# 3.5.3 Experimental Therapies and Biomarkers in Cancer Group

Publications: 8
Q1: 4

## COMPOSITION

**María Inmaculada Ibáñez de Cáceres.** Investigadora Senior (Miguel Servet). Jefe de Laboratorio. FIBHULP

**Javier de Castro Carpeño.** Jefe de Sección de Oncología. Hospital Universitario La Paz. Profesor Asociado. Universidad Autónoma de Madrid

**Miranda Burdiel Herencia.** Investigadora Predoctoral. Universidad Autónoma de Madrid

**Julián Colmenarejo Fernández.** Investigador Predoctoral. Universidad Autónoma de Madrid

**Patricia Cruz Castellanos.** Facultativo Especialista de Área en Oncología Médica. Hospital Universitario La Paz

**María Dolores Diestro Tejada.** Facultativo Especialista de Área en Ginecología y Obstetricia. Unidad de Ginecología Oncológica. Hospital Universitario La Paz

**María Isabel Esteban Rodríguez.** Facultativo Especialista de Área en Anatomía Patológica. Hospital Universitario La Paz

**Álvaro García Guede.** Investigador Predoctoral. FIBHULP

**Julia Jiménez Hernández.** Investigadora Predoctoral. Universidad Autónoma de Madrid

**Cristina Manguán García.** Técnico de Laboratorio. IIb "Alberto Sols"

**Rocío Moreno Velasco.** Técnico de Laboratorio. FIBHULP

**Olga Pernía Arias.** Investigadora Predoctoral. Universidad Autónoma de Madrid

**Carlos Rodríguez Antolín.** Bioinformático. FIBHULP

**Rocío Rosas Alonso.** Investigadora Postdoctoral (Juan Rodés). Hospital Universitario La Paz

**Olga Vera Puente.** Investigadora Postdoctoral (Sara Borrell). FIBHULP


## STRATEGIC OBJECTIVE

Genetic and epigenetic mechanisms play significant roles in tumor progression and the development of resistance to treatment. The dynamic nature of tumors and their ability to adapt and resist therapies pose critical challenges in clinical practice. In our research, we have employed diverse strategies to address these challenges. Firstly, we have focused on the identification of novel markers throughout the course of lung cancer, aiming to uncover crucial indicators of disease progression. Additionally, we have pursued various approaches to identify specific targets involved in drug response, striving to enhance treatment efficacy. Our investigations have transcended the realm of theory, extending into the realm of clinical practice through the meticulous analysis of human samples. It is through this granular examination that we have unraveled the alterations occurring at the individual patient level. Moreover, we have successfully pinpointed epigenetic changes in tumor suppressor genes that are strongly associated with drug resistance. Furthermore, we have made significant strides in understanding the role of epigenetic regulators in lung and melanoma, particularly in the context of oxidative stress. These findings shed light on novel avenues for therapeutic interventions and provide valuable insights into the complex interplay between genetic, epigenetic, and environmental factors in cancer progression and treatment resistance.

Through the application of genomic, transcriptomic, and expression reactivation techniques,

we have made significant strides in identifying a diverse array of biomarkers, including genes and microRNAs. These biomarkers hold immense potential for non-invasive cancer diagnosis, particularly in the context of non-small cell lung cancer (NSCLC). Our pioneering research has demonstrated the efficacy of liquid biopsy as a reliable method for detecting these biomarkers, providing a promising avenue for early detection and diagnosis of lung cancer. In addition, we have focused our attention on assessing chronic obstructive pulmonary disease (COPD) patients to establish the presence of early-stage lung cancer. By leveraging these advanced techniques, we have successfully unraveled the intricate transcriptomic alterations at miRNA level, occurring during the establishment of lung cancer in COPD patients. These groundbreaking findings not only hold great promise for improving the accuracy and efficiency of cancer diagnosis but also pave the way for personalized treatment approaches that can potentially enhance patient outcomes.

## RESEARCH LINES

1. Identification of predictive epigenetic biomarkers in the appearance of resistance to treatment in solid tumors. Within the oncological markers, those for predictive use are the most necessary to help direct therapies since the vast majority of patients are diagnosed when the tumor needs to be treated. Platinum-derived compounds are the standard treatment for high-incidence tumors such as those of the lung, ovary, and rectum, so the fact of finding markers of response to their use would allow the selection of patients, optimizing treatment and associated healthcare costs.

   **1.1 Lung cancer:** In this line we have identified the methylation of the IGFBP3 gene promoter, whose epigenetic silencing is related to platinum resistance, extending its validation to cohorts of lung cancer patients likely to benefit from its use. In addition, the effectiveness of this biomarker is being tested in liquid biopsy as a non-invasive test. This line of research has given rise to three concatenated publications (Oncogene 2010 PMID: 20023704, Oncogene 2013 PMID: 22543588, Epigenetics 2014 PMID: 25482372) and a patent in the joint exploitation phase with a Spanish biotechnology company that has licensed said patent. This patent has passed a Pre-commercial Public Purchase in SERGAS and its validation in national phases has had the support of two concatenated RETOS projects.

   **1.2 Brain Tumors:** Regarding our line with brain tumors, we assess the methylation status of the MGMT gene in glioblastomas, as a care and research task since 2014 in our laboratory, developing advanced high-sensitivity technology for its detection in liquid biopsy. The data obtained to date in more than 200 patients in a prospective trial has given rise to a recent publication (Clinical epigenetics 2021 PMID: 33750464) and a second article in process, in addition to a European patent that has just passed PCT extension, and the award of two competitive public projects, one of them a DTS20 technological project for diagnosis and blood monitoring of patients with glioblastomas, and a PLEC project (RETOS) in collaboration with Val`deHebron for fine-tuning diagnostic technologies and monitoring with tracers PET. In addition, these results have allowed the defense in 2021 of the doctoral thesis of Rocío Rosas, a member of our team, who has just started her independent line in January 2022 as a "Juan Rodés" researcher.

   **1.3 Ovarian Cancer:** We also have an open line in ovarian cancer, in which we have published a recent article (Clinical Epigenetics 2021 PMID: 34454589) and has allowed us to participate as work package leaders in a Transcan European project led by Italy, which has just successfully passed the first round of evaluation.

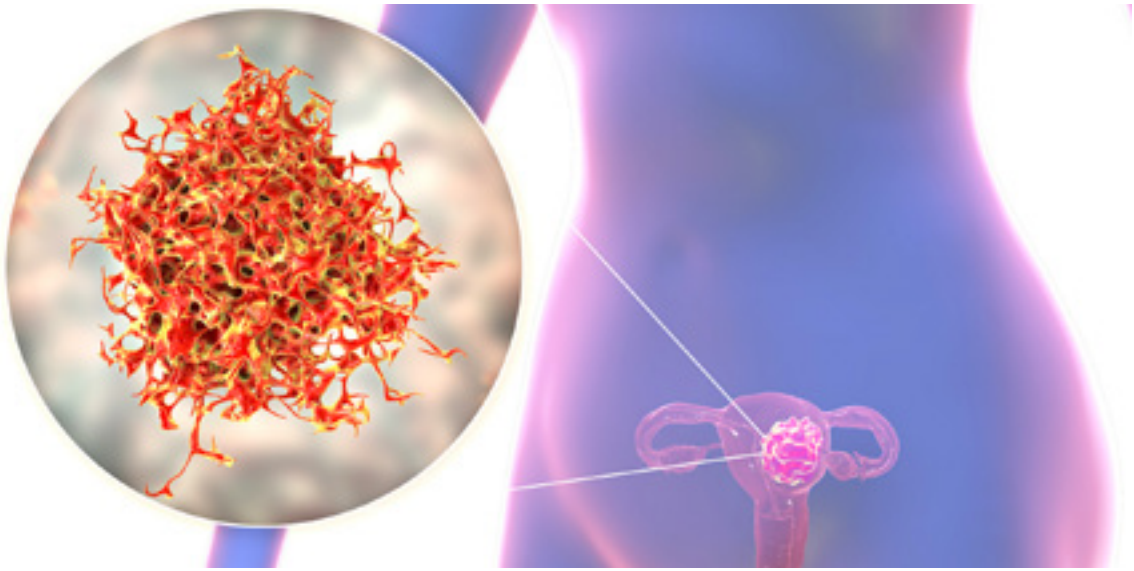
   **1.4 Melanoma**. In this emerging line, we are focusing on the characterization of the oncogenic role of MAFG in the response to immunotherapy in melanoma. Dr. Olga Vera, recently has incorporated to the group as a Sara Borrell postdoctoral researcher to lead this line. Previous studies of Olga have identified MAFG as a potential oncogene in melanoma and with potential therapeutic applications. The successful completion of our study will significantly advance our understanding of the role of MAFG in melanoma, determine new therapeutic targets and open new lines of research focused on dissecting the oncogenic role of MAFG.

2. Study of the molecular mechanisms underlying simultaneous resistance to platinum in cancer, through the epigenetic regulation of regulatory non-coding RNAs. In this line, changes in the expression of microRNAs and lncRNAs in platinum-sensitive and -resistant human NSCLC and ovarian cancer cell lines established in our research group are studied. We have identified 7 microRNAs whose expression appears to be under epigenetic regulation. One of them under the epigenetic regulation of its regulatory region (miRNA-7) as a potential predictive biomarker of response to platinum in ovarian cancer in terms of overall survival and time to progression. Product of the development of this line has been the publication of an article in the journal (Theranostics 2017 PMID: 29158814), as well as a patent that is in the PCT phase. Based on these findings, in 2016 we began a collaboration with the MOFFITT cancer center in Tampa (USA) to study Long Non-Coding RNAs (lnc-RNAs) and their possible regulation through DNA methylation in these cell lines. With this project we assess the changes in the expression of lncRNAs and their epigenetic regulation at the level of DNA methylation, characterizing two groups of lncRNAs differentially regulated in the development of resistance to cisplatin, and thus opening the way for the identification of new ones. As a result of the activity of this collaboration, highly innovative results were obtained in this field (Epigenetics PMID: 29436261 and Translational Research 2018, PMID: 30053382), and the research activity focused on the characterization of these novel biomarkers is maintained thanks to the funding supported for the PI21/00145 and Caixa Impulse projects.

3. Identification of new therapeutic targets. In recent years we have also identified the direct regulation of the MAFG gene through miR-7 in our experimental models. The function of MAFG is associated with detoxification in a situation of oxidative stress and our in vitro studies have shown its involvement in the appearance of cisplatin-resistant phenotypes. Our translational approach indicates that MAFG could be a diagnostic

marker in patients with lung and ovarian cancer treated with platinum-based chemotherapy. To date, this line has provided four articles (Translational Research 2018, PMID: 30053382; Cell Biosci. 2019 PMID: 31406565; Arch Bronconeumol (Engl Ed). 2020. PMID: 31780284; Antioxidants (Basel).PMID: 32492865) and one European patent that has just been extended to national phases in the USA and Europe, which describes the clinical use of MAFG in patients with lung and ovarian cancer. We have currently addressed the study and use of MAFG as a therapeutic target through in vitro and in vivo assays after editing the MAFG gene using CRISPR/Cas9 technology, a project funded by the ISCIII (PI18/00050, P21/000145 ) in addition to extending and validating its use with the potential development of a kit for clinical use thanks to obtaining a RETOS project (RTC2019-007229-1) from the 2019 call and which is ongoing with the collaboration of H. Ramón y Cajal and the companies Aptus and Atrys.

4. Identification of biomarkers in exosomes such as liquid biopsy in patients with lung and ovarian cancer. With this line we intend, through a first basic approach, to characterize and compare the protein and microRNA content of exosomes from the secretome of paired sensitive and resistant lung cancer cell lines. In the translational study of the project, the candidates identified in the cell lines in circulating exosomes from samples of lung and ovarian cancer patients are being validated, which have given rise to different results. On the one hand, two candidate miRNAs with prognostic significance in this pathology, and on the other hand, a miRNA with possible universal value has been identified as endogenous capable of normalizing the value of the content of the exosomal miRNoma, both in healthy individuals and in individuals with different tumor types. These results have given rise to a European patent that is in national phases and the obtaining of a Caixa Impulse Validate project for the constitution of a Spin-off, in our institution focused on the development of a first RUO product for the normalization of exosomal content. in human blood samples, in addition to two manuscripts in preparation, as well as the defense of Julia Jiménez's thesis in July 2019.



5. Identification of pharmacogenetic biomarkers associated with efficacy and toxicity of cancer treatments. Led by Dr R Rosas.

   Pharmacogenetics is the field of knowledge that seeks to identify genetic variants to provide information that will allow a better understanding of drug response in terms of efficacy and toxicity, thus contributing to personalised precision medicine. Despite progress in the research and development of new cancer treatments, the efficacy and safety of these drugs vary widely between patients. In this context, this line of research aims to understand how genetic variations in individuals may influence the efficacy and toxicity of cancer treatments. The use of pharmacogenetic biomarkers is a reality in routine clinical practice and has been shown to improve the efficacy and reduce the side effects of treatments, resulting in a better quality of life for patients and reduced costs for the national healthcare system. Our ultimate goal is to identify new pharmacogenetic biomarkers that will allow better selection of cancer treatments for each patient, thus promoting the medicine of the future with a personalised and individualised approach. This line currently has two projects awarded in public (PI22/00128) and private (Jose Luis Castaño-SEQC Foundation) competitive calls, led by Dr Rocío Rosas."

6. Identification of microRNA hypermethylation patterns associated with an increased risk of developing non-small cell lung cancer in patients with mild COPD and moderate to high tobacco consumption. In recent years, the potential role of epigenetic alterations in the development of lung cancer in COPD patients, mediated by changes in the activity of various microRNAs, small non-coding RNA molecules (19-25 nucleotides) with a regulatory function of gene expression, which induce the degradation of messenger RNA or inhibit its translation, has gained particular importance. It is therefore interesting to consider whether there may be hypermethylation profiles of different microRNAs that are associated with an increased risk of lung cancer in COPD patients, which would facilitate appropriate risk selection for screening programmes.This line currently has one project, which was awarded in a competitive public call (PI22/001764), under the co-direction of Olga Pernía Arias.

7. Fine-tuning of high performance techniques available to the National Health System (NHS). (NGS and Characterization of DNA methylation status). Implicit in the group's cross-cutting lines and in our commitment to support the implementation in the NHS of the technological advances derived from our research activity, we have fine-tuned the characterization of the methylation status at the PAZ genetics facilities of DNA through the use of these new aspects of NGS applied to the field of epigenetics, both from a global approach and limited to certain regions, to implement its possible care applicability in cancer patients through personalized panels in solid tumors including glioblastomas, through the use of Methylseq technology and the 850K EPIC-arrays. Likewise, in these years we have fine-tuned the use of commercial NGS panels in strict compliance with quality regulations to address the characterization of the genetic pro-

file of tumors in patients with lung cancer. Thanks to the addition to our team such as Dra Rocío Rosas, Juan Rodés from 2022, we are starting the hospital implementation phase, in which we have already tested careers with various platforms from different commercial houses. Its fine-tuning would allow its use both for research activities and its future healthcare applicability, especially in the classification of brain tumors. This activity is financed by the Spanish Group of Transversal Oncology and Rare Orphan Tumors (Getthi), which has just financed the group with a competitive project for this purpose. Given the experience acquired by the group in the use of massive data, we have been able to participate in the EU ISIDORE project and have begun the study of predictive bioinformatic matrices of response to platinum treatment. We intend to combine the information available in public domain databases with relevant clinical information associated with our own experimental results (methylation and gene expression microarrays and microRNAs, bisulfite sequencing, RNAseq and miRNAseq) to generate a predictive matrix of response to treatment. With these analytical models, we intend to identify "global markers" that define a predictive profile for treatment with platinum in lung and ovarian cancer based on the transcriptome, microRNome, and/or methylome.

# RESEARCH ACTIVITY

## Doctoral theses

### Final Degree Theses

**Cruz Castellanos P.** Estudio de miARNs exosomales en respuesta a platinos en cáncer de ovario: Validación en biopsia líquida.[dissertation]. Madrid: UCM: 2022(03/06/2023).

Director: Ibáñez de Cáceres I.

## Publications

- Sooy RA, Han JY, Dafni U, Cho BC, Yeo CM, Nadal E, Carcereny E, de Castro J, Sala MA, Bernabee R, Coate L, Pulla MP, Campelo RG, Cuffe S, Hashemi SMS, Fruh M, Massuti B, García-Sánchez J, Domine M, Majem M, Sánchez-Torres JM, Britschgi C, Pless M, Dimopoulou G, Roschitzki-Voser H, Ruepp B, Rosell R, Stahel RA, Peters S. A randomised phase II study of osimertinib and bevacizumab versus osimertinib alone as second-line targeted treatment in advanced NSCLC with confirmed EGFR and acquired T790M mutations: the European Thoracic Oncology Platform (ETOP 10-16) BOOSTER trial. Ann Oncol. 2022; 33(2): 181-92. Article. IF: 50,5; D1
- Remón J, Girard N, Novello S, de Castro J, Bigay-Game L, Bernabe R, Greillier L, Mosquera J, Cousin S, Juan O, Sampayo M, Besse B. PECATI: A multicentric, open-label, single-arm phase II study to evaluate the efficacy and safety of pembrolizumab and lenvatinib in pretreated b3-thymoma and thymic carcinoma patients. Clin Lung Cancer. 2022; 23(3): E243-6. Article. IF: 3.6; Q2
- Dafni U, Soo RA, Peters S, Tsourti Z, Zygoura P, Vervita K, Han JY, de Castro J, Coate L, Fruh M, Hashemi SMS, Nadal E, Carcereny E, Sala MA, Bernabe R, Provencio M, Cuffe S, Roschitzki-Voser H, Ruepp B, Rosell R, Stahel RA. Impact of smoking status on the relative efficacy of the EGFR TKI/angiogenesis inhibitor combination therapy in advanced NSCLC-a systematic review and meta-analysis. ESMO Open. 2022; 7(3): 100507. Review. IF: 7.3; Q1
- Wolf J, Helland A, Oh IJ, Migliorino MR, Dziadziuszko R, Wrona A, de Castro J, Mazieres J, Griesinger F, Chlistalla M, Cardona A, Ruf T, Trunzer K, Smoljanovic V, Novello S. Final efficacy and safety data, and exploratory molecular profiling from the phase III ALUR study of alectinib versus chemotherapy in crizotinib-pretreated ALK-positive non-small-cell lung cancer. ESMO Open. 2022; 7(1): 100333. Article. IF: 7.3; Q1
- Arriola E, González-Cao M, Domine M, de Castro J, Cobo M, Bernabe R, Navarro A, Sullivan I, Trigo JM, Mosquera J, Crama L, Isla D. Addition of immune checkpoint inhibitors to chemotherapy vs chemotherapy alone as first-line treatment in extensive-stage small-cell lung carcinoma: a systematic review and meta-analysis. Oncol The. 2022; 10(1): 167-84. Review. IF: 2.7; Q4
- Lacal JC, Perona R, de Castro J, Cebrian A. Choline kinase alpha Inhibitors MN58b and RSM932A enhances the antitumor response to cisplatin in lung tumor cells. Pharmaceutics. 2022; 14(6): 1143. Article. IF: 5.4; Q1
- Cruz-Castellanos P, Ortiz-Cruz E, Sánchez-Mendez JI, Tapia M, Morera R, Redondo A. The impact of the first wave of the COVID-19 pandemic on oncological patients in a tertiary hospital. Rev Esp Patol . 2022; 55(2): 77-84. Article. Not Indexed
- Pacheco-Barcia V, Gómez D, Obispo B, Gongora LM, San Gil RH, Cruz-Castellanos P, Gil-Raga M, Villalba V, Ghanem I, Jiménez-Fonseca P, Calderón C. Role of sex on psychological distress, quality of life, and coping of patients with advanced colorectal and non-colorectal cancer. World J Gastrointest Oncol. 2022; 14(10): 2025-37. Article. IF: 3; Q3

## Research projects

**Burdiel Herencia M.** Contrato predoctoral (FI19/00061). ISCIII-MICINN. 2021-2023.

Managment centre: FIBHULP

**Cruz Castellanos P.** App respira. Boehringer Ingelheim España S.A. 2019-Ongoing.

Managment centre: FIBHULP

**de Castro Carpeño J.** Avanzando en el tratamiento del cáncer de pulmón con terapia dirigida. Un paso más: de la investigación a la práctica clínica. Pfizer S.L.U. 2022-Ongoing.

Managment centre: FIBHULP

**de Castro Carpeño J.** Comite de gestión de programa: diseño, mediante inteligencia artificial, de algoritmos predictivos para la identificación de individuos en riesgo de desarrollar sobrepeso/obesidad y sus patologías asociadas: aportación del análisis genético (S2017/BMD-3773). CM. 2018-2021.

Managment centre: FIBHULP

**de Castro Carpeño J.** Desarrollo de las tareas necesarias para la puesta en marcha del estudio clínico ml40221 título: estudio de práctica clínica en condiciones reales para evaluarla toma de decisiones en el tratamiento de segunda línea conforme a las normas asistenciales y basado en los perfiles de foundation medicine en pacientes con cáncer de pulmón no microcítico (cpnm) localmente avanzado o metastásico con histologia de adenocarcinoma en españa. Roche Farma S. A. 2018-Ongoing.

Managment centre: FIBHULP

**de Castro Carpeño J.** Determinación mediante inmunohistoquímica de la expresion de PDL-1 en carcinoma de célula no pequeña de pulmón. Fundación ECO. 2016-Ongoing.

Managment centre: FIBHULP

**de Castro Carpeño J.** Eluxa 2: estudio de fase III, abierto, aleatorizado y controlado con producto activo, multicéntrico e internacional, para evaluar la eficacia de BI1482694 frente a un doblete de quimioterapia estandar que incluye platino en pacientes con cáncer de pulmón no microcítico localmente avanzado o metastásico, con la mutación T790 M, cuya enfermedad ha progresado con el tratamiento previo con un inhibidor de la tirosina cinasa del receptor del factor de crecimiento epidérmico (EGFR-TKI). Parexel International (Irl) Limited. 2016-Ongoing.

Managment centre: FIBHULP

**de Castro Carpeño J.** Identificación de nuevos mecanismos genéticos y epigenéticos de resistencia a la inmunoterapia de primera linea en pacientes con cáncer de pulmón no microcítico metastásico (cpnmm) con alta expresión pd-l1. Estudio Keypredict. Fundación Mutua Madrileña. 2022-Ongoing.

Managment centre: FIBHULP

**de Castro Carpeño J.** Prestación de servicios para el desarrollo de las tareas necesarias en el estudio Estudio observacional de alectinib en pacientes con CPNM ALK+ en el programa de acceso precoz en España. Roche Farma S. A. 2018-Ongoing.

Managment centre: FIBHULP

**Esteban Rodríguez MI.** Proyecto para la evaluación retrospectiva de muestras pareadas de biopsia y citología para la detección de reordenamientos de alk y expresión de pd-l1 en cpcnp. Roche Farma S.A. 2017-Ongoing.

Managment centre: FIBHULP

**Esteban Rodríguez MI.** Proyecto para la evaluación retrospectiva de muestras pareadas de biopsia y citología para la detección de reordenamientos de alk y expresión de pd-l1 en cpcnp. Roche Farma S.A. 2017-Ongoing.

Managment centre: FIBHULP

**Ibáñez de Cáceres MI.** Early molecular nanoDIAGnostics of brain tumors using ImmunePET (DIAGBI) (PLEC2021-008034 ). MICIIN. 2021-2024.

Managment centre: FIBHULP

**Ibáñez de Cáceres MI.** Estudio de la Plasticidad Tumoral Epigenética a través de la carcinogénesis y progresión del CPNM en biopsia líquida . SETuP (PI21/00145). ISCIII. 2022-2024.

Managment centre: FIBHULP

**Ibáñez de Cáceres MI.** Estudio de los mecanismos moleculares y celulares responsables de la aparición de resistencia a quimioterapia mediados MOR MAFG y su implicación como nueva diana diagnóstica y terapéutica en cancer de pulmón no microcítico (PI18/00050). ISCIII. 2019-2021¡3.

Managment centre: FIBHULP

**Ibáñez de Cáceres MI.** Estudio de los mecanismos moleculares y celulares resposnables de la aparición de resistencia a quimioterapia mediados por mafg y su implicación como nueva diana diagnóstica y terapéutica. FIBHULP. 2022-Ongoing.

Managment centre: FIBHULP

**Ibáñez de Cáceres MI.** Evalución y puesta a punto del biomarcardor epigenético MGMT en biopsia líquida como prueba no invasiva de seguimiento, en pacientes con gliomas. Juan Cuesta Barrio. 2017-Ongoing.

Managment centre: FIBHULP

**Ibáñez de Cáceres MI.** First bio-Tool for Exosomal normalization in Liquid biopsy and its clinical applicability for Lung cancer patients stratification. LUCADIA (CI20-00182). CaixaImpulse Validate. 2020-ongoing.

Managment centre: FIBHULP

**Ibáñez de Cáceres MI.** Plataforma del grupo de investigación de terapias experimentales y biomarcadores en cáncer (TEBC). Helicon Medical S.L. 2021-Ongoing.

Managment centre: FIBHULP

**Ibáñez de Cáceres MI.** Prediapt: desarrollo de un sistema predictivo de respuesta al tratamiento con derivados del platino en cáncer de pulmón basado en aptámeros (RTC-2019-007229-1). MICIU. 2020-2023.

Managment centre: FIBHULP

**Ibáñez de Cáceres MI.** Validación del biomarcador epigenético MGMT en biopsia líquida como prueba no invasiva en pacientes con gliomas (DTS20/00029 ). ISCIII. 2021-2023.

Managment centre: FIBHULP

**de Castro Carpeño J.** Resistencia a la inmunoterapia de primera línea en pacientes con cáncer de pulmón no microcítico metastásico con expresión de PD-L1 mayor o igual al 50%. Fudación Mutua Madrileña. 2022-ongoing.

Managment centre: FIBHULP

**Rodríguez Antolín C.** Aplicación del metiloma en el diagnóstico de tumores del sistema nervioso central de difícil clasificación a través de algoritmos de aprendizaje automático. Fundación de la Comunidad Valenciana Hospital Provincial de Castellón. 2022-Ongoing.

Managment centre: FIBHULP

**Rodríguez Antolín C.** Aplicacion del metiloma en el diagnostico del sistema nervioso central de difícil clasificaición a través de algoritmos de aprendizaje automático. Ghetti. 2022-Ongoing.

Managment centre: FIBHULP

**Rodríguez Antolín C.** Implementación diagnóstica del análisis de metilación dirigida en plataformas de secuenciación masiva de cáncer. Roche Farma S. A. 2019-Ongoing.

Managment centre: FIBHULP

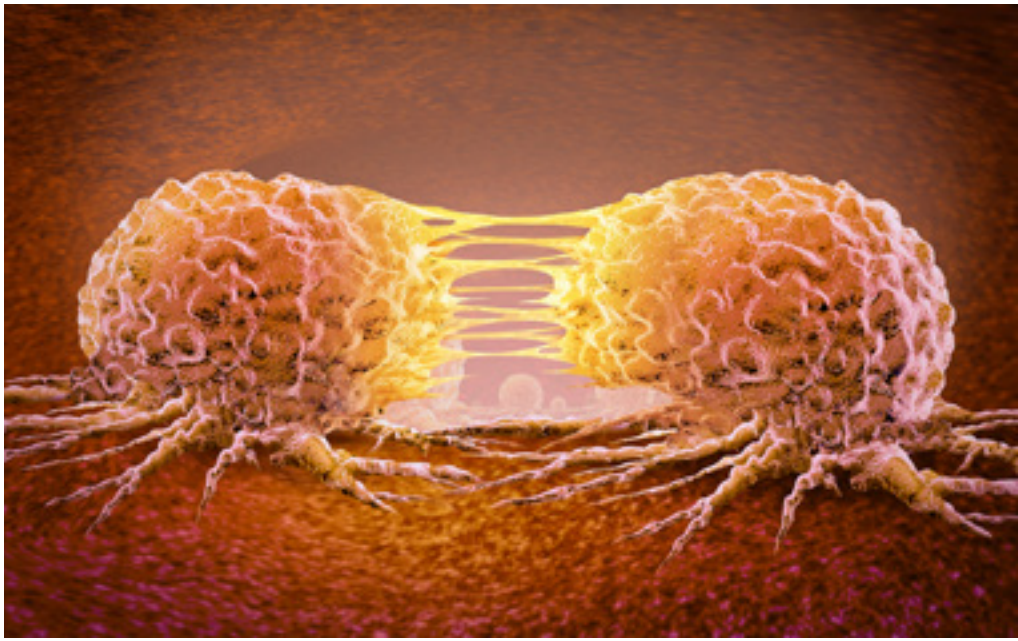
**Rodríguez Antolín C.** Implementación diagnóstica del análisis de metilación dirigida en plataformas de secuenciación masiva de cáncer. Roche Farma S. A. 2019-Ongoing.

Managment centre: FIBHULP

**Rosas Alonso R.** Contrato Río Hortega (CM19/00100). ISCIII. 2020-2021.

Managment centre: FIBHULP

**Rosas Alonso R.** Estudio de nuevas variantes asociadas a toxicidad por fluoropirimidinas. Fundación José Luis Castaño para el De-



sarrollo del Laboratorio Clínico. 2022-Ongoing.

**Managment centre:** FIBHULP

## Cibers and Retics

**de Castro Carpeño J.** Dinamización e innovación de las capacidades industriales del SNS y su transferencia al sector productivo (PT20/0002). ISCIII. (31/12/2023). FIBHULP

**Ibáñez de Cácerres I.** European Infraestructure for Translational Medicine. (EATRIS). EU. (31/12/2023). FIBHULP

## Clinical trials

**de Castro Carpeño J.** Estudio en fase II abierto, de un solo grupo y multicéntrico para evaluar la eficacia y la seguridad de taletrectinib en pacientes con cpnm ros1 positivo avanzado o metastásico y otros tumores sólidos.

**Type:** Clinical Trials, phase II. 5975 AB-106-G208.
**Sponsored by:** Anheart Therapeutics Inc.
**Signed date:** 25/01/2022

**de Castro Carpeño J.** Estudio de fase I-II para evaluar la seguridad, tolerabilidad y eficacia de pm01183 y atezolizumab en pacientes con cáncer de pulmón de células pequeñas avanzado que haya progresado tras el tratamiento con quimioterapia de platino.

**Type:** Clinical Trials, phase II. 5966 2SMALL.
**Sponsored by:** Fundacion Oncosur.
**Signed date:** 19/01/2022

**de Castro Carpeño J.** Ensayo de fase 3, abierto, aleatorizado y multicéntrico que compara selpercatinib con una terapia basada en platino y pemetrexed, con o sin pembrolizumab, como tratamiento inicial del cáncer de pulmón no microcítico avanzado o metastásico, positivo para fusión de ret..

**Type:** Clinical Trials, phase III. ANEXO 2 5442.
**Sponsored by:** Lilly, S.A..
**Signed date:** 22/02/2022

**de Castro Carpeño J.** A phase I/II, open-label, multicenter study to assess the safety, tolerability, pharmacokinetics and anti-tumor efficacy of dzd9008 in patients with advanced non-small cell lung cancer (nsclc) with egfr or her2 mutation / estudio en fase I/II, abierto, multicéntrico para evaluar la eguridad, la tolerabilidad, la farmacocinética y la eficacia antitumoral de dzd9008 en pacientes con cáncer de pulmón no microcítico (cpnm) avanzado con mutación de egfr o her.

**Type:** Clinical Trials, phase I. 5936 DZ2019E0001.
**Sponsored by:** Dizal(Jiangsu) Pharmaceutical Co, Ltd.
**Signed date:** 08/03/2022

**de Castro Carpeño J.** Estudio en fase II, aleatorizado, doble ciego de relatlimab más nivolumab en combinación con quimioterapia frente a nivolumab en combinación con quimioterapia como tratamiento de primera línea para los participantes con cáncer de pulmón de células no pequeñas (cpcnp) en estadio iv o recurrente.

**Type:** Clinical Trials, phase II. ANEXO 1 5809.
**Sponsored by:** Bristol-Myers Squibb International Corporation (Bmsic).
**Signed date:** 03/03/2022

**de Castro Carpeño J.** Estudio global de fase III, multicéntrico, aleatorizado, controlado y abierto de capmatinib en combinación con osimertinib, frente a quimioterapia basada en doblete de platino y pemetrexed, en pacientes con nsclc localmente avanzado o metastásico con mutaciones activadoras del egfr que hayan progresado a un tratamiento previo con tki del egfr y cuyos tumores presenten mutación t790m negativa y amplificación de met (geometry-e.

**Type:** Clinical Trials, phase III. 6049 CINC280L12301.
**Sponsored by:** Novartis Farmaceutica, S.A..
**Signed date:** 10/03/2022

**de Castro Carpeño J.** Estudio de fase I-III multicéntrico para evaluar la eficacia y seguridad de múltiples tratamientos en cohortes de pacientes seleccionados basándose en el estado de los biomarcadores, con cáncer de pulmón no microcítico en estadio III localmente avanzado, no resecable.

**Type:** Clinical Trials, phase I. 6099 BO42777.
**Sponsored by:** F.Hoffmann-La Roche Ltd.
**Signed date:** 16/03/2022

**de Castro Carpeño J.** Estudio fase 3 aleatorizado de la combinación de amivantamab y lazertinib frente a osimertinib como tratamiento de primera línea en pacientes con cáncer de pulmón no microcítico localmente avanzado o metastásico con mutación del egfr. mariposa.

**Type:** Clinical Trials, phase III. ANEXO 1 5636.
**Sponsored by:** Janssen Cilag International Nv.
**Signed date:** 25/03/2022

**de Castro Carpeño J.** Estudio de fase III, abierto y aleatorizado para evaluar la eficacia y seguridad de alectinib adyuvante frente a la quimioterapia adyuvante con un derivado del platino en pacientes con carcinoma de pulmón no microcítico positivo para la cinasa del linfoma anaplásico en estadio Ib (tumores ≥ 4 cm) a IIIa completamente extirpado.

**Type:** Clinical Trials, phase III. ANEXO 1 5014.
**Sponsored by:** F.Hoffmann-La Roche Ltd.
**Signed date:** 17/03/2022

**de Castro Carpeño J.** Observación del cáncer residual mediante evaluación por biopsia líquida (observation of residual cancer with liquid biopsy evaluation, oracle).

**Type:** No EPA. PI-5196.
**Sponsored by:** Guardant Health, Inc..
**Signed date:** 21/10/2022

**Cruz Castellanos P.** Implementación de una herramienta de telemedicina para mejorar la continuidad de la atención de pacientes oncológicos.

**Type:** No EPA. PI-5131.
**Sponsored by:** Cureety Sas.
**Signed date:** 29/04/2022

**de Castro Carpeño J.** Estudio de fase III, abierto, aleatorizado, global y multicéntrico de sacituzumab govitecán frente a docetaxel en pacientes con cáncer de pulmón no microcítico (cpnm) avanzado o metastásico con progresión durante o después de la quimioterapia a base de pl.

**Type:** Clinical Trials, phase III. 6041.
**Sponsored by:** Gilead Sciences, S.L..
**Signed date:** 15/02/2022

**de Castro Carpeño J.** Estudio de fase III aleatorizado, multicéntrico y abierto de lurbinectedina como agente único o lurbinectedina en combinación con irinotecán frente a la elección del investigador (topotecán o irinotecán) en pacientes con cáncer de pulmón de células pequeñ.

**Type:** Clinical Trials, phase III. 6083.
**Sponsored by:** Pharmamar, S.A..
**Signed date:** 25/04/2022

**de Castro Carpeño J.** Estudio de fase II, abierto, de un solo grupo y multicéntrico para evaluar la eficacia y la seguridad de pemigatinib en participantes con cáncer pulmonar no microcítico avanzado con una alteración del receptor del factor de crecimiento fibroblástico que p.

**Type:** Clinical Trials, phase II. 6089.

**Sponsored by:** Incyte Corporation.
**Signed date:** 18/05/2022

**de Castro Carpeño J.** Estudio en fase II, abierto y multicéntrico de la combinación de rmc-4630 y sotorasib para pacientes con cáncer de pulmón no microcítico (cpnm) con mutación krasg12c tras el fracaso de tratamientos estándar previos.

**Type:** Clinical Trials, phase II. 6132.
**Sponsored by:** Revolution Medicines Inc.
**Signed date:** 26/09/2022

**de Castro Carpeño J.** Estudio fase 3, aleatorizado, abierto, para comparar nivolumab más quimiorradioterapia concurrente (qrtc) seguidos por nivolumab más ipilimumab o nivolumab más qrtc seguidos por nivolumab frente a qrtc seguida por durvalumab en el cáncer de pulmón no microcítico localmente avanzado (cpnm la) no tratado previamente.

**Type:** Clinical Trials, phase III. Appendix 2 5403.
**Sponsored by:** Bristol-Myers Squibb International Corporation (Bmsic).
**Signed date:** 23/03/2022

**de Castro Carpeño J.** Ensayo fase III, internacional, multicéntrico, doble ciego, aleatorizado y controlado con placebo de durvalumab tras el tratamiento con radioterapia estereotáctica corporal (sbrt), para el tratamiento de pacientes con cáncer de pulmón no microcítico, estadio I/II no resecado, con ganglios linfáticos negativos (pacific -4/rtog-3515).

**Type:** Clinical Trials, phase III. Appendix 1 5241.
**Sponsored by:** Astrazeneca Farmaceutica Spain, S.A.
**Signed date:** 05/04/2022

**de Castro Carpeño J.** A phase 3, open-label, randomized study of lazertinib with subcutaneous amivantamab administered via manual injection compared with intravenous amivantamab or subcutaneous amivantamab administered via on body delivery system in patients with egfr-mutated advanced or metastatic non-small cell lung cancer after progression on osimertinib and chemotherapy (paloma-3).

**Type:** Clinical Trials, phase III. 2022.069.
**Sponsored by:** Janssen Cilag International Nv.
**Signed date:** 16/06/2022

**de Castro Carpeño J.** Estudio de screening maestro para determinar el estado de los biomarcadores y su potencial elegibilidad en ensayos para pacientes con tumores malignos.

**Type:** No EPA. 2022.139.
**Sponsored by:** Roche Farma, S.A..
**Signed date:** 04/05/2022

**de Castro Carpeño J.** Estudio observacional retrospectivo sobre la eficacia y seguridad de lorlatinib en pacientes con cáncer de pulmón de células no pequeñas metastásico alk o ros1 tratados dentro del programa de uso compasivo en españa.

**Type:** Clinical Trials, phase . 2022.286.
**Sponsored by:** Fundacion Gecp.
**Signed date:** 30/06/2022

**de Castro Carpeño J.** A randomised phase II trial of osimertinib and bevacizumab versus osimertinib alone as second-line treatment in stage IIIb-ivb nsclc with confirmed egfrm and t790m.

**Type:** Clinical Trials, phase II. 2022.300.
**Sponsored by:** Grupo Español Cancer Pulmon.
**Signed date:** 20/06/2022

**de Castro Carpeño J.** Phase 1/2 open-label platform study to evaluate the safety and efficacy of multiple amivantamab-based therapeutic combinations in participants with advanced, unresectable lung cancer (lc) kaleidoscope. investigation-specific appendix 1 to master protocol platformpansc2001 (kaleidoscope) a phase 1/2 study evaluating the safety and efficacy of amivantamab and capmatinib combination therapy in unresectable metastatic non-small cell lung cancer (metalmark).

**Type:** Clinical Trials, phase I. 2022.340.
**Sponsored by:** Janssen Cilag International Nv.
**Signed date:** 08/11/2022

**de Castro Carpeño J.** Estudio de fase 1 para evaluar la seguridad, tolerabilidad y farmacocinética de amg 757 en sujetos con cáncer de pulmón microcítico.

**Type:** Clinical Trials, phase I. 2022.349.
**Sponsored by:** Amgen, S.A..
**Signed date:** 06/07/2022

**de Castro Carpeño J.** Estudio de fase I-III multicéntrico para evaluar la eficacia y seguridad de múltiples tratamientos en cohortes de pacientes seleccionados basándose en el estado de los biomarcadores, con cáncer de pulmón no microcítico en estadio III localmente avanzado, no resecable.

**Type:** Clinical Trials, phase I. 2022.380.
**Sponsored by:** F.Hoffmann-La Roche Ltd.
**Signed date:** 14/07/2022

**de Castro Carpeño J.** A phase 2, open-label, parallel cohort study of subcutaneous amivantamab in multiple regimens in patients with advanced or metastatic solid tumors including epidermal growth factor receptor mutated non-small cell lung cancer (paloma-2).

**Type:** Clinical Trials, phase II. 2022.401.
**Sponsored by:** Janssen Cilag International Nv.
**Signed date:** 21/09/2022

**de Castro Carpeño J.** Ensayo fase II, de un solo brazo, para evaluar la eficacia de osimertinib en combinación con savolitinib en pacientes con cáncer de pulmón no microcítico localmente avanzado o metastásico, con mutación egfrm positivo y met positivo, que hayan progresado después de un tratamiento con osimertinib (ensayo savannah.

**Type:** Clinical Trials, phase II. 2022.512.
**Sponsored by:** Astrazeneca Farmaceutica Spain, S.A.

**Signed date:** 20/09/2022

**de Castro Carpeño J.** Ensayo de plataforma de fase 2 basdo en biomarcardores en pacientes con cancer de pulmon no microcítico avanzado cuya enfermedad ha progresado durante el tratamiento con osimertinib en primera línea (orchard).

**Type:** Clinical Trials, phase II. 2022.513.
**Sponsored by:** Astrazeneca Farmaceutica Spain, S.A.
**Signed date:** 08/09/2022

**de Castro Carpeño J.** Características clínicas, manejo y uso de los recursos del hospital en pacientes con estadío temprano y localmente avanzado de cáncer de pulmón de célula no pequeña: un estudio multicéntrico y retrospectivo de s ehr (electronic health record) historias clínicas electrónicas utilizando el procesamiento del lenguaje natural (nlp).

**Type:** EPA-OD. 2022.578.
**Sponsored by:** Merck Sharp and Dohme de España, S.A.
**Signed date:** 21/12/2022

**de Castro Carpeño J.** Estudio en fase II, aleatorizado, doble ciego de relatlimab más nivolumab en combinación con quimioterapia frente a nivolumab en combinación con quimioterapia como tratamiento de primera línea para los participantes con cáncer de pulmón de células no pequeñas (cpcnp) en estadio iv o recurrente.

**Type:** Clinical Trials, phase II. 2023.085.
**Sponsored by:** Bristol-Myers Squibb International Corporation (Bmsic).
**Signed date:** 14/12/2022

## Patents and trademarks

**Ibáñez de Cáceres I, de Castro Carpeño J, Jiménez Hernández J, Rodríguez Antolín C, Rodríguez Jiménez C, Rosas Alonso R, Cruz Castellanos P, Burdiel Herencia M, Pernía Arias O, Diestro Tejada MD, Esteban Rodríguez MI,** inventors; FIBHULP, assignee. miR-151A-3p as an universal endogenous control for exosome cargo normalization. EP19382252.5 (Publication Number pending); 2019 April 05.

**Ibáñez de Cáceres I, de Castro Carpeño J, Jiménez Hernández J, Rodríguez Antolín C, Vera Puente O, Rosas Alonso R, Pernía Arias O, Losantos García I,** inventors; FIBHULP, assignee. Method for determining the response to treatment of a patient affected by non-small cell lung carcinoma (NSCLC). EP19382614.6 (Publication Number pending); 2019 July 19.

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**Ibáñez de Cáceres I, Pernía Arias O, de Castro Carpeño J, Vera Puente O, Jiménez Hernández J, Perona Abellón R, Rojo Todo F,** inventors; FIBHULP, CSIC, UAM, Instituto de Investigación Sanitaria FJD, assignees. Determination of methylation and miRNA levels in response to a platinum-based antitumor compound. P201530997, PCT/ES2016/070516; 2015 July 09.

**Perona Abellón R, Sastre Garzón L, Pintado Berninches L, Carrillo García J, Molina Pachón A, Irradiccio Silva L, Manguán García C**, inventors; CSIC, UAM, Advanced Medical Projects, Centro de Investigación Biomédica en Red (CIBER), assignees. Peptides derived from GSE 24.2 for treating diseases caused by oxidative stress and damage to DNA. P201331573, AU2014338820, CA2931429, EP3061815 PCT/ES2014/070803; 2013 October 25.

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**Cejas Guerrero P, Belda Iniesta C, Feliú Batlle J, de Castro Carpeño J, Moreno García V, Burgos Lizalde E, Casado Sáenz E, Sánchez Hernández JJ,** inventors; FIBHULP, UAM, Empresa Pública Hospital del Norte, assignees. Genomic fingerprint for predicting the clinical response to an antitumor therapy in colorectal cáncer. P201130863, PCT/ES2012/070379; 2011 May 26.

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**Perona Abellón R, Sastre Garzón L, Machado Pinilla R, Sánchez Pérez I,** inventors; CSIC, UAM, assignees. Use of inductor agents GSE24.2 for producing pharmaceutical compositions for treating illnesses relating to cellular senescence. P200703106, PCT/ES2008/070212, EP2216043, US2011300115, JP2011504483, CA2706467; 2007 November 23.

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