

3.5.3 Experimental Therapies and Biomarkers in Cancer



Publications: 9 | Q1: 7

COMPOSITION

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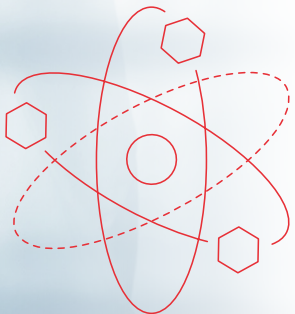
- **Ana Arauzo Cabrera.** Investigadora Predoctoral. FIBHULP
- **María José Beato Merino.** Facultativo Especialista de Área en Anatomía Patológica Hospital Universitario La Paz
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- **César Casado Sánchez.** Profesor Asociado Universidad Autónoma de Madrid
- **Patricia Cruz Castellanos.** Facultativo Especialista de Área en Oncología Médica. Hospital Universitario La Paz
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- **Olga Pernía Arias.** Investigadora Predoctoral. Universidad Autónoma de Madrid
- **Carlos Rodríguez Antolín.** Bioinformático. FIBHULP
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STRATEGIC OBJECTIVES

- 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.



3 Research areas and groups

3.5. Cancer and Human Molecular Genetics Area

RESEARCH LINES

- 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.
 - 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.
 - 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 de Hebron 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.
 - 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.
 - 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.
- 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.

- 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.
- 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.
- 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

3 Research areas and groups

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."

- 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.
- 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 Methyseq 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. Breast cancer**

RESEARCH ACTIVITY

Master Theses

- **Arauzo Cabrera A.** Estudio del perfil de expresión diferencial de miARNs en la detección temprana del cáncer de pulmón no microcítico [dissertation]. Madrid: Universidad Autónoma de Madrid: 2024(26/06/2024). Director: Ibáñez de Cáceres I

Final Degree Theses

- **Ruiz Buceta S.** Caracterización de los genes diana de MAFG en la progresión del melanoma [dissertation]. Madrid: Universidad Francisco de Vitoria: 2024(01/07/2024). Director: Vera Puente O

Publications

- **Arriola E, de Castro J, García-Campelo R, Bernárdez B, Bernabé R, Bruna J, Dómine M, Isla D, Juan-Vidal O, López-Fernández T, Nadal E, Rodríguez-Abreu D, Vares M, Asensio U, García LF, Felip E.** Expert Consensus on the Management of Adverse Events of Lorlatinib in the Treatment of ALK plus Advanced Non-small Cell Lung Cancer. *Clin Drug Invest.* 2024; 44(8): 553-76. Review. IF: 2.7; Q2
- **Conde E, Hernández S, Carrillo JLR, Martínez R, Alonso M, Curto D, Jimenez B, Caminoa A, Benito A, Garrido P, Clave S, Arriola E, Esteban-Rodríguez I, De Castro J, Sansano I, Felip E, Rojo F, Dómine M, Abdulkader I, García-Gonzalez J, Teixido C, Reguart N, Compañ D, Insa A, Mancheño N, Palanca S, Juan-Vidal O, Baixeras N, Nadal E, Cebollero M, Calles A, Martín P, Salas C, Provencio M, Aranda I, Massuti B, López-Vilaro L, Majem M, Paz-Ares L, López-Rios F.** RET Fusion Testing in Patients With NSCLC: The RETING Study. *JTO Clin Res Rep.* 2024; 5(4): 100653. Article. IF: 3.5; Q1
- **Molina-Alejandre M, Perea F, Calvo V, Martínez-Toledo C, Nadal E, Sierra-Rodero B, Casarrubios M, Casal-Rubio J, Martínez-Martí A, Insa A, Massuti B, Viteri S, Aranda IB, Rodríguez-Abreu D, de Castro J, Martínez JM,**

- Cobo M, Wistuba II, Parra ER, Martín-López J, Megias D, Muñoz-Viana R, Garrido F, Aptsiauri N, Ruiz-Cabello F, Provencio M, Cruz-Bermúdez A.** Perioperative chemoimmunotherapy induces strong immune responses and long-term survival in patients with HLA class I-deficient non-small cell lung cancer. *J Immunother Cancer.* 2024; 12(10): e009762. Article. IF: 10.6; D1
- **Peña-López J, Gutiérrez-Sainz L, Jiménez-Bou D, Ruiz-Gutiérrez I, Navas-Jiménez C, Alonso-Eiras JJ, García-Zamarriego A, Sánchez-Cabrero D, Ruiz-Giménez L, Pertejo-Fernández A, Villamayor-Sánchez J, Cruz-Castellanos P, Higuera-Gómez O, de Castro J.** Assessing Prognosis: Factors Influencing Outcomes in Hospitalized Lung Cancer. *Oncology (Basel).* 2024; 4(4): 458-70. Article. Not Indexed
- **Peressini M, García-Campelo R, Massuti B, Martí C, Cobo M, Gutiérrez V, Dómine M, Fuentes J, Majem M, de Castro J, Córdoba JF, Diz MP, Isla D, Esteban E, Carcereny E, Vila L, Moreno-Vega A, Ros S, Moreno A, García EJ, Huidobro G, Aguado C, Cebey-López V, Valdivia J, Palmero R, Lianes P, López-Brea M, Vidal OJ, Provencio M, Arriola E, Baena J, Herrera M, Bote H, Molero M, Adradas V, Ponce-Aix S, Núñez-Buiza A, Uceros A, Hernández S, López-Rios F, Conde E, Paz-Ares L, Zugazagoitia J.** Spatially Preserved Multi-Region Transcriptomic Subtyping and Biomarkers of Chemoimmunotherapy Outcome in Extensive-Stage Small Cell Lung Cancer. *Clin Cancer Res.* 2024; 30(14): 3036-49. Article. IF: 10.2; D1
- **Provencio M, de Lope LR, Serna-Blasco R, Nadal E, Tain PD, Massuti B, González-Larriba JL, Insa A, Sánchez-Hernández A, Casal-Rubio J, García-Campelo R, López SS, Rogado J, Martínez-Martí A, Bosch-Barrera J, Bernabé R, Estévez SV, Ponce S, de Castro J, Sarto JC, Reguart N, Dómine M, Aguilar A, Majem M, Estival A, Cabia SP, Martín AL, González MAS, Cobo M, Camps C, Barneto I, Calvo V,**



Collazo-Lorduy A, Cruz-Bermúdez A, Romero A. BRAF mutational status is associated with survival outcomes in locally advanced resectable and metastatic NSCLC. *Lung Cancer.* 2024; 194: 107865. Article. IF: 4.4; Q1

- **Provencio M, Nadal E, Insa A, Campelo RG, Casal J, Dómine M, Massuti B, Majem M, Rodríguez-Abreu D, Martínez-Martí A, de Castro J, de Antonio DG, Macia I, Figueroa S, Vago LF, Calvo V, Palmero R, Sierra-Rodero B, Martínez-Toledo C, Molina-Alejandre M, Serna-Blasco R, Romero A, Cruz-Bermúdez A.** Perioperative chemotherapy and nivolumab in non-small-cell lung cancer (NADIM): 5-year clinical outcomes from a multicentre, single-arm, phase 2 trial. *Lancet Oncol.* 2024; 25(11): 1453-64. Article. IF: 35.9; D1
- **Rosas-Alonso R, Colmenarejo-Fernández J, Pernía O, Burdiel M, Rodríguez-Antolín C, Losantos-García I, Rubio T, Moreno-Velasco R, Esteban-Rodríguez I, Martínez-Marín V, Yubero P, Costa-Fraga N, Díaz-Lagares A, López-López R, Díaz-Martín E, García JF, Sánchez CV, Gandía-González ML, Moreno-Bueno G, de**

Castro J, de Cáceres II. Evaluation of the clinical use of MGMT methylation in extracellular vesicle-based liquid biopsy as a tool for glioblastoma patient management. *Sci Rep-Uk.* 2024; 14(1): 11398. Article. IF: 3.9; Q1

- **Soo RA, Dafni U, Han JY, Cho BC, Nadal E, Yeo CM, Carcereny E, de Castro J, Sala MA, Coate L, Provencio M, Britschgi C, Vagenknecht P, Dimopoulou G, Kammler R, Finn SP, Peters S, Stahel RA.** ctDNA Dynamics and Mechanisms of Acquired Resistance in Patients Treated with Osimertinib with or without Bevacizumab from the Randomized Phase II ETOP-BOOSTER Trial. *Clin Cancer Res.* 2024; 30(22): 5180-91. Article. IF: 10.2; D1

Research projects

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

Management 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 histología de adenocarcinoma en España. Roche Farma S. A. 2018-Ongoing. **Management centre: FIBHULP**
- **de Castro Carpeño J.** Determinación mediante inmunohistoquímica de la expresión de PDL-1 en carcinoma de célula no pequeña de pulmón. Fundación ECO. 2016-Ongoing. **Management 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 estándar 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. **Management 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. **Management 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. **Management centre: FIBHULP**
- **de Castro Carpeño J.** Identificación de nuevos mecanismos genéticos y epigenéticos de resistencia a la inmunoterapia de primera línea en pacientes con cáncer de pulmón no microcítico metastásico (CPNMM) con alta expresión PD-1. Estudio keypredict. Fundación Mutua Madrileña.

2022-Ongoing. **Management centre: FIBHULP**

- **de Castro Carpeño J.** Plataforma del grupo de investigación de terapias experimentales y biomarcadores en cáncer. Helicon Medical S.L. 2021-Ongoing. **Management 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. **Management centre: FIBHULP**
- **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. **Management centre: FIBHULP**
- **de Castro Carpeño J.** Título: INtegrative GENomic, digital Imaging and clinical information towards Precision Oncology Optimization (PMP21/00107). ISCIII-MICIIN. 2022-2025. **Management 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-1 en cpcnp. Roche Farma S.A. 2017-Ongoing. **Management centre: FIBHULP**
- **Galera Martínez R, Pernía Arias O.** Evaluación del perfil de hipermetilación de micrnas para la estimación de riesgo de cáncer de pulmón en pacientes con EPOC (PI22/01764). ISCIII. 2023-2025. **Management 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. **Management 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. **Management centre: FIBHULP**

3 Research areas and groups

- **Rodríguez Antolín C.** aplicación del metiloma en el diagnóstico del sistema nervioso central de difícil clasificación a través de algoritmos de aprendizaje automático. Ghetti. 2022-Ongoing. **Management 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. **Management centre:** FIBHULP
- **Rodríguez Antolín C.** Personal técnico bioinformático de apoyo a investigación (CA22/00002). ISCIII. 2023-Ongoing. **Management centre:** FIBHULP
- **Rosas Alonso R.** Estudio de nuevas variantes asociadas a toxicidad por fluoropirimidinas. Fundación Jose Luis Castaño para el Desarrollo del Laboratorio Clínico. 2022-Ongoing. **Management 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. **Management 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 Jose Luis Castaño para el Desarrollo del Laboratorio Clínico. 2023-Ongoing. **Management 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. **Management centre:** FIBHULP
- **Vera Puente O.** Early molecular nanoDIAGnostics of brain tumors using Immune-PET (DIAGBI) (PLEC2021-008034). MICIIN. 2021-2024. **Management centre:** FIBHULP
- **Vera Puente O.** Evaluación y puesta a punto del biomarcador epigenético MGMT en biopsia líquida como prueba no invasiva de seguimiento, en pacientes con gliomas. Cuesta Barrio, Juan. 2017-Ongoing. **Management centre:** FIBHULP
- **Vera Puente O.** Validación clínica en biopsia líquida de una firma genética y epigenética

- como herramienta pronóstica frente a quimioinmunoterapia en pacientes con cáncer de pulmón (CPP2022-009545). MICIIN. 2023-2026. **Management centre:** FIBHULP
- **Vera Puente O.** Caracterización de las funciones inmunosupresoras de mafg en melanoma y sus potenciales implicaciones para la terapia del cáncer (GEM2023_OVP). Grupo Español Multidisciplinar de Melanoma. 2024-2026. **Management centre:** FIBHULP
 - **Vera Puente O.** Dinamización de ciencia disruptiva en predictores de enfermedades tumorales, infecciosas y hereditarias como base de la medicina personalizada (FORT23/00006_ GRUPO III). ISCIII. 2024-2028. **Management centre:** FIBHULP

Cibers and Retics

- **de Castro Carpeño J.** Plataforma de Dinamización e Innovación de las Capacidades Industriales del SNS y su Transferencia Efectiva al Sector Productivo (PT23/00035). ISCIII. (31/12/2026). FIBHULP
- **de Castro Carpeño J.** Dinamización e innovación de las capacidades industriales del SNS y su transferencia al sector productivo (PT20/00002). ISCIII. (31/12/2024). FIBHULP

Clinical trials

- **de Castro Carpeño J.** a first-in-human (fih) phase I/II open-label, multicentre, dose escalation and expansion trial of vert-002 in patients with locally advanced or metastatic solid tumors including non-small cell lung cancer (nscl) harboring met alterations. **Type/Phase:** I **Sponsored by:** Pierre Fabre Medicament S.A.S. **Signature date:** 26/09/2024
- **de Castro Carpeño J.** a multicentre, phase II, single-arm, interventional study of neoadjuvant durvalumab and platinum-based chemotherapy (ct), followed by either surgery and adjuvant durvalumab or chemoradiotherapy (crt) and consolidation durvalumab, in participants with resectable or borderline resectable stage IIb-IIIb non-small cell lung cancer (nscl). **Type/Phase:** II

Sponsored by: Astrazeneca Ab
Signature date: 18/01/2024

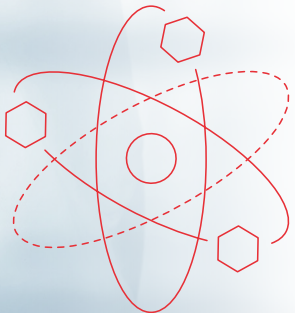
- **de Castro Carpeño J.** a phase 1/2, dose escalation, dose expansion, and dose optimization study of the safety, tolerability, and anti-tumor activity of sar444881 administered alone and in combination with pembrolizumab, cetuximab, and/or chemotherapy in participants with advanced solid tumors. **Type/Phase:** I **Sponsored by:** Sanofi-Aventis Recherche Et Developp **Signature date:** 02/07/2024
- **de Castro Carpeño J.** a phase 2, open-label, parallel cohort study of subcutaneous amivantamab administered 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 **Signature date:** 12/01/2024
- **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 **Signature date:** 28/11/2024
- **de Castro Carpeño J.** a phase 3, open-label, randomized, multi-center study of dzd9008 versus platinum-based doublet chemotherapy as first-line treatment for patients with locally advanced or metastatic non-small cell lung cancer harboring epidermal growth factor receptor exon 20 insertion mutation. **Type/Phase:** III **Sponsored by:** Dizeal Pharmaceuticals Inc. **Signature date:** 05/02/2024
- **de Castro Carpeño J.** a randomized phase 2 platform study to evaluate cemiplimab plus chemotherapy versus cemiplimab plus

3 Research areas and groups

3.5. Cancer and Human Molecular Genetics Area

chemotherapy plus other cancer treatments for the perioperative treatment of patients with resectable non-small cell lung cancer.

- Type/Phase:** II
Sponsored by: Regeneron Pharmaceuticals Inc.
Signature date: 30/10/2024
- **de Castro Carpeño J.** a randomized, double-blind, placebo-controlled, multi-regional phase III clinical study of toripalimab alone or in combination with tificemalimab (js004/tab004) as consolidation therapy in patients with limited-stage small cell lung cancer without disease progression following chemoradiotherapy. **Type/Phase:** III **Sponsored by:** Shanghai Junshi Biosciences Co Ltd. **Signature date:** 09/07/2024
 - **de Castro Carpeño J.** an open-label, randomized phase 3, global multi-center trial to assess the efficacy and safety of zipalertinib (tas6417) plus pemetrexed and cisplatin or carboplatin, versus pemetrexed and cisplatin or carboplatin, in patients with previously untreated, locally advanced or metastatic non-squamous non-small cell lung cancer (nscl) with epidermal growth factor receptor (egfr) exon 20 insertion (ex20ins) mutations. **Type/Phase:** III **Sponsored by:** Taiho Oncology Inc. **Signature date:** 24/01/2024
 - **de Castro Carpeño J.** an open-label, randomized phase 3, global multi-center trial to assess the efficacy and safety of zipalertinib (tas6417) plus pemetrexed and cisplatin or carboplatin, versus pemetrexed and cisplatin or carboplatin, in patients with previously untreated, locally advanced or metastatic non-squamous non-small cell lung cancer (nscl) with epidermal growth factor receptor (egfr) exon 20 insertion (ex20ins) mutations. **Type/Phase:** III **Sponsored by:** Taiho Oncology Inc. **Signature date:** 07/11/2024
 - **de Castro Carpeño J.** beamion lung-2: a phase III, open-label, randomized, active-controlled, multi-centre trial evaluating orally administered bi 1810631 compared with standard of care as first-line treatment in patients with unresectable,



locally advanced or metastatic nonsquamous non-small cell lung cancer harbouring her2 tyrosine kinase domain mutations.

Type/Phase: III

Sponsored by: Boehringer Ingelheim International GmbH

Signature date: 05/03/2024

- **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 (l1) y quimioterapia (costar lung).

Type/Phase: II

Sponsored by: Glaxosmithkline Research And Development Limited; Glaxosmithkline Research And Development Limited

Signature date: 20/03/2024

- **de Castro Carpeño J.** ensayo clínico fase III de tratamiento adyuvante con sacituzumab y zimberelimab para pacientes con cáncer de pulmón no microcítico (cpnm) en estadio ib-IIIa-IIIb (n2) previamente operados (r0) que no alcanzaron una respuesta patológica completa tras el tratamiento neoadyuvante.

Type/Phase: III

Sponsored by: Fundación Gepec

Signature date: 01/10/2024

- **de Castro Carpeño J.** ensayo en fase III, aleatorizado, con el anticuerpo monoclonal anti-pd-1 pembrolizumab (mk-3475), en comparación con placebo para pacientes con cpnm en fase temprana después de resección y finalización del tratamiento complementario de referencia (pearls).

Type/Phase: III

Sponsored by: Merck & Co. Inc.

Signature date: 13/12/2024

- **de Castro Carpeño J.** ensayo en fase III, aleatorizado, sin enmascaramiento para comparar la eficacia y la seguridad de ose2101 frente a docetaxel en pacientes positivos para hla-a2 con cáncer de pulmón no microcítico (cpnm) metastásico y con resistencia secundaria a los inhibidores de puntos de control inmunitario (inhibidores del pci) - estudio artemia.

Type/Phase: III

Sponsored by: Ose Immunotherapeutics

Signature date: 03/09/2024

- **de Castro Carpeño J.** estudio aleatorizado, doble ciego, multicéntrico internacional, de fase III para evaluar la eficacia antitumoral y la seguridad de hlx10 (inyección de anticuerpos monoclonales humanizados anti-pd-1 recombinantes) o placebo, en combinación con quimioterapia (carboplatino/cisplatino-etopósido) y radioterapia concomitante en pacientes con cáncer de pulmón de células pequeñas en estadio limitado (cpcp-el).

Type/Phase: III

Sponsored by: Shanghai Henlius Biotech

Signature date: 15/04/2024

- **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

Signature date: 08/04/2024

- **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.

Signature date: 05/08/2024

- **de Castro Carpeño J.** estudio de fase ib/II, abierto y aleatorizado de vudalimab en combinación con quimioterapia o pembrolizumab en combinación con quimioterapia como tratamiento de primera línea en pacientes con cáncer de pulmón no microcítico avanzado.

Type/Phase: II

Sponsored by: Xencor Inc.

Signature date: 21/06/2024

- **de Castro Carpeño J.** estudio de fase III aleatorizado, controlado y multirregional de ivonescimab en combinación con quimioterapia frente a pembrolizumab en combinación con

quimioterapia para el tratamiento de primera línea del cáncer de pulmón no microcítico escamoso metastásico (harmoni-3).

Type/Phase: III

Sponsored by: Summit Therapeutics Inc.

Signature date: 09/09/2024

- **de Castro Carpeño J.** estudio de fase III aleatorizado, doble ciego de tiragolumab más atezolizumab comparado con placebo más atezolizumab, en participantes con cáncer de pulmón no microcítico completamente reseccionado, en estadio IIb, IIIa o IIIb selectivo, pd-11 positivo, que hayan recibido quimioterapia adyuvante basada en platino.

Type/Phase: III

Sponsored by: F.Hoffmann-La Roche Ltd.

Signature date: 23/04/2024

- **de Castro Carpeño J.** estudio de fase III, multicéntrico, aleatorizado, en doble ciego y controlado con placebo, para evaluar la eficacia y la seguridad de azd9291 frente a placebo en pacientes con carcinoma de pulmón no microcítico con mutación del receptor del factor de crecimiento epidérmico, en estadio ib-IIIa, tras la resección completa del tumor, con o sin quimioterapia adyuvante (adaura).

Type/Phase: III

Sponsored by: Astrazeneca Farmaceutica Spain S.A.

Signature date: 08/04/2024

- **de Castro Carpeño J.** estudio de la respuesta inmune antitumoral generada tras quimio-radioterapia concurrente (qrtc) y tratamiento con io en pacientes con estadio IIIa/b y IIIc nsclc no reseccionados en el mundo real. sienna.

Type/Phase: EOm prospectivo

Sponsored by: Fundación Gepec

Signature date: 17/09/2024

- **de Castro Carpeño J.** estudio en fase i, abierto, de escalada y ampliación de la dosis para evaluar la seguridad, la tolerabilidad, la farmacocinética, la farmacodinámica y la eficacia preliminar de d3s-001 en monoterapia en sujetos con tumores sólidos avanzados con mutación p.g12c en kras.

Type/Phase: I

Sponsored by: D3 Bio

Signature date: 07/11/2024

- **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.

Signature date: 28/07/2024

- **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.

Signature date: 27/11/2024

- **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/Phase: II

Sponsored by: Bristol-Myers Squibb International Corporation (Bmsic)

Signature date: 28/06/2024

- **de Castro Carpeño J.** estudio en fase III abierto y aleatorizado del tratamiento combinado de amivantamab y lazertinib con quimioterapia basada en platino en comparación con quimioterapia basada en platino en pacientes con cáncer de pulmón no microcítico con mutación del egfr localmente avanzado o metastásico tras el fracaso de osimertinib.

Type/Phase: III

Sponsored by: Janssen Cilag International Nv

Signature date: 25/10/2024

- **de Castro Carpeño J.** estudio en fase III multicéntrico, abierto, randomizado para evaluar la eficacia y la seguridad de divarasib comparado con sotorasib o adagrasib en pacientes con cáncer de pulmón no microcítico kras g12c positivo avanzado o metastásico, tratados previamente.

Type/Phase: III

Sponsored by: F.Hoffmann-La Roche Ltd.

Signature date: 20/06/2024

- **de Castro Carpeño J.** estudio en fase

III, multicéntrico, aleatorizado y sin enmascaramiento de ifinatamab deruxtecán (i-dxd), un conjugado anticuerpo-fármaco (caf) b7-h3 frente al tratamiento elegido por el médico (tpc) en participantes con carcinoma pulmonar de células pequeñas (cpcp) recidivante (ideate-lung02)".

Type/Phase: III
Sponsored by: Daiichi Sankyo Inc.
Signature date: 19/06/2024

- **de Castro Carpeño J.** estudio fase 3 abierto y aleatorizado de la combinación de la terapia amivantamab y carboplatino-pemetrexed, frente a carboplatino-pemetrexed, en pacientes con cáncer de pulmón no microcítico localmente avanzado o metastásico con egfr mutado por inserciones en el exon 20.

Type/Phase: III
Sponsored by: Janssen Cilag International Nv; Janssen-Cilag España S.A.
Signature date: 23/04/2024

- **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/Phase: III
Sponsored by: Janssen Cilag International Nv
Signature date: 20/12/2024"

- **de Castro Carpeño J.** estudio multicéntrico de fase 3, aleatorizado, doble ciego, controlado con placebo, para comparar niraparib añadido a pembrolizumab versus placebo añadido a pembrolizumab como terapia de mantenimiento en participantes cuya enfermedad se haya mantenido estable o haya respondido a una primera línea de quimioterapia basada en platino y pembrolizumab en cáncer de pulmón no microcítico estadio IIIb o iv.

Type/Phase: III
Sponsored by: Glaxosmithkline S.A.
Signature date: 22/02/2024

- **de Castro Carpeño J.** fase I/II first-in-human open-label trial to assess safety and efficacy of stx-241 in participants with locally advanced

or metastatic non-small cell lung cancer (nslc) resistant to egfr tyrosine kinase inhibitors (tkis).

Type/Phase: I
Sponsored by: Sas Pierre Fabre Medicament
Signature date: 18/07/2024

- **Vera Puente O.** estudio farmacogenómico en la quimioterapia con platinos.

Type/Phase: EPA-OD
Sponsored by: Dupont Investigación Y Desarrollo S.L
Signature date: 18/06/2024

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 trefol 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 cancer. P201130863, PCT/ES2012/070379; 2011 May 26.

- **Martínez Mániz 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.