

BIOGRAPHICAL SKETCH

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NAME: Carlos Simon

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POSITION TITLE: Professor, Department of Pediatrics, Obstetrics and Gynecology, Valencia University, Adjunct Professor, Department of Obstetrics and Gynecology, Stanford University School of Medicine

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)	Completion Date MM/YYYY	FIELD OF STUDY
University of Valencia, School of Medicine, Spain	M.D.	09/1985	Medicine and Surgery
University of Valencia, School of Medicine, Spain	Excellence Award	09/1986	Medicine and Surgery
University of Valencia, School of Medicine, Spain	Ph.D.	09/1987	Reproductive Genetics
University Clinic Hospital, Valencia, Spain	Resident	09/1991	Board Certified Obs/Gyn
Stanford University, CA, USA	Post-doc Fellow	09/1994	Reproductive Endocrinology

A. Personal Statement

My interest is in the understanding of the human embryonic implantation, a critical process to the survival of the species that it is relatively inefficient. I did my clinical residency in Obstetrics and Gynecology, my PhD in Reproductive Genetics and my postdoctoral fellowship in Reproductive Immunology in the lab of Prof. Mary Lake Polan at Stanford University. After my clinical and research training I become an independent investigator as Associate Professor since March 1994 in Spain, I have been productive in both basic and clinical research, with my commitment to excellence demonstrated by the publication of **423 papers** in peer-reviewed journals with an accumulated **impact factor of 1,962.505** (www.ncbi.nlm.nih.gov/myncbi/simon_c) Research ID: G-2186-2014. My papers have been cited **16,459 times** with an average of **39** citations/paper. My **H-Index is 71**, and I am the editor of **18 books** in English, Spanish, and Portuguese. An independent bibliometric analysis (Gonzalez-Alcaide G et al., Fertil Steril. 2008) classifies Carlos Simon as the 9th most productive author in reproductive biology in the world. My commitment to excellence in clinical care is demonstrated by my instrumental role in establishing the clinical practice and research program of IVI as the world's largest and most successful reproductive clinics (www.ivi.es). As inventor, my research has originated **16** patent applications that have enabled the creation of Igenomix SL in 2011 (www.igenomix.com), a biotech venture devoted to personalized genetic services in human reproduction, of which I am Scientific Director and Founder. Finally, my educational commitment has been recognized by the Serono Symposia International Foundation in 2011, with the prestigious award "Rewarding Scientific Excellence in Medical Education" ([2011 SSIF AWARD](#)). www.carlos-simon.com

B. Positions and Honors**Positions and Employment**

1991 - 1991 Assistant Professor, Dept of Ob/Gyn, School of Medicine, University of Valencia, Spain.
 1994 - 2016 Scientific Director, Instituto Valenciano de Infertilidad (IVI), Valencia, Spain.
 1994 - 2007 Associate Professor, Dept of Ob/Gyn, School of Medicine, University of Valencia, Spain.
 2007 - present Professor, Dept of Ob/Gyn, School of Medicine, University of Valencia, Spain.
 2009 - 2011 Scientific Director, Prince Felipe Research Center, Valencia, Spain.
 2011- present Co-Founder & CSO, Igenomix (www.igenomix.com).
 2009 - 2012 President, Valencian Bioregion (BIOVAL), Valencia, Spain.
 2013 - present Adjunct Clinical Professor, Dept of Ob/Gyn, School of Medicine, Stanford University, CA, USA.
 2014 - present Adjunct Professor, Dept of Ob/Gyn, Baylor College of Medicine, TX, USA.

Other Experience and Professional Memberships

1997 - 2014 Member of the Human Reproduction Program. Advisor of the Scientific and Ethical Review Group, World Health Organization. Switzerland
 1997 - present Scientific Reviewer, National Health and Medical Research Council. Australia
 1999 - present Grant Referee, National Agency of Evaluation and Prospective, Spanish Government. Spain

- 2002 - present Research Project Referee, Instituto de Salud Carlos III, Spanish Government. Spain
- 2002 - 2002 Scientific Reviewer, Fundación Centro Nacional de Investigaciones Cardiovasculares, Instituto de Salud Carlos III, Spanish Government. Spain
- 2002 - 2006 Expert Referee, 6th Framework Program, European Commission. Belgium
- 2004 – present Scientific Reviewer, The Israel Science Foundation. Israel
- 2004 - 2005 Member of the Working Group for the Spanish Biomedicine Research Law, Ministry of Health, Spanish Government. Spain
- 2005 - 2007 Spanish Nanomedicine Platform, Coordinator of Regenerative Medicine Working Group. Spain
- 2006 - 2006 Secretary of the National Faculty Selection Committee, Ministry of Education and Science, Spanish Government. Spain
- 2006 - 2006 Research Project Referee, Colombian Institute for the Development of Science and Technology. Colombia
- 2006 - 2011 Member of the National Stem Cell Bank Committee, Ministry of Health, Spanish Government. Spain
- 2007 - 2007 Referee for Projects of Excellence, Ministry of Innovation and Science, Andalusian Agency of University Quality Evaluation Accreditation. Spain
- 2008 - present Member of the Expert Panel, Program for the National Accreditation ACADEMIA, National Agency for Quality Assessment and Accreditation (ANECA). Spanish Government. Spain
- 2008 - 2008 Scientific Reviewer, The Estonian Science Foundation. Estonia
- 2008 - 2008 Member of the Scientific Advisory Committee, Valencian Agency of Evaluation and Prospective. Valencian Government. Spain
- 2015 - present Member of the Endometrium, Placentation and Implantation (EPI) Research Focus Group (RFG), National Institutes of Health. USA

Associate Editor: Fertil Steril (2011-present); Human Reproduction (2001-2007)

Reviewer for journals including Nature Medicine, Lancet, New England Journal of Medicine, Cell Stem Cell, Nature Communications, PNAS, Stem Cells, and Nature Protocols.

Invited Speaker: Gordon Conferences, Keystone Meeting, American Society for Reproductive Medicine, Society for Gynecological Investigation, Cold Spring Harbor Conferences, and many others.

Honors

- 1984 López Sancho Graduate Fellow Award in Ob/Gyn, University of Valencia. Spain
- 1986 M.D. Degree Excellence Award, School of Medicine, University of Valencia. Spain
- 1992 José A Portuondo Award, Spanish Fertility Society. Spain
- 1993, 2002 President's Poster Awards. Society for Reproductive Investigation (SRI) (former SGI), USA.
- 1993/95/97/99/2001/ Prize Paper Awards. American Society for Reproductive Medicine (ASRM), USA.
05/08/16
- 1995 Vicente Zaragoza Orts Award, Valencian Obs/Gyn Society. Spain
- 1999 Research Award, Spanish Society of Obs/Gyn. Spain
- 2000, 2002 Prize Paper Award, Spanish Fertility Society. Spain
- 2004 Innovation Award. "Two First Stem Cells Lines in Spain", World Academy of Science, Technology, Education and Humanities. Spain
- 2006 University Clinic Hospital of Valencia, Clinical Research Award. III Edition. Spain
- 2009 Award for the Innovation, Quality & Image in Assist. Reprod., Merck Serono. Spain
- 2011 Rey Jaime I Medical Research Award. Spain
- 2011/12/13/14/15/16 Star Award, American Society for Reproductive Medicine. USA
- 2011 Rewarding Scientific Excellence in Medical Education, Serono Symposia International Foundation. Sweden
- 2012 Basic Science Oral Presentation Award, European Society of Human Reproduction and Embryology (ESHRE)
- 2014 KY Cha Award in Stem Cell Technology, American Society for Reproductive Medicine. USA
- 2009/14/15 President's Presenter Award, Society for Reproductive Investigation (SRI). USA
- 2016 Prize Paper. Society for Reproductive Endocrinology and Infertility (SREI). USA
- 2016 Distinguished Research Award. American Society for Reproductive Medicine (ASRM), USA.

C. Contribution to Science

1. My main interest is in the understanding of the human embryonic implantation process, considering as key elements the embryo, the maternal endometrium, and the cross-communication between them using different scientific perspectives.

- a. Thouas GA, Dominguez F, Green MP, Vilella F, Simon C, Gardner DK. Soluble ligands and their receptors in human embryo development and implantation. *Endocr Rev.* 2015 Feb;36(1):92-130. PubMed PMID: [25548832](#).
 - b. Ruiz-Alonso M, Blesa D, Simón C. The genomics of the human endometrium. *Biochim Biophys Acta.* 2012 Dec;1822(12):1931-42. PubMed PMID: [22634130](#).
 - c. Vilella F, Moreno-Moya JM, Balaguer N, Grasso A, Herrero M, Martínez S, Marcilla A, Simon C. Hsa-miR-30d, secreted by the human endometrium, is taken up by the pre-implantation embryo and might modify its transcriptome. *Development.* 2015 Sep 15;14(18):3210-21. PMID: [26395145](#)
2. Using microarray technology, I discovered the transcriptomic signature of human endometrial receptivity (a), publishing our findings in 20 works as first or last author; one of them is the 2nd most-cited article in the journal *Molecular Human Reproduction* (b). Clinical translation of this work resulted in a patent for the creation of a customized endometrial receptivity array (ERA) for the molecular diagnosis of endometrial receptivity in infertile patients (c), the creation of a biotech company (www.igenomix.com), and a free access endometrial database (www.endometrialdatabase.com) managed by the University of Valencia.
 - a. Díaz-Gimeno P, Horcajadas JA, Martínez-Conejero JA, Esteban FJ, Alamá P, Pellicer A, Simón C. A genomic diagnostic tool for human endometrial receptivity based on the transcriptomic signature. *Fertil Steril.* 2011 Jan;95(1):50-60, 60.e1-15. PubMed PMID: [20619403](#).
 - b. Riesewijk A, Martín J, van Os R, Horcajadas JA, Polman J, Pellicer A, Mosselman S, Simón C. Gene expression profiling of human endometrial receptivity on days LH+2 versus LH+7 by microarray technology. *Mol Hum Reprod.* 2003 May;9(5):253-64. PubMed PMID: [12728018](#).
 - c. Simón C, Horcajadas JA, Diaz-Gimeno P, Pellicer A. 2012. Gene expression profile as an endometrial receptivity marker. E.U. Patent [EP2333107A1](#), filed July 22, 2000, and issued Feb 16, 2012.
 3. I discovered the functional relevance of the interleukin-1 system in endometrial receptivity regulation and human embryonic implantation and demonstrated the deleterious effect of high levels of estradiol on endometrial receptivity in patients with high response to gonadotrophins, modifying established clinical practice and initiating the concept of mild stimulation.
 - a. Simón C, Frances A, Piquette GN, el Danasouri I, Zurawski G, Dang W, Polan ML. Embryonic implantation in mice is blocked by interleukin-1 receptor antagonist. *Endocrinology.* 1994 Feb;134(2):521-8. PubMed PMID: [8299552](#).
 - b. Simón C, Cano F, Valbuena D, Remohí J, Pellicer A. Clinical evidence for a detrimental effect on uterine receptivity of high serum oestradiol concentrations in high and normal responder patients. *Hum Reprod.* 1995 Sep;10(9):2432-7. PubMed PMID: [8530680](#).
 4. Using the human endometrial side population in a xenograft murine model, my lab demonstrated the existence and the functional proof of concept for the existence of human endometrial stem cells.
 - a. Cervelló I, Gil-Sanchis C, Mas A, Delgado-Rosas F, Martínez-Conejero JA, Galán A, Martínez-Romero A, Martínez S, Navarro I, Ferro J, Horcajadas JA, Esteban FJ, O'Connor JE, Pellicer A, Simón C. Human endometrial side population cells exhibit genotypic, phenotypic and functional features of somatic stem cells. *PLoS One.* 2010 Jun 24;5(6):e10964. PubMed PMID: [20585575](#).
 - b. Cervelló I, Mas A, Gil-Sanchis C, Peris L, Faus A, Saunders PT, Critchley HO, Simón C. Reconstruction of endometrium from human endometrial side population cell lines. *PLoS One.* 2011;6(6):e21221. PubMed PMID: [21712999](#).
 - c. Cervelló I, Gil-Sanchis C, Mas A, Faus A, Sanz J, Moscardó F, Higuera G, Sanz MA, Pellicer A, Simón C. Bone marrow-derived cells from male donors do not contribute to the endometrial side population of the recipient. *PLoS One.* 2012;7(1):e30260. PubMed PMID: [22276168](#).
 5. My work in human embryology allowed me to expand my research into the field of stem cells, resulting in the derivation, characterization, and registration in the National Stem Cell Bank (BNLC) of 10 human embryonic stem cell lines (VAL-3,4,5,6M,7,8,9,9 /Oct-4, 10B & 11B). I pioneered the first derivation of embryonic stem cell lines in Spain and described a new system for freezing these cells in the absence of animal contaminants. I derived VAL-6M, the first Spanish line with a monogenic disorder (Myotonic Dystrophy Type I) used as disease model by other researchers. My pioneering work in this field made possible the creation of the Valencia Node of the Spanish Stem Cell Bank in 2004, located in the Prince Felipe Research Center. From September 2009 to September 2011 I was

Scientific Director of this Research Center. Now, my lab has been working on the direct reprogramming with 6 germ line-related factors in human somatic cells to produce meiotic germ cells.

- a. Simón C, Escobedo C, Valbuena D, Genbacev O, Galan A, Krtolica A, Asensi A, Sánchez E, Esglagues J, Fisher S, Pellicer A. First derivation in Spain of human embryonic stem cell lines: use of long-term cryopreserved embryos and animal-free conditions. *Fertil Steril*. 2005 Jan;83(1):246-9. PubMed PMID: [15652923](#).
 - b. Valbuena D, Sánchez-Luengo S, Galán A, Sánchez E, Gómez E, Poo ME, Ruiz V, Genbacev O, Krtolica A, Pellicer A, Moreno R, Simón C. Efficient method for slow cryopreservation of human embryonic stem cells in xeno-free conditions. *Reprod Biomed Online*. 2008 Jul;17(1):127-35. PubMed PMID: [18616900](#).
 - c. Mosher JT, Pemberton TJ, Harter K, Wang C, Buzbas EO, Dvorak P, Simón C, Morrison SJ, Rosenberg NA. Lack of population diversity in commonly used human embryonic stem-cell lines. *N Engl J Med*. 2010 Jan 14;362(2):183-5. PubMed PMID: [20018958](#).
 - d. Medrano JV, Martínez-Arroyo A, Miguez JM, Moreno-Gimeno I, Martínez S, Quiñonero A, Díaz-Gimeno P, Marques-Mari AI, Pellicer A, Remohi J, Simon C. Human somatic cells subjected to genetic reprogramming with 6 germ line-related factors display meiotic germ cell-like features. *Stem Cell Reports*. 2015 Submitted
6. We have created a prediction model for aneuploidy in early human embryo development revealed by single-cell analysis, together with the impact of mitochondrial DNA content as a viability score in human euploid embryos. My opinion on this topic was requested and presented in a recent article in *Cell Stem Cell*.
- a. Vera-Rodriguez M, Chavez SL, Rubio C, Reijo Pera RA, Simon C. Prediction model for aneuploidy in early human embryo development revealed by single-cell analysis. *Nat Commun*. 2015 Jul 7;6:7601. PubMed PMID: [26151134](#); PubMed Central PMCID: [PMC4506544](#).
 - b. Díez-Juan A, Rubio C, Marin C, Martínez S, Al-Asmar N, Riboldi M, Díaz-Gimeno P, Valbuena D, Simón C. Mitochondrial DNA content as a viability score in human euploid embryos: less is better. *Fertil Steril*. 2015 Sep;104(3):534-541.e1. PubMed PMID: [26051102](#).
 - c. Díez-Juan A, Simón C. Converting a Problem into an Opportunity: mtDNA Heteroplasmy Shift. *Cell Stem Cell*. 2015 May 7;16(5):457-8. PubMed PMID: [25957899](#).

Complete list of publications can be found at: http://www.ncbi.nlm.nih.gov/myncbi/simon_c

D. Research Support

Ongoing Research Support

BFU2015-72131-EXP, Spanish Ministry of Economy and Competitiveness. Simon, Carlos (PI) 09/01/16-08/31/18
Cryptochromes, the Inexplicable Presence of Light Sensors in the Darkness Connecting Early Embryo with the Cosmos. The main objective of the project is to identify whether the metabolic activity of the embryo is capable of producing light, so in theory modulate signaling cryptochrome. The secondary objective is to identify whether external factors that alter the signaling cryptochrome are able to modulate their targets, altering the metabolism of the embryo and potentially adult physiology

SAF2015-67154-R, Spanish Ministry of Economy and Competitiveness. Simon, Carlos (PI) 01/01/16-12/31/18
Maternal Transcriptomic Regulation of the Pre-implantation Embryo. A novel mechanism to understand the origin of adult diseases such as obesity and/or related to tobacco exposure.
We investigate this novel maternal-embryonic transcriptomic regulatory mechanism as the basis for the developmental origin of adult diseases that can be induced during embryonic implantation either by metabolic disorders of future mothers such as obesity, or by the exposure of contaminants such as tobacco.
Role: PI

R1 – NIH Grant, National Institute of Health. Simon, Carlos (PI) 01/01/15-12/31/19
Genetics of Male Infertility Initiative (GEMINI)
A five-year project aimed at discovering the genetic causes of infertility, and looking at how best to address them in a clinical setting through personalized genomic medicine. The GEMINI team will be specifically studying men who suffer from azoospermia, a condition in which no sperm are produced.
Role: PI

Completed Research Support

- 2R01HD032067-19, National Institutes of Health Grant (NIH). Matzuk, Martin (PI) 07/01/15-06/30/16
Bone Morphogenic Protein Signaling Pathways In Uterine Biology.
The Specific Aims of these proposed studies are: 1) Mechanistically and genetically define the BMP signaling components required for implantation, 2) Characterize BMP signaling pathways in post-implantation uterine biology and diseases of pregnancy, and 3) Create small-molecule BMP receptor type 2-specific regulators
Role: Sub-project PI. Aim 2.
- SARM 324509, FP-7 Marie Curie Program European Commission. Simon, Carlos (PI) 01/01/13-12/31/16
Endometrial and Embryonic Genomics, Searching for Biomarkers in Assisted Reproduction.
The primary objective is to unravel the molecular nature of human preimplantation embryo development and endometrial maturation, which will be achieved by exploiting highly sophisticated single-cell genomic tools.
Role: Sub-project PI.
- Prometeo II/2013/018, Generalitat Valenciana. Simon, Carlos (PI) 01/01/13-12/31/16
Identification of Endometrial Stem Cell Markers. From Animal Models to Human Endometrial Stem Cell Therapy.
The present study aims to elucidate the specific subset of markers for the identification of endometrial stem cells located at the endometrial niche and the contribution of the bone marrow in the endometrial regeneration.
Role: PI
- KY Cha Award In Stem Cell Technology, ASRM. Simón, Carlos (PI) 10/19/15-10/19/16
Direct Conversion of Human Somatic Cells to Meiotic Germ-Like Cells by Genetic Reprogramming.
The goal of this grant is the transcriptomic, epigenetic and functional characterization of reprogrammed cells to a germ cell-like phenotype using 6 germ line-related key factors.
Role: PI
- SAF2012-31017, Spanish Ministry of Economy and Competitivity. Simon, Carlos (PI) 01/01/13-12/31/15
Demonstration of Leucine-Rich Repeat-Containing G-Protein Coupled Receptor 5 (Lgr5) as an Endometrial Stem Cell Marker. From Animal Models to Human Endometrial Stem Cell Therapy and Tissue Engineering.
The major goal of this grant is the analysis of LGR5 as specific human endometrial stem cell marker.
Role: PI
- Grant for Fertility Innovation, EMD Serono. Simon, Carlos (PI) 06/01/13-12/31/15
Analysis of miRNAs in endometrial fluid as a tool for noninvasive diagnosis of endometrial receptivity.
The goal of this grant is to create an atlas of the expression profiles of secreted miRNAs in endometrial fluid and peripheral blood to design a non-invasive diagnostic method to predict endometrial receptivity in assisted reproductive treatments.
Role: PI
- E!6478-NOTED, Eurostars-Eureka Programme, European Commission. Simon, Carlos (PI) 12/01/12-05/30/15
Non-invasive Tests for Endometrial Dysfunction – Novel Clinical Perspectives for Infertility and Endometriosis Diagnostics.
The first goal was to develop non-invasive tests for endometrial quality based on transcript and proteome profiling of blood and endometrial fluid samples.
Role: PI
- EC11-299, Spanish Ministry of Health. Simon, Carlos (PI) 01/01/12-06/30/15
New Strategies in the Therapeutics of Asherman's Syndrome and Endometrial Atrophy Based in the Autologous Transplantations of Bone Marrow Stem Cells.
The aim of this grant was piloting endometrial regeneration in patients with Asherman's Syndrome using isolated stem cells from peripheral blood.
Role: PI
- PROMETEO/2008/163, Generalitat Valenciana. Simon, Carlos (PI) 05/01/09-12/31/12
Isolation and characterization of endometrial somatic stem cells in endometriosis. Pathogenic and therapeutic implications.
The goal of this grant was the identification of the endometrial somatic stem cell population patients with endometriosis to search for therapeutic targets to treat endometriosis.
Role: PI