EF Clif

EUROPEAN
FOUNDATION
FOR THE STUDY
OF CHRONIC
LIVER FAILURE

SUMMARY OF ACTIVITIES **2016**

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Letter of the Chairman

2016 has been the first full year of the European Foundation for the Study of Chronic Liver Failure (EF Clif). The Foundation was constituted on April 8th 2015, from July 2015 became fully operational and in the following November, we were able to start working in our new headquarters. During this year, we have made a lot of progress in finalizing some ongoing studies, while designing and initiating new studies, both clinical (through the EASL Chair) and translational (through the Grifols Chair).

In the clinical research area, we have set up the foundation prospective, for the new key observational multicentre study, following the pathway of the CANONIC, called PREDICT Study. An experienced Principal Investigator has been appointed for two years (starting in January 2017), Prof Jonel Trebicka, to lead this study that is expected to include 1,200 patients with decompensated cirrhosis from more than 50 hospitals from all over Europe.

In the translational research area, under the leadership of Prof's Richard Moreau and Joan Clària, we initiated several translational research studies, focusing on the antioxidative and antiinflamatory effects of albumin and on the profile of metabolites in serum samples form patients with cirrhosis with and without ACLF by untargeted functional metabolomics and lipidomics.

A major event during 2016 was the organization of the Symposium SYSTEMIC INFLAMMATION AND ORGAN FAILURE IN CIRRHOSIS. THE ACUTE-ON-CHRONIC LIVER FAILURE SYNDROME (ACLF), on April 12th in Barcelona, which was the first international meeting of the EF Clif. Over 200 specialists from all over the world, mostly European hepatologists, participated in in just before the start of the 51st Annual congress of the European Association for the Study of the Liver (EASL 2016).

We have already established an ambitious and exciting plan for the 2017 and the following year, with both clinical and translational studies, by optimizing the resources that we will receive from our donors.

Vicente Arroyo, MD
Chairman

Mission

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

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

Vision

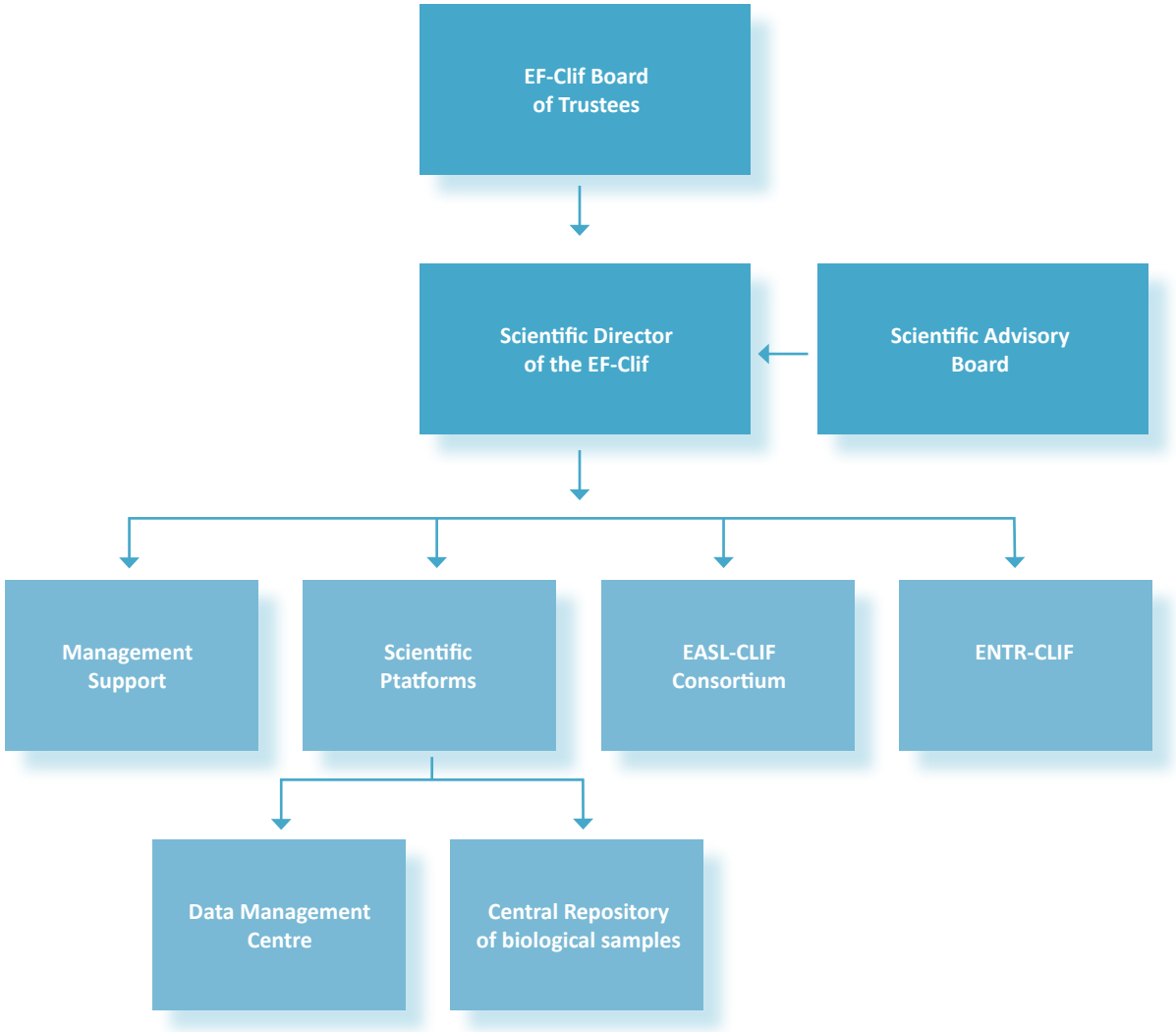
Our vocation is helping investigators to achieve their projects and getting the best results. To this end, we finance Research and provide technical support, driven by the idea that research is fundamental to obtain effective treatments for cirrhosis.

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

Values

Our organization

European Foundation for the Study of Chronic Liver Failure (EF-Clif)



Board of Trustees

VICENTE ARROYO
M.D.

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

Chairman of the EASL Clif Consortium.

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

Main research interest:

Chronic liver failure, ascites acute bacterial infection in cirrhosis, and acute on chronic liver failure

MAURO BERNARDI
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Professor of Internal Medicine Bologna University, Italy.

Director, Postgraduate School in Internal Medicine Treasurer, European Association for the Study of the Liver.

Vice-chairman of EASL Clif Consortium.

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

Main research fields:

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

JAVIER JORBA
M.D.

President of Grifols Bioscience Industrial Group.

Member of the Grifols Executive Committee.

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)

He specializes in Company Law, Competition and Industrial Property.

The EASL Chair and Steering Committee

EASL CLIF **CONSORTIUM**

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

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GRIFOLS CHAIR OF **RESEARCH** ON CLIF

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

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

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Richard Moreau / Hôpital Beaujon, Clichy

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Facts and figures

The EF Clif is a Foundation that gives support to the EASL CLIF Consortium and European CLIF Network for Translational Research (ENTR-CLIF) to promote clinical and translational research in cirrhosis.

The EF Clif in numbers

Only in Europe, about **170,000 citizens** die from cirrhosis every year.

The cost of cirrhosis represents more than **€15.8 billion** per year in health care and a huge loss in economic productivity[1].

This has been our contribution to the fight against this silent disease.

A network of almost **100 hospitals** in Europe.

Almost **200 investigators** working on EF Clif sponsored projects.

More than **1,500,000 €/year** in supporting research.

2 chairs with a continuous commitment to education.

19 papers published in 2016.

[1] Murray CVJ, et al. The global burden of disease study 2010. Lancet 2012; 380: 2053-60.

Icons 1, 4, 5, 6 in made by Vectors Market from www.flaticon.com; Icons 2, 7, 8 made by Freepik from www.flaticon.com

Scientific publications

The scientific production of the EF CLIF Consortium during 2016 consists of 19 articles.

1. TREATMENT WITH NON-SELECTIVE BETA-BLOCKERS IS ASSOCIATED WITH REDUCED SEVERITY OF SYSTEMIC INFLAMMATION AND IMPROVED SURVIVAL OF PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE. Mookerjee RP, Pavesi M, Thomsen KL, Mehta G, Macnaughtan J et al. Journal of Hepatology 2016;64:574-582.

2. MACROPHAGE ACTIVATION MARKERS PREDICT MORTALITY IN PATIENTS WITH LIVER CIRRHOSIS WITHOUT OR WITH ACUTE-ON-CHRONIC LIVER FAILURE (ACLF). Gronbaek H, Rodgaard-Hansen S, AAgaard NK, Arroyo V, Moestrup SK et al. Journal of Hepatology 2016;64:813-822.

3. NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN IS A BIOMARKER OF ACUTE-ON-CHRONIC LIVER FAILURE AND PROGNOSIS IN CIRRHOSIS. Ariza X, Graupera I, Coll M, Solà E, Barreto R et al. Journal of Hepatology 2016;65:57-65.

4. CHARACTERISTICS, DIAGNOSIS AND PROGNOSIS OF ACUTE-ON-CHRONIC LIVER FAILURE IN CIRRHOSIS ASSOCIATED TO HEPATITIS B. Li H, Chen LY, Zhang Nn, Li Sht, Zeng B et al. Scientific Reports 2016; 5: 25487.

5. ACUTE-ON-CHRONIC LIVER FAILURE: A DISTINCT CLINICAL CONDITION. Jalan R, Moreau R, Kamath PS, Arroyo V. Seminars in Liver Disease 2016;36:107-108.

6. ACUTE-ON-CHRONIC LIVER FAILURE: DEFINITION, DIAGNOSIS, AND CLINICAL CHARACTERISTICS. Arroyo V, Jalan R. Seminar in Liver Disease 2016;36:109-116.

7. ACUTE-ON-CHRONIC LIVER FAILURE IN CIRRHOSIS. Arroyo V, Moreau R, Kamath P, Jalan R, Ginès P et al. Nature Reviews Disease Primers 2016; 2:16041.

8. BREXIT FROM CURRENT GUIDELINE RECOMMENDATIONS? Angeli P, Piano S, Arroyo V on behalf of the ICA. Gut. 2016 Jul 27. DOI: 10.1136/gutjnl-2016-312422.

9. SYSTEMIC INFLAMMATION IN DECOMPENSATED CIRRHOSIS: CHARACTERIZATION AND ROLE IN ACUTE-ON-CHRONIC LIVER FAILURE. Clària J, Stauber RE, Coenraad MJ, Moreau R, Jalan R et al. Hepatology 2016; 64:1249-1264.

10. CLINICAL COURSE AND SHORT-TERM MORTALITY OF CIRRHOTIC PATIENTS WITH INFECTIONS OTHER THAN SPONTANEOUS BACTERIAL PERITONITIS. Fernández J, Acevedo J, Prado V, Mercado M, Castro M et al. Liver International 2016; Aug 25. DOI: 10.1111/liv.13239. [Epub ahead of print].

11. PROGNOSTIC VALUE OF C-REACTIVE PROTEIN IN CIRRHOSIS: EXTERNAL VALIDATION FROM THE CANONIC COHORT. Cervoni JP, Amoros A, Bañares R, Montero JL, Soriano G et al. European Journal of Gastroenterology and Hepatology 2016; 28:1028-1034.

12. NEW CONCEPTS IN ACUTE-ON-CHRONIC LIVER FAILURE: IMPLICATIONS FOR LIVER TRANSPLANTATION. Putignano A, Gustot T. Liver Transplantation 2016 Oct 17. doi: 10.1002/lt.24654. [Epub ahead of print].

13. NEUROINFLAMMATION IN LIVER DISEASE: SESSIONAL TALKS FROM ISHEN. Wright G, Swain M, Annane D, Saliba F, Samuel D et al. Metabolic Brain Disease 2016; Oct 11. DOI:10.1007/s11011-016-9918-7. [Epub ahead of print].

14. PLASMA COPEPTIN AS BIOMARKER OF DISEASE PROGRESSION AND PROGNOSIS IN CIRRHOSIS. Sola E, Kerbert AJC, Verspaget HW, Moreira R, Pose E et al. Journal of Hepatology 2016;65:914-920.

15. SIGNALING AND IMMUNORESOLVING ACTIONS OF RESOLVIN D1 IN INFLAMED HUMAN VISCERAL ADIPOSE TISSUE. Titos E, Rius B, López-Vicario C, Alcaraz-Quiles J, Garcia-Alonso V et al. Journal of Immunology 2016; 197:3360-3370.

16. POLYMORPHISMS IN THE INTERLEUKIN (IL)-1 GENE CLUSTER INFLUENCE SYSTEMIC INFLAMMATION IN PATIENTS AT RISK FOR ACUTE-ON-CHRONIC LIVER FAILURE. Alcaraz-Quiles J, Titos E, Casulleras M, Pavesi M, López-Vicario C et al. Hepatology 2016 Oct 24 doi:10.1002/hep 28896 (Epub ahead of print).

17. THE ACUTE-ON-CHRONIC LIVER FAILURE, OR WHEN THE INNATE IMMUNE SYSTEM GOES ASTRAY. Claria J, Arroyo V, Moreau R. J Immunol 2016; 197:3755-3761.

18. NOVEL APPROACHES AND THERAPEUTICS IN ACUTE ON-CHRONIC LIVER FAILURE Jalan R Liver Transpl. 2016; 22 S14-.

19. USING EQ-5D-3L AND OAB-5D TO ASSESS CHANGES IN THE HEALTH-RELATED QUALITY OF LIFE IN MEN WITH LOWER URINARY TRACT SYMPTOMS ASSOCIATED WITH BENIGN PROS Hakimi Z, Herdman M, Pavesi M, Devlin N, Nazir J et al. Qual Life Res. Nov 2016; DOI:10.1007/s11136-016-1460-x [Epub ahead of print].

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EASL CLIF CONSORTIUM

Hospital network

The increase of the projects in which the EF Clif is getting involved has given the opportunity to include new hospitals during 2016. (*) New centres 2016

1	AUSTRIA	KLAGENFURT AM WÖRTHESEE HOSPITAL	Markus Peck Radosavljevic
2	AUSTRIA	MEDICAL UNIVERSITY OF GRAZ	Rudolf Stauber
3	AUSTRIA	MEDICAL UNIVERSITY OF INSBRUCK	Wolfang Vogel, Heinz Zoller
4	AUSTRIA	MEDICAL UNIVERSITY OF VIENNA	Thomas Reiberger
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8	BELGIUM	UZ GASTHUISBERG LEUVEN	Frederik Nevens
9	CROATIA	ZAGREB UNIVERSITY HOSPITAL	Irena Hrstic
10	CZECH REPUBLIC	INSTITUTE FOR CLINICAL AND EXPERIMENTAL MEDICINE, PRAGA	Jan Sperl
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12	DENMARK	HVIDOVRE UNIVERSITY HOSPITAL	Flemming Bendtsen
13	DENMARK	NYKOBING FALSTER	Lars Martinsen
14	DENMARK	RIGSHOSPITALET- COPENHAGEN	Fin Stolze Larsen
15	DENMARK	ODENSE UNIVERSITY HOSPITAL	Aleksander Krag
16	ESTONIA	WEST TALLIN CENTRAL HOSPITAL	Vadim Brjalin, Külliki Suurmaa
17	FRANCE	CHU TOULOUSE	Jean-Marie Peron, Christophe Bureau
18	FRANCE	CHU AMIENS –PICARDIE	Nguyen-Khac
19	FRANCE	HÔPITAL AVICENNE BOBIGNY	Dominique Roulot
20	FRANCE	HÔPITAL BEAUJON	Claire Francoz
21	FRANCE	HÔPITAL CLAUDE HURIEZ - LILLE	Philippe Mathurin
22	FRANCE	HÔPITAL HENRI MONDOR - CRÉTEIL	Christophe Duvoux
23	FRANCE	HÔPITAL JEAN VERDIER	Roland Amathieu

24	FRANCE	HÔPITAL MINJOZ, BESANÇON	Thierry Thevenot
25	FRANCE	HÔPITAL PAUL BROUSSE	Faouzi Saliba
26	FRANCE	HÔPITAL PITIÉ SALPÊTRIÈRE - PARIS	Dominique Thabut
27	FRANCE	HÔPITAL TENON- PARIS	Jean Didier Grange
28	FRANCE	CHU ANGERS	Frédéric Oberti
29	FRANCE	RENNES UNIVERSITY HOSPITAL	Pierre Brissot
30	GEORGIA	GEORGIAN NATIONAL HEPATOBILIARY CENTER	V Katsarava, Gocha Barbakadze
31	GERMANY	AACHEN UNIVERSITY HOSPITAL	Christian Trautwein
32	GERMANY	DUSSELDORF UNIVERSITY HOSPITAL	Dieter Häussinger
33	GERMANY	HAMBURG-EPPENDORF UNIVERSITY HOSPITAL	Ansgar Lohse, Valentin Fuhrmann
34	GERMANY	HANNOVER MEDICAL SCHOOL	Thomas von Hahn, Michael Manns
35	GERMANY	J W GOETHE UNIVERSITY HOSPITAL-FRANKFURT	Stefan Zeuzem
36	GERMANY	JENA UNIVERSITY HOSPITAL	Tony Bruns
37	GERMANY	KLINIKUM DER UNIVERSITÄT MÜNCHEN	Alexander Gerbes
38	GERMANY	MÜNSTER UNIVERSITY HOSPITAL	Hartmut Schmidt
39	GERMANY	UNIVERSITY HOSPITAL HALLE-WITTENBERG	Alexander Zipprich
40	GERMANY	UNIVERSITY HOSPITAL LEIPZIG	Cornelius Engelmann
41	GERMANY	UNIVERSITY HOSPITAL OF ESSEN	Guido Gerken
42	GERMANY	UNIVERSITY HOSPITAL OF FREIBURG	Robert Thimme
43	GERMANY	UNIVERSITY HOSPITAL OF HEIDELBERG	Wolfgang Stremmel, Dr. Uta Merle
44	GERMANY	UNIVERSITY HOSPITAL OF HOMBURG	Frank Lammert
45	GERMANY	UNIVERSITY HOSPITAL OF MAGDEBURG	Ali Canbay
46	GERMANY	UNIVERSITY HOSPITAL WÜRZBURG	Andreas Geier
47	GERMANY	UNIVERSITY OF BONN	Jonel Trebicka; Alessandra Pohlman
48	GERMANY	UNIVERSITY OF MAINZ HOSPITAL	Peter R. Galle; Marcus-A. Wörns
49	HUNGARY	UNIVERSITY OF DEBRECEN	Mária Papp
50	ICELAND	LANDSPITALI UNIVERSITY HOSPITAL- REYKJAVIK	Sigurdur Olafsson
51	IRELAND	ST VINCENT'S UNIVERSITY HOSPITAL	Aiden McCormick

52	ITALY	ALMA MATER STUDIORUM. UNIVERSITÀ DI BOLOGNA	Mauro Bernardi, Paolo Caraceni
53	ITALY	ASL BRINDISI	Pietro Gatti
54	ITALY	AZIENDA OSPEDALIERA CITTÀ DELLA SALUTE E DELLA SCIENZA DI TORINO	Carlo Alessandria
55	ITALY	AZIENDA OSPEDALIERA DI PADOVA	Paolo Angeli, Salvatore Piano
56	ITALY	POLICLINICO SAN DONATO- UNIVERSITY OF MILAN	Francesco Salerno
57	ITALY	UNIVERSITY OF ROME	Manuela Merli
58	ITALY	OSPEDALE NIGUARDA, MILAN	Luca Saverio Belli
59	ITALY	POLICLINICO OF PALERMO	Vito di Marco
60	ITALY	INTERNAL MEDICINE- UNIVERSITY OF UDINE	Pierluigi Toniutto
61	LATVIA	RIGA EAST UNIVERSITY HOSPITAL	Ieva Tolmane
62	LITHUANIA	HOSPITAL OF LITHUANIAN UNIVERSITY OF KAUNAS	Limas Kupcinskas
63	LITHUANIA	SIAULIAI HOSPITAL	Gitana Acute
64	NETHERLANDS	ERASMUS UNIVERSITY MEDICAL CENTER ROTTERDAM	Rob de Man; Rosalie Oey
65	NETHERLANDS	LEIDEN UNIVERSITY MEDICAL CENTER	Minneke J Coenraad
66	NORWAY	OSLO UNIVERSITY HOSPITAL	Zbigniew Konopski
67	POLAND	POMERIAN MEDICAL UNIVERSITY	Anna Borón Kaczmarska
68	PORTUGAL	CENTRO HOSPITALAR DO PORTO	Filipe Nery
69	PORTUGAL	CHTMAD VILA REAL	José A Presa Ramos
70	PORTUGAL	HOSPITAL SANTA MARIA FACULTADE DE MEDICINA DA UNIVERSIDADE DE LISBOA	José Velosa
71	SLOVACK REPUBLIC	PAVOL JOZEF SAFARIK UNIVERSITY IN KOSICE ROOSEVELT UNIVERSITY HOSPITAL. BANSKA BYSTRICA	Martin Janicko, Peter Jarcuska
72	SPAIN	CLINICA UNIVERSITARIA NAVARRA	Jorge Quiroga
73	SPAIN	FUNDACIÓ HOSPITAL UNIVERSITARI VALL D'HEBRON - INSTITUT DE RECERCA	Víctor Vargas
74	SPAIN	HOSPITAL CLINIC BARCELONA	Pere Ginès
75	SPAIN	HOSPITAL DE LA SANTA CREU I SANT PAU	German Soriano

76	SPAIN	HOSPITAL GENERAL UNIVERSITARIO GREGORIO MARAÑÓN	Rafael Bañares
77	SPAIN	HOSPITAL UNIVERSITARI BELLVITGE	José Castellote
78	SPAIN	HOSPITAL UNIVERSITARI GERMANS TRIAS I PUJOL	Rosa Mª Morillas
79	SPAIN	HOSPITAL UNIVERSITARIO RAMÓN Y CAJAL	Agustín Albillos
80	SPAIN	HOSPITAL UNIVERSITARIO wwREINA SOFÍA- CÓRDOBA	Manuel de la Mata
81	SPAIN	HOSPITAL VIRGEN DEL ROCÍO	Manuel Romero Gómez, Javier Ampuero
82	SWEDEN	LINKÖPIN UNIVERSITY HOSPITAL	Stergios Kechagias
83	SWITZERLAND	INSELSPITAL BERNE	Andrea De Gottardi
84	SWITZERLAND	LAUSANNE UNIVERSITY HOSPITAL CHUV	Pierre Deltenre
85	SWITZERLAND	UNIVERSITY HOSPITAL OF GENEVE	Dr Laure Elkrief
86	SWITZERLAND	ST GALL CANTONAL HOSPITAL	Christine Bernsmeier
87	SWITZERLAND	ZÜRICH UNIVERSITY HOSPITAL	Beat Mühlhaupt
88	TURKEY	ANKARA UNIVERSITY FACULTY OF MEDICINE	Ramazan Idilman
89	TURKEY	KARADENIZ SCHOOL OF MEDICINE - TRABZON	Mehmet Arslan
90	TURKEY	MARMARA UNIVERSITY SCHOOL OF MEDICINE - ISTANBUL	Osman Ozdogan
91	UK	GLASGOW ROYAL INFIRMARY	Ewan Forrest
92	UK	IMPERIAL COLLEGE	Harry Antoniades
93	UK	KING'S COLLEGE HOSPITAL	Debbie Shawcross, William Bernal, Julia Wendon
94	UK	PLYMOUTH HOSPITAL TRUST	Juan Acevedo, Matthew Cramp
95	UK	QUEEN ALEXANDRA HOSPITAL -PORTSMOUTH	Richard Aspinall
96	UK	UNIVERSITY COLLEGE LONDON- ROYAL FREE HOSPITAL	Rajiv Jalan, Raj Mookerjee
97	UK	UNIVERSITY HOSPITALS BIRMINGHAM	Ahmed Elsharkawy, Neil Rajoriya
98	UK	UNIVERSITY HOSPITALS NOTTINGHAM	Stephen Ryder
99	UKRAINE	IVANO-FRANKIVSK NATIONAL MEDICAL UNIVERSITY	Virstyk Nataliya

Activities

12 April 2016

1st Meeting of the EF Clif in Barcelona.

The symposium was the first major scientific event organized by the Foundation, since its establishment in mid-2015, and has served as a public presentation of its activities and projects to the international scientific community in the field of Hepatology. Over two hundred specialists from all over the world, mostly European hepatologists, attended the lectures on the Acute-on-Chronic Liver Failure (ACLF) Syndrome.

27 May 2016

Call for the PREDICT study.

This is the first study which starts under the sponsorship of the EF Clif Foundation and will represent a further advance in the knowledge of ACLF

19 September 2016

Investigators of the EF Clif hold a workshop in the XXIV Congress of the Latin American Association for the Study of Liver in Santiago de Chile.

The presentations focused on new developments on the characterization, mechanisms and treatments of the ACLF.

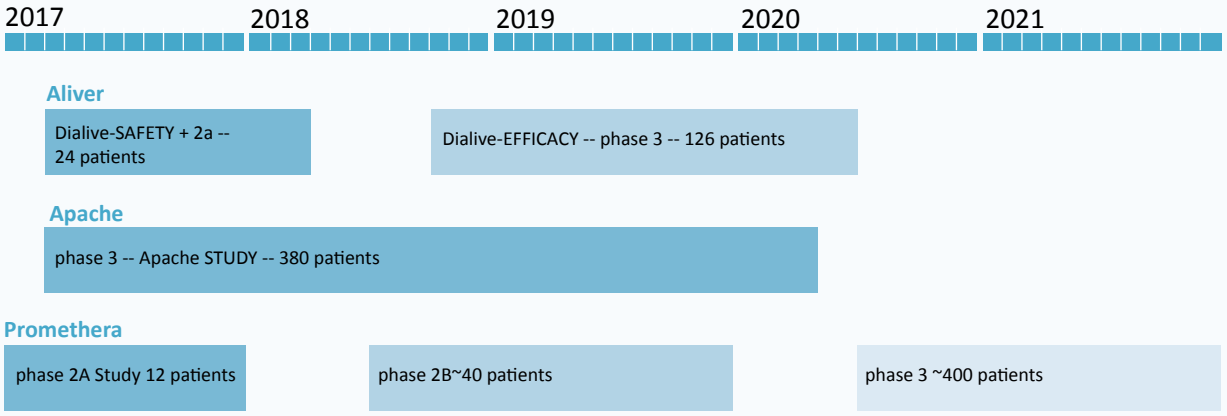
12 December 2016

The Cellex Foundation contributes with a donation for the PREDICT Study.

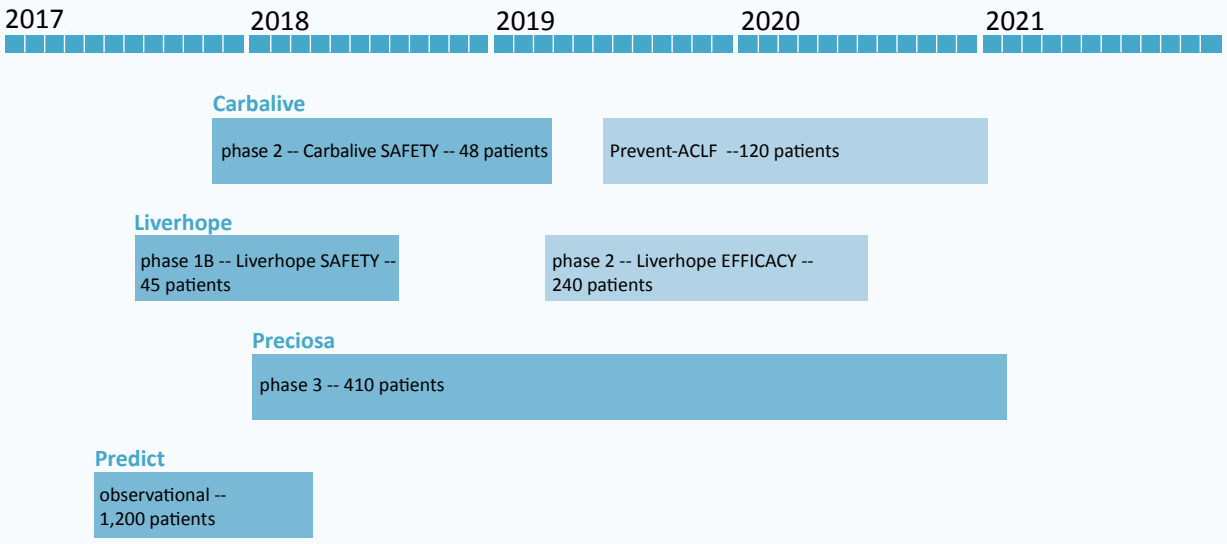
This contribution will allow Dr Jonel Trebicka to join the EF Clif as a Visiting Professor in 2017 and 2018 to lead the future flagship study of the EF Clif.

New studies calendar

STUDIES ON ACLF



STUDIES ON DECOMPESATED CIRRHOSIS



EASL CLIF CONSORTIUM

EASL Chair Studies

Finalized studies

CANONIC Study

(2010-2013)

This study was aimed to assess the diagnosis criteria, prevalence, clinical features, prognosis and mechanisms of Acute on Chronic Liver Failure in cirrhosis.

Principal Investigator: Richard Moreau (Hôpital Beaujon, Clichy, France).

Data were collected from 1343 hospitalized patients with cirrhosis and acute decompensation from 29 liver units in 8 European countries.

Organ failure and mortality data were used to define ACLF grades, assess mortality, and identify differences between ACLF an acute decompensation.

Diagnostic criteria for ACLF were established based on analysis of patients with organ failure (defined by the CLIF-SOFA score) and high 28-day mortality rate (>15%).

- The results of this prospective observational study were published in 2013 and they have allowed to identify the ACLF as a new clinical entity.
- The description of the natural history of ACLF has led to establish diagnostic criteria and open new perspectives in the study of chronic liver diseases.
- Thirteen ancillary studies have been published, focusing on different aspects of ACLF.
- Eleven additional core and ancillary studies are currently performed, using the database and biological samples from the Canonic Study, which will give a total number of 25 Canonic derived original articles.

(April 2014-December 2016))

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

Principal Investigator: Javier Fernández (Hospital Clínic, Barcelona, Spain).

This is a phase IV, open-label, multicenter European RCT. Patients with advanced cirrhosis and frequent non-SBP infections were randomized to receive antibiotics or antibiotics plus albumin. The primary goal of the study was to evaluate if albumin administration improves in-hospital survival in this target population. The sample size initially calculated was 512 patients (256 per treatment arm).

From April 2014 to December 2016, 776 patients were screened and 136 patients (17.5%) were included in the study. Hospital Clinic of Barcelona (n=37), University of Padova (n=15), Sapienza University in Rome (n=10), University Hospital in Bonn (n=8), and Erasme Hospital, Brussels and San Giovanni Battista Hospital, Turin (n=8, each) were the centers with the highest inclusion rates. The study has been prematurely interrupted in December 31st 2016 due to the low recruitment rate and the expiration of the study drug. All sites will be closed by the end of April 2017. The final study report will be published no later than 12 months after the finalization of the study.

Ongoing studies

(June 2015-2019)

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

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

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

Eight centers are currently active to recruit: Belgium (n=2), Spain (n=4) and Italy and Czech Republic (n=1, each). Regulatory issues are still pending in Germany (n=1), Austria (n=1) and United Kingdom (n=2). Until now, 136 patients have been screened and 31 patients (23%) have been included in the study. We estimate that the inclusion will finish at the end of 2019.

New projects

Predicting Acute-on-Chronic Liver Failure in Cirrhosis (PREDICT)
(January 2017-2018)

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

Principal Investigator: Jonel Trebicka (Bonn University Hospital, Germany).

The aim of this study is to assess prospectively the critical period prior to the development of ACLF (1), to uncover mechanistic and pathophysiological processes associated with the development and clinical course of ACLF (2) and to identify the precipitating events of ACLF (3).
Specific goals of the study are:

- To identify early clinical predictors, biomarkers, mechanisms and precipitating events during the critical period prior to and involved in the development and clinical course of ACLF (with special emphasis to medical trajectory and drug history) in patients admitted/referred to study centre with acute decompensation of cirrhosis (ascites, GI-hemorrhage, overt encephalopathy, new onset of non-obstructive jaundice and/or bacterial infections) and the chronological relationship of the events with occurrence and dynamics of ACLF development.
- To develop a score predicting ACLF development (CLIF-PREDICT score) and assess 28- day, 90-day, 6-month and 1-year all-cause mortality in cirrhotic patients with acute AD, but without ACLF.
- To serve as a core (hub) study for prospective ancillary studies regarding diagnosis, prognosis and pathogenesis of AD and ACLF.

The population of patients would include ca. 1,200 cirrhotic patients over a twelvemonths period. These patients will be admitted/referred to the study centre because of acute decompensation of cirrhosis (ascites, overt encephalopathy, GI-hemorrhage, new onset of non-obstructive jaundice and/or bacterial infections), without ACLF (as defined according to the CANONIC study) at hospitalization.

After the enrolment visit, the patients will be stratified into two groups:

- Group 1: patients with high risk of ACLF development (CLIF-C AD score ≥ 60).

- Group 2: patients with low risk of ACLF (CLIF-C AD score <60).

The whole cohort will be followed for 3 months, while Group 1 will be followed more closely. Development of ACLF is an end-point and in this case a final visit 7-10 days after ACLF development is planned. Data on liver transplantation, mortality and causes of mortality 3 months, 6 months and 12 months will be collected in the whole cohort.
Prospective collection of biological material and performance of ancillary studies investigating predictors for development and pathogenesis of ACLF.

GRIFOLS CHAIR OF **RESEARCH** ON CLIF

Studies

Ongoing studies

ALBUMIN AS A DRUG: ANTIOXIDATIVE, ANTI-INFLAMATORY AND TISSUE PROTECTIVE ACTIONS OF HUMAN ALBUMIN.

Principal Investigator: Joan Clària (Hospital Clínic, Barcelona, Spain).
(June 2016- December 2017)

Albumin plays a modulatory role in systemic inflammation and oxidative stress through its ability to bind and sequester soluble mediators. The main goal of this project is to investigate the mechanisms of action of the anti-inflammatory and anti-oxidative properties of albumin in two ex vivo models. The first model is in leukocytes, which is an appropriate experimental tool for studying the systemic effects of albumin, and the second model is in precision-cut liver slices, which is an appropriate experimental tool for studying the effects of albumin on tissues.

ALBUMIN AS A DRUG: EFECTS OF ALBUMIN ON GENE EXPRESSION AND SIGNALING IN LEUKOCYTES ISOLATED FROM PATIENTS WITH ACLF.

Principal Investigator: Richard Moreau (Hôpital Beaujon, Clichy, France).
(June 2016-December 2017)

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

COMPREHENSIVE UN-TARGETTED METABOLOMIC AND LIPIDOMIC PROFILING OF ORGAN DYSFUNCTION IN PATIENTS WITH DECOMPENSATED CIRRHOSIS AND ACLF.

Principal Investigators: Christophe Junot (CEA, Saclay, France), Richard Moreau (Hôpital Beaujon, Clichy, France) and Joan Clària (Hospital Clínic, Barcelona, Spain).
(June 2016-December 2017)

The main goal of this project is to characterize the profile of metabolites in serum samples from patients with cirrhosis by un-targeted functional metabolomics and lipidomics using liquid chromatography-tandem mass spectrometry (LC-MS/MS). The predicted outcomes include the identification of a metabolic signature of ACLF patients, to discriminate patient groups accordingly to etiology (alcohol, virus) or presence of infections and the identification of organ-specific metabolic signatures in these patients.

External projects

New studies

During 2016, the EF Clif has participated in the design and preparation of the following studies.

The APACHE TRIAL (Promoter: Grifols)

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

Principal Investigators: Javier Fernández (Hospital Clínic, Barcelona, Spain) and Fin Stolze Larsen (Rigshospitalet, Copenhagen, Denmark).
(2017-2020)

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

The study will be performed in 39 centres, 28 from Europe and 11 from North America. The submission process will start within the second quarter of 2017. The estimated duration of the study is 36 months.

The ALADDIN STUDY (Promoter: Grifols)

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

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

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

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

The PRECIOSA STUDY (Promoter: Grifols)

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

Principal Investigator: Paolo Caraceni (Policlinico S Orsola-Malpighi, Bologna, Italy).
(2017-2020)

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

The study will be performed in about 40 European centres. The submission process will start within the second quarter of 2017. The estimated duration of the study is 36 months

ALIVER

(European Union Horizon 2020 Program)

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

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

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

CARBALIVE (European Union Horizon 2020 Program)

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

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

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

LIVERHOPE (European Union Horizon 2020 Program)

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.

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

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

PROMETHERA

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

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

The EF Clif has collaborated in the running safety study, in its design and statistical planning, and also in the discussions of a future follow-up efficacy study.

Future projects

In late 2016, The EF Clif has been evaluating new projects to increase the knowledge and understanding of cirrhosis. As a result, some new studies will be designed during 2017.

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"Omics" characterization of the ACLF syndrome.

Principal Investigators: Pierre Emmanuel Rautou (Hôpital Beaujon, Clichy, France) and Wim Laleman (Gasthuisberg University Hospital, Leuven, Belgium).

Up to now, the ACLF syndrome has been characterized in patients from the Canonic Study by clinical and standard laboratory data and inflammation and circulatory biomarkers (cythokines, renin and oxidized albumin). In the next two years, the characterization of the syndrome will be completed by genomic, proteomic, lipidomic and metabolomic studies and systemic biological analysis.

Microbiota in ACLF

Principal Investigator: Jonel Trebicka (Bonn University Hospital, Germany).

The PREDICT Study is designed to prospectively observe patients with an Acute Decompensation (AD) at risk of developing ACLF within three months and to discover clinical, laboratory and patho-physiological (using prospective ancillary studies) predictors and mechanisms involved in the development and clinical course of ACLF. Especially gut microbiota has been in the focus of modifying and influencing health and disease in the last years. The overall objective of MICROB-PREDICT is the understanding, prediction and treatment of acute on chronic liver failure. The specific aims are: (A) To define specific gut microbiome and associated host genome, transcriptome and metabolome risk signatures that predict the development of AD and progression to ACLF. (B) From these signatures to develop novel omics-based biomarkers for early diagnosis, prognosis and treatment monitoring. (C) Use the identified risk signatures and biomarkers to evaluate interventions based on microbiome modulation to prevent AD and ACLF development.

EASL CLIF CONSORTIUM

Prospective observational study in Acute Alcoholic Hepatitis in Europe

Principal Investigators: Christophe Moreno (Erasme University Hospital, Bruxelles, Belgium) and Ramón Bataller (University of Pittsburgh, USA).

Acute Alcoholic Hepatitis (ASH) is a major cause of ACLF. This association, however, is poorly characterized. Following the end of the PREDICT Study, the EF Clif has decided to explore Acute Alcoholic hepatitis with a project reproducing the methodology used in the Canonic and in the PREDICT STUDY. Samples will be obtained for later translational studies.

The Chinese Canonic Study

Principal Investigator: Hai Li (Ren Ji Hospital, Shanghai, China).

Chinese CLIF Consortium has finished a Chinese Canonic observational Study in 14 University Hospitals from East China. Clinical data and biological samples have been obtained from 1458 patients with cirrhosis. The European CLIF Consortium will participate in the data analysis and exploitation of the results.

The Latin American Canonic Study

Principal Investigator: Flair Carrilho (University of Sâo Paolo, Brasil).

The Latin American CLIF Consortium in collaboration with the EASL-Clif Consortium is planning to develop the Latin American Canonic Study in 1000 patients admitted to a hospital for an acute decompensation in cirrhosis, in University hospitals from Brazil, Argentina, Chile and Mexico.
EF Clif supports the project with the design of the e CRF and the economic support for the collection of biological samples and biobanking.

EF Clif

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