BITRECS: Biomedicine International Training Research Programme for Excellent Clinician-Scientists

Research Lines

RL1. Surgical advances in gynaecologic (within the research IDIBAPS line "Gynaecology, human reproduction and women's health")

Key words: Gynecologic oncology, endometriosis, minimally invasive surgery

Description of the research line: our goal is to leverage scientific and technical advancements to provide our patients with more personalized and less invasive surgery, reducing surgical morbidity and allowing a faster recovery after surgery. Within the scope of our research line, we have several ongoing research projects aimed at:

- Pre-surgically: incorporating the most recent knowledge on gynecological conditions into treatment planning (i.e. molecular classification of gynecological tumors for surgical planning, ultrasonographic pre-surgical evaluation of tumors, endometriosis and benign gynecological diseases, cervical cancer screening and HPV-related diseases)
- In the operating room: developing and validating surgical techniques (i.e. sentinel lymph node mapping in ovarian and endometrial cancer, laparoscopically assisted radical vaginal hysterectomy, robotic surgery in gynecologic oncology, robotic surgery in gynecologic endometriosis, uterus transplantation), devising less invasive therapeutic options tailored to the patient's preferences and needs (i.e. fertility-sparing surgery in women with endometriosis and gynecological tumors)
- After surgery: improving recovery and minimizing morbidity (i.e. prehabilitation and enhanced recovery after major gynecological surgery, preventing and improving sexual disfunction after cervical cancer treatment, medical and molecular factors involved in comorbidities and mental health of patients with endometriosis and pelvic pain, long-term evolution of medical-surgical treatments for endometriosis and adenomyosis)

Hence, our research line aims to translate the technological innovations and the findings from translational and clinical research into tangible improvements clinical practice.

Principal investigator: Berta Díaz-Feijoo (bdiazfe@clinic.cat)

Research group: Gynecology, human reproduction and women's health. The research team primarily consists of gynaecologists from the Gynaecology Department at Hospital Clinic de Barcelona. Additionally, we collaborate on translational research initiatives with other departments within the hospital and participate in multicenter projects involving national and international institutions.

Our primary scientific aim is to enhance the diagnosis and treatment of gynaecological conditions.

Our research activities are primarily conducted within the Gynaecology Department of HCB, where the researcher will have access to various facilities, including the operating room, diagnostic area, and outpatient clinic. The techniques employed by our research group are integral to both the diagnostic and therapeutic processes for gynaecological diseases, encompassing ultrasonography, various imaging modalities, pathology, and surgical techniques.

Additional information about the research group:

- **Importance of the clinician-scientists within the group:** The research group comprises solely gynecologists, thus engaging in both research and clinical activities within the Gynecology Department. While historically, emphasis has been placed on basic research and medical aspects of gynecology, we recognize the essential role of research in the field of gynecological surgery for the benefit of our patients. One challenge we encounter is the extended timeframe required for research findings, particularly translational research, to be incorporated into surgical practices for patient care. Recognizing this, clinician-scientists within the group strive to develop research projects with direct applicability in clinical settings, aiming to bridge the gap between research outcomes and the operating room. This approach not only advances scientific knowledge but also enhances the medical care provided to our patients, ensuring they have access to the latest innovations and treatments available.

- **Interest of the group to recruit a clinician-scientist:** A clinician-scientist, fully focused on research projects, would enhance our research activity as well as its applicability in clinical practice, particularly in the operating room. We seek to develop translational/technological research projects whose results directly improve clinical practice, thus the role of a clinician-scientist fully focused on research projects is essential for our group.

RL2. Alcohol-associated neurocognitive impairment: clinical and socioeconomic implications

Key words: Alcohol Use Disorder (AUD), Alcohol associated Liver Disease, Alcohol-associated cognitive impairment (AACI)

Description of the research line: Alcohol is a leading cause of preventable mortality and morbidity worldwide and receives scarce research attention. Alcohol-associated liver disease is the leading cause of liver- related mortality and related health expenditure.

Challenge 1: Determine the prevalence of, and optimize diagnostic tools for identifying, alcohol-associated cognitive impairment (AACI).

Challenge 2: Study the mechanisms and role of AACI in patients with early and advanced alcohol-associated liver disease.

Challenge 3: Test novel therapeutic approaches for patients with AACI, alcohol use disorder (AUD) and liver disease (digital health solutions, brain stimulation and microbiota transplantation).

Challenge 4: Assess the impact of AACI on health expenditure (ER visits and hospitalizations), loss of productivity, and quality of life indicators.

This research project involves two integrated clinical and research groups (Addiction Unit and Liver Unit) that share the management of patients with AUD and associated liver disease. Seventy per cent of these patients present with AACI, with higher rates in those with more severe AUD. Therefore, there is an urgent need to develop novel diagnostic and therapeutic tools to address this clinical problem. Patients with AACI have worse adherence and treatment retention, more alcohol relapse, lower motivation, and more anxiety and depressive symptoms. This leads to impaired quality of life, higher mortality, and loss of functionality and productivity. Patients with alcohol associated liver disease are at risk of AACI. Improving diagnosis and identifying novel therapies will improve the outcomes of this complex population.
To successfully carry out this project, a clinician-scientist with training in both addictions and organ damage such as liver diseases is required. Our aim is to select a clinical specialist in addictions that has worked with patients with organ damage, especially alcohol-associated liver disease.

Principal investigator: Hugo López Pelayo (hlopez@clinic.cat); Ramon Bataller Alberola (co-PI) (bataller@clinic.cat)

Research group: Our scientific objective is to develop novel diagnostic tools and pathophysiological based targeted therapies for people with alcohol-related organ damage. Our research team is highly multidisciplinary, including the Addictions and the Steatohepatitis and Liver Transplantation groups in IDIBAPS. We provide integrated patient care, sharing patient management across the Addiction and Liver Units that include day hospital, inpatient, and outpatient services.

Research methods available for this project include standardized clinical assessment including neuropsychological evaluation, systematic reviews and meta-analyses, metabolomics, co-creation and participatory research.

Additional information about the research group:

- **Importance of the clinician-scientists within the group:** Our two groups contain 51 members including 19 clinically active postdoctoral researchers (liver specialists, psychiatrists and psychologists, two with long-term experience in neuropsychological assessment), 1 emeritus researcher, 5 research technicians and 14 PhD students (3 of them under contract with Hospital Clínic Barcelona and clinically active).

- **Interest of the group to recruit a clinician-scientist:** We aim to incorporate a clinician scientist with interest experience in addiction, neurocognition, and related organ damage to foster research and clinical collaboration in the assessment and treatment of patients with alcohol use disorder and alcohol-associated liver disease.

RL3. CD70, a novel target of CART-cell therapy for MCL

Key words: Non-Hodgkin lymphomas (NHL); Mantle cell lymphoma (MCL), CD19, CD70, CAR-T cell Therapy.

Description of the research line: The research lines of my scientific group are based on the study of the tumour microenvironment of mantle cell lymphoma (MCL) and other non-Hodgkin lymphomas (NHL) and the complex protein interplay between SOX11 and key oncogenic factors in lymphoid neoplasms.

The main scientific challenges of my research are: 1) To identify new candidates and signalling networks responsible for the onset, maintenance, and aggressive behaviour of lymphomas, from clinical samples of patients with NHL. 2) To characterize the functional role and clinical impact of these new identified oncogenic factors and signalling pathways in aggressive lymphomas using innovative molecular and cellular biology tools and animal models for a better understanding of the pathogenesis and to find potential candidates for targeted therapies. 3) In order to contribute to the bench-bedside translation research of upcoming results my group aims to develop lymphoma in vitro and in vivo mouse modes and assay treatments providing the bases of new therapies for the treatment of aggressive lymphomas.

The Relevance is the translation of the identified promising target therapies to clinical trials, to improve the life quality of NHL patients.

Principal investigator: Virginia Amador (vamador@recerca.clinic.cat); Julio Delgado (co-IP) (jdelgado@clinic.cat)

Research group: Functional Characterization of oncogenic mechanism in lymphomagenesis. CD70 is playing an essential role in tumour progression by promoting immune suppression, as well as tumour cell proliferation and survival in aggressive MCL (Balsas P, et al., Blood. 2021). Our preliminary data has shown that antiCD70 blocking antibodies increased IFN-γ secretion and tumour cell death in MCL/T-cells co-culture systems. Our key objective is to develop a new dual anti-CD19/CD70 CART-cell based immunotherapy, trying to overcome anti-CD19 CART-cell therapy failures. If our dual CART-cells product is superior to anti-CD19 CART-cells, in pre-clinical assays, we plan to manufacture clinical-grade dual anti-CD19/CD70 CART-cells from patients, using the CliniMACS Prodigy system, to clinical translate this product for a phase I clinical trial, aiming to improve outcome and life quality of patients with MCL.

Additional information about the research group:

- **Importance of the clinician-scientists within the group:** If our hypothesis is confirmed, and the dual anti-CD19/CD70 CAR cell product is superior to anti-CD19 CART-cells, we plan to bring this product to MCL patients with the aim to improve their outcome. Dr. J. Delgado, head of the Oncoimmunotherapy Unit at HCB, is a haematologist with experience in the translation of academic CART-cells into clinical trials for the treatment of B-cell malignancies. So far, he has designed 3 different trials and has collaborated in the design of two others. One of the products developed in-house (var-cell, targeting CD19) has been approved in Spain for the treatment of adult acute lymphoblastic

leukemia and has been granted PRIME designation by the EMA. Almost 200 patients have been treated at HCB with academic CART-cell products manufactured in house.

- **Interest of the group to recruit a clinician-scientist:** Our project would lead to the development of a new promising dual CAR-T-cell based product. Our interest is to recruit a Clinician-scientist to design and conduct academic CAR-T clinical trials for the treatment of patients with NHL overexpressing CD70.

RL4. Novel theranostic opportunities for liver diseases coursing with vascular dysfunction.

Key words: Liver sinusoidal endothelial cells; hepatic stellate cells; liver sinusoid; portal hypertension; liver fibrosis

Description of the research line: The liver microcirculation, specifically involving sinusoidal endothelial cells, stellate cells, and resident macrophages (Kupffer cells), plays a pivotal role in the initiation and progression of liver diseases. Consequently, these cells constitute a significant therapeutic target for enhancing the treatment outcomes of individuals with liver damage. Our research group is dedicated to investigating the molecular and biomechanical processes governing the phenotype of these sinusoidal cells, as well as the mechanisms of intercellular communication within the hepatic environment. Our focus spans healthy conditions, responses to acute liver injuries, chronic liver diseases (such as steatosis and cirrhosis), and the impact of aging.

The outcomes of our research provide the foundation for the development of novel therapeutic strategies aimed at enhancing liver microcirculation, mitigating fibrosis, and optimizing overall liver function. To achieve these objectives, we employ a diverse array of experimental methodologies, encompassing the use of tissues and primary cells sourced from both human and rodent subjects. Additionally, our investigations extend to in vivo and in vitro models of liver disease, cell co-culture facilitated by liver-on-a-chip technology, the analysis of extensive datasets through advanced bioinformatic tools and liquid biopsies characterization using omics.

Principal investigator: Jordi Gràcia-Sancho (jgracia@recerca.clinic.cat); JC Garcia-Pagan (co-IP) (jcgarcia@clinic.cat)

Research group: The Liver Vascular Biology Group and the Hepatic Hemodynamic Unit (Regulation of liver microcirculation in cirrhosis and hepatic vascular diseases) stand as a leading force in the investigation of liver vascular disorders and the development of innovative therapeutic methodologies. Our extensive research contributions, reflected in over 300 publications in esteemed international scientific journals, underscore our commitment to advancing the understanding and treatment of liver-related conditions. Comprising approximately 30 researchers specializing in biology, biochemistry, physiology, and clinical expertise, our team operates within the esteemed IDIBAPS Biomedical Research Institute, the Hospital Clínic, the University of Barcelona, and the Biomedical Research Networking Centre on Hepatic and Digestive Disease (CIBEREHD). These affiliations offer our MD and PhD scientists a rich and diverse scientific milieu, characterized by cutting-edge technologies, advanced core units, and comprehensive training programs of the highest quality.

Our research initiatives encompass a multidisciplinary approach, integrating fundamental studies at the cellular and molecular levels with in vivo investigations employing animal models and sophisticated genetically modified murine models. Furthermore, our collaborations with clinical entities focused on liver pathology allow us to bridge the gap between laboratory discoveries and clinical applications. This convergence of expertise uniquely positions us to

advance scientific knowledge and revolutionize the treatment paradigms for chronic liver diseases.

Additional information about the research group:

- **Importance of the clinician-scientists within the group:** We, as close collaborators of the Hepatic Hemodynamic Unit, have several scientists performing clinical and basic research activities. Our sister unit at the Hospital Clinic is a referent in the field of chronic liver disease and vascular liver diseases. At the same time, close collaboration between clinical scientists and research scientists allows us to develop novel and very updated research projects that combine bench research with human samples analysis. These projects ultimately aim at better understanding liver diseases coursing with vascular dysfunction, developing novel therapeutic approaches and proposing novel biomarkers.

- **Interest of the group to recruit a clinician-scientist:** Our group is highly translational and therefore we always seek to create new projects that investigate clinically relevant problems using cutting-edge technology. To accomplish this, our group is multidisciplinary and therefore require incorporation of highly motivated clinical researchers that will, for sure, develop excellent work and give further clinical insight.

RL5. Clinical and Translational Research on Infective Endocarditis

Key words: Infective endocarditis, experimental endocarditis, *in vitro* studies, cohort studies, clinical trials, antimicrobial studies.

Description of the research line: Infective endocarditis (IE) is a cardiac infection involving natural valves and intra-cardiac devices (mechanical and biological valve prosthesis, TAVI, pacemakers and defibrillators) with overall rates of cardiac surgery and mortality of 50% and 20%, respectively. Although the prevalence is relatively low (1 episode per 1,000 hospital admissions), the disorder has a significant burden in terms of both clinical management and severity, requiring a multidisciplinary approach ("an Endocarditis team") to achieve the best outcomes. This research line undertakes both clinical and translational studies. On the clinical side, we are researching: (1) epidemiological and prognostic-factor studies on several types of endocarditis (at local, Spanish and International [International collaboration on Endocarditis [ICE], European IE Registry [Euro-ENDO] levels); (2) the association between *Enterococcus faecalis* endocarditis of unknown source and colonic cancer (Enterocolonus project); (3) the diagnostic yield of molecular diagnosis of infective endocarditis (16S, microbial cfDNA); (4) the usefulness of cardiac PET/CT scans for the diagnosis and management of device-related infections; and (5) clinical trials and cohort studies on the treatment of *S. aureus*, enterococci, and *Candida* bacteraemia and endocarditis (OROPAT RCT).

On the translational side, we are performing *in vitro* and *in vivo* studies focused on the pathophysiology and treatment of experimental endocarditis caused by susceptible and resistant Gram-positive cocci. We have been evaluating the activity of new antibiotics or new antibiotic combinations against *Staphylococcus aureus* (MSSA with different vancomycin MICs, MRSA and GISA), *S. epidermidis* (MRSE, VRSE), *Enterococcus faecalis, E. faecium* and penicillin-resistant *Streptococcus mitis* endocarditis. The experimental endocarditis model in rabbits is an ideal model for the evaluation of antimicrobials, and most of the data from successful preclinical trials were shown to be effective in clinical trials of bacteraemia and endocarditis in the human being. It is, therefore, a very good example of "from bench to bedside".

Principal investigator: Jose M. Miró (jmmiro@ub.edu)

Research group: The Hospital Clinic Infective Endocarditis Research Group ("the Endocarditis Team") was created in 1986 (Dr. Miro is the Chair) and includes 20 researchers specialized in cardiovascular diseases and infections: cardiologists, cardiovascular surgeons, infectious-diseases specialists with broad experience in cardiovascular infections, electrophysiologists, microbiologists, nuclear-medicine specialists, pathologists, biologists with expertise in animal models of endocarditis, toxicologists, pharmacologists and statisticians. It is a consolidated research group that has received continuous funding from national and international agencies for more than 30 years and has been an international research group both at clinical and translational levels. In 1979 the Hospital Clinic Infective Endocarditis Database was started, and we have collected more than 1,800 consecutive cases of infective endocarditis. Since 2014 the Hospital Clinic of Barcelona has been the referral hospital of 10 hospital centers for patients with infective endocarditis needing cardiac surgery in Catalonia, and it has created a Catalonian research network that evaluates 90–100 cases of endocarditis per year. Since 1994 it has also

operated a microbiological repository of samples isolated from blood cultures or valve vegetations from patients with infective endocarditis and currently stores more than 1,500 well-characterized microbiological isolates.

Additional information about the research group:

- **Importance of the clinician-scientists within the group:** Dr. Jose M. Miro has been working on a clinical and experimental endocarditis model using human-like pharmacokinetics for over 30 years, including a six-month pre-doctoral stay at Mayo Clinic, Rochester, MN, USA. Dr. Miro currently has an 80:20 IDIBAPS Research Contract obtained through a competition for the period 2017–24. The major component of this contract is work focused on clinical and translational research, and he expects to transfer and apply scientific-technical knowledge to improving the prevention, diagnosis, and treatment of infective endocarditis.

- **Interest of the group to recruit a clinician-scientist:** We are a group with both clinical and translational activities, and we are therefore very interested in recruiting a clinician-scientist (e.g., MD-PhD). Our research line has a strong component in both areas: working both with patients and in the laboratory with an experimental endocarditis model. We are looking for someone who can integrate data coming from the two fields, which may help us to understand the disease and thereby improve its prognosis, diagnosis, and antimicrobial therapy.

RL6. Clinical and Translational Research in Autoimmune and Cholestatic Liver Diseases

Key words: autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, translational research

Description of the research line: The team of autoimmune and cholestatic liver diseases, part of the group of viral, genetic and immune-mediated liver diseases (Led by Dr. Xavier Forns) performs clinical and translational research in autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC). Our team participates in international networks of autoimmune liver diseases (ERN-RARE LIVER, International Autoimmune Hepatitis Group, Global PBC Study Group and International PSC Study Group) and in international clinical and research protocols.

Recently, our group is running various clinical studies with national and international collaborations. In the field of AIH we focus on the evolution of the disease in special populations (pregnancy, decompensated cirrhosis) and on the role of liver elastography in disease prognosis. In the field of PBC we are working on the early diagnosis and prediction of non-cirrhotic portal hypertension and on the role of extrahepatic manifestations (fatigue) in the disease course trying to establish a multidisciplinary prehabilitation program that will improve the quality of life of the patients. Regarding PSC, we are participating in international randomized control trials trying to discover effective treatments.

At the translational level, we are performing a simultaneous immunological and transcriptomic analysis at single cell level of peripheral and intrahepatic lymphocytes using cutting edge techniques (scRNAsec, spectral cytometry) in patients with well characterized AIH to identify the role of different lymphocytic populations (B-cells, T follicular helper-cells, T regulatory-cells) in disease pathogenesis, treatment response and outcome. We believe that the simultaneous interrogation of blood and liver tissue, enabled by new and advanced laboratory techniques, is the key for identifying the molecular and cellular drivers that are lying behind the pathogenesis and affect the prognosis of autoimmune and cholestatic liver diseases.

Principal investigator: María-Carlota Londoño (mlondono@clinic.cat); Xavier Forns (co-PI) (xforns@clinic.cat)

Research group: Viral, genetic and immune-mediated liver diseases/team of autoimmune and cholestatic liver diseases. The research team of autoimmune and cholestatic liver diseases is performing clinical and translational research protocols focused on the knowledge of the phenotype, natural history, diagnosis, prognosis and treatment of AIH, PBC and PSC. Our research lines implement cutting edge technologies such as scRNA sequencing of fine needle aspirates and spectral cytometry analysis, in combination with robust in-depth analysis tools like next generation sequencing of liver biopsies, all in the framework of state-of-the-art facilities at the Hospital Clinic of Barcelona and IDIBAPS.

Additional information about the research group:

- **Importance of the clinician-scientists within the group:** Our team combines clinical activity with translational research and consists of one clinician-accredited researcher, one clinician-post-doctoral researcher, one pre-doctoral researcher, a technician and a nurse. Our experienced clinical scientists are dedicated to the diagnosis, clinical management and treatment of AIH, PBC and PSC. Our team is also running a number of clinical studies with national and international collaborations and is participating in international randomized control clinical trials aiming to discover new therapeutic agents in cholestatic liver diseases.

- **Interest of the group to recruit a clinician-scientist:** We are interested in recruiting a clinician-scientist with experience in basic research and clinical management of autoimmune and cholestatic liver diseases, to perform a translational research project related to the pathogenesis, treatment and prognosis of autoimmune and cholestatic liver diseases.

RL7. Elevating Hepatocellular Carcinoma Therapy: Unifying Radiomics and Liquid Biopsy for Targeted Interventions (ELEVATE project)

Key words: Liver cancer, immunotherapy, immune evasion, radiomics, circulating non-coding RNAs

Description of the research line: Immunotherapy (IT) is the first line treatment for advanced hepatocellular carcinoma (HCC) patients. Although patients' survival has improved significantly, there is still a percentage of patients in which treatment has no effect. Immune evasion is the main responsible for HCC progression and it can take place early during treatment (non-responder patients) but even the ones who respond will eventually relapse after 3-4 years of treatment. It would be ground-breaking to have the information that could show us which patients are leading which way.
Disease progression is analysed by means of radiology. Our group has previously demonstrated that tumour progression patterns associate to differences in disease evolution and consequently in patients' prognosis. Radiomics is a novel technology that integrates multiple imaging data that can be associated to specific biological characteristics: genetic profile or differences in tissue microenvironment, for instance. Thus, specific changes in imaging data might be tracing the changes in tumour biology.
We hypothesize that these changes will be also seized in circulating blood samples. We will be working with cell-free circulating non-coding RNA (cf-ncRNA) species which are extremely stable in circulating blood. In fact, it is well known that ncRNA expression profiles are tissue specific and consequently they might be also mirroring differences in tumour response to IT.

Our goal is to improve HCC patients' management through the optimisation of patient treatment allocation and precision oncology development in HCC. Although this project is focused on IT treatment in HCC, the results obtained will be applicable to patients with liver cancer independently of treatment received. The combination of radiomics and data coming from liquid biopsy is going to be key in identifying the patients who are no longer benefiting from the treatment so they can be given other treatment options even before the worsening of their disease.

Principal investigator: Maria Elisa Reig Monzón (mreig1@clinic.cat); Loreto Boix (co-PI) (lboix@recerca.clinic.cat)

Research group: Liver Cancer (BCLC) group. Our goal is to predict HCC patients' responses to immunotherapy using advanced radiomics and liquid biopsy.
Join our multidisciplinary research team at BCLC (http://www.bclc.cat) and Hepatic Oncology Unit (https://www.clinicbarcelona.org/unidad/oncologia-hepatica). With 360 new patient visits annually, you'll have access to extensive facilities, to experts in different fields and to the BCLC network (+70 hospitals) for research, education, and innovation.
Our translational lab specializes in cellular and molecular studies, liver cancer models, innovative human sample investigations from investigator-initiated clinical trials/projects and pathology/radiology AI https://eucanimage.eu/

Additional information about the research group:

- **Importance of the clinician-scientists within the group:** BCLC's research focuses on liver cancer knowledge for the benefit of patients. Led by Dr. Reig, we embrace a multidisciplinary approach, involving clinician-scientists from different disciplines such as Hepato-oncologists, pathologists, and radiologists. This collaboration has sparked new research areas such as microbiome and liver cancer, immunotherapy response markers, radiomics, and AI in radiology, alongside partnerships with other institutions. We've welcomed new researchers, fostering knowledge exchange and teamwork towards a common goal. This synergy, combined with Win-Win collaborations, enhances the clinician-scientific balance within BCLC, driving impactful research.

- **Interest of the group to recruit a clinician-scientist:** BCLC recruits' clinician-scientists since 1986 for clinical insights in liver cancer. We host BCLC meetings weekly, journal clubs monthly, and encourage discipline-specific and all IDIBAPs meeting participation. Candidates lead projects, secure funding, and join our global networks for growth.

RL8. Fetal Therapy and Surgery

Key words: Fetal development, Fetal surgery, perinatology, maternofetal research, artificial placenta.

Description of the research line: We are an internationally recognized research group in the field of maternofetal Medicine and one of our research lines is Fetal Therapy and Surgery.

The goal of this research line is to pioneer innovative intrauterine treatments and interventions designed to overcome the existing limitations associated with fetal conditions. The main challenge for this research line is the prevention and treatment of fetal-origin pathologies. To achieve this, our dedicated research team assesses targeted therapeutic approaches, which can prove beneficial in addressing specific fetal-origin diseases. Thus, we are committed to improve fetal treatment and to develop innovative surgeries to palliate fetal diseases. Several complications can arise during prenatal period, for instance, there is a 7-10% prevalence of fetal growth restriction (FGR) in pregnancies, which leads to a deleterious fetal neurodevelopment. We aim to overcome this condition with our Fetal Brain Care (FBC) project.

Our research aims at finding solutions to palliate the aforementioned prevalent conditions and other fetal rare diseases. For example, we have been within the first groups worldwide to perform surgery in congenital diaphragmatic hernia, prevalent in 1 every 2,500 gestations. In addition, we are actively researching to find solutions for extreme prematurity with our Artificial Placenta project.

We have a high translational capacity of research findings and technological results into clinical practice. Most of our research have led to medical innovations and improvements, which are currently offered to patients in clinical practice.

Altogether, we believe that our research contributes to develop solution to significantly reduce fetal complications that presented nowadays.

Principal investigator: Eduard Gratacós Solsona (gratacos@clinic.cat); Elisenda Eixarch Roca (co-PI) (eixarch@clinic.cat)

Research group: Fetal and perinatal medicine (BCNatal-FMRC) is a research group associated to UB, a multidisciplinary team specialized in fetal and perinatal Medicine. Our goal is to improve the health of future generations from the beginning of life (fetal period).

We have allocated 750sqm for research, and our researchers have access to the wet lab, animal facility, fetal image acquisition and post-processing facilities and operation theatre among others.

Our team is multidisciplinary, composed by specialist in maternofetal medicine, cardiology, neurodevelopment, biologists, pharmacists, bioengineers, epidemiologists and statisticians.

Additional information about the research group:

- **Importance of the clinician-scientists within the group:** Our research group is composed by an interdisciplinary team including several clinical professionals. In addition to the Principal Investigator, co-investigators and researchers are medical

doctors actively engaged in clinical work at the Hospital Clínic of Barcelona. These experts represent the fusion of several medical disciplines: neonatology, fetal medicine, and critical pediatric care; alongside with researchers with biotechnological and engineering expertise.

- **Interest of the group to recruit a clinician-scientist:** The nature of the work conducted within our research group encompasses both clinical and scientific domains. It is only through the combination of these two backgrounds that our research can advance. Recruiting a BITREC's fellow with clinician-scientist background and specialized in Biology will reinforce an area where we lack of expertise.

RL9. Innovative diagnostic and preventive strategies for hereditary colorectal cancer

Key words: Colorectal cancer, Lynch syndrome, immune interception, prevention, endoscopy

Description of the research line: The clinical research team is part of the Gastrointestinal and Pancreatic Oncology Research Group integrated in Area 3 of IDIBAPS. The scientific activity of the group is aimed at deepening the knowledge of the mechanisms involved in the development and progression of premalignant and malignant gastrointestinal, with the ultimate aim of establishing new diagnostic, therapeutic and / or preventive strategies in these neoplasms. The research carried out is basic, clinical and translational, so the group has several lines of research fully interrelated. One of the main aims is the characterization and improvement in the management of the hereditary forms of CRC. A key element in this line has been the leadership of one of the most ambitious cooperative projects carried out in Spain in recent years, the EPICOLON project. This project is based on an epidemiological, prospective and multicenter study, national-wide and population based, aimed at establishing the incidence and characteristics of the hereditary and familial forms of CRC in Spain as well as to deepen the molecular basis of these forms of CRC. The results of this project have allowed, among other things, to characterize the incidence of hereditary CRC in Spain as well as to describe relevant molecular keys. In 2006, a program for the prevention of CRC was started in individuals and patients with an increased risk of developing CRC based on their personal and family history. Our "High Risk Colorectal Cancer Clinic" (CAR-CCR), pioneer in our country, is coordinated by Dr. Balaguer. As a result of collaboration with national and international groups, the applicant and members of the research group have developed a number of studies focusing on the identification of Lynch syndrome and serrated polyposis syndrome.

Scientific challenges: Many challenges lie ahead in the clinical, molecular and endoscopic characterization of high-risk conditions for colorectal cancer. Herein we describe the most relevant for our group:

- A strong immunological response to Lynch syndrome tumors has been described to be a common and relevant feature in this syndrome. However, the molecular basis and the potential role of immunological intervention in Lynch syndrome tumors are still poorly understood. Our group is currently leading a phase I study evaluating a dendritic-cell based vaccine for cancer prevention in Lynch syndrome.
- Endoscopy has experienced a very important advance in recent years and its role as the main tool for the prevention of colorectal cancer is still to be determined.
- There is a lack of biomarkers for early diagnosis, prognosis and treatment in colorectal cancer in the high-risk CRC setting.

Relevance of the research line for the improvement of the clinical practice / health: Hereditary forms of colorectal cancer are rare diseases. To improve its clinical management, it is necessary to do research in a multidisciplinary and collaborative context. Our research group has extensive experience in multicenter collaboration, has made relevant contributions in the understanding of molecular mechanisms in this context, and has a long clinical experience.

Principal investigator: Francesc Balaguer (fprunes@clinic.cat)

Research group: Gastrointestinal and Pancreatic Oncology Research Group, consisting mainly of clinicians with basic training has extensive experience in translational research in digestive cancer, leading both clinical and molecular projects that have contributed to the characterization, diagnosis and treatment of digestive cancer. The scientific objectives are:

1. To develop immune approaches for cancer prevention in individuals with Lynch syndrome with the ultimate goal of developing a vaccine.
2. Evaluating new endoscopic techniques in high-risk conditions for colorectal cancer.
3. Developing biomarkers with clinical utility for early diagnosis, prognosis and treatment in high-risk conditions for CRC.

Researchers will have access to the facilities of the IDIBAPS (laboratory of the group) needed to develop the project, as well as access to the Endoscopy Unit of the Gastrointestinal Department of the Hospital Clínic for the endoscopy studies. Moreover, for multicenter studies, access to the centralized database from the EPICOLON project will also be available.

Additional information about the research group:

- **Importance of the clinician-scientists within the group:** The research group consists mainly of clinicians (board certified gastroenterologists) with basic training with extensive experience in translational research in digestive cancers. Also, the clinician-scientists have a broad experience in endoscopy, specifically in the management of hereditary forms of colorectal cancer.
- **Interest of the group to recruit a clinician-scientist:** The interest of the group in recruiting a clinician-scientist is to be able to develop the objectives of the group by the hand of a highly motivated clinician, and to be able to offer him all the tools for his professional development. The research team is comprised of clinical experts in the management of high-risk CRC conditions. The synergy of the group with a new member will allow the successful achievement of our and her/his objectives.

RL10. Advances imaging in neuroimmunological diseases

Key words: Multiple sclerosis, magnetic resonance imaging, optic coherence tomography, neurodegeneration, disability.

Description of the research line: The Advanced Imaging in Neuroimmunological Diseases Research Group (ImaginEM) from FCRB-Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) was founded in 2015 and is coordinated by Dr. Sara Llufriu, neurologist of Neuroscience Institute at the Hospital Clinic in Barcelona. The group is part of the Neuroimmunology and Multiple Sclerosis (MS) Unit in Hospital Clinic, that attends 800 patients with MS and has large experience in the clinical research of MS and other neuroimmune diseases. We are part of the MAGNIMS european research network.

The primary objectives of our group encompass the development and application of imaging biomarkers to gain insights into the pathogenesis of physical and cognitive dysfunction in patients with MS and other demyelinating diseases of the central nervous system. Our mission also involves predicting disease progression and advocating for personalized medicine. Additionally, we are dedicated to showcasing the efficacy of stem cell therapy and cognitive rehabilitation in the context of MS.

MS stands as a significant cause of disability in young adults, and it manifests as a highly heterogeneous condition among patients. While numerous new therapies have emerged, it's important to acknowledge that high-efficacy drugs often carry a heightened risk of adverse events. Therefore, the ability to identify patients at a higher risk of experiencing clinical deterioration or non-responsiveness to treatment is paramount. This approach enables us to tailor therapeutic interventions and enhance the benefit-risk ratio.
One of our main research focuses is to understand the underpinnings of disease progression, particularly related to the neurodegenerative component and chronic inflammation, while concurrently developing predictive biomarkers. We employ cutting-edge imaging techniques, including magnetic resonance imaging and optical coherence tomography for retinal assessment, along with analyzing serum biomarkers and genetic profiles. The projects involve technological development of new magnetic resonance imaging processing techniques and clinical investigation. This facet of our research holds immense significance as it carries the potential for significant advancements in the field and the application of the results to the clinical setting.

Principal investigator: Sara Llufriu (sllufriu@clinic.cat)

Research group: Advanced Imaging in Neuroimmunological diseases group (ImaginEM). The main goal of the group is the development and application of neuroimage biomarkers to understand the basis of disability in patients with MS, and to predict disease evolution and guide personalized medicine approaches.

The ImaginEM group unites engineers, neurologists and neuropsychologists. This diverse team enables us to tackle multifaceted clinical research, encompassing the study of various

neuroimmune diseases, the development of advanced imaging techniques, and the analysis large amount of information using machine learning technology. We have carefully observed a cohort of 300 MS patients for 10 years, amassing extensive data on imaging, serum, genetic markers, and physical and cognitive function. This abundance of information empowers us to explore the predictive factors of disease progression. Moreover, the collaborations with other MAGNIMS members grant us access to large cohort data and the opportunity to work with globally renowned experts.

Also, the FCRB-IDIBAPS and Hospital Clinic offers all the necessary infrastructure to develop the research.

Additional information about the research group:

- **Importance of the clinician-scientists within the group:** The research group comprises members with a clinical background and staff exclusively dedicated to research performing imaging processing and data analysis and acquisition. Dr. Llufriu is a neurologist at the Neuroimmunology and MS Unit in Hospital Clinic and dedicates part of her time to the care of patients with neuroimmune disease. She is a member of the program 50/50 IDIBAPS-Hospital Clinic (50% protected time for research). Additionally, Dr. Blanco, a group member, serves as the coordinator of the MS Unit, and juggles responsibilities between unit coordination, patient care, and research.

- **Interest of the group to recruit a clinician-scientist:** The ImaginEM group is actively seeking a clinician-scientist researcher with a keen focus on multiple sclerosis (MS). We are looking for an individual who can bridge the gap between clinical understanding of the disease's impact on patients and the technical and fundamental aspects of research. This unique combination will enable the translation of valuable insights from clinical data into practical knowledge for the clinical setting. With the assistance of this candidate, we aim to deliver outcomes that will significantly enhance the management of individuals affected by MS.

RL11. Unraveling the Complexities of the Intra-tumor Immune Landscape in Endometrial Cancers (The ImmunoGyn Project)

Key words: Endometrial cancer, immune landscape

Description of the research line: Endometrial carcinoma is Spain's most prevalent gynecologic cancer, causing significant morbidity and mortality with over 7,300 new cases and nearly 1,800 deaths annually. Although early-stage disease has a favorable prognosis, high relapse rates and limited treatment responses in advanced stages highlight the need for precision oncology-based approaches.

Scientific challenges: Endometrial carcinomas exhibit heterogeneity, requiring tailored treatment strategies. Understanding the immune microenvironment's role in treatment outcomes and survival is crucial. The ImmunoGyn Project proposes a translational approach to explore immune cell composition and function, aiming to enhance therapy response and survival. The overall objective is to deeply understand the functions of the immune infiltrate and its role in prognosis in different histologically and molecular subtypes of endometrial cancer. To do so, we will use a retrospective series of tumors of patients diagnosed with early-stage endometrial cancer at Hospital Clinic Barcelona, and we will employ RNA sequencing techniques to characterize gene expression, spatial profiling using the GeoMx platform to characterize the tumor microenvironment, single cell RNA sequencing to further determine immune cell populations and to study T cell receptor and and B cell receptor repertoires.

Relevance of the research line: This research could lead to new diagnostic and therapeutic approaches, improving treatment effectiveness and patient outcomes while potentially facilitating patient selection for treatments like immunotherapy, thereby advancing drug development and reducing costs.

Principal investigator: Aleix Prat (alprat@clinic.cat)

Research group: Translational genomics and targeted therapies in solid tumors. The research of the Translational Genomics and Targeted Therapies in Solid Tumors Lab led by Prof Aleix Prat focuses on the diagnostics and treatment of solid tumors. The main objectives are (1) to identify genomic biomarkers predictive of response to targeted therapies; (2) to understand the mechanisms of drug resistance and tumor progression; (3) to identify and validate new therapeutic targets; and (4) to characterize the interaction between tumor cells and the tumor microenvironment.

Additional information about the research group:

- **Importance of the clinician-scientists within the group:** Recruiting a clinician-scientist with expertise in endometrial cancer can provide invaluable clinical insights, can help bridge the gap between basic science discoveries and clinical applications, and ensure that research efforts are directly aligned with addressing the most pressing clinical needs of patients. Their clinical expertise, translational potential, and ability to foster multidisciplinary collaboration make them invaluable assets in the quest to develop effective strategies for the prevention, diagnosis, and treatment of endometrial cancer.

In our team, approximately 50% of the members are medical oncologists who perform both clinical and research activities.

- **Interest of the group to recruit a clinician-scientist:** We seek a highly motivated clinician-scientist willing to provide expertise in field of diagnostics, treatment and unmet medical needs for patients with endometrial cancer. The clinician-scientist will have the opportunity to learn cutting-edge technologies including single cell sequencing and digital spatial profiling.

RL12. Translational research in non-antibiotic strategies for the prevention and treatment of pulmonary infections

Key words: Antibiotic resistances, severe pulmonary infections, non-antibiotic treatments, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*

Description of the research line:

1) Translational research in non-antibiotic strategies for the prevention and treatment of pulmonary infections
2) The current practices to fight against pulmonary infections, in addition to vaccines, are mainly based on the administration of antibiotics. The broad use of antibiotics is now challenged by the appearance of resistances of microorganisms to antibiotics which is now one of the major global health threats. The use of non-antibiotic strategies has the main aim of decreasing the global use of antibiotics, and consequently, to decrease or stop the emergence and spread of antibiotic resistances. The predictions of WHO is that antibiotic resistances will kill more than 50 million people in 2050. Our group is focussed in the investigation and development of non-antibiotic strategies to treat or prevent pulmonary infections as follows: A-Corticosteroids as immunomodulatory treatments in severe pulmonary infections, both community-acquired (CAP) and hospital-acquired (HAP) with the aim to decrease the severity of the disease and shorten the duration of antibiotic treatment. This line includes animal studies in our models of CAP and HAP in mechanically ventilated piglets, "in vitro" studies in defensive cells, and randomized clinical trials in HAP (in the frame of the Horizon grant currently ongoing).
   B-Avirulent bioengineered *Mycoplasma pneumoniae* chassis: In the last five years and in collaboration with Centre for Genomic Regulation (CRG) we have performed *in vitro* and *in vivo* animal studies developing an avirulent *Mycoplasma pneumoniae* pulmonary chassis to prevent and treat ventilator-associated pneumonia (VAP) caused by *Pseudomonas aeruginosa*, Including the biofilms formed in the endotracheal tubes. The next step in this line is to test this chassis in humans, moving to phase I and II studies.

   C-The administration of phages (Oliveira, V.C. et al. *Antibiotics* **2021**, *10*, 78.) is a promising strategy to treat severe infections avoiding totally or partially the administration of antibiotics. We performed "in vitro" studies comparing antibiotics to antibiotics + phages or phages alone, in biofilms formed by *Pseudomonas aeruginosa*, one of the most challenging microorganisms in VAP. These preliminary results indicate synergism between Phages and ceftolozane/tazobactam in a way that reduce *P.aeruginosa* burden up to 6 log after 48 hours of treatment exposure. We have an SGR grant 01148 (2021) from Generalitat de Catalunya to undergo next steps and we have also applied for extra funds to conduct the preclinical validation of these promising findings in our pig model of VAP.

   D-Macrolides are used in severe CAP to immunomodulate the excessive inflammatory response generated by the host. *S.pneumoniae* is the most frequent microorganism causing CAP. The concentration of macrolides in the spleen macrophages is 10 times of the blood. We applied for an JPIAMR2024_IMPACT-121 European action as coordinators

to study both the anti-inflammatory and antibacterial activity of azithromycin "in vitro" and in mice and piglet animal models of *S.pneumoniae.*

3) The relevance of the research line is in line with the global necessity to reduce and optimize antibiotic consumption and consequently to reduce the global burden of resistances.

Principal investigator: Antoni Torres (atorres@clinic.cat); Laia Fernández Barat (lfernan1@recerca.clinic.cat)

Research group: Applied research in infectious respiratory diseases and critically ill patients. Our translational perspective has the final aim to improve clinical care for patients with respiratory infectious diseases. We are a multidisciplinary team comprising researchers and ICU clinicians whose complementary skills have driven successful results to date.

Facilities: CELLEX microbiology Lab, Animal Facility (UB), Biobank, comprising the Neurological Tissue Bank, the Tumour Biobank, and the Blood and Fluid Biobank, Functional Genomics, Cytometry and cell sorting facility, Medical Statistics, Magnetic resonance imaging, HCB-IDIBAPS Clinical Research Support Unit, Proteomics Unit (UB/IDIBAPS), Advanced optical microscopy facility (UB), Electron microscopy unit (UB), DNA Unit (HCB), Knowledge and Technology Transfer Office (KTT).

Additional information about the research group:

- **Importance of the clinician-scientists within the group:** The group include 4 clinicians performing investigations. All the three are respiratory Intensive Care clinicians. Some of them have a large trajectory in clinical and translational investigation. Antoni Torres and Miquel Ferrer are senior investigators with a well-recognized reputation. Enric Barbeta, Ricard Mellado, and Carlos Ferrando are post doc-investigators working in intensive care unit and focused in acute lung injury. Flavia Galli is a pre-doc Intensive Care physician involved coordinating animal studies in our group. Finally, Andrea Palomeque is a pre-doc clinician working in intensive care. Her PhD deals with the rapid diagnosis of pulmonary infections using molecular platforms.

- **Interest of the group to recruit a clinician-scientist:** The group is interested in recruiting a clinician skilled in intensive care, with in-depth knowledge of pulmonary infections and previous research experience in the field of severe pulmonary infections. The ideal candidate should also be capable of performing animal studies, applying for grants, and writing manuscripts generated by the proposed research lines.

RL13. Predictors of CAR-T cell activity in multiple myeloma

Key words: Immunotherapy, CAR-T cells, myeloma, monoclonal gammopathies

Description of the research line: Multiple myeloma (MM) is the second most frequent hematologic malignancy. Despite numerous clinical advances and the approval of new drugs, MM remains an almost incurable disease, particularly in patients with relapsed/refractory (RR) MM. Chimeric antigen receptor T-cell (CART) therapy against BCMA has shown outstanding results, with two products approved for use. These products have yielded impressive overall response rates. Despite the exceptional efficacy, relapses have been observed in most patients. Antigen escape and T-cell exhaustion are thought to play a key role. The former refers to the decrease or lost expression of BCMA following the administration of CARTs. This escape may occur due to acquired biallelic loss of BCMA or the selection of BCMA negative subclones under the immunological pressure exerted by CARTs. The latter is characterized by reduced effector function, increased inhibitory receptor expression, and altered transcriptional program. We are evaluating several strategies to overcome relapse, in the pre-clinical setting, that can increase the persistence or even CAR-T cells able to recognize other antigens beyond BCMA. Our institution has been a pioneer in academic CART development in Europe. In the MM field, our BCMA CART, ARI0002h, has demonstrated outstanding results in a clinical trial for RRMM and the first case report for AL amyloidosis. Our research group has a platform for developing academic antibodies and CARTs against novel antigens (such as CD229) in MM. The study of transcriptomic, metabolic and proteomic profile of the CAR-T cells to identify the best characteristic of the cells and the pathways to be improved in these T lymphocytes , as well the molecular characteristics of the malignant plasma cells in the bone marrow and the cell free DNA in peripheral blood, could help us not only to identify those in higher risk of progression, but also to tune these autologous immunotherapeutic strategy for a better final outcome.

Principal investigator: Carlos Fernández de Larrea (cfernan1@clinic.cat)

Research group: Myeloma, amyloidosis, macroglobulinemia and other gammopathies. Our group is devoted to the study of multiple myeloma and other plasma cell malignancies. A main objective is to study the mechanisms in asymptomatic or premalignant monoclonal gammopathies to develop myeloma, amyloidosis, or macroglobulinemia. We are developing and evaluating immunotherapy treatments, based on modifying the patient's immune system. In this regard, an academic CAR-T therapy against BCMA has confirmed its clinical activity in a clinical trial. The goal is to study the factors related to the activity of this CAR-T, and to increase the activity in preclinical models.

Additional information about the research group:

- **Importance of the clinician-scientists within the group:** The incorporation of clinician-scientists within the group if part of our core. The PI of this group is one, part of program from IDIBAPS-Clinic and sharing clinical activity with lab coordination. One of the members is also staff of the haematology department and performing research lab activities. Together with PhD students and post-doc researchers, there are always haematologists performing translational investigations; we believe this nourishes our research with clinical questions with potential impact and accelerates the time from bench from bedside and vice versa.

- **Interest of the group to recruit a clinician-scientist:** The incorporation of this profile will be of great relevance by allowing clinical and translational studies to be linked in those patients who have received CAR-T cells inside and outside of a clinical trial, with impact on the results of our group and the professional development of the candidate.

RL14. Clinical and Experimental Neuroscience

Key words: Autoimmune encephalitis, synaptic receptors, animal models, NMDA, systems immunology

Description of the research line: My line of research is focuses in antibody-mediated diseases of the central nervous system, particularly the antibody-mediated encephalitis (or autoimmune encephalitis). Projects range from discovery of novel autoimmune encephalitis (such anti-NMDA receptor encephalitis or anti-GABAbR encephalitis), characterization of the syndrome and associated antibodies and antigens, development of clinical diagnostic tests and other biomarkers, and characterization of the mechanisms involved at the neurobiological and immunobiological levels through animal models of the disease. These models include the use of state-of-the art techniques such as confocal and high-resolution microscopy to determine how antibodies alter the structure and function of the targets, mechanisms that link adaptive with innate immunity through machine-learning guided deep antibody profiling to establish signatures associated with disease severity/outcomes, and behavioural animal studies. Finally, we develop new treatment strategies that derive from laboratory studies or implement treatments via clinical trials.

Principal investigator: Josep Dalmau (PI) (jdalmau@clinic.cat); Marianna Spatola (Co-PI) (spatola@recerca.clinic.cat)

Research group: Clinical and Experimental Neuroimmunology. The group includes 20 researchers whose specialties range from clinical neurologists focused on autoimmune neurologic disorders to basic scientists specialized in animal models, synaptic confocal imaging, systems immunology, and neurophysiology. The goal is the discovery and clinical and neurobiological characterization of autoimmune synaptopathies. In addition, the PI leads a multidisciplinary program that includes 5 additional groups (psychiatry, advance neuroimaging, theoretical neurobiology of cortical circuits, cortical circuit dynamics, clinical neurophysiology and multimodal imaging)

Additional information about the research group:

- **Importance of the clinician-scientists within the group:** Our group is primarily involved in translational research, and clinician-scientists play a critical role in the design and execution of projects. Therefore, multiple members of the group are involved in clinical activities at Hospital Clínic. The PI and co-PI are clinical-scientists who are regularly consulted or involved in clinical projects. Active clinical neurologists of the group include: Eugenia Martinez-Hernandez, Mar Guasp, Thais Armangué, Elianet Fonseca. The team also includes international clinical fellows who are involved in clinical activity and translational research projects.

- **Interest of the group to recruit a clinician-scientist:** We are interested in a clinical-scientist who will be involved in studies of patients with anti-NMDAR encephalitis, focusing on the interplay between antibodies and innate immunity and on the functional effects of the Fc antibody region according to stage of the disease, trigger (virus, tumor), age, serum/CSF, and response to treatment.

RL15. Liver Cancer

Key words: Hepatocellular carcinoma, Clinical trial, Immune therapies, Cancer Vaccines, Single cell -spatial transcriptomics

Description of the research line: Hepatocellular carcinoma (HCC) represents the third leading cause of cancer-related mortality globally with a 5-year survival rate < 30% in Spain. Patients at early stages can be treated with resection, transplantation and local ablation, but outcomes are plagued by a recurrence rate of 30-50% at 3 years. The current proposal entitled **Neoadjuvant-adjuvant immunotherapy and cancer vaccines to improve survival in hepatocellular carcinoma** has an overarching goal of improving outcomes of HCC and is designed to be conducted in 25 centres (15 Hospitals, and 10 research institutes) coordinated by Dr Llovet. We expect the BITRECS candidate to co-coordinate this study. We **will be addressing three unmet needs: 1) clinical trials exploring strategies to decrease recurrence after resection; 2) molecular studies identifying mechanisms and biomarkers of response/resistance; and 3) experimental studies exploring strategies to overcome resistance**. Our hypothesis is that neoadjuvant + adjuvant immunotherapies alone or in combination with a personalized cancer vaccines will provide relevant clinical benefits for early-stage HCC patients. To prove this hypothesis, we have three aims. Aim 1: to assess the **efficacy and safety of neoadjuvant atezolizumab +bevacizumab alone or combined with a personalized cancer vaccine in the adjuvant setting in resectable high-risk HCC** by conducting a phase II trial (AECC-ASPIRE trial: n=120). The dendritic cells -based vaccine will be prepared in Hospital Clinic of Barcelona. The CRO of the trial will be led by the CTU of our institution. A companion translational component using cutting-edge methodologies -**single nuclei RNA seq, spatial transcriptomics, microbiome profiling and artificial intelligence**- will enable to characterize changes in tumor microenvironment related to therapies, and to develop markers of response/resistance (aim 2). In collaboration with other teams, we plan to use patient **derived organoids (PDO)** co-cultured with autologous immune components and **patient derived xenografts (PDX**) to understand mechanisms of resistance and identify novel therapies (aim 3).

Principal investigator: Josep Maria Llovet (jmllovet@clinic.cat)

Research group: Liver Cancer Translational Research Group & and ASPIRE Consortium. Our group (~15 members) aims to improve the knowledge on HCC development, biomarkers of response and resistance to therapies. We have published > 300 articles in liver cancer, with > 110.000 citations. We are currently leading international Consortiums (>40 collaborators) and EU- and NCI funded grants. The group has also access to a large cohort of clinically annotated liver cancer samples (> 3000). In the setting of all these studies we are currently applying cutting-edge technologies, such as **single-cell RNA seq, spatial transcriptomics, microbiome analysis, artificial intelligence**, RNA sequencing, whole exome sequencing as well as HCC experimental models, flow cytometry and molecular biology techniques.

Additional information about the research group:

- **Importance of the clinician-scientists within the group:** The group has a long-standing track record of clinician-scientists (~15) who have significantly contributed to research, either as Ph D students or Post-docs. They have been leading studies and published as 1st- authors: (1) Montironi et al, Gut 2023; (2) Haber et al, Gastroenterology 2023; (3) Castet et al, Clin Cancer Res. 2021; (4) Montal et al, J Hepatol. 2020; (5) Puigvehí et al, JHEP Rep 2019; (6) Hernandez-Gea et al, Gastroenterology 2013; (7) Lachenmayer et al,

J Hepatol. 2012; (8) Mínguez et al, J Hepatol. 2011. All of the above are currently performing clinical activity and translational research in Hospital Clinic, Hospital Vall D'Hebron, Hospital de Lleida, Hospital Charitté in Berlin and University Bearn.

- **Interest of the group to recruit a clinician-scientist:** The recruited clinician scientist will be offered the responsibility to co-coordinate the AECC-ASPIRE trial described in the proposal, which includes 15 Hospitals in Spain, and involves our Immmunology Service and CTU. He will have the support of the rest of the steering committee team and will be supervised by the PI.