BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Alarcón-Riquelme, Marta Eugenia	Head of Medical Genomics, Center for Genomics and Oncological Research (GENYO), Spain
eRA COMMONS USER NAME (credential, e.g., agency login) MALARCON	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
LaSalle University (UNAM) Mexico	MD	1980-1985	Medicine
Stockholm University, Stockholm, Sweden	PhD	1987-1994	Immunology

A. Personal Statement

My background in Medicine, Immunology and Genetics make a unique combination and provide me with the tools I need to successfully carry out this project. For over 20 years of my research career I have focused in the identification of the genetic basis of SLE as a first building block towards understanding how such genes lead to cellular abnormalities that eventually lead to clinical disease. In this context, animal models provide possibilities where human studies have limitations. A main goal of my research is to understand the mechanisms behind disease pathogenesis, identify new biomarkers for disease, develop new therapies and find new targets, understand the mechanisms of non-response to therapies, and define the heterogeneity of autoimmune diseases. I am totally committed to the work for lupus and other autoimmune diseases, and I believe that only through careful longitudinal analysis of the patients will we be able to understand this disease. I am focusing importantly on systems biology approaches, -omics data integration and clustering and bioinformatics approaches to the understanding of these diseases.

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B. Positions and Honors

Positions

1985-1986 Medical Internship, Universidad LaSalle
1986-1987 Research Fellow in Immunology, Instituto Nacional de la Nutrición, Mexico City, Mexico
1988-1994 PhD in Immunology, Stockholms University
1994-1996 Postdoctoral Research Fellow, Uppsala University
1996-2000 Assistant Professor in Medical Genetics, Uppsala University (award)
2001-2009 Associate Professor in Medical Genetics (Docent), Uppsala University
2004- 2009 Royal Swedish Academy of Sciences Research Fellow (award)
2008- 2009 Esther Z. Greenberg Scholar, Oklahoma Medical Research Foundation
2009-2011 Professor in Genetic Epidemiology of Inflammatory Diseases, Uppsala University
2009-2015 Associate Member, Oklahoma Medical Research Foundation
2011- Head of Medical Genomics, Center for Genomics and Oncological Research (GENYO) Granada, Spain
2014-2019 Visiting Professor (20%), Department of Environmental Medicine, Karolinska Institute, Sweden

C. Contribution to Science

1. My early publications have dealt with the genetics of lupus, primarily focusing on the identification of genes for lupus. The first studies involved multicase families, particularly extended pedigrees that we obtained from Iceland and Sweden. This led us to identify the gene *PDCD1* as involved in lupus susceptibility. *PDCD1* (PD-1) is a target for therapy. The *PDCD1* work was one of the first to analyze functional variants and their influence in the function of the gene. After this, other studies followed, including the analyses of several genes.

a. Prokunina L, Castillejo-Lopez C, Oberg F, Gunnarsson I, Berg L, Magnusson V, Brookes AJ, Tentler D, Kristjansdottir H, Grondal G, Bolstad AI, Svenungsson E, Lundberg I, Sturfelt G, Jonssen A,

Truedsson L, Lima G, Alcocer-Varela J, Jonsson R, Gyllensten UB, Harley JB, Alarcon-Segovia D, Steinsson K, **Alarcon-Riquelme ME**. A regulatory polymorphism in PDCD1 is associated with susceptibility to systemic lupus erythematosus in humans. *Nat Genet*. 2002 Dec; 32(4):666-669.

b. **Alarcón-Riquelme, M.E**. "A Runx Trio with a Taste for Autoimmunity." *Nat Genet*, 35 (4): 299-300, 2003.

c. Graham, R.R.*, Kozyrev, S.V.*, Baechler, E.C., Reddy, MVP, Plenge, R.M., Bauer, J.W., Ortmann, W.A., Koeuth, T., González-Escribano, M.F., Argentine and Spanish Collaborative Groups, Pons-Estel, B., Petri, M., Daly, M., Gregersen, P.K., Martin, J., Altshuler, D., Behrens, T.W., and **Alarcón-Riquelme, M.E**. A Common Haplotype of Interferon Regulatory Factor 5 (IRF-5) Regulates Splicing and Expression, and is Associated with Increased Risk of systemic lupus erythematosus. *Nat Genet* 38(5): 550-555, 2006.

d. Kozyrev, S.V., Lewén, S., Reddy, M.V.P., Pons-Estel, B.A., Argentine Collaborative Group, Witte, T., The German Collaborative Group, Junker, P., Laustrup, H., Gutiérrez, C., Suárez, A., González-Escribano, M.F., Martín, J., The Spanish Collaborative Group and **Alarcón-Riquelme, M.E**. Structural insertion/deletion Variation in IRF5 is Associated with a Risk Haplotype and Defines the Precise IRF5 Isoforms Expressed in systemic lupus erythematosus. *Arthritis Rheum* 56(4): 1234-41, 2007

2. With the advent of genome-wide association arrays and the creation of the SLEGEN consortium, new possibilities opened for the study of the genetics of lupus and the identification of genes for the disease. As a founder member of SLEGEN, I participated in the GWAS that identified several new genes, but also had an independent study that allowed my identification of BANK1, and participated in the identification of ITGAM. These papers were all published in the same issue of *Nat Genet*. In collaboration with Tim Vyse and John Rioux we embarked in a larger GWAS in Europeans that resulted in a top publication in *Nat Genet* and we have done the same publishing the first GWAS in the Hispanic admixed population focusing on the Native American ancestry. More recently our transancestral immunochip study was published. Lately, I have focused on rare variants: through exome sequencing of families with multiple cases of lupus, and using very stringent imputation approaches and aggregate analyses to identify candidate genes.

a. International Consortium for Systemic Lupus Erythematosus Genetics (SLEGEN), Harley JB, **Alarcón Riquelme ME**, Criswell LA, Jacob CO, Kimberly RP, Moser KL, Tsao BP, Vyse TJ, Langefeld CD, Nath SK, Guthridge JM, Cobb BL, Mirel DB, Marion MC, Williams AH, Divers J, Wang W, Frank SG, Namjou B, Gabriel SB, Lee AT, Gregersen PK, Behrens TW, Taylor KE, Fernando M, Zidovetzki R, Gaffney PM, Edberg JC, Rioux JD, Ojwang JO, James JA, Merrill JT, Gilkeson GS, Seldin MF, Yin H, Baechler EC, Li QZ, Wakeland EK, Bruner GR, Kaufman KM, Kelly JA. Genome-wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in ITGAM, PXK, KIAA1542 and other loci. *Nat Genet*. 2008 Feb; 40(2):204-210. PMCID:PMC3712260

b. Kozyrev SV, Abelson AK, Wojcik J, Zaghlool A, Linga Reddy MV, Sanchez E, Gunnarsson I, Svenungsson E, Sturfelt G, Jonsen A, Truedsson L, Pons-Estel BA, Witte T, D'Alfonso S, Barizzone N, Danieli MG, Gutierrez C, Suarez A, Junker P, Laustrup H, Gonzalez-Escribano MF, Martin J, Abderrahim H, **Alarcon-Riquelme ME.** Functional variants in the B-cell gene BANK1 are associated with systemic lupus erythematosus. *Nat Genet*. 2008 Feb; 40(2):211-216

c. Bentham, J., Morris, D.L., Cunninghame-Graham, D.S., Pinder, C.L., Tombleson, P., Behrens, T.W., Criswell, L.A., Gaffney, P., Martin, J., Fairfax, B., Knight, J., Syvannen, AC., Ronnblom, L., Graham, R.R., Wither, J.E., Rioux, J.D., **Alarcón-Riquelme, M.E**., and Vyse, T.J. Genetic Association Analyses Implicate aberrant gene regulation of the innate and adaptive immunity genes in the pathogenesis of SLE implicated by genetics. *Nat Genet* 47: 1457–1464, 2015.

d. **Alarcón-Riquelme,M.E**.*, Ziegler,J.T., Molineros,J., Howard, T.D., Moreno-Estrada, A., Sánchez-Rodríguez, E., Ainsworth, H.C., Ortiz-Tello, P., Comeau, M.E., Rasmussen, A., Kelly, J.A., Adler, A., Acevedo-Vázquez, E., Cucho, J.M., García-De la Torre, I., Cardiel, M.H., Miranda, P., Catoggio, L., Maradiaga-Ceceña, M., Gaffney, P., Vyse, T., Criswell, L.A., Tsao, B., Sivils, K.M., James, J.A., Kimberly, R., Kaufman, K., Harley, J.B., Esquivel-Valerio, J., Moctezuma, J.F., García, M.A., Berbotto, G., Babini, A., Scherbarth, H., Toloza, S., Baca, V., Nath, S.K., Orozco, L., Tusié-Luna, T., Zidovetzki,

R., Pons-Estel, B.A., Langefeld, C.D., and Jacob, C.O. GWAS in an Amerindian ancestry population reveals novel systemic lupus erythematosus risk loci and the role of European admixture. *Arthritis Rheumatol* 68(4): 932-43, 2016. *corresponding author.

e. Langefeld, C.D., et al. Transancestral mapping and genetic load in systemic lupus erythematosus. *Nat Comm*. 8:16021/DOI: 10.1038/ncomms16021

f. Delgado-Vega, A.M., Martínez-Bueno, M., Oparina, N.Y., López Herráez, D., Kristjansdottir, H., Steinsson, K., Kozyrev, S.V., and **Alarcón-Riquelme, M.E**. Whole Exome Sequencing of Patients from Icelandic Multicase Families Identifies Functionally Related Genes Enriched for Rare Variants in Systemic Lupus Erythematosus *Sci Rep* 8(1):8775, 2018.

g. Martínez-Bueno, M. and **Alarcón-Riquelme, M.E**. Exploring Impact of Rare Variation in Systemic Lupus Erythematosus by a Stringent Genome Wide Imputation Approach. *Front Immunol* 10:258, 2019.

3. From here, my work has derived towards the use of genomics methods for the reclassification of systemic autoimmune diseases and systems biology approaches with the idea that autoimmune diseases are a clinical constellation of the same or nearly similar disease processes. Our most recent publications point towards those approaches by creating software and performing analyses of gene expression data to identify drug targets and learning systems medicine methods for clustering of patients. Our first work focuses on lupus, but is planned to extend to other related autoimmune diseases. As PI of the PRECISESADS project, a high degree of coordination has been necessary. In this role, I have acquired enormous experience on the organization of large projects and recruitment of patients, most recent ethical rules. I have also acquired learning on the subject of machine learning bioinformatic methods, clustering and classification of the autoimmune diseases, and QTL analyses across autoimmune diseases.

a. Muchmore, B. and **Alarcón-Riquelme, M.E.** CymeR: cytometry analysis using KNIME, Docker and R. Bioinformatics 33(5): 776-778**,** 2017.

b. Toro, D., Carmona, P., and **Alarcón-Riquelme, M.E**. Support for PI3K and mTOR Inhibitors as treatment of SLE using *In Silico* Drug Repurposing Analysis *Arthritis Res Ther* 19(1):54, 2017.

c. Toro, D., Martorell-Marugán, J., Goldman, D., Petri, M., Carmona-Sáez, P., and **Alarcón-Riquelme, M.E**. Longitudinal Stratification of Gene Expression Reveals Three SLE Groups of Disease Activity Progression *Arthritis Rheum* 70(12):2025-2035, 2018.

d. Barturen, G., Beretta, L., Cervera, R., Van Vollenhoven, R., and **Alarcón-Riquelme, M.E**. Moving Towards a Molecular Taxonomy of Autoimmune Rheumatic Diseases. *Nat Rev Rheumatol* 14(2):75-93, 2018. (Peer-reviewed)

e. Carnero-Montoro, E., Barturen, G., Povedano, E., Kerick, M., Martínez-Bueno, M., PRECISESADS Clinical Consortium, Ballestar, E., Martín, J., Teruel, M., and **Alarcón-Riquelme, M.E.** Epigenome-wide Study Reveals Key Differences between MCTD and related Systemic Autoimmune Diseases. *Front Immunol*. doi.org/10.3389/fimmu.2019.01880.

4. The second path relates to the use of animal models for testing potential new drug targets, new genes and specific hypotheses. We have now obtained extensive experience in such models and are defining those that may be more effective to test given systems. We have focused on TLR7 due to the importance of this pathway in autoimmunity and in the genes we have studied such as BANK1. We have also used biochemistry to understand the function of BANK1.

a. Wu, Y.Y., Kumar, R., Haque, S.M., Castillejo-López, C., and **Alarcón-Riquelme, M.E.** BANK1 Controls CpG-induced IL-6 Secretion Via a p38 and MNK1/2- eIF4E Translation Initiation Pathway. *J Immunol* 191(12): 6110-6116, 2013. PMCID: PMC3858538

b. Wu, Y.Y., Kumar, R., Iida, R., Bagavant, H., and **Alarcón-Riquelme, M.E**. BANK1 Regulates IgG Production in a Lupus Model by Controlling STAT1 Activation. *PLoS One*. 11(5):e0156302, 2016.

c. Georg, I., Díaz-Barreiro, A., Morell-Hita, M., Pey, A.L., and **Alarcón-Riquelme, M.E**. BANK1 Interacts with TRAF6 and MYD88 in Innate Immune Signaling in B Cells. *Cell Mol Immunol* (*In Press*). doi: 10.1038/s41423-019-0254-9

Current funding

SAF2016-78631-P Alarcón (PI) 01/01/2017 - 12/31/2020
Ministerio de Economía y Competitividad (Spain) (20%)
Plan Estatal de Fomento de la Investigación Científica y Técnica de Excelencia 2016
Defining the role of BANK1 in TLR signaling and autoimmunity
No overlap, this has financed the paper by Georg, et al, which deals with the biochemical interactions of BANK1 and MYD88 and TRAF6. Right now it is paying the salary of Maria Morell to finalize the Pateamine A work as treatment for SLE (Manuscript under preparation).

ISCIII CD18/00149 Alarcón (PI) 01/01/2018 - 31/12/2021
Sara Borrell support for postdoc Guillermo Barturen.

European Commission GAP-806975 Mariette (PI) 01/01/2019 - 31/12/2025
NECESSITY: New Clinical Endpoints in Primary Sjogren´s Syndrome: An Interventional Trial Based on Stratifying Patients.

European Commission GAP-831434-2
IMI2-RIA - 14th Call Alarcón (PI) 01/09/2019 - 31/08/2026
3TR: Treatment, Targets, Therapies and Remission: *Identification of the Molecular Mechanisms of non-response to Treatments, Relapses and Remission in Autoimmune, Inflammatory, and Allergic Conditions.*

European Commission GAP-838548 Alarcón (PI) 16/09/2019 - 15/09/2022
H2020-MSCA-IF-2018
RoBE: Study of the Role of BANK1 in Antibody Production and Antibody-Independent Functions of B Cells in SLE. Support for a Marie Sklodowska Curie research fellow, Georgina Galicia, for 3 years with Dr Alarcón.

Consejería de Salud y Familias
Programa Nicolás Monardes Marañón (PI) 01/05/2020 - 30/04/2024
Program to support the salary of Concepción Marañón
Searching for biomarkers for the precise diagnosis of systemic autoimmune diseases.

Consejería de Salud
PE-0297-2019 Alarcon (PI) 01/01/2020 - 31/12/2023
El papel de genes de susceptibilidad al Lupus Eritematoso Sistémico en la Función molecular de una subpoblación Pro-inflamatoria de Linfocitos B.
This grant proposes the study of pro-inflammatory B cells in patients with SLE having the risk alleles of BANK1

Pending

Junta de Andalucía
PAIDI-Excelencia Alarcón (PI)
SIDT1 as Key for the Induction of Type I IFN and Development of Autoimmunity.

Inactive

GA-115565 Alarcón (PI) 02/01/2014-01/31/2019
IMI-JU (European Union) (30%)
PRECISESADS: Molecular Reclassification to Find Clinically Useful Biomarkers for Systemic Autoimmune Diseases A joint undertaking between Academia and pharmaceutical companies to identify clusters of patients independently of their clinical diagnoses using the latest techniques for genomics, transcriptomics, epigenomics, flow cytometry, metabolomics and serology (cytokines and autoantibodies). A centralized resource was created with samples from 2000 patients and 600 healthy controls that includes electronically monitored clinical information, cells, DNA, RNA, urine, plasma and serum and all with OMICS data.