3.5.3 Experimental Therapies and Biomarkers in Cancer Group

Publications:17 | **Q1:**10

COMPOSITION

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STRATEGIC OBJETIVES

- 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. 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 (José 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 profile 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. **This research line is led by Carlos Rodríguez Antolín, Bioinformatic of the group.**

RESEARCH ACTIVITY

Publications

- **Alonso-Espías M, Alonso-García M, García-Pineda V, Gracia M, Siegrist J, Diestro MD, Hernández A, Zapardiel I.** Beyond bladder dysfunction: assessing the full impact of radical hysterectomy on cervical cancer patients. Eur J Gynaecol Oncol. 2023; 44(6): 60-6. Article. IF: 0.5; Q4
- **Burdiel M, Jiménez J, Rodríguez-Antolín C, García-Guede A, Pernía O, Sastre-Perona A, Rosas-Alonso R, Colmenarejo J, Rodríguez-Jiménez C, Diestro MD, Martínez-Marín V, Higueras O, Cruz P, Losantos-García I, Peinado H, Vera O, de Castro J, de Cáceres II.** MiR-151a: a robust endogenous control for normalizing small extracellular vesicle cargo in human cancer. Biomark Res. 2023; 11(1): 94. Letter. IF: 9.5; D1
- **de Castro J, Insa A, Collado-Borrell R, Escudero-Vilaplana V, Martínez A, Fernández E, Sullivan I, Arrabal N, Carcedo D, Manzaneque A.** Economic burden of locoregional and metastatic relapses in resectable early-stage non-small cell lung cancer in Spain. BMC Pulm Med. 2023; 23(1): 69. Article. IF: 2.6; Q2
- **Escudero-Vilaplana V, Collado-Borrell R, De Castro J, Insa A, Martínez A, Fernández E, Sullivan I, Flores A, Arrabal N, Carcedo D, Manzaneque A.** Cost-effectiveness of adjuvant atezolizumab versus best supportive care in the treatment of patients with resectable early-stage non-small cell lung cancer and overexpression of PD-L1. J Med Econ. 2023; 26(1): 445-53. Article. IF: 2.9; Q2
- **Gracia M, Rodríguez E, Diestro MD, Spagnolo E, García V, Siegrist J, Pérez Y, Zapardiel I, Hernández A.** Impact of the Covid-19 pandemic on the management of gynecologic cancer: a Spanish survey. Observational, multicenter study. Bmc Womens Health. 2023; 23(1): 488. Article. IF: 2.4; Q2
- **Guijarro-Eguinoa J, Arjona-Hernández S, Stewart S, Pernía O, Arias P, Losantos-García I, Rubio T, Burdiel M, Rodríguez-Antolín C, Cruz-Castellanos P, Higuera O, Borobia AM, Rodríguez-Novoa S, de Castro-Carpeño J, de Cáceres II, Rosas-Alonso R.** Prognostic impact of dihydropyrimidine dehydrogenase germline variants in unresectable non-small cell lung cancer patients treated with platin-based chemotherapy. Int J Mol Sci. 2023; 24(12): 9843. Article. IF: 4.9; Q1
- **Ibáñez-Navarro M, Fernández A, Escudero A, Esteso G, Campos-Silva C, Navarro-Aguadero MA, Leivas A, Caracuel BR, Rodríguez-Antolín C, Ortiz A, Navarro-Zapata A, Mestre-Durán C, Izquierdo M, Balaguer-Pérez M, Ferreras C, Martínez-López J, Valés-Gómez M, Pérez-Martínez A, Fernández L.** NKG2D-CAR memory T cells target pediatric T-cell acute lymphoblastic leukemia in vitro and in vivo but fail to eliminate leukemia initiating cells. Front Immunol. 2023; 14: 1187665. Article. IF: 5.7; Q1
- **Isla D, Lozano MD, Paz-Ares L, Salas C, de Castro J, Conde E, Felip E, Gómez-Román J, Garrido P, Enguita AB.** New update to the guidelines on testing predictive biomarkers in non-small-cell lung cancer: a National Consensus of the Spanish Society of Pathology and the Spanish Society of Medical Oncology. Clin Transl Oncol. 2023; 25(5): 1252-67. Article. IF: 2.8; Q2
- **Isla D, Lozano M D, Paz-Ares L, Salas C, de Castro J, Conde E, Felip E, Gómez-Román J, Garrido P, Belén Enguita A.** New update to the guidelines on testing predictive biomarkers in non-small-cell lung cancer: a National Consensus of the Spanish Society of Pathology and the Spanish Society of Medical Oncology. Rev Esp Patol. 2023; 56(2): 97-112. Review. Not indexed
- **Marín-Candón A, García-García I, Arias P, Carcas AJ, Díaz-García L, Ochoa RF, Cano NH, Pinto PH, González MJ, López-Granados E, Martínez-Feito A, Mayor-Ibarguren A, Rosas-Alonso R, Seco-Meseguer E, Borobia AM.** Identifying biomarkers of treatment response to ciclosporin in atopic dermatitis through multio-

mic predictive modelling: DERMATOMICS study protocol. BMJ Open. 2023; 13(7): e072350. Article. IF: 2.4; Q1

- **Nadal E, Rodríguez-Abreu D, Simó M, Massutí B, Juan O, Huidobro G, López R, de Castro J, Estival A, Mosquera J, Sullivan I, Felip E, Blasco A, Guirado M, Pereira E, Vilariño N, Navarro V, Bruna J.** Phase II trial of atezolizumab combined with carboplatin and pemetrexed for patients with advanced nonsquamous non-small-cell lung cancer with untreated brain metastases (Atezo-Brain, GECP17/05). J Clin Oncol. 2023; 41(28): 4478-85. Article. IF: 42.1; D1
- **Provencio M, Nadal E, González-Larriba JL, Martínez-Martí A, Bernabé R, Bosch-Barrera J, Casal-Rubio J, Calvo V, Insa A, Ponce S, Reguart N, de Castro J, Mosquera J, Cobo M, Aguilar A, Vivanco GL, Camps C, López-Castro R, Morán T, Barneto I, Rodríguez-Abreu D, Serna-Blasco R, Benitez R, de la Rosa CA, Palmero R, Hernando-Trancho F, Martín-López J, Cruz-Bermúdez A, Massuti B, Romero A.** Perioperative nivolumab and chemotherapy in stage iii non-small-cell lung cancer. New Engl J Med. 2023; 389(6): 504-13. Article. IF: 96.2; D1
- **Quevedo IC, García IC, Gracia M, García-Pineda V, Alonso-Espias M, Siegrist J, Diestro MD, Hernández A, Zapardiel I.** Personalized sentinel node mapping in endometrial cancer by the indocyanine green implementation as single tracer: a case control study. J Pers Med. 2023; 13(2): 170. Article. IF: 3.0; Q2
- **Salloum FN, Tocchetti CG, Ameri P, Ardehali H, Asnani A, de Boer RA, Burridge P, Cabrera JA, de Castro J, Córdoba R, Costa A, Dent S, Engelbertsen D, Fernández-Velasco M, Fradley M, Fuster JJ, Galán-Arriola C, García-Lunar I, Ghigo A, González-Neira A, Hirsch E, Ibáñez B, Kitsis RN, Konety S, Lyon AR, Martín P, Mauro AG, Vega MMM, Meijers WC, Neilan TG, Rassaf T, Ricke-Hoch M, Sepulveda P, Thavendiranathan P, van der Meer P, Fuster V, Ky B, López-Fernández T.** Priorities in cardio-oncology basic and translational science gcos 2023 symposium proceedings: JACC: CardioOncology State-of-the-Art Review. JACC Cardiooncol. 2023; 5(6): 715-31. Review. IF: 12.0; Q1
- **Sánchez-Cabrero D, García-Guede A, Burdiel M, Pernia O, Colmenarejo-Fernández J, Gutiérrez L, Higuera O, Rodríguez IE, Rosas-Alonso R, Rodríguez-Antolín C, Losantos-García I, Vera O, de Castro-Carpeño J, de Cáceres II.** miR-124 as a liquid biopsy prognostic biomarker in small extracellular vesicles from NSCLC patients. Int J Mol Sci. 2023; 24(14): 11464. Article. IF: 4.9; Q1
- **Sánchez-Cazorla E, González-Atienza C, López-Vázquez A, Arruti N, Nieves-Moreno M, Noval S, Mena R, Rodríguez-Jiménez C, Rodríguez-Solana P, González-Iglesias E, Guerrero-Carretero M, Mardero OD, Coca-Robinot J, Acal JC, Blasco J, Castañeda C, Maya JF, Del Pozo A, Gómez-Pozo MV, Montaño VEF, Dios-Blázquez LD, Rodríguez-Antolín C, Gómez-Cano MD, Delgado-Mora L, Vallespín E.** Whole-exome sequencing of 21 families: candidate genes for early-onset high myopia. Int J Mol Sci. 2023; 24(21): 15676. Article. IF: 4.9; Q1
- **Stewart S, Dodero-Anillo JM, Guijarro-Eguinoa J, Arias P, de las Huertas AGL, Seco-Meseguer E, García-García I, García ER, Rodríguez-Antolín C, Carcas AJ, Rodríguez-Novoa S, Rosas-Alonso R, Borobia AM.** Advancing pharmacogenetic testing in a tertiary hospital: a retrospective analysis after 10 years of activity. Front Pharmacol. 2023; 14: 1292416. Article. IF: 4.4; Q1

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.** 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.** 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*
- **de Castro Carpeño J.** Evaluación del perfil de hipermetilación de microRNAs para la estimación de riesgo de cáncer de pulmón en pacientes con EPOC (PI22/01764). ISCIII. 2023-2025. *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 Madrilena. 2022-Ongoing. *Managment centre: FIBHULP*
- **de Castro Carpeño J.** Plataforma del grupo de investigación de terapias experimentales y biomarcadores en cáncer (tebc). Helicon Medical S.L. 2021-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*
- **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%. Mutua Madrileña. 2022-ongoing. *Managment centre: FIBHULP*

3.5 Cancer and Human Molecular Genetics Area

- **de Castro Carpeño J.** SurvAI: Plataforma web para la automatización de la anotación, clasificación e interpretación de variantes genéticas en cáncer a través de algoritmos basados en deep learning. Predicción de supervivencia y efecto de variantes de significado incierto (DTS22/00145). ISCIII. 2023-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.** Digittal PCR Systems (IFEQ22/00003). ISCIII. 2023-2024. *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. 2019-2023. *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). Caixa-Impulse Validate. 2020-2023. *Managment centre: FIBHULP*
- **Ibáñez de Cáceres MI.** In-Vivo Imaging_IVIS (IFEQ22/00004). ISCIII. 2023-2024. *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.** Primera bioherramienta para la normalización del contenido exosomal en biopsia líquida y su aplicabilidad clínica para la estratificación y diagnóstico de pacientes con cáncer de pulmón. (Lucadia). FIBHULP. 2021-Ongoing. *Managment centre: FIBHULP*
- **Ibáñez de Cáceres MI.** Ultracentrífuga preparativa de alta eficacia y rendimiento (IFEQ22/00002). ISCIII. 2023-2024. *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*
- **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 Castelló. 2022-Ongoing. *Managment centre: FIBHULP*
- **Rodríguez Antolín C.** Aplicacion del metiloma en el diagnostico del sistema nervioso central de dificil clasificaicón a través de algoritmos de aprendizaje automatico. 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.** Personal técnico bioinformático de apoyo a investigación (CA22/00002). ISCIII. 2023-Ongoing. *Managment centre: FIBHULP*
- **Rosas Alonso R.** Estudio de nuevas variantes asociadas a toxicidad por fluoropirimidinas. Fundación José Luis Castaño para el Desarrollo del Laboratorio Clínico. 2022-Ongoing. *Managment centre: FIBHULP*
- **Rosas Alonso R.** Farmacogenética de inhibidores tirosina-quinasa en cáncer de pulmón: medicina de precisión más allá de un solo gen (PI22/00128). ISCIII. 2023-2025. *Managment centre: FIBHULP*
- **Rosas Alonso R.** Identificación de biomarcadores farmacogenéticos asociados a eFicacia y toxicidad a tratamientos en pacientes con Artritis Reumatoide: estudio BIOFAR (PI-5318). Fundación José Luis Castaño para el Desarrollo del Laboratorio Clínico. 2023-Ongoing. *Managment centre: FIBHULP*
- **Rosas Alonso R.** Identificación de biomarcadores farmacogenéticos asociados a eficacia y toxicidad a tratamientos en pacientes con artritis reumatoide: estudio BIOFAR (2022.26). Fundación José Luis Castaño para el Desarrollo del Laboratorio Clínico. 2023-Ongoing. *Managment centre: FIBHULP*
- **Vera Puente O.** Caracterización de las funciones inmunosupresoras de MAFG en melanoma y sus potenciales implicaciones para la terapia del cáncer (PI 5815). FIBHULP. 2024-Ongoing. *Managment centre: FIBHULP*
- **Vera Puente O.** Early molecular nanoDIAGnostics of brain tumors using Immune-PET (DIAGBI) (PLEC2021-008034). MICIIN. 2021-2024. *Managment centre: FIBHULP*
- **Vera Puente O.** 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*

Cibers and Retics

- **de Castro Carpeño J.** Dinamización e innovación de las capacidades industriales del SNS y su transferencia al sector productivo. 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.** A phase 1 study to assess the effect of hepatic impairment on the pharmacokinetics of repotrectinib in advanced cancer patients.
  Type/Phase: I
  Sponsored by: Turning Point Therapeutics, Inc
  Signed date: 21/06/2023
- **de Castro Carpeño J.** A phase iii, open-label, randomised, multicentre study of ceralasertib plus durvalumab versus docetaxel in patients with advanced or metastatic non-small cell lung cancer without actionable genomic alterations, and whose disease has progressed on or after prior anti-pd-(l)1 therapy and platinum-based chemotherapy: latify.

Type/Phase: III
Sponsored by: Astrazeneca Ab
Signed date: 12/01/2023

- **de Castro Carpeño J.** Estudio abierto seguido de un estudio aleatorizado, doble ciego, controlado con placebo, de grupos paralelos y un estudio de extensión para investigar la seguridad y eficacia de gb1211 (un inhibidor de la galectina-3) en combinación con atezolizumab en pacientes con cáncer de pulmón no microcítico (cpnm).
  Type/Phase: I
  Sponsored by: Galecto Biotech Ab
  Signed date: 07/02/2023

- **de Castro Carpeño J.** Estudio de diseño abierto de 2 partes, multicentro y de fase 1b de datopotamab deruxtecan (dato-dxd) en combinación con inmunoterapia con o sin carboplatino en participantes con cáncer de pulmón de células no pequeñas metastásico o avanzado.
  Type/Phase: I
  Sponsored by: Astrazeneca Ab
  Signed date: 31/05/2023

- **de Castro Carpeño J.** Estudio de fase I, con aumento escalonado de la dosis y ampliación de cohortes de tsr-022, un anticuerpo monoclonal anti-tim-3, en pacientes con tumores sólidos avanzados (amber).
  Type/Phase: I
  Sponsored by: Tesaro Inc.
  Signed date: 18/04/2023

- **de Castro Carpeño J.** Estudio en fase II de tratamiento combinado con adagrasib en pacientes con carcinoma pulmonar no microcítico avanzado con mutación del gen kras g12c.
  Type/Phase: II
  Sponsored by: Mirati Therapeutics, Inc
  Signed date: 21/06/2023

- **de Castro Carpeño J.** Ensayo clínico fase II de quimio-inmunoterapia neoadyuvante seguida de tratamiento adyuvante según el estado de resección para el tratamiento de pacientes con cáncer de pulmón no microcítico (cpnm) con diagnóstico de tumor de pancoast. un estudio exploratorio multicéntrico.
  Type/Phase: II
  Sponsored by: Fundacion Gecp
  Signed date: 06/02/2023

- **de Castro Carpeño J.** Estudio de fase 1/2a, multicéntrico y abierto para evaluar la seguridad, la tolerabilidad, la farmacocinética y los indicios preliminares de actividad antitumoral basados en terapias combinadas con jab-3312 en pacientes adultos con tumores sólidos avanzados.
  Type/Phase: I
  Sponsored by: Jacobio Pharmaceuticals Co, Ltd
  Signed date: 21/04/2023

- **de Castro Carpeño J.** Estudio de fase III aleatorizado y doble ciego de bgba1217, un anticuerpo anti-tigit, en combinación con tislelizumab frente a pembrolizumab en pacientes con cáncer de pulmón no microcítico irresecable o metastásico no tratado previamente, con expresión de pd-l1 y localmente avanzado.
  Type/Phase: III
  Sponsored by: Beigene Usa, Inc
  Signed date: 14/02/2023

- **de Castro Carpeño J.** A randomized, double-blind, multi-center, phase III study of ak112 or placebo combined with pemetrexed and carboplatin in patients with egfr-mutant locally advanced or metastatic non-squamous nsclc who have failed egfr-tki treatment (harmoni).
  Type/Phase: III
  Sponsored by:
  Signed date: 28/09/2023

- **de Castro Carpeño J.** Estudio en fase IB/IIA, abierto y multicéntrico para evaluar la eficacia, la seguridad, la tolerabilidad y la farmacocinética del inhibidor de atr m1774 en combinación con cemiplimab en participantes con cáncer de pulmón no microcítico no escamoso que ha progresado a pesar de haber recibido tratamiento anti-pd-(l)1 y tratamiento con un derivado del platino.
  Type/Phase: I
  Sponsored by: Merck Healthcare Kgaa
  Signed date: 14/09/2023

- **de Castro Carpeño J.** Estudio abierto, en fase I/II, sobre t3p-y058-739, una cepa genéticamente modificada de la bacteria yersinia enterocolitica, en pacientes con tumores sólidos avanzados.
  Type/Phase: I
  Sponsored by: T3 Pharmaceuticals Ag
  Signed date: 12/06/2023

- **de Castro Carpeño J.** Rosy-d: estudio maestro de continuación en pacientes que hayan completado un estudio en oncología previo con durvalumab y que el investigador considere que van a beneficiarse clínicamente de continuar el tratamiento.
  Type/Phase: III
  Sponsored by: Astrazeneca Ab
  Signed date: 25/04/2023

- **de Castro Carpeño J.** A phase 3, multicenter, randomized, open-labelstudy evaluating efficacy of sotorasib platinum doublet combination versus pembrolizumab platinum doublet combination as a front-line therapy in subjects with stage iv or advanced stage iiib/c nonsquamous non–small cell lung cancers, negative for pd-l1, and positive for kras p.g12c (codebreak 202).
  Type/Phase: III
  Sponsored by: Amgen, Inc
  Signed date: 16/10/2023

- **de Castro Carpeño J.** Estudio de plataforma de fase 2, aleatorizado, abierto que utiliza el protocolo maestro para evaluar nuevas combinaciones con inmunoterapia en participantes con cáncer de pulmón no microcítico localmente avanzado/metastásico, seleccionados según la expresión del ligando de muerte programada 1, que no han recibido tratamiento previo.
  Type/Phase: II
  Sponsored by: Glaxosmithkline Research And Development Limited ,
  Signed date: 26/07/2023

- **de Castro Carpeño J.** Estudio en fase IB/IIA de la seguridad y la tolerabilidad de bemcentinib con pembrolizumab/carboplatino/pemetrexed en sujetos con cáncer de pulmón no microcítico (cpnm) no epidermoide avanzado o metastásico con/sin mutación de stk11 no tratado previamente.
  Type/Phase: I
  Sponsored by: Bergenbio Asa
  Signed date: 20/10/2023

- **de Castro Carpeño J.** An open-label, phase 2b, global multicenter cohort trial to assess the safety and efficacy of zipalertinib in patients with locally advanced or metastatic non-small cell lung cancer with exon 20 insertion and uncommon/single or compound epidermal growth factor receptor mutations.
  Type/Phase: IIb
  Sponsored by: Taiho Oncology, Inc
  Signed date: 07/11/2023

- **de Castro Carpeño J.** Ensayo abierto de un solo brazo para evaluar la actividad antitumoral, la seguridad y la farmacocinética de sar408701 utilizado en combinación con ramucirumab en pacientes con carcinoma pulmonar no microcítico no escamoso metastásico (cpnm nem) con tumores ceacam5 positivos, tratados previamente con quimioterapia a base de platino y con un inhibidor de puntos de control inmunitario.
  Type/Phase: II
  Sponsored by: Sanofi-Aventis Recherche & Developpement
  Signed date: 30/05/2023

- **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/Phase: II
  Sponsored by: Janssen Cilag International Nv
  Signed date: 04/10/2023

- **de Castro Carpeño J.** Estudio en paraguas de fase ib/ii, sin enmascaramiento, multicéntrico y aleatorizado para evaluar la eficacia y la seguridad de combinaciones de tratamientos basados en múltiples inmunoterapias en pacientes con carcinoma de pulmón no microcítico metastásico (morpheus pulmonar.
  Type/Phase: I
  Sponsored by: Genentech Inc
  Signed date: 18/10/2023

- **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/Phase: II
  Sponsored by: Anheart Therapeutics Inc
  Signed date: 27/10/2023
- **de Castro Carpeño J.** Estudio en fase III, aleatorizado y abierto para evaluar zimberelimab y domvanalimab en combinación con quimioterapia frente a pembrolizumab con quimioterapia, como tratamiento de primera línea de pacientes con cáncer de pulmón no microcítico metastásico sin aberraciones tumorales genómicas del receptor del factor de crecimiento epidérmico ni de la quinasa del linfoma anaplásico.
  Type/Phase: III
  Sponsored by: Gilead Sciences Inc
  Signed date: 29/11/2023
- **de Castro Carpeño J.** Observación del cáncer residual mediante evaluación por biopsia líquida (observation of residual cancer with liquid biopsy evaluation, oracle).
  Type/Phase: No EPA
  Sponsored by: Guardant Health, Inc.
  Signed date: 29/11/2023
- **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/Phase: III
  Sponsored by: Janssen Cilag International Nv
  Signed date: 14/12/2023
- **de Castro Carpeño J.** Comparación de la eficacia entre cobolimab + dostarlimab + docetaxel y dostarlimab + docetaxel y docetaxel en monoterapia en participantes con cáncer de pulmón no microcítico avanzado que hayan progresado al tratamiento previo con anti-pd (l)1 y quimioterapia (costar lung.
  Type/Phase: II
  Sponsored by: Glaxosmithkline Research And Development Limited Glaxosmithkline Research And Development Limited ,
  Signed date: 15/12/2023

Patents and trademarks

- **Perona Abellón R, Sánchez Pérez I, Machado Pinilla R, Sastre Garzón L, Murguía Ibáñez JR, inventors; CSIC, UAM, Universidad Politécnica de Valencia, assignees.** Sequence of nucleotides and peptides GSE 24.2 of dyskerin, which can induce telomerase activity, method for obtaining same, therapeutic compositions and applications thereof. P200502511, PCT/ES2006/070152, EP1947175, US20090202503, US2015337022, AT469212, CA2625981, DK1947175, JP2009511036, JP5560398, PT1947175; 2005 October 14.
- **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.
- **Cejas Guerrero P, González Barón M, Casado Sáenz E, Sánchez Hernández JJ, Perona Abellón R, inventors; FIBHULP, UAM, CSIC, assignees.** Use of trefoil factor family 3 (TFF3) in the prognosis of patients diagnosed with colorectal cancer. P200703230, PCT/ES2008/000757, EP2236625; 2007 December 04.
- **Cejas Guerrero P, Belda Iniesta C, Feliú Batlle J, González Barón M, de Castro Carpeño J, Casado Sáenz E, Sánchez Hernández JJ, inventors; FIBHULP, UAM, assignees.** Genomic fingerprint for the prognosis of the evolution of colorectal adenocarcinoma. P200703229, PCT/ES2008/000756, EP2236626; 2007 December 04.
- **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.
- **Martínez Máñez R, Murguía Ibáñez JR, Perona Abellón R, Agostini A, Mondragón Martínez L, Moreno Torres M, Manguán García C, Marcos Martínez MD, Soto Camino J, Sancenón Galarza F, inventors; Universidad Politécnica de Valencia, CSIC, Centro de Investigación Biomédica en Red en Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), assignees.** Release of substances into senescent cells. P201231370, PCT/ES2013/070581, EP2893923, JP2015529216, US2015306037; 2012 September 04.
- **Ibáñez de Cáceres I, Belda Iniesta C, Pernía Arias O, Perona Abellón R, Cortés Sempere M; inventors.** FIBHULP, CSIC, UAM, Fundación Hospital de Madrid, assignees. Method for predicting the response to a treatment consisting of radiotherapy combined with cisplatin-based chemotherapy. P201330783, PCT/ES2014/070433, EP3006572, US20160122828; 2013 May 29.
- **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.
- **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.
- **Ibáñez de Cáceres I, de Castro Carpeño J, Vera Puente O, Pernía Arias O, Rodríguez Antolín C, González Muñoz VM, Martín Palma ME, Salgado Figueroa AM, inventors; FIBHULP, FIBIOHRC, assignees.** MAFG as a potential therapeutic target to restore chemosensitivity in platinum-resistant cancer cells. EP17382610.8 (Publication Number pending), PCT/EP2018/068156; 2017 September 15.
- **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, Rosas Alonso R, Pernía Arias O, Martínez Marín V, Esteban Rodríguez MI, inventors; FIBHULP, assignee.** Method for determining the percentage of methylation of the promoter of the gene O6-methylguanine-DNA methyltransferase (MGMT) in circulating exosomes. EP19382299.6 (Publication Number pending); 2019 April 16.
- **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.