LINEA DE INVESTIGACIÓN:

Genómica funcional de enfermedades autoinmunes sistémicas

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RESUMEN LÍNEA DE INVESTIGACIÓN

My research work as an independent scientist has been focused on the genetic basis of autoimmune diseases, mainly those with a rheumatologic component such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and more recently systemic sclerosis (SSc) and giant cell arteritis (GCA). Our main objective is to identify genetic factors that influence susceptibility and/or severity to these pathologies, which on one hand will help us to know the pathophysiological mechanisms that underlie the development of these diseases, and on the other can allow us to develop new and more specific diagnostic tools and therapeutic targets.

We have participated in large-scale international consortia that have yielded a remarkable progress in the identification of risk genes for the aforementioned autoimmune diseases, and which results have been published in the best rheumatology journals: Ann Rheum Dis (#57) and Arthritis Rheum (#56). Noting our participation in large-scale genetic studies, GWAS o Immunochip, with international consortia that have yielded a remarkable progress in the identification of risk genes for autoimmune diseases, and which results were published in prestigious journals such as Nature (#1), Nat Genet (#8), Nat Commun (#3) or Am J Hum Genet (#8), Plos Genet (#4) or Hum Mol Genet (#8).

However, our most noteworthy scientific achievements come from the work on SSc genetics that have positioned our group as the international leader in the genetic/genomics of SSc, mainly since the publication of the first complete genome study - GWAS - in SSc *(Nat Genet*, 2010) that was co-directed by our group. Subsequently we performed fine-mapping studies in SSc together with several meta-GWAS in autoimmunity that have provide new insight in the knowledge of the genetic basis of systemic autoimmune disease. Very recently

we firmly established the association of 30 loci with SSc (*Nat Commun*, 2019) through a large GWAS study, that included around 30.000 individuals around the world, and identified specific loci for the different subtypes of the disease. . Furthermore, data mining analysis of SSc GWAS data allowed us a comprehensive analysis of the MHC region in SSc identifying differential HLA associations by clinical and serological subtypes with possible application as biomarkers of disease severity and progression (Acosta-Herrera et al, *Ann Rheum Dis*, 2021). In addition, based on GWAS data, we successfully implemented a genomic risk score (GRS) in SSc with potential application in the clinic (Bossini-Castillo et al., *Ann Rheum Dis*, 2021). Recently we described that copy number (CN) polymorphisms of complement C4 are implicated in the sex-biased vulnerability observed in SSc (Kerick et al, *NPJ Genome Med*, 2022).On the other hand, we have contributed to the better understanding of the pathogenesis of SSc by investigating the differential whole blood gene expression occurring in SSc patients through a genome-wide transcriptome analysis (*Beretta et al., Ann Rheum Dis, 2020*) and by the identification of the genetic variants that affect gene expression (eQTLs) in SSc (*Kerick et al., Arthritis Rheum, 2021*). In a recent study, we used promoter capture HiC (pCHi-C) in two of the most relevant cell types in SSc pathogenesis, CD4+ T cells and CD14+ monocytes from SSc patients and healthy controls, identifying new target genes and confirming others for SSc GWAS loci in these two cell types (Gonzalez-Serna et al, *Arthritis Rheum, 2023; 75:1007-1020*).

Our medium-term research is aimed at deciphering the functional consequences of genetic variants associated to SSC through the application of new genomic, epigenomic and transcriptomic techniques.

H-index: ISI/ Scopus=75; Google Scholar=92 / i10-index= 496
Total citations: Scopus= 27664; Google Scholar= 38286
Last five years Google Scholar: H-index= 55, i10-index=303, citations= 16624

PUBLICACIONES RECIENTES (15 destacadas, últimos cinco años)

1. Martínez-López J, Márquez A, Pegoraro F, et al., **Martín J*,** Vaglio A*. Genome-wide association study identifies the first germline genetic variant associated with Erdheim Chester disease. . ***Arthritis Rheumatol.*** 2023 Aug 10. doi: 10.1002/art.42673. Online ahead of print. shared senior authorship.
2. Villanueva-Martin G, Acosta-Herrera M, Carmona EG et al., **Martin J**. (12/12). Non-classical circulating monocytes expressing high levels of microsomal prostaglandin E2 synthase-1 tag an aberrant IFN-response in systemic sclerosis. ***J Autoimmun***. 2023 Aug 24;140:103097. doi: 10.1016/j.jaut.2023.103097. Online ahead of print
3. Ortiz-Fernández L, Carmona EG, Kerick M et al., **Martin J*,** Marquez A* .Identification of new risk loci shared across systemic vasculitides points towards potential target

genes for drug repurposing. ***Ann Rheum Dis.*** *2023* Jun;82(6):837-847.* shared senior authorship.

4. González-Serna D, Shi C, Kerick M, et al., **Martin J*,** Orozco G*. Functional genomics in primary T cells and monocytes identifies mechanisms by which genetic susceptibility loci influence systemic sclerosis risk. ***Arthritis Rheumatol.*** 2023; 75:1007-1020. * shared senior authorship.
5. Ortíz-Fernández L, **Martín J,** Alarcón-Riquelme ME. A Summary on the Genetics of Systemic Lupus Erythematosus, Rheumatoid Arthritis, Systemic Sclerosis, and Sjögren's Syndrome. ***Clin Rev Allergy Immunol.*** 2023 Jun;64(3):392-411.
6. Ishigaki K, Sakaue S, Terao C, et al., [**Martín J]** et al., Raychaudhuri S. (88/91) Multi-ancestry genome-wide association analyses identify novel genetic mechanisms in rheumatoid arthritis. ***Nat Genet.*** 2022 Nov;54(11):1640-1651,
7. Estupiñán-Moreno E, Ortiz-Fernández L, *et al.* **Martín J.** (13/13) Methylome and transcriptome profiling of giant cell arteritis monocytes reveals novel pathways involved in disease pathogenesis and molecular response to glucocorticoids. ***Ann Rheum Dis.*** 2022; 81:1290–1300.
8. Kerick M, Acosta-Herrera M, Simeón-Aznar et al., **Martin J.** Complement component C4 structural variation and quantitative traits contribute to sex-biased vulnerability in systemic sclerosis. ***NPJ Genom Med***. 2022 Oct 5;7(1):57. doi: 10.1038/s41525-022-00327-8.
9. Acosta-Herrera M, Kerick M, Lopéz-Isac E, et al., **Martin J** . Comprehensive analysis of the major histocompatibility complex in systemic sclerosis identifies differential HLA associations by clinical and serological subtypes. ***Ann Rheum Dis.*** 2021;80:1040–1047.
10. Bossini-Castillo L, Villanueva-Martin G, Kerick M et al., and, **Martin J.** Genomic Risk Score impact on susceptibility to systemic sclerosis. ***Ann Rheum Dis.*** 2021;80:118-127.
11. Casares-Marfil D, Strauss M, Bosch-Nicolau P et al., **Martín J***, Acosta-Herrera M*. A genome-wide association study identifies novel susceptibility loci in chronic Chagas cardiomyopathy. ***Clin Infect Dis*** 2021;73:672-679..**equal contribution*
12. Kerick M, González-Serna D, Carnero-Montoro E, et al., **Martin J.** eQTL analysis in systemic sclerosis identifies new candidate genes associated with multiple aspects of disease pathology. ***Arthritis Rheumatol.*** *2021;* 73:1288–1300.
13. Beretta L, Barturen G, Vigone B, et al., and **Martin J.**. Genome-wide whole blood transcriptome profiling in a large European cohort of systemic sclerosis patients. ***Ann Rheum Dis*** 2020;79:1218-1226.
14. López-Isac E, Acosta-Herrera M, Kerick M, et al., and **Martin J**. GWAS for systemic sclerosis identifies multiple risk loci and highlights fibrotic and vasculopathy pathways. ***Nat Commun*** 2019 Oct 31;10(1):4955.
15. Acosta-Herrera M, Kerick M, González-Serna D et al., and **Martin J.**Genome-wide meta-analysis reveals shared new loci in systemic seropositive rheumatic diseases. ***Ann Rheum Dis*** 2019 Mar;78(3):311-319.

PROYECTOS DE INVESTIGACIÓN (Últimos 5 años)

2023-2026. Proyecto financiado por el Ministerio de Ciencia e Innovación. Reference: **PID2022-13929208-I00.** Title: *Functional characterization of the genetic regions associated to systemic sclerosis (FunES)*. PI: Javier Martin. Duration: 1/09/2023/ - 31/08/2027. Financing received: 425,000 €.

2023.- Proyecto financiado por la Consejería de Universidad, Investigación e Innovación, Junta de Andalucía Plan Complementario de I+D+I en el área de Biotecnología aplicada a la salud, incluido en el Plan de Recuperación, Transformación y Resiliencia. **BIOT22_00018_4**. Título: *Implementación de tecnologías de Transcriptómica espacial de resolución celular con aplicación biosanitaria y desarrollo de métodos coordinados de análisis bioinformáticos estandarizados* . Investigador Principal: Javier Martín Ibáñez. Subvención: 265.006,58 euros

2022-2024. Red de Enfermedades Inflamatorias (REI) **RD21/0002/0039**. Programa (Red de Investigación Cooperativa Orientadas a Resultados en Salud (RICORS). Instituto de Salud Carlos III. Investigador Principal: Javier Martín Ibáñez. Subvención: 109.403,80 euros

2022-2023. Project funded by the Erheim Chester Global Alliance.Title: *Exploring the genetic landscape of Erdheim-Chester disease by integrating GWAS and -omic data.* PI: Francesco Pegoraro; co-PI: Javier Martín Financing: 50.000 dolars

2021-2023. Project funded by EFSA.European Food Safety Authority. U. Title: *Evaluating the impact on/by gastro-intestinal (GI) tract microbiomes (human and domestic animal) in assessments under EFSA's remit*. PI: Javier Moreno; Colaborador: Javier Martín Ibáñez: Financing to the group: 45.000 €

2020-2022- Proyecto financiado por la Consejería de Transformación Económica, Industria, Conocimiento y Universidades, Junta de Andalucía, Ref: **P18-RT-4442**. Título: *Estudio de las bases moleculares de la esclerosis sistémica mediante secuenciación del transcriptoma de linfocitos T y fibroblastos a nivel de una única célula*. Investigador Principal: Javier Martín Ibáñez. Subvención: 140.352,00 €

2020-2021. Project funded by Consejería de Economía, Conocimiento, Empresas y Universidad. Junta de Andalucía. **CV20-77708.** Title: *Análisis Multi-Ómico en Pacientes Con Covid-19 Como Predictor de la Evolución de la Enfermedad y Su Respuesta al Tratamiento.* Coordinator: Julio Gálvez. Collaborator: Javier Martín Ibáñez. Financing: 75.000€

2021-2024. Project funded by Fundació la Marató de TV3. **339/C/2020.** Title: *Design of an integrative patients stratification approach for the systemic sclerosis management.* Coordinator: Javier Narvaez. IP subproject: Javier Martín Ibáñez. Financing: 379.020,52 €

2019-2025. Innovative Medicines Initiative (IMI) Program of the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA). Title: Taxonomy, Treatment, Targets and Remission

Identification of the Molecular Mechanisms of non-response to Treatments, Relapses and Remission in Autoimmune, Inflammatory, and Allergic Conditions (**3TR**). Coordinadora: Marta Alarcón Riquleme. PI: Javier Martín Ibáñez. Financing received to the group: 285,000 €

2019-2022. Proyecto financiado por el Ministerio de Ciencia, Innovación y Universidades. **RTI2018101332-B-100***. Descifrando las Bases Genéticas de la Esclerosis Sistémica.* Investigador Principal: Javier Martín Ibáñez. Subvención total: 350.900 euros

2019.- Proyecto financiado por el Ministerio de Ciencia, Innovación y Universidades. Convocatoria de Adquisión de Equipamiento Científico-Técnico del año 2019. Subprograma Estatal de Infraestruutras de Investigación y Equipamiento Científico-Técnico. **EQC2019-005592-P.** Título: *Plataforma de Secuenciación de Célula Única de Alto Rendimiento.* Investigador Principal: Javier Martín Ibáñez. Subvención total: 227.509,04 euros

2019-2021. Project funded by the Histiocytosis UK Title: *Genome-wide and epigenome-wide association study in patients with Erdheim-Chester Disease*. PI: Augusto Vaglio; co-PI: Javier Martín. Financing: 50,000 GBP

2019-2022. Project reference: H2020- Marie Skłodowska-Curie Actions- Innovative Training Networks- European training networks (MSCA- ITN-ETN) Title: Health Data Linkage for Clinical Benefit (***HELICAL***). Funding entity: European Union. Coordiantor: Mark Little. Principal investigator: Javier Martín Ibáñez. Financing received to the group: 265,000 €

2018-2021. Proyecto financiado por FOREUM Foundation for Research in Rheumatology. Título: ***START****: Molecular stratification of patients with giant cell arteritis to tailor glucocorticoid therapy.* Coordinador: Nicolo Pipitone. Investigador Principal: Javier Martín Ibáñez.Subvención total: 600.000 € / Subvención al grupo: 65.000 €

2017-2021. Proyecto financiado por CYTED: Programa Iberoamericano de Ciencia y Tecnología para el Desarrollo. Título: Red Iberoamericana de Medicina Genómica en la Enfermedad de Chagas - **RIMGECH**- Coordinador: Javier Martín Ibáñez. Subvención: 150.000 euros

2016-2018. Proyecto financiado por el Ministerio de Economía y Competitividad. **SAF2015-66761-P.** Título: *Bases moleculares de la esclerosis sistémica: integrando genómica y transcriptómica.* Investigador Principal: Javier Martín Ibáñez. Subvención total: 296.450 euros

2017-2021. Red de Investigación en Inflamación y Enfermedades Reumáticas (RIER). **RD16/0012/0013**. Programa RETIC (Redes Temáticas de Investigación Cooperativa). Instituto de Salud Carlos III. Investigador Principal: Javier Martín Ibáñez. Subvención: 249.744 euros