

Candidate: **Francisco Sánchez-Madrid**

## PERSONAL INFORMATION

First and Family name	Francisco Sánchez Madrid		
ID number	30409868G	Age	64
Researcher numbers	Researcher ID	M-7889-2016	
	Orcid code	0000-0001-5303-0762	

### A.1. Current position

Name of University/Institution	Hospital Universitario de la Princesa. Universidad Autónoma de Madrid.		
Department	Instituto Investigación Sanitaria Princesa. Hospital de la Princesa.		
Address and Country	Diego de León, nº 62 – 28006 Madrid		
Phone number	+34915202307	E-mail	<a href="mailto:fsmadrid@salud.madrid.org">fsmadrid@salud.madrid.org</a>
Current position	Professor Immunology	From	March 1990
Espec. cód. UNESCO	2412		
Palabras clave	Immunology/Inflammation/Activation receptors /Immunological Synapse/Mechanisms of Intercellular Communication		

### A.2. Education

PhD	University	Year
<b>Licenciate Biology</b>	Universidad de Sevilla	1976
<b>Ph. D. Biochemistry</b>	Universidad Autónoma de Madrid	1980

Who Am I: I am full Professor of Immunology University Autónoma of Madrid. Over the last 10 years, I have directed the Immunology Department, and served as Scientific Director of the Health Research Institute of University Hospital Princesa in Madrid.

Major achievements: During my scientific career to date I have made leading contributions to knowledge about the mechanisms of **leukocyte adhesion, polarity, migration and activation**. This contribution has pioneered the identification and **characterization of the first families of leukocyte adhesion molecules**, their physiological **role in the control of migration and cellular traffic**, and their **immense relevance to chronic inflammatory pathologies**. These contributions have formed the **basis for novel anti-adhesion therapies that are being used** to treat diseases such as **multiple sclerosis, psoriasis and Crohn's** (granulomatous colitis). My main achievements are the following: i) Identification, biochemical characterization and functional regulation of the integrin VLA-4 ( $\alpha 4\beta 1$ ) and its implications in leucocyte interactions, mainly in T cell migration and infiltration in inflammatory diseases; ii) Mechanisms of chemokine-induced leukocyte polarity: Identification of the molecular components implicated and identification of the function of two subcellular compartments: "leading edge" and "trailing edge" or uropod; iii) Dynamic interactions of adhesion molecules (ICAMs, tetraspanin/integrin complexes) with cytoskeleton components that regulate leucocyte-endothelium interactions and early stages of the T cell-antigen presenting cell (APC) interaction during the immune synapse; iv) Our group has identified and characterized the leucocyte activation antigen CD69 and its regulation mechanisms. We generated the first CD69 knock-out mice and described the CD69 *in vivo* function as negative immuno-modulator in autoimmune diseases mainly by regulating Th17 expansion. Galectin-1 and oxLDL have been identified as CD69 cellular ligands. More recently, CD69 has been characterized as a new metabolic gatekeeper in inflammation through the control of amino-acid transporter CD98/LAT1. v) In the most recent years, my research group has made key contributions to understanding the functional relevance and mechanisms of genetic transfer of miRNA from T cell to APC during the immune synapse. We have also addressed the composition and sorting into exosomes of proteins and miRNA and their role in cell-cell communication in the immune response.

Our laboratory research on migration and activation receptors of human leukocytes is documented in more than **440 publications** in international journals, **including many recent articles in highly prestigious journals**; for example several articles in Nature journals, in Immunity, and many others in journals such as J. Clin. Invest. J. Exp. Med., J. Cell Biol, EMBO J, NEJM. This track record has given me ample experience in the **creation of a high-quality research team, collaboration in translational biomedical research programmes and training of researchers**. As many as 25 alumni from my group are now university teachers and research leaders in national and international centers, including **three ERC Grant awardees**. In parallel with my research activity, I have also carried out an intense **teaching activity since 1990** in the Faculties of Medicine and Biological Sciences at the *Universidad Autónoma de Madrid*. As part of this activity, **I have supervised 35 doctoral theses** and presented more than 200 lectures and seminars at diverse research centres and universities in Spain and abroad. **I have been invited to give Plenary and Keynote Lectures** in numerous international scientific Workshops, Meetings and Congresses (Keystone Meetings, Gordon Conferences, FASEB and EFIS Meetings, etc).

## **B. Positions and Honors**

### **Positions and Employment**

2009-to date Scientific Director, Instituto de Investigación Sanitaria Princesa (IIS-IP). UAM. Madrid.  
2009-to date Head of Immunology Service, Service of Immunology. Hospital de la Princesa.  
1989-to date Full Professor Immunology. Universidad Autónoma de Madrid (UAM), Madrid  
1992-2009 Associate Professor Immunology, Service of Immunology.  
1984-1991 Assistant Professor Immunology, Service of Immunology. Hospital de la Princesa. Madrid.  
1980-1983 Research Fellow, Harvard Medical School, Harvard University, Boston, MA.  
1977-1980 Ph. D. Student, Centro de Biología Molecular (CSIC-UAM), Madrid.

### **Other Experience and Professional Memberships**

Current Member of the Scientific Advisory Board of the following scientific institutions:

- Health Research Institute IDIBAPS-Hospital Clínico, Barcelona, Spain
- Cancer Research Center , Salamanca, Spain
- Institute CABIMED-CSIC-Universidad de Sevilla, Spain
- Health Research Institute Maimónides. Hospital Reina Sofía-Universidad de Córdoba, Spain
- Dpt of Health and Life Sciences-Universidad Pompeu Fabra-Barcelona.

2007-2010. Member, Evaluation Panel LS6 of European Research Council for Young Investigator Grants.  
2001-2005 Coordinator of the National Biomedicine Plan (Plan Nacional de Biomedicina).  
1998-2000 President, Immunology Commission of the Spanish Health Research Fund (FIS)

**Member of Editorial Boards:** Eur J Immunol; Front Immunol;

### **Honors and Awards**

2018 Award Biomedicine Career “Constantes y Vitales”. Atresmedia/ La Sexta.  
2018 Recipient of a Health Research Grant from La Caixa  
2012 Recipient of an ERC Advance Grant  
2009 Science Prize from the Community of Madrid “Miguel Catalán”.  
2008 National Society of Neurology. “Multiple Sclerosis” award.  
2005 Basic Research award from Foundation Pfizer  
2005 Lilly Foundation. Pre-Clinical Research award.

2004	“Severo Ochoa” award from Foundation Ferrer
2003	Award, Francisco Cobos Foundation-CSIC.
2001	Award, CEOE Biomedicine
2001	Award, Life Sciences Foundation.
2002	Grant for Basic Research from Juan March Foundation.
1996	Elected member of EMBO.

### C. Contribution to Science

During my scientific career, I have defined several key lines of research in human immunology through leading contributions regarding the molecular and cellular mechanisms of **leukocyte adhesion, polarity, migration and activation**, and their **crucial relevance in chronic inflammatory pathologies**, has led to **basic and translational breakthroughs**. My publications have to date received a total of **30.700 citations** (ISI-WOK), and my **H Factor is 88 (105 in google scholar)**.

*The most important achievements during my scientific career are:*

**- Novel modes of cell-to-cell communication and transfer of genetic information through the immune synapse (2011- ).** Our group has recently addressed novel forms of **cell-to-cell communication in the immune system, including the transfer of genetic information through antigen-dependent contacts**. A major breakthrough was the demonstration that **genetic information is transferred between T cells and antigen-presenting cells contained in exosomes** harbouring specific repertoires of proteins, miRNAs and Mitochondrial DNA. **For this activity, I was awarded an Advanced ERC Grant in 2012, and the Health Research Grant form La Caixa (2019-2021).**

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| 1. Mittelbrunn et al., 2011 Nature Commun          | 6. Martin-Cófreces et al., 2014. Trends Cell Biol. |
| 2. Baixauli et al., 2011 EMBO J.                   | 7. Barreiro et al., 2016 Elife.                    |
| 3. Martin-Cófreces et al., 2012 EMBO J.            | 8. Blas-Rus et al., 2016 Nature Commun             |
| 4. Mittelbrunn et al., 2012 Nat Rev Mol Cell Biol. | 9. Villarroya-Beltrí et al., 2016 Nature Commun.   |
| 5. Villarroya-Beltrí et al., 2013 Nature Commun.   | 10. Cruz-Adalia et al., 2017. Nature Commun        |
|  | 11. Torralba et al., 2018. Nature Commun.          |

**-T-lymphocyte activation receptors and the regulation of the inflammatory response (1988-Presently).** A long-term research line pioneered by my group was the identification CD69 as the earliest activation antigen expressed by lymphocytes. During last 30 years, we characterized the functional role of CD69, cloned and localized the gene and characterized the molecular regulation of its expression. We generated genetically-modified mice deficient for CD69, which we used to **demonstrate that CD69 is a physiological negative regulator of the inflammatory immune response** through the control of differentiation and expansion of the pro-inflammatory Th17 cells. Recently, we have identified CD69 physiologic ligands, and discovered the regulatory mechanism by which CD69 governs the immune inflammatory response, acting as a metabolic gatekeeper.

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| 1. Cebrián et al., 1988 J. Exp. Med.       | 8. Martin et al 2011 Science Signaling.       |
| 2. López-Cabrera et al., 1993 J. Exp. Med. | 9. González-Amaro et al.,2013 Trends Mol Med. |
| 3. Esplugues et al., 2003, J. Exp. Med.    | 10. de la Fuente et al., 2014, Mol Cell Biol. |
| 4. Sancho et al., 2003, J Clin Invest.     | 11. Cibrián et al., 2016 Nat Immunol.         |
| 5. Sancho et al., 2005, Trends Immunol.    | 12. Tsilingiri et al., 2019. Circulation      |
| 6. Martin et al., 2010 Mol Cell Biol.      |   |
| 7. Cruz-Adalia et al., 2010, Circulation.  |   |

**- Protein microdomains that facilitate cell-to-cell communication (2004-2010).** These studies include breakthroughs in understanding how cells generate finely regulated molecular subdomains that facilitate cell-to-cell communication in connection to the cellular cytoskeleton.

1. Vicente-Manzanares *et al.*, 2004 *Nat Rev Immunol.*
2. Mittelbrunn *et al.*, 2004. *Proc Natl Acad Sci.*
3. Barreiro *et al.*, 2005. *Blood.*
4. Ibiza *et al.*, 2006 *Immunity.*
5. Martín-Cófreces *et al.*, 2008 *J Cell Biol.*
6. Barreiro *et al.*, 2008 *J Cell Biol.*
7. Yáñez-Mo *et al.*, 2008. *Blood.*
8. Yáñez-Mo *et al.*, 2009 *Trends Cell Biol.*
9. Sánchez-Madrid and Serrador. 2009 *Nat Rev Mol Cell Biol.*

**-Molecular mechanisms of leukocyte migration, orientation and cell polarity in the inflammatory immune response (1995-2003).** Our group made pivotal contributions to unravel the mechanisms underlying leukocyte orientation during directional migration, which is a cornerstone of inflammation, as well as the process of antigenic presentation established between T cells and antigen presenting cells. **Our contributions have led to a new model of molecular polarity in leukocytes and endothelium that guides migration and facilitates cell-to-cell communication during antigenic and inflammatory contacts.** These discoveries have been reported in many studies published in leading journals in the fields of Immunology and Cell and Molecular Biology.

1. del Pozo *et al.*, 1995 *J Cell Biol*
2. del Pozo *et al.*, 1997 *J Cell Biol*
3. Nieto *et al.*, 1997 *J Exp Med*
4. Serrador *et al.*, 1997 *J Cell Biol*
5. Yáñez-Mó *et al.*, 1998 *J Cell Biol*
6. Sánchez-Madrid *et al.*, 1999 *EMBO J*
7. Sancho *et al.*, 2000 *J Cell Biol*
8. Montoya *et al.*, 2002 *Nature Immunol.*
9. Barreiro *et al.*, 2002 *J. Cell Biol*
10. Urzainqui *et al.*, 2002 *Immunity*
11. Gil *et al.*, 2002 *Cell*
12. Serrador *et al.*, 2004 *Immunity*

**-Leukocyte adhesion and its relevance in inflammatory diseases (1985-1994).** In 1985, I began a career as an independent researcher in the *Servicio de Inmunología* at the *Hospital Universitario de la Princesa* in Madrid. My research comprised seminal studies characterizing the molecular mechanisms that regulate leukocyte adhesion, polarity and activation. Some examples include the characterization of several receptors essential for leukocyte migration and trafficking, for example the integrin VLA-4 and the receptor ICAM-3. These studies, both *in vitro* and *in vivo*, using models of inflammatory diseases are the conceptual foundation of novel anti-adhesion therapies for the treatment of human chronic inflammatory diseases such as multiple sclerosis, and Crohn's disease.

1. Campanero *et al.*, 1990, *J. Cell Biol.*
2. Campanero *et al.*, 1993, *J. Cell Biol.*
3. Campanero *et al.*, 1994, *J Cell Biol.*
4. Arroyo *et al.*, 1992, *J. Cell Biol.*
5. Arroyo *et al.*, 1994 *J Cell Biol.*
6. Yednock *et al.*, 1992 *Nature.*
7. Laffón *et al.*, 1992 *J. Clin. Invest.*
8. Postigo *et al.*, 1993 *J. Clin. Invest.*
9. Gonzalez-Amaro *et al.*, 1994 *J Exp. Med.*

**-Identification of the first families of leukocyte adhesion molecules (1980-1983).** In 1980, I moved to the Pathology Department at Harvard Medical School, where I worked under the direction of Drs. B. Benacerraf (Nobel Laureate in Medicine, 1980) and T. A. Springer on the molecular mechanisms of the cytotoxic T lymphocytes and the cell receptors implicated in this phenomenon. The most important discoveries during this period were the identification and functional characterization of the first family of human leukocyte adhesion receptors, LFA-1/Mac-1, and of the family of beta2 integrins, which are crucial mediators of inflammatory processes.

1. Sánchez-Madrid *et al.*, 1982, *PNAS.*

2. *Sánchez-Madrid et al., 1983a, J. Exp. Med.*
3. *Sánchez-Madrid et al., 1983b, J. Exp. Med.*

**-Collaboration in translational biomedical research programmes in mechanisms of Chronic Inflammatory Diseases. I have also been a staunch proponent of the interaction between basic and translational research.** The translational activity involved specialists in rheumatology, nephrology, gastroenterology, dermatology and pathological anatomy working on various clinical aspects of inflammatory processes. These collaborations have borne fruit in numerous publications in prestigious clinical journals. Some key examples include studies published in journals of **maximum impact on the pathophysiological mechanisms of inflammatory diseases.**

1. *Garcia-Monzon et al., 1990 Gastroenterology*
2. *Garcia-Monzon et al., 1992 Gastroenterology*
3. *Acevedo et al., 1993 Am J Pathol.*
4. *Díaz-González et al., 1995 J Clin Invest*
5. *Garcia-Monzon et al., 1995 Gastroenterology*
6. *Yáñez-Mó et al., 2003 New Engl. J Med.*
7. *de la Fuente et al., 2012 J. Pathol.*

**D. Granted Patents:** The candidate has participated in the invention of **16 Patents and Licenses;** some of these are being exploited by Biogen, Pharma-Mar, Albor Biologics Ltd, Immunotech, Pharmingen, Coulter and Caltag through contracts and licensing agreements with the Technology Transfer Office of the Universidad Autónoma Madrid.

**(Selected patents within the last five years)**

- Electrochemical biosensors for diagnosing acute myocarditis. P Martín, R Blanco Domínguez, R Sánchez Díaz, **F Sánchez Madrid**. EPI17382324. Entidad titular: Canaan R&D and CNIC
- CD81 as therapeutic target for control of intracellular levels of DNTPs. M Yáñez-Mó, H Suárez Montero, **F Sánchez Madrid**, V Rocha Perugini. N: P201700345. Institution: UAM
- Transinfected lymphocytes for anti-tumor therapy. E Veiga Chacón, A Cruz Adalia, G Ramírez Santiago, B Alarcón **F Sánchez-Madrid**. PCT/ES2016/070597WO2017/025657. Institutions.: CSIC and UAM
- Antibody Drug Conjugates. M Garranzo García-Ibarrola, A Francesch Solloso, JM Domínguez Correa, MJ Muñoz Alonso, **F Sánchez Madrid**, JM Zapata, AG Arroyo, MA Ursa, C Cuevas Marchante. PCT/EP2014/061392. Company PharmaMar. European Patent Office. The Hague.
- Therapeutic application of inhibitory agents for CD44 against human acute lymphoblastic leukemia (ALL) humana. M Luisa Toribio, M García Peydró, **F Sánchez Madrid**. (Patent ES201231274): PCT/ES2013/070576. 2013

**E. Previous Grants**

<i>Project Title</i>	<i>Funding source</i>	<i>Amount (Euros)</i>	<i>Period</i>	<i>Role of the PI</i>	<sup>1</sup>
GENTRIS: "Mechanisms of MTOC guidance and Genetic Transfer at the Immune Synapse: novel modes of Immunomodulation."	ERC-2011-ADG_20110310  ERC	2,049,000€	2012-2017	PI	

Immunoregulatory molecules in inflammation: Function of exosomes in cell-to-cell communication	SAF2014-55579-R MINECO	550,000€	2015-2017	PI	
Immunoregulatory molecules and miRNAs as targets in coronary heart disease and acute coronary syndrome.	La Marató 2015 Fundació La Marató	150,000 €	2016-2018	PI	
Identification of new anti-tumoral agents against cancer target : topoisomerase and regulatory molecules of the immune response	IMMUNOTOP RTC-2016-4611-1 MINECO	310,000 €	2016-2019	PI	

### On-going Grants

<i>Project Title</i>	<i>Funding source</i>	<i>Amount (Euros)</i>	<i>Period</i>	<i>Role of the PI</i>	
Immunoregulatory mechanisms of cell-cell communication: Synaptic Contacts Induce an Alert State in Immune Cells”.	Spain Ministry of Science and Universities	441,000	2018 - 2020	PI	
Readying immune cells prior to disease-inducing encounters :	Health Foundation “la Caixa”	500.000	2019-2021	PI	

### **F. Mentoring the Early Careers of Excellent Researchers (PhD students and Postdocs)**

I am deeply involved in teaching and mentoring activities at multiple levels. Accordingly, many of my former pre- and post-doctoral fellows are currently directing their own laboratories. Among them, I can mention:

**Ph. D. Students:** **Rafael Pulido**. Ikerbasque Professor. Hospital Cruces Bilbao; **Miguel R Campanero**. Associate Professor. Institute for Biomedical Research-CSIC, Madrid; **Paloma Sánchez-Mateos**. Assistant Professor Dpt Immunology, Hospital Gregorio Marañón, Madrid; **Alicia G Arroyo**. Associate Professor. Center for Biology Research. CSIC. Madrid; **Rosario Garcia-Vicuña**. Chief. Service of Rheumatology and Assistant Professor Clinical Research Rheumatology Service Hospital Universitario de la Princesa. UAM; **Federico Díaz González**. Chief Unit of Rheumatology and Assistant Professor Clinical Research Rheumatology Service Hospital Clínico-Universidad de la Laguna. Tenerife; **Miguel A del Pozo**. Full Professor- National Center for Cardiovascular Research (CNIC) Madrid. **EURYI Awardee 2005**; **Marta Nieto** Associate Professor. National Center of Biotechnology (CSIC) Madrid; **JM Serrador**. Associate Professor. Center for Molecular Biology UAM-CSIC. Madrid ; **David Sancho**. Associate Professor (CNIC). Madrid. **Starting ERC Awardee 2010, and Consolidator ERC Awardee 2016**; **María Yáñez-Mó**: Assistant Professor. Center for Molecular Biology UAM-CSIC **Miguel Vicente-Manzanares**. Associate Professor. Center for Cancer Research, CSIC. Salamanca; **María Mittelbrunn**. Miguel

Servet Investigator. Research Associate. Center for Molecular Biology UAM-CSIC. Madrid.  
**Starting ERC Awardee 2016**

**Postdoctoral Fellows:** **Angel L Corbi**. Professor. Center for Biological Research CSIC. Madrid; **Joaquin Teixidó**. Professor. Center for Biological Research CSIC. Madrid; **Manuel López-Cabrera**. Associate Professor. Center for Molecular Biology. CBM-UAM. Madrid; **Agustín Valenzuela**. Assistant Professor. Dpt Pharmacology. Facultad de Medicina. Universidad de La Laguna; **Pilar Martín** Assistant Professor. (CNIC) Madrid; **Esteban Veiga**. Associate Professor. National Center of Biotechnology (CSIC). Madrid.

#### **G. Invited Presentations to Conferences (Selection of 10, in last five years)**

1. "*Centrosomes and Exosomes: Pacemakers of T cell activation*". **Plenary Lecture. ECI Meeting, Amsterdam 2018.** 2. "*Centrosomes in T cell activation*". **Lecture "Severo Ochoa" Center Molecular Biology, Madrid. 2017.** 3. **NIH Strategic Workshop on Extracellular RNA Transport. Washington DC, USA 2017.** 4. "*Immune cell-to-cell communication: Mechanisms of genetic and protein transfer*". Distinguished Ludwig Lecture Series in **Cancer Research. Ludwig Cancer Institute. Lausanne, Switzerland 2017.** 5. "*The role of the leukocyte activation receptor in the immune Inflammatory response: its ligands and associated molecules*" **Plenary Lecture. 7<sup>th</sup> EMBO Meeting, Mannheim 2016.** 6. "*New modes of Cell-Cell Communication in the Immune System*". Invited Lecture. **University of Manchester, UK 2016.** 7. "*Immune Cell-to-Cell communication: Mechanisms of miRNA and proteins sorting into exosomes*" **Plenary Lecture. 5<sup>th</sup> Annual Meeting ISEV, Rotterdam 2016.** 8. "*Immune cell-to-cell communication: Mechanisms of miRNA and proteins sorting into exosomes*". Invited Symposia. **4<sup>th</sup> ECI Vienna 2015.** 9. "*T cell membrane microdomain and microvesicle sorting at the immune Synapse*" Invited Symposia. **Lymphocyte Signalling. EMBO Conference, Bertinoro, Italy. 2014.** 10. "*Immune Cell-to-Cell communication: Mechanisms of miRNA and proteins sorting into exosomes*". **Cellular synapsis for cell-cell signalling, EMBO Workshop. El Escorial, Spain- 2015.**