BIOGRAPHICAL SKETCH

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NAME: Jose A. Martinez-Climent

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POSITION TITLE: Professor of Medicine

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of Valencia School of Medicine, Valencia, Spain	MD	1986	Medicine
La Fe Children´s Hospital, University of Valencia, Valencia, Spain	Board Certification	1992	Pediatrics and Pediatric Hematology/Oncology
The University of Chicago Medical Center, Chicago, IL, US; and University of Valencia	PhD	1996	Cancer Genetics

A. Personal Statement. I am Professor of Medicine in the Department of Hemato-Oncology at the University of Navarra in Spain. I obtained an MD degree (1986) and a board certification (MIR) in pediatrics and pediatric hematology/oncology from La Fe University Hospital in Valencia, Spain (1992). Then I received training in cancer genetics and cell biology at the University of Chicago and University of California San Francisco USCF, earning a PhD degree in 1996. Upon my return to Spain, I was Attending Physician and Assistant Professor in the Department of Hematology/Oncology at University of Valencia Clinic Hospital (1996-2004). There I started my first research lab and founded the cancer genetics lab for the centralized genetic diagnosis of cancer patients in public hospital at the Valencia region, which I directed for 8 years. In 2005 I moved to the University of Navarra as a Ramon y Cajal Scientist and Associate Professor of Medicine to start full dedication to translational research. Since 2010 I am Professor of Medicine and Head of Preclinical Therapy Research at Center for Applied Medical Research, Clinica Universidad de Navarra Cancer Center, and School of Medicine.

The goal of my research has been to understand the nature of hematological cancers, exploiting scientific discoveries in the lab to advance early therapies to the clinic. My work and expertise span from basic studies on leukemia, lymphoma and myeloma biology, genomics, and immunology to the development of novel therapeutic approaches based on tumor features. We have made substantial contributions on the genomic and immune profiling of B-cell lymphomas, the mechanisms underlying acquired therapeutic resistance and how it can be overcome, and the role of endogenous retroelements in drug therapy response and cancer development. More recently, we have developed genetically engineered mouse models of human-like multiple myeloma, leukemias and mature B-cell lymphomas, which are allowing to link tumor genetic and immunological features during malignant transformation at unprecedented levels. Remarkably, genomic and immune portraits condition responses to preclinical immunotherapy and, accordingly, we are using the models to evaluate drug efficacy, mechanisms of response/resistance, and toxicity. The final goal is prioritizing which targeted and immune-based drug combinations should be clinically tested in selected disease subsets, particularly in cancer patients without optimal therapeutic options, with the aim of reaching a cure.

I currently direct a research lab of 18 people fully dedicated to research, with 4 junior scientists and 1 lab manager who coordinate the work of 5 post-doctoral fellows, 2 computational biologists, 4 lab technicians (3 with PhD degree), and 2 PhD students. We are part and routinely collaborate with our clinical colleagues in the Hemato-Oncology department at the Clinica Universidad de Navarra Cancer Center. To support our research in the lab, I receive regular funding through competitive grants from national and international agencies. In addition, my group is supported by the major pharmaceutical companies through research collaborations, which now account for >80% of our budget dedicated to research (total budget since 2020, 2MM€/year). In this line, I founded MIMO

(Modeling IMmunotherapy in Oncology) Biosciences in 2023, a spin-off company at the University of Navarra, dedicated to the generation, development and use of genetically engineered mouse models for advancing cancer immunotherapy. Through such collaborations with pharma companies, we facilitate the translation of scientific knowledge and pre-clinical therapeutics to clinical trials.

I have published >110 scientific articles (70% in D1 of JCR) and have an H-factor of 44, with 4 EU/US patent applications. I have regularly presented our work at >100 international meetings from scientific and clinical hematology/oncology societies (ASH, EHA, AACR, ASCO, IMS, etc.). As a Professor, I have directed 16 doctoral thesis and 6 master's degrees, and have supervised >25 post-doctoral MD or PhD fellows for at least 1 year.

B. Positions, Scientific Appointments, and Honors

Positions

2023-present	Founder and Scientific Director, MIMO Biosciences
2010-present	Professor of Medicine and Head of Preclinical Therapy Research. Department of Hemato-Oncology. Center for Applied Medical Research (CIMA), Clinica University of Navarra Cancer Center and School of Medicine, University of Navarra
2005-2009	Associate Professor of Medicine, Departments of Hematology and Oncology, and "Ramon y Cajal" Program Investigator. CIMA and School of Medicine, University of Navarra
2000-2001	Visiting Scientist, University of California San Francisco, UCSF Comprehensive Cancer Center, San Francisco, CA, US; mentor, Professor Daniel Pinkel, PhD
1996-2004	Attending Physician and Assistant Professor, Department of Hematology and Medical Oncology, Hospital Clinic; and Founder and Director, Cancer Genetics Core Diagnostic Laboratory, University of Valencia, Spain
1993-1995	Pre-doctoral Research Fellow, Cancer Genetics Lab, Section of Hematology and Oncology, The University of Chicago, IL, US; mentor, Professor Janet D. Rowley, MD
1990-1992	Clinical Fellow, Pediatric Hematology-Oncology, La Fe Childen´s Hospital, Valencia, Spain
1987-1989	Resident, General Pediatrics, La Fe Childen´s Hospital, University of Valencia, Spain
1986-1987	Army Medical Officer, Military Hospital Valencia and Gomez-Ulla Hospital Madrid, Spain

Honors and Awards

Spanish Pediatric Association leukemia research award (1992); International ISCIII research award for PhD thesis, Spanish Ministry of Health (1992-1996); International ISCIII visiting professorship travel awards to The University of Chicago, Spanish Ministry of Health (years 1999, 2000 and 2001); International Union Against Cancer UICC-ICRET award (2001); Clinical Investigation award, University of Valencia/Clinic Hospital (2002); Emilio Rodríguez Vigil annual award (2002); Spanish Hematology Association-Schering Research Award in Lymphomas (years 2001, 2003, 2005 and 2007); Yamagiwa-Yoshida Memorial International cancer research award for UICC (2005); Ramon y Cajal award (Ministry of Science) (2005-2010); Ortiz de Landazuri award (Navarra Health Dept.) (2006); Maria Jose Jove research award in breast cancer (2006); Lymphoma Research Foundation award (2010); Spanish Cancer Network award (Ministry of Health) (2011); Roche International Research Award in Hemato-Oncology (2014); International Waldeström Macroglobulinemia and Leukemia Lymphoma Society award (2017); International Myeloma Society TRP research award (2022).

C. Contributions to Science

1. Genetics of pediatric leukemias. After finishing a clinical fellowship in pediatric hematology/oncology, I joined Prof. Janet Rowley´s lab at the University of Chicago. Under her extraordinary mentorship, I decided to dedicate my work to cure incurable patients by understanding their tumor biology. I published my first 10 papers in leukemia genetics, focused on *MLL* rearrangements in childhood ALL/AML, leading to a PhD thesis (1996): *Molecular genetics of childhood AML*. I closed this line of research years ago. The papers I am prouder of are:

a) **Martinez-Climent JA**, Lane NJ, Rubin CM, …, Vardiman JW, Larson RA, Le Beau MM, Rowley JD. Clinical and prognostic significance of chromosomal abnormalities in childhood acute myeloid leukemia de novo. **Leukemia**. 9(1):95-101, 1995. IF: 12,897 (D1, 7/96; Hematology). Citations: 92

b) **Martinez-Climent JA**, Thirman MJ, Espinosa R 3rd, Le Beau MM, Rowley JD. Detection of 11q23/MLL rearrangements in infant leukemias with fluorescence in situ hybridization and molecular analysis. **Leukemia**. 9(8):1299-304, 1995. IF: 12,897 (D1, 7/96; Hematology). Citations: 56

c) Dreyling MH, **Martinez-Climent JA**, Zheng M, Mao J, Rowley JD, Bohlander SK. The t(10;11)(p13;q14) in the U937 cell line results in the fusion of the AF10 gene and CALM, encoding a new member of the AP-3 clathrin assembly protein family. **Proc Natl Acad Sci U S A**. 93(10):4804-9, 1996. IF: 12,779 (D1, 9/135; Multidisciplinary Sciences). Citations: 256

2. Genomic and transcriptomic deregulation across B-cell malignancies. Upon my return to Spain in 1996, I started my own lab dedicated to the genetic study of B-cell malignancies. We pioneered the simultaneous high-throughput genomic and transcriptomic analyses of lymphomas using paralleled DNA and RNA microarrays. Following my first paper as senior author in Leukemia in 2000, we published five consecutive papers in Blood, defining genetic characteristics in different B-cell lymphoma subtypes that correlated with pathological and clinical features (Martinez-Climent, Blood 2001 and 2003; Sanchez-Izquierdo, Blood 2003; Rubio-Moscardo, Blood 2004 and 2005). A major discovery was to define the paracaspase MALT1 as an oncogenic factor in lymphoma (Sanchez-Izquierdo, Blood 2003), which was followed by studies to inhibit its enzymatic activity for lymphoma therapy (Vicente-Dueñas, Fontan, PNAS 2012; Fontan, Cancer Cell 2102). This research line continues today in the lab, where we evaluate MALT1 inhibitors undergoing clinical development in combination with drugs in clinical use. The main papers during this period were:

a) **Martinez-Climent JA**(*), Alizadeh AA, Segraves R, Blesa D, Rubio-Moscardo F, Albertson DG, Dyer MJ, Levy R, Pinkel D, Lossos IS(*). Transformation of follicular lymphoma to diffuse large B-cell lymphoma is associated with a heterogeneous set of DNA copy number and gene expression alterations. **Blood**, 101:3109-3117, 2003. (*) Co-senior authors. IF: 25,476 (D1, 1/76; Hematology). Citations: 178

b) Sanchez-Izquierdo D, Buchonnet G, Siebert R, Gascoyne RD, Climent J, Karran L, Blesa D, Horsman D, Rosenwald A, Staudt LM, Albertson DG, Du MQ, Ye H, Marynen P, Pinkel D, Dyer MJ, **Martinez-Climent JA**. MALT1 gene is deregulated by both chromosomal translocation and amplification in B-cell non-Hodgkin lymphoma. **Blood**, 101:4539-4546, 2003. IF: 25,669 (D1, 2/96; Hematology). Citations: 166

c) Rubio-Moscardo F, Climent J, Siebert R, Piris MA, Martín-Subero JI, Nieländer I, Garcia-Conde J, Dyer MJ, Terol MJ, Pinkel D, **Martinez-Climent JA**. Mantle cell lymphoma genotypes identified with CGH to BAC microarrays define a leukemic subgroup of disease and predict patient outcome. **Blood**, 105:4445-54, 2005. IF: 25,669 (D1, 2/96; Hematology). Citations: 146

3. Mechanisms of therapeutic resistance in cancer. I moved to the University of Navarra in 2005, and focused on the mechanistic characterization of primary and acquired therapeutic resistance in cancer cells, with the goal of learning how it can be overcome. We found changes in intrinsic and extrinsic apoptosis pathways that conferred primary therapy resistance (Mestre-Escorihuela, Blood 2007; Richter-Larrea, Blood 2010). We discovered a non-canonical function of cyclin-D1 in deregulating mitochondrial apoptosis through sequestering cytosolic BAX that restricted BCL2 inhibition therapy responses (Beltran, PNAS 2011). We reported acquired mutations in apoptotic genes following venetoclax treatment in experimental leukemia/lymphoma models (Fresquet, Blood 2014), which anticipated the development of such mutations in clinical trials. We defined the mechanistic basis underlying sensitivity and resistance to epigenetic agents combined with venetoclax in multiple cancer types (Fresquet, Cancer Discovery 2021):

a) Mestre-Escorihuela C, Rubio-Moscardo F, …, Staudt LM, Pinkel D, Dyer MJ, **Martinez-Climent JA**. Homozygous deletions localize novel tumor suppressor genes in B-cell lymphoma. **Blood** 109:271-280, 2007. IF: 25,669 (D1, 2/96; Hematology). Citations: 195

b) Beltran E, Fresquet V, Martinez-Useros J, …, Prosper F, Lossos IS, Piris MA, Fernandez-Zapico ME, **Martinez-Climent JA**. A cyclin-D1 interaction with BAX underlies its oncogenic role in mantle cell lymphoma. **Proc Natl Acad Sci U S A** 108:12461-12466, 2011. IF: 12,779 (D1, 9/135; Multidisciplinary Sciences). Citations: 50

c) Fresquet V, Rieger M, Carolis C, García-Barchino MJ, **Martinez-Climent JA**. Acquired mutations in BCL2 family proteins conferring resistance to the BH3 mimetic ABT-199 in lymphoma. **Blood**. 23(26):4111-9, 2014. IF: 25,669 (D1, 2/96; Hematology). Citations: 141

d) Fresquet V, Garcia-Barchino MJ, …, Prosper F, **Martinez-Climent JA**. Endogenous retroelement activation by epigenetic therapy reverses the Warburg effect and elicits mitochondrial-mediated cancer cell death. **Cancer Discovery**. 11(5):1268-1285, 2021. IF: 38,272 (D1, 9/245; Oncology). Citations: 32

4. Advancing targeted and immune-based drug therapies in experimental models of B-cell malignancies. More recently, we have modeled human-like hematological malignancies in mice by triggering patient´s mutations at cells that originate the disease. Following this strategy, we generated the first model of MALT lymphoma by activating *MALT1* oncogene in immature lymphoid cells (Fontan, PNAS 2012). We also modeled different lymphoma subtypes in mice (MCL, SMZL, GC and ABC DLBCL) through activating selected oncogenic drivers at specific cell stages (Beltran, PNAS 2011; Sagardoy, Blood 2013; Romero, Nat Comm 2013; Green, Nat Comm 2014; Robles, Nat Comm 2016; Pascual, Blood 2019). More recently, we have recapitulated the broad pathological spectrum $MYD88^{L265P}$ indolent and aggressive lymphomas in mice carrying oncogenic MYD88 with selected secondary mutations (Rodriguez, Sci Adv 2022; Sacco, Blood 2023; Celay, submitted). Finally, we have generated 15 mouse models that reflect the principal pathogenetic elements in multiple myeloma, defining different genetic paths of progression that conditioned immune escape mechanisms and dictated repose to immunotherapy (Larrayoz, Nature Med 2023; Jimenez, Nature Comm 2023). These lymphoma and myeloma models constitute unique platforms to study mechanisms of therapy response/refractoriness, while they are also used to advance personalized immunotherapy combinations. This line of research has opened multiple collaborations with academic centers and pharmaceutical companies across Europe and the US (see Funding section), aiming to translate pre-clinical knowledge to the clinic:

a) Vicente-Dueñas C*, Fontan L*, …, Cobaleda C, Sanchez-Garcia I(*), **Martinez-Climent JA**(*). Expression of MALT1 oncogene in mouse hematopoietic stem/progenitor cells recapitulates the pathogenesis of human MALT lymphoma. **Proc Natl Acad Sci U S A** 109:10534-10539, 2012. IF: 12,779 (D1, 9/135; M.Sciences). Citations: 62 - Cited by Faculty of 1.000. (*) co-senior/corresponding
b) Pascual M, Mena-Varas M, …, Melnick A, **Martinez-Climent JA**(*), Roa S(*). PD-1/PD-L1 immune checkpoint and p53 loss facilitate tumor progression in activated DLBCL. **Blood**. 30;133(22):2401-2412, 2019. (*) co-senior/corresponding. IF: 25,669 (D1, 2/96; Hematology). Citations: 51
c) Rodriguez S, Celay J, …, Roccaro AM, San Miguel JF, **Martinez-Climent JA**(*), Paiva B(*). Preneoplastic somatic mutations including $MYD88^{L265P}$ in lymphoplasmacytic lymphoma. **Science Advances** Jan 21;8(3):eabl4644, 2022. (*) co-senior. IF: 14,957 (D1, 7/135; Multidisciplinary Sc.). Citations: 11
d) Larrayoz M, Garcia-Barchino MJ, Celay J, …, San Miguel J, Paiva P, Prosper F, **Martinez-Climent JA**. Pre-clinical models for predicting immune evasion mechanisms and clinical immunotherapy outcomes in genetically heterogeneous multiple myeloma. **Nature Medicine** 29(3):632-645, 2023. IF: 87,24 (D1, 1/139; Medicine Experimental). Citations: 3
e) Jimenez C, Botta C, Larrayoz M, …, San Miguel J, **Martinez-Climent JA**, Paiva B. Single-cell profiles in multiple myeloma reveals dysfunction of large T-cell clones and phenotypic markers of response to lenalidomide-based combinations. **Nature Communications.** 2023. IF: 17,694 (D1, 6/135; M. Sciences).

Patents

1. Authors: **Martinez-Climent JA**, Climent J, Albertson D, Pinkel D. Title: Chromosome 11q deletion as a molecular genetic marker in breast cancer. Patent number: US 2007-264637-A1. University of Navarra and University of California UCSF. May 2006
2. Authors: Sanchez-García I, Cobaleda C, Fontán L, Vicente-Dueñas C, **Martinez-Climent JA**. Title: A non-human animal model of mucosa-associated lymphoid tissue (MALT) lymphoma. Patent number: EP 11382319. University of Navarra and CSIC/Universidad de Salamanca. October 2011
3. Authors: Fresquet, V; Oyarzabal, J; Prosper, F; **Martinez-Climent, JA**; Agirre, X. Title: New epigenetic agents and drug combinations. Patent number: EP18382435.8. University of Navarra. June 2018
4. Authors: Larrayoz M, Celay J, Garcia-Barchino MJ, **Martinez-Climent JA**. Title: Genetically engineered animal models for multiple myeloma. Patent number: EP18382435.8. University of Navarra. July 2022

Funding for Research in last three years (total budget from 2020; 2MM€/year.)

Martinez-Climent as coordinator/PI

Title: Modeling, unraveling, and beating acquired resistance to BCMA and GPRC5D targeted agents in MM. Funded by Intl. Myeloma Society, Translational Research Grant. From 03/2023 to 03/2025. PI: Martinez-Climent.

Title: Understanding and overcoming acquired resistance to IMiDs in mouse models of MM. Funded by ISCIII Institute, Spanish Ministry of Health (PI22/00983). From 01/2023 to 01/2026. PI: Martinez-Climent

Title: Optimizing CART therapy in murine models of MM. Funded by German Jose Carreras Foundation. From 11/2022 to 11/2025. PI: Martinez-Climent (co-PI: Sophia Danhof, University of Würzburg).

Title: Advancing personalized targeted therapy and immunotherapy in hematologic malignancies through using mouse models. Funded by Carlos III Health Institute, Spanish Ministry of Health (ISCIII/FIS) (Grant no. PI19/00818). From 01/2020-01/2023. PI: Martinez-Climent.

Research agreements with pharmaceutical companies

Title: Understanding the alterations in the BM microenvironment during MGUS to MM transition and immunotherapy responses using mouse models and patient samples to inform future treatment strategies. Funded by Immunotherapy Centers of Research Excellence (imCORE-Roche). Grant no. NAV15-H/2020. From 10/2020 to 10/2023. PI: Martinez-Climent (co-PI: Bruno Paiva).

Title: Screening effectiveness of immunotherapeutic drug combinations in genetically engineered mouse models of human-like B-cell lymphomas. Funded by Immunotherapy Centers of Research Excellence (imCORE-Roche). Grant no. NAV4/2017. From 01/2018 to 01/2023. PI: Martinez-Climent (co-PI: Sergio Roa).

Title: Targeting regulatory T (Treg) cells in multiple myeloma with a novel CD25 depleter moAb. Funded by Roche (research agreement). From 01/2022 to 01/2024. PI: Martinez-Climent.

Title: Evaluation of BCMA-CD3 T cell bispecific, PD1-IL2v, and BCMA-co-stimulatory molecules in mouse models of multiple myeloma. Funded by Immunotherapy Centers of Research Excellence (imCORE-Roche). From 03/2023 to 06/2024. PI: Martinez-Climent.

Title: Biological study of high-risk disease features, therapeutic responses, and resistance mechanisms in genetically engineered MM models (BMS research agreement). From 06/2021 to 12/2023. PI: Martinez-Climent.

Title: Therapeutic inhibition of NSD2/MMSET in mouse models of multiple myeloma with t(4;14) (BMS research agreement). From 05/2023 to 11/2023. PI: Martinez-Climent.

Title: Targeting the immune microenvironment in extranodal lymphomas with MALT1 and BTK inhibitors (Janssen research agreement). From 01/2022 to 12/2023. PI: Martinez-Climent.

Title: Antitumor and mechanistic studies of BCMAxCD3 in humanized mouse models of MM (Regeneron research agreement). From 04/2022 to 12/2023. PI: Martinez-Climent.

Title: Harnessing glycobiology to direct immune responses in mouse models of multiple myeloma (Palleon research agreement). From 02/2022 to 06/2023. PI: Martinez-Climent.

Title: CAR T cell therapy in combination with the sphingosine-1 phosphatase inhibitor Mocravimod (Priothera research agreement). From 08/2022 to 6/2023. PI: Martinez-Climent.

Title: Mocravimod and BCMAxCD3 bi-specific moAb combination in experimental models of MM (Priothera research agreement). From 01/2023 to 09/2023. PI: Martinez-Climent.

Title: Understanding mechanisms of Mocravimod effectiveness and resistance in B-cell lymphoma (Priothera research agreement). From 06/2023 to 02/2024. PI: Martinez-Climent.

Title: Defining therapeutic targets across chromosome 1q genomic amplification in mouse and human MM (AstraZeneca research agreement). From 07/2023 to 1/2024. PI: Martinez-Climent.

Title: Novel CDK9 inhibitors to treat multiple myeloma in experimental models (AstraZeneca research agreement). From 05/2023 to 11/2023. PI: Martinez-Climent.

Title: Therapy combinations to enhance GPRC5D targeted therapies in mouse models of multiple myeloma with humanized targets (research agreement). To be signed. PI: Martinez-Climent.

Ongoing Collaborative Projects

Title: Beating multiple myeloma. Funded by Paula and Rodger Riney Foundation. From 06/2021 to 06/2023. PI: Jesus San Miguel, U Navarra (M-Climent JA, team member).

Title: Early detection and intervention in incurable hematological malignancies. Funded by Spanish AECC, Cancer Research UK, and AIRC (Accelerator Grant 2018). From 11/2018 -11/2023. PI: Jesus San Miguel (M-Climent JA, team member).

Title: Spanish Cancer Network CIBER ONCOLOGY. Funded by Spanish Ministry of Health. From 01/2017 to 01/2025. PI: Felipe Prosper (M-Climent JA, team member).