease, by decreasing mortality and improving quality of life of patients and their families, and will reduce costs, by decreasing the number of hospitalizations.

SCOTCH Trial Supplemental Corticosteroids in Cirrhotic Hypotensive Patients with Suspicion of Sepsis

Randomised controlled clinical trial

Alexander Wilmer (UZ Leuven. Leuven, Belgium)
Julia Wendon (King's College. London, United Kingdom)
Javier Fernández (Hospital Clínic Barcelona-IDIBAPS; EF Clif. Barcelona, Spain)

Promoter: Catholic University of Leuven
Start date: 01/04/2015
End date: 31/12/2020 (early terminated)

Double-blind, phase IV, randomized, placebo-controlled multicentre trial, involving 356 patients with cirrhosis and septic shock, aimed at evaluating if intravenous low-dose hydrocortisone improves 28-d survival in comparison with standard therapy.

The study started in April 2015 and until the end of 2020 included 94 patients. Ten centres were theoretically active but just two were currently recruiting. A total of 244 were screened, but not included (screening failure). Due to the low recruitment rate, the study was prematurely stopped on December 31, 2020.

The next steps are the finalization of online monitoring, cleaning of the database and initiation of the analysis of clinical data and samples. Cortisol metabolism will be analysed in Leuven. The rest of the analysis (inflammation and omics) will be performed by EF Clif investigators.

APACHE Trial. Effects of Plasma Exchange with Human Serum Albumin 5% (PE-A 5%) on Short-term Survival in Subjects with "Acute-On-Chronic Liver Failure" (ACLF) at High Risk of Hospital Mortality

Randomised controlled clinical trial

Javier Fernández (Hospital Clínic Barcelona-IDIBAPS; EF Clif. Barcelona, Spain)
Fin Stolze Larsen (Rigshospitalet. Copenhagen, Denmark)

Promoter: Grifols, SA
Start date: 21/02/2019
End date: 31/12/2022

It is a phase III, multicentre, randomized, open-label trial in 380 patients with ACLF-1b, ACLF grade 2 or ACLF-3a, aimed to determine whether plasma exchange with 5% albumin (from 4 to 9 plasma exchange [PE] sessions) improves 90-day survival, in comparison with standard medical therapy.

The study is being performed in 30 centres, 20 from Europe and 10 from North America. Most hospitals had their site open visit at the end of 2019, or in the first quarter of 2020. Until now, 105 patients have been enrolled. The estimated additional duration of the study is 24 months, considering the problems of recruitment associated with the COVID-19 pandemic.

ALADDIN Study

Clinical translational research

Joan Clària (Hospital Clínic Barcelona-IDIBAPS; EF Clif. Barcelona, Spain)

Promoter: EF Clif
Start date: 01/02/2020
End date: 31/12/2022

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 recruitment of patients for study inclusion is ongoing.

PRECIOSA Study Prevention of Mortality with Long-Term Administration of Human Albumin in Subjects with Decompensated Cirrhosis and Ascites

Randomized controlled clinical trial

Javier Fernández (Hospital Clínic Barcelona-IDIBAPS; EF Clif. Barcelona, Spain)
Paolo Angeli (University of Padova. Padova, Italy)

Funder: Grifols, SA
Start date: 20/04/2018
End date: 31/12/2023

This is a phase IV, multicentre, randomized open-label trial, in 410 patients with decompensated liver cirrhosis with ascites, aimed to determine if long-term albumin administration (1.5 g/kg body weight every 10 days for 12 months) prevents ACLF and improves 1-year transplant-free survival in comparison with standard medical therapy.

The study is being performed in 29 European and 10 North American centres. The first site was opened in April 2018. Until now, 115 subjects have been included. The estimated additional duration of the study is 30 months, given the problems of recruitment caused by the COVID-19 pandemic.

HEPASTEM

• HEP101-PHASE Multicenter Phase II safety and preliminary efficacy study of 2 dose regimens of HEPASTEM in patients with acute-on-chronic liver failure

Phase II randomised controlled clinical trial

Frederik Nevens (UZ Leuven. Leuven, Belgium)

Funder: Promethera Biosciences
Start date: 16/12/2016
End date: 21/08/2020

An interventional, multicentre, open, safety study of 2 dose regimens of HepaStem, given in subsequent cohorts with approximately 24 hospitalized ACLF patients. Its primary objective is to assess the safety administration of different doses of HepaStem up to D28, and the secondary one is to evaluate preliminary efficacy parameters up D28, up to M3 and up to 1 year.

The clinical part of this study has been completed in the period under review. LPLV was on 21August 2020. The CSR is not available at the time of this report. Subject exposure: 24 patients. Safety results: 2 patients with underlying coagulation disturbances/ failure (due to their disease) experienced severe bleeding, caused by severe coagulopathy in the highest dose cohort (5 Mio cells/kg). 21/24 patients treated in the reduced dose cohorts (0.6 to 1.2 single and double doses 1 week apart) did not experience coagulopathy. The coagulation parameters stayed within the set safety limits for fibrinogen and platelets.

• HEP102-RANDOMIZED, placebo controlled, double blind, multi-center PHASE IIB study to evaluate the efficacy and safety of HEPASTEM in patients with acute-on-chronic liver failure (ACLF)

Phase IIB randomised controlled clinical trial

Frederik Nevens (UZ Leuven. Leuven, Belgium)

Funder: Promethera Biosciences
Start date: 21/01/2020
End date: 31/12/2023

Interventional, double blind, randomised (2:1) and placebo-controlled study on one dose regimen of HepaStem. 1-week double-blind treatment period with 2 i.v. infusions of HepaStem at 1.0 x 106 cells/ kg BW or Placebo.

The primary objective is to demonstrate the efficacy of 2 infusions (i.v.) of HepaStem at 1.0 million of cells/kg (7-day interval) on the overall survival proportion at D90 days.

FPFV: 21 January 2020. Recruitment has been strongly impacted for the COVID-19 situation. 12 Patients were exposed to HepaStem or placebo up to 08-12-20. The randomization ratio is 2:1 Therefore, an estimated number of 8 patients received HepaStem. No safety concerns have been observed in the treated population so far.

Liposomal peritoneal dialysis for the management of hepatic encephalopathy

Phase I randomised controlled clinical trial

Jonel Trebicka (Goethe University Frankfurt. Frankfurt, Germany; EF Clif. Barcelona, Spain)

Funder: Versantis GmbH
Start date: 01/09/2019
End date: 11/03/2021

Versantis, a clinical-stage company developing novel therapies for orphan liver and paediatric diseases, performs a Phase 1b clinical trial of VS-01 in decompensated liver cirrhosis. VS-01 was tested in a first-in-human, single-ascending and multiple dose study.

The primary objective of the study is to evaluate the safety and tolerability of i.p.-administered VS-01 on top of standard of care in cirrhotic patients with ascites and mild hepatic encephalopathy, following single and multiple intraperitoneal administrations. The secondary objectives are to gather preliminary PK, PD and clinical efficacy data. In total, 12 patients were successfully treated, 9 in the single ascending dose part (3 doses) and 3 in the multiple dose (daily treatment for 4 days) part of the study.

The results show that VS-01 was safe and well tolerated, with no dose-limiting toxicities or unexpected safety signals. No serious adverse events (AE) are reported, and no patients discontinued because of an AE. Patients receiving multiple doses of VS-01 show improvements in selected biomarkers and clinical cognitive tests, which support the clinical potential of VS-01 and encourage its further investigation in a Phase 2a study in the target indication of ACLF.

10

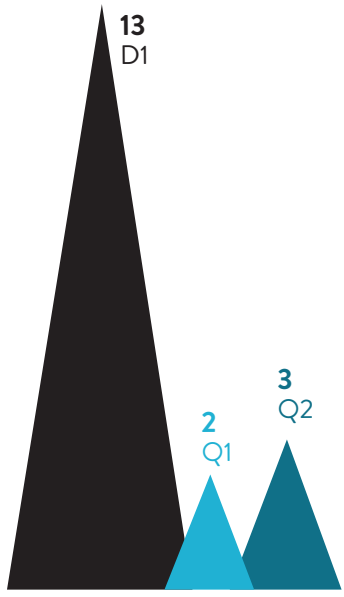
SCIENTIFIC PUBLICATIONS

18
SCIENTIFIC ARTICLES

9
ORIGINAL RESEARCH ARTICLES

8
REVIEW ARTICLES

1
EDITORIALS



18
ARTICLES PUBLISHED

13 articles **D1**
(8 in 2019)

2 articles **Q1**
(3 in 2019)

3 articles **Q2**
(4 in 2019)

MEAN IF
22.69
10,61 in 2019

TOTAL IF
385.73
159,19 in 2019

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

2
ARTICLES ARE SIGNED
by authors from
15 or more EASL-Clif
Consortium Members

SCIENTIFIC ARTICLES

01. ALBUMIN IN DECOMPENSATED CIRRHOSIS: NEW CONCEPTS AND PERSPECTIVES.

Bernardi M, Angeli P, Claria J, Moreau R, Gines P, Jalan R, Caraceni P, Fernandez J, Gerbes A, O'Brien A, Trebicka J, Thevenot T, Arroyo V. 2020. Gut. 69:1127-1138

02. ACUTE-ON-CHRONIC LIVER FAILURE: A NEW DISEASE OR AND OLD ONE HIDING IN PLAIN SIGHT?

Jalan R, Perricone G, Moreau R, Arroyo V, Williams R. 2020. Clinical in Liver Disease. 15; 1

03. GENETIC VARIANTS OF INNATE IMMUNITY RECEPTORS ARE ASSOCIATED WITH MORTALITY IN CIRRHOTIC PATIENTS WITH BACTERIAL INFECTION.

Schaapman J, Amoros A, van der Reijden J, Laleman W, Zeuzem S, Bañares R, Jalan R, Arroyo V, Claria J, Versoaget H, Coenraad M. 2020. Liver International. 40; 3:646-653

04. HDL-RELATED BIOMARKERS ARE ROBUST PREDICTORS OF SURVIVAL IN PATIENTS WITH CHRONIC LIVER FAILURE.

Trieb M, Rainere F, Stadlbauer V, Douschan P, Horvath A, Binder L, Trakaki A, Knuplez E, Stojakovic T, Heinemann A, Pitarch C, Amoros A, Gerbes A, Caraceni P, Alessandria C, Moreau R, Clària J, Marsche G, Stauber R. 2020. Journal of Hepatology. 73: 113-120

05. ALBUMIN INTERNALIZES AND INHIBITS ENDOSOMAL TLR SIGNALING IN LEUKOCYTES FROM PATIENTS WITH DECOMPENSATED CIRRHOSIS.

Casulleras M, Flores-Costa R, Duran-Güell M, Alcaraz-Quilez J, Sanz S, Titos E, Lopez.Vicario C, Fernandez J, Horrillo R, Costa M, De La Grange P, Moreau R, Arroyo V, Clària J. 2020. Science Translational Medicine. 12 (566):eaax5135

06. TARGETED LIPIDOMICS REVEALS EXTENSIVE CHANGES IN THE BLOOD LIPID MEDIATOR PROFILE IN ACUTELY DECOMPENSATED CIRRHOSIS.

Lopez-Vicario C, Checa A, Aguilar F, Alcaraz-Quiles , Caraceni P, Amorós A, Pavesi M, Gomez-Cabrero D, Trebicka J, Oettl K, Planell N, Arroyo V, Wheelock C, Clària J. 2020. Journal of Hepatology. 73;4:817-828

07. IMPROVED PREDICTION OF MORTALITY BY COMBINATIONS OF INFLAMMATORY MARKERS AND STANDARD CLINICAL SCORES IN PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE AND ACUTE DECOMPENSATION.

Gronbaek H, Moller H, Saliba F, Zeuzem S, Albillos A, Ariza X, Graupera I, Solà E, Amoros A, Pavesi M, Bossen L, Jalan R, Gines P, Arroyo V. 2020. Journal of Gastroenterology and Hepatology. 36(1):240-248

08. THE PREDICT STUDY UNCOVERS THREE CLINICAL COURSES IN ACUTELY DECOMPENSATED CIRRHOSIS WITH DISTINCT PATHOPHYSIOLOGY.

Trebicka J, Fernandez J, Papp M, Caraceni P, Laleman W, Gambino C, Giovo I, Uschner F, Jimenez C, Mookerjee R, Gustot T, Albillos A, Bañares R, Janicko M, Steib Ch, Reiberger T, Acevedo J, Gatti P, Bernal W, Zeuzem S, Zipprich A, Piano S, Berg T, Bruns T, Gluud L, Coenraad M, Merli M, Stauber R, Zoller H, Cristino A, Solè C, Soriano G, Gottardi A, Gronbaek H, Saliba F, Trautwein Ch, Ozdogan O, Sven F, Ryder S, Nahon P, Romero-Gomez M, Van Vlierberghe H, Francoz C, Manns M, García E, Tufoni M, Amorós A, Pavesi M, Sanchez C, Putignano A, Moreno E, Shawcross D, Aguilar F, Clària J, Ponzo P, Jansen Ch, Vitalis Z, Zaccherini G, Balogh B, Vargas V, Montagnese S, Alessandria C, Bernardi M, Ginès P, Jalan R, Moreau R, Angeli P, Arroyo V. 2020. Journal of Hepatology. 74(4):842-854

09. ACUTE-ON-CHRONIC LIVER FAILURE.
Arroyo V, Moreau R, Jalan R. 2020. New England Journal of Medicine. 382:2137-2145

10. LIVER TRANSPLANTATION FOR ACUTE-ON-CHRONIC LIVER FAILURE: SCIENCE OR FICTION?
Trebicka J, Sundaram V, Moreau R, Jalan R, Arroyo V. 2020. Liver Transplantation. 26;7: 906-915

11. ACLF: DEFINITIONS, PATHOPHYSIOLOGY AND PRINCIPLES OF TREATMENT.
Zaccherini G, Weiss E, Moreau R. 2020. Journal of Hepatology. Vol 3; 1:100176

12. ACUTE-ON-CHRONIC LIVER FAILURE.
Rajiv Jalan, Richard Moreau, Vicente Arroyo. 2020. New England Journal of Medicine. 382:2137-2145

13. ORGAN ALLOCATION FOR PATIENTS WITH ACLF: TIME TO LOOK BEYOND MELD-SODIUM.
Jalan R, Arroyo V. 2020. Journal of Hepatology. 73; 6:1316-1318

14. PREDICT IDENTIFIES PRECIPITATING EVENTS ASSOCIATED WITH THE CLINICAL COURSE OF ACUTELY DECOMPENSATED CIRRHOSIS.
Trebicka J, Fernandez J, Papp M, Caraceni P, Laleman W, Gambino C, Giovo I, Uschner F, Jimenez C, Mookerjee R, Gustot T, Albillos A, Bañares R, Janicko M, Steib Ch, Reiberger T, Acevedo J, Gatti P, Bernal W, Zeuzem S, Zipprich A, Piano S, Berg T, Bruns T, Gluud L, Coenraad M, Merli M, Stauber R, Zoller H, Cristino A, Solè C, Soriano G, Gottardi A, Gronbaek H, Saliba F, Trautwein Ch, Ozdogan O, Sven F, Ryder S, Nahon P, Romero-Gomez M, Van Vlierberghe H, Francoz C, Manns M, García E, Tufoni M, Amorós A, Pavesi M, Sanchez C, Putignano A, Moreno E, Shawcross D, Aguilar F, Clària J, Ponzo P, Jansen Ch, Vitalis Z, Zaccherini G, Balogh B, Vargas V, Montagnese S, Alessandria C, Bernardi M, Ginès P, Jalan R, Moreau R, Angeli P, Arroyo V. 2020. Journal of Hepatology. 74; 5: 1097-1108

15. ASSESSING THE ROLE OF AMINO ACIDS IN SYSTEMIC INFLAMATORY RESPONSES AND ORGAN FAILURES IN PATIENTS WITH ACLF.
Zaccherini G, Aguilar F, Caraceni P, Clària J, Lozano J, Fenaille F, Junot Ch, Formentin Ch, Weiss E, Bernardi M, Jalan R, Angeli P, Moreau R, Arroyo V. 2020. Journal of Hepatology. 74; 5: 1117-1131

16. THE SYSTEMIC INFLAMMATION HYPOTHESIS: TOWARDS A NEW PARADIGM OF ACUTE DECOMPENSATION AND MULTIORGAN FAILURE IN CIRRHOSIS.
Arroyo V, Angeli P, Moreau R, Jalan R, Clària J, Trebicka J, Fernandez J, Gustot T, Caraceni P, Bernardi M. 2020. Journal of Hepatology. Vol 74; 670-685

17. UTILIZING THE GUT MICROBIOME IN DECOMPENSATED CIRRHOSIS AND ACUTE-ON-CHRONIC LIVER FAILURE.
Trebicka J, Bork P, Krag A, Arumugam M. 2020. Nature Reviews Gastroenterology & Hepatology. 18(3); 167-180

18. MACROPHAGE ACTIVATION MARKERS, CD163 AND CD206, IN ACUTE-ON-CHRONIC LIVER FAILURE (ACLF).
Nielsem M, Gantzel R, Clària J, Trebicka J, Moller H, Gronbaek H. 2020. Cells. 9; 1175

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01. A DOUBLE-BLIND RANDOMIZED PLACEBO-CONTROLLED TRIAL OF PROBIOTIC LACTOBACILLUS CASEI SHIROTA IN STABLE CIRRHOTIC PATIENTS.
Macnaugtan J, Figorilli F, García E, Lu H,Jones H, Sawhney R, Suzuki K, Fairclough S, Marsden J, Moratella A, Cox I J, Thomas L, Davies N, Williams R, Mookerjee R, Wright G, Jalan R. 2020. Nutrients. 12; 1650

02. GENOMEWIDE ASSSOCIATION STUDY OF SEVERE COVID-19 WITH RESPIRATORY FAILURE.
Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, Invernizzi P, Fernandez J, Prati D,Baselli G, Asselta R, Grimsrud M, Milani Ch et al fot The Severe Covid-19 GWAS Group. 2020. New England Journal of Medicine. 386;16

03. THE ROLE OF MACROPHAGE-INDUCIBLE C-TYPE LECTIN IN DIFFERENT STAGES OF CHRONIC LIVER DISEASE.
Schierwagen R, Uschner FE, Ortiz C, Torres S, Brol M, Tyc O, Gu W, Grimm Ch, Zeuzem S, Plamper A, Pfeifer P, Zimmer S, Welsch Ch, Schaefer L, Rheinwalt K, Clària J, Arroyo V, Trebicka J, Klein S. 2020. Frontiers in Immunology. vol 11 art 1352

04. PLASMA EXCHANGE: AN EFFECTIVE RESCUE THERAPY IN CRITICALLY ILL PATIENTS WITH COVID-19 INFECTION".
Fernández J, Gratacos-Ginès J, Olivas P, Costa M, BS, Nieto S, Mateo D, Sanchez M, Aguilar F, Bassegoda O, Ruiz P, Caballol B, Pocurull A, Llach J, Mustieles M, Cid J, Reverter E, Toapanta N, Hernández-Tejero M, Martínez J, Clària J, Fernández C, Mensa J, Arroyo V, Castro P, Lozano M. 2020. Critical Care Medicine. 48(12):e1350-e1355

05. DIFFERENTIAL INFLAMMASOME ACTIVATION PREDISPOSES TO ACLF IN HUMAN AND EXPERIMENTAL CIRRHOSIS WITH AND WITHOUR PREVIOUS DECOMPENSATION.
Monteiro S, Grandt J, Uschner F, Kimer N, Madsen J, Schierwagen R, Klein S, Welsch Ch, Schäfer L, Jansen Ch, Clària J, Alcaraz-Quiles J, Arroyo V, Moreau R, Fernández J, Bendtsen F, Mehta G, Gluud L, Moller S, Praktiknjo M, Trebicka J. 2020. Gut. 70;379-387

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