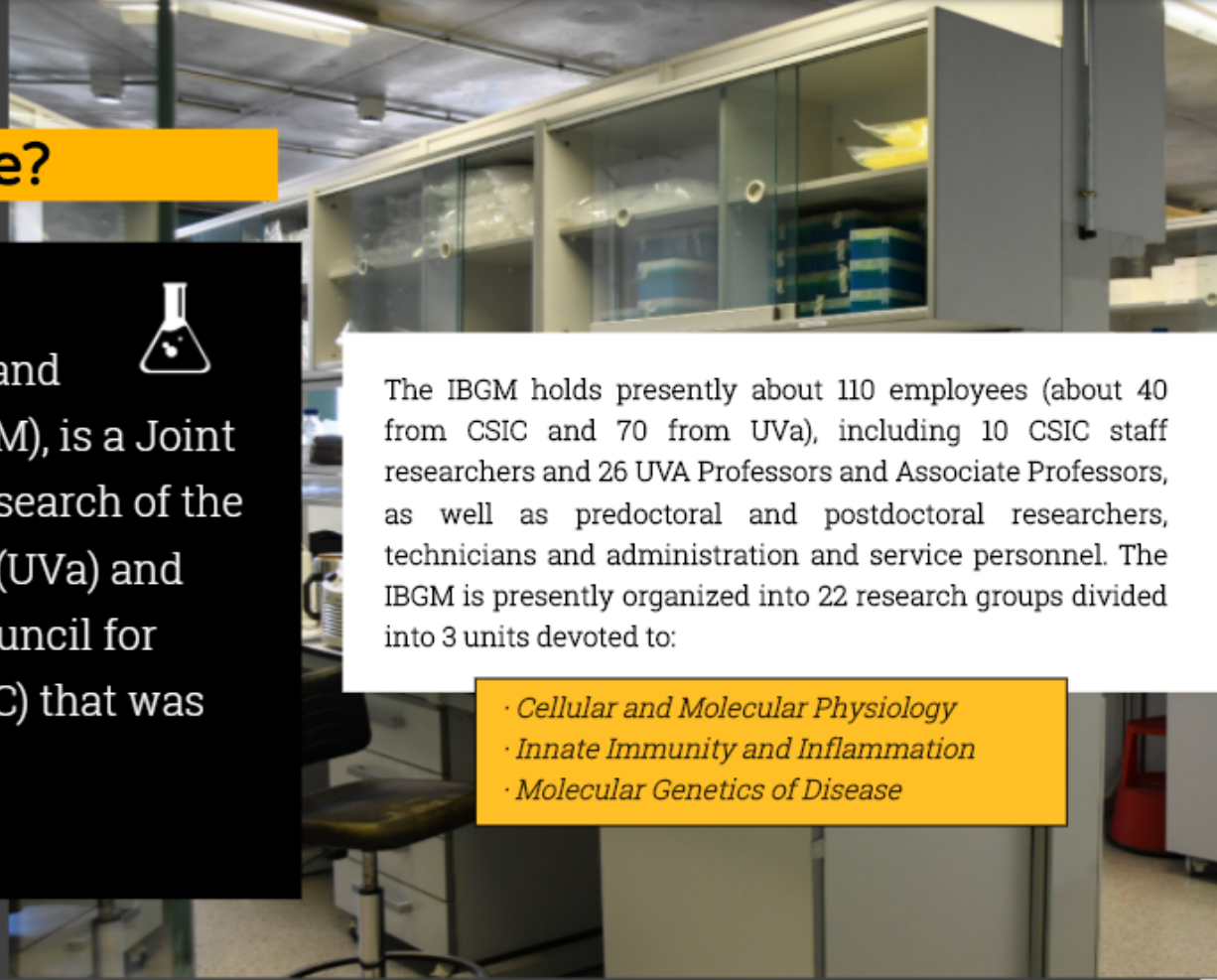
Scientific Report 2019

Instituto de Biología y Genética Molecular

Who are we?

The Institute of Biology and Molecular Genetics (IBGM), is a Joint Center of Biomedical Research of the University of Valladolid (UVa) and the Spanish National Council for Scientific Research (CSIC) that was founded in 1998.



The IBGM holds presently about 110 employees (about 40 from CSIC and 70 from UVa), including 10 CSIC staff researchers and 26 UVA Professors and Associate Professors, as well as predoctoral and postdoctoral researchers, technicians and administration and service personnel. The IBGM is presently organized into 22 research groups divided into 3 units devoted to:

- *Cellular and Molecular Physiology*
- *Innate Immunity and Inflammation*
- *Molecular Genetics of Disease*

The IBGM hosts 8 groups of excellence (GIR) of the University of Valladolid and 8 Units of Consolidated Research (UIC) of the Junta de Castilla y León.

UVA Groups of Excellence (GIR) @ IBGM

* Calcio y Función Celular / Calcium and Cell Function. PI Javier García-Sancho. Teresa Alonso, Jonathan Rojo, Carlos Villalobos, Lucía Núñez, Jonathan Rojo.

*Edición Génica para el Estudio de Canales Ionicos Vasculares y Proteínas mitocondriales /Gene edition for research on ion channels and mitochondrial proteins
PI José Ramón López López. Miguel Angel de la Fuente, Teresa Pérez García, Pilar Cidad.

*Estudio de una Poblacion Estromal Medular para Tratamiento de Enfermedades Degenerativas / Study of a Medullary Stromal Population for the Treatment of Degenerative Diseases
PI Ana Sánchez. Mercedes Alberca, Thomas Schimmang.

*Enfermedades Metabólicas y Neurodegeneración /Metabolic diseases and Neurodegeneration.PI Lola Ganfornina. Diego Sánchez, Irene Cózar, Carmen Domínguez, Alfredo Moreno.
Quimiorreceptores Arteriales y Fisiopatología Vascular / Arterial Chemoreceptors and Vascular Pathophysiology.
PI Ana Obeso. Asunción Rocher, Ricardo Rigual, Angela Gómez Niño.
Transporte Iónico Celular / Cell Ion Transport
PI Javier Alvarez Martín. Mayte Montero, Rosalba Fonteriz.

*Inmunidad de las Mucosas y Alergia: de la Inmunopatología a la Terapia / Mucosal Immunology and Alergy.PIs Eduardo Arranz & David Bernardo. José Antonio Garrote, Luis Fernández Salazar.

JCyL Consolidated Research Units (UIC) @IBGM

UIC 041 PI Teresa Pérez García (UVA).
José R. López, Pilar Cidad, Miguel Angel de la Fuente, Mercedes Roqué.

UIC 043, PI Mariano Sánchez Crespo (CSIC).
Carmen García, Nieves Fernández, Andrés Alonso, Yolanda Bayón.

UIC 059, PI Jesús Balsinde Rodríguez (CSIC).
Angeles Balboa, Clara Meana, Julio Rubio.

UIC 093, PI Carlos Villalobos Jorge (CSIC).
Lucía Núñez, Eva Muñoz, Javier Núñez.

UIC 138, PI Javier García-Sancho (UVA).
Ana Sánchez, Mª Teresa Alonso, Thomas Schimmang, Mercedes Alberca, Jonathan Rojo, Verónica García.

UIC 211, PI Asunción Rocher Martín (UVA).
Ana Obeso, Ricardo Rigual, Angela Gómez, Elvira González.

UIC 224, PI Dolores Ganfornina (UVA).
Diego Sánchez, Irene Cózar, Germán Perdomo, Carmen Domínguez, Alfredo Moreno.

UIC 236, PI Eladio Velasco Sampedro (CSIC).
Mª José Caloca, Concepción Lázaro, Miguel de la Hoya, Mercedes Durán, Mar Infante

What do we do?

The IBGM studies Cell and Molecular bases of the most prevalent groups of diseases including cardiovascular and respiratory system diseases, immune system and inflammatory and metabolic diseases, cancer, aging and neurological and neurodegenerative diseases, as well as advanced methods of molecular diagnostics and new therapies, particularly Cell Therapy and Immunotherapy.

What do we produce?

MÁSTER EN INVESTIGACIÓN BIOMÉDICA
Escuela de Doctorado Universidad de Valladolid

UVa DOCTORADO EN INVESTIGACIÓN BIOMÉDICA

The IBGM provides essentially all teachers for the Master in Biomedical Research (15 students / year) and the PhD Program in Biomedical Research (50 students approx.) of the University of Valladolid, producing about 10 new PhD researchers each year.

IBGM also participates in a growing series of Cell Therapy and Regenerative Medicine Clinical Trials throughout Spain and Europe, having generated a Spin off company (Citospin). IBGM also is the origin and main contributor to genetic diagnosis of familial breast and colon types of cancer in Castilla y León, Spain.

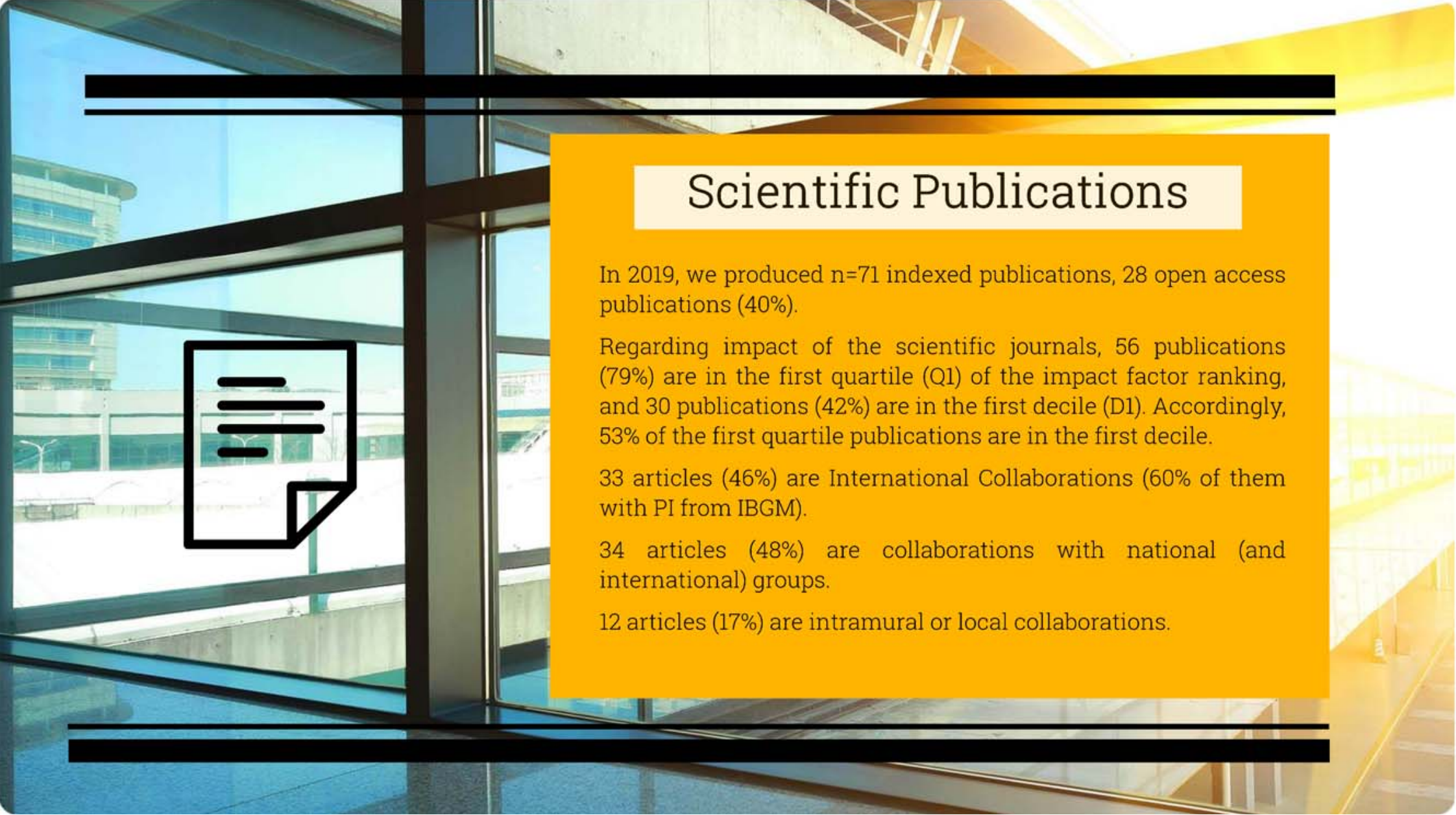
IBGM researchers capture most of its funding on competitive basis amounting 2 M â,¬ / year on competitive research funds that contribute about â,¬ 400,000 â,¬ in overheads to both institutions. These funds cover the expenses of the research projects including personnel hired from these funds.

Competitive funding is obtained mainly from the National I+D+i plan of the Government of Spain, European projects, regional funds of the Castilla y LeÃ³n, various foundations such as the AECC, La Caixa, BBVA etc. and research contracts with companies (PharmaMar, Matarromera, etc.).

The IBGM receives funds for its current expenses from UVa (approximately € 20,000 / year) and from the CSIC (approximately € 60,000 / year). The UVa covers running expenses including telephone, water, electricity, security and cleaning expenses of the Benito Herreros building (for around € 80,000 / year), and CSIC provides the "overheads" of the research projects of CSIC members.

Therefore, the total running expenses of the IBGM are around 150,000-200,000 € / year that is paid essentially in equal parts by UVa and CSIC. IBGM staff works in two locations: the IBGM building and the Valladolid University Medical School, both being very close to the Valladolid University Hospital.

IBGM (front) is located near the University Hospital of Valladolid (back)



Scientific Publications

In 2019, we produced n=71 indexed publications, 28 open access publications (40%).

Regarding impact of the scientific journals, 56 publications (79%) are in the first quartile (Q1) of the impact factor ranking, and 30 publications (42%) are in the first decile (D1). Accordingly, 53% of the first quartile publications are in the first decile.

33 articles (46%) are International Collaborations (60% of them with PI from IBGM).

34 articles (48%) are collaborations with national (and international) groups.

12 articles (17%) are intramural or local collaborations.

Cell and Molecular Physiology Unit

1. Etxaniz A, González-Bullón D, Martín C, **Alonso MT**, Ostolaza H (2019) Irreversible versus repairable membrane poration: differences in permeabilization elicited by Bordetella Adenylate Cyclase Toxin and its hemolysin domain in macrophages. *FEBS J*. 2019 Oct 24. doi: 10.1111/febs.15106. Q1 / IF: 3,62

2. Calatayud C, Carola G, Fernández-Carasa I, Valtorta M, Jiménez-Delgado S, Díaz M, Soriano-Fradera J, Cappelletti G, **García-Sancho J**, Raya Á, Consiglio A (2019) CRISPR/Cas9-mediated generation of a tyrosine hydroxylase reporter iPSC line for live imaging and isolation of dopaminergic neurons. *Sci Rep*. 2019 May 2;9(1):6811. doi: 10.1038/s41598-019-43080-2. D1 / IF: 4,29 / OPEN ACCESS

3. García-Casas P, Arias-Del-Val J, Alvarez-Illera P, Wojnicz A, de Los Ríos C, Fonteriz RI, **Montero M, Alvarez J** (2019) The Neuroprotector Benzothiazepine CGP37157 Extends Lifespan in C. elegans Worms. *Front Aging Neurosci*. 2019 Jan 17;10:440. doi: 10.3389/fnagi.2018.00440. eCollection 2018. Q1 / IF: 3,73 / OPEN ACCESS

4. Arias-Del-Val J, Santo-Domingo J, García-Casas P, Alvarez-Illera P, Núñez Galindo A, Wiederkehr A, Fonteriz RI, **Montero M, Alvarez J** (2019) Regulation of inositol 1,4,5-trisphosphate-induced Ca^{2+} release from the endoplasmic reticulum by AMP-activated kinase modulators. *Cell Calcium* 2019 Jan;77: 68-76. doi: 10.1016/j.ceca.2018.12.004. Q1 / IF: 3,53

5. Parys JB, Pereira CF, **Villalobos C** (2019) The Eighth ECS Workshop on "Calcium Signaling in Aging and Neurodegenerative Diseases". *Int J Mol Sci* 2019 Dec 12;20(24). pii: E6263. Q1 / IF: 4,32 / OPEN ACCESS

6. **Villalobos C**, Hernández-Morales M, Gutiérrez LG, **Núñez L** (2019) TRPC1 and Orai1 channels in colon cancer. *Cell Calcium* 81, 59–66. IF: 3.707 / Q1

7. **Núñez L**, Bird GS, Hernando-Pérez E, Pérez-Riesgo E, Putney JW, **Villalobos C** (2019) Store-operated Ca^{2+} entry and Ca^{2+} responses to hypothalamic-releasing hormones in anterior pituitary cells from Orai1 and heptaTRPC knockout mice. *Biochim Biophys Acta Mol Cel Res* 1866, 1124–1136.IF: 5.128 / Q1

8. Calvo-Rodriguez M, Hernando-Pérez E, **Núñez L**, **Villalobos C** (2019) Amyloid β oligomers increase ER-mitochondria Ca^{2+} cross talk in young hippocampal neurons and exacerbate aging-induced intracellular Ca^{2+} remodeling. *Front Cell Neurosci* 13:22. IF 4,3 / Q1 / OPEN ACCESS

9. Gutiérrez LG, Hernández-Morales M, **Núñez L**, **Villalobos C** (2019) Inhibition of polyamine biosynthesis reverses Ca^{2+} channel remodeling in colon cancer cells. *Cancers* 2019 Jan 13;11(1). pii: E83. IF: 5.326 / D1 / OPEN ACCESS

10. Arévalo-Martínez M, Cidad P, García-Mateo N, Moreno-Estar S, Serna J, Fernández M, Swärd K, **Simarro M**, **de la Fuente MA**, **López-López JR**, **Pérez-García MT** (2019) Myocardin-Dependent Kv1.5 Channel Expression Prevents Phenotypic Modulation of Human Vessels in Organ Culture. *Arterioscler Thromb Vasc Biol*. 2019 Dec;39(12):e273-e286. doi: 10.1161/ATVBAHA.119.313492. D1 / IF: 4,65 / OPEN ACCESS

11. Alonso-Carbajo L, Alpizar YA, Startek JB, **López-López JR**, **Pérez-García MT**, Talavera K (2019) Activation of the cation channel TRPM3 in perivascular nerves induces vasodilation of resistance arteries. *J Mol Cell Cardiol*. 2019 Apr;129:219-230. doi: 10.1016/j.yjmcc.2019.03.003. D1 / IF: 4,72

12. Sacramento JF, Olea E, Ribeiro MJ, **Prieto-Lloret J**, Melo BF, Gonzalez C, Martins FO, Monteiro EC, Conde SV (2019) Contribution of adenosine and ATP to the carotid body chemosensory activity in ageing. *J Physiol*. 2019 Oct;597(19):4991-5008. doi: 10.1113/JP274179. Q1 / IF: 3,54

13. Gallego-Martin T, Prieto-Lloret J, Aaronson PI, **Rocher A**, **Obeso A** (2019) Hydroxycobalamin Reveals the Involvement of Hydrogen Sulfide in the Hypoxic Responses of Rat Carotid Body Chemoreceptor Cells. *Antioxidants (Basel)*. 2019 Mar 13;8(3). pii: E62. doi: 10.3390/antiox8030062. D1 / IF: 4,88 / OPEN ACCESS

14. Fernández-Díaz CM, Escobar-Curbelo L, López-Acosta JF, (...), Perdomo G, **Cózar-Castellano I** (2019) Insulin degrading enzyme is up-regulated in pancreatic β cells by insulin treatment. Histol Histopathol 33(11), pp. 1167-1180. Q2 / IF: 1,77

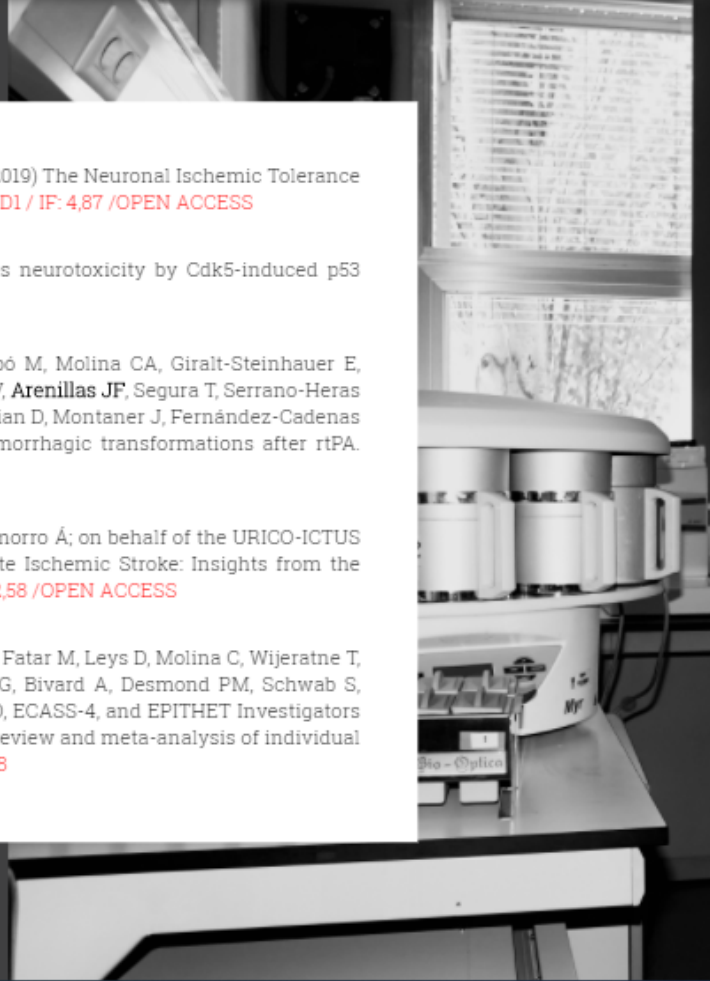
15. Merino B, Fernández-Díaz CM, **Cózar-Castellano I**, Perdomo G (2019) Intestinal Fructose and Glucose Metabolism in Health and Disease. *Nutrients*. 2019 Dec 29;12(1). pii: E94. doi: 10.3390/nu12010094. D1 / IF: 4,51

16. García-Calvo J, Torroba T, Brañas-Fresnillo V, Perdomo G, **Cózar-Castellano I**, Li YH, Legrand YM, Barboiu M (2019) Manipulation of Transmembrane Transport by Synthetic K+ Ionophore Depsipeptides and Its Implications in Glucose-Stimulated Insulin Secretion in β-Cells. *Chemistry*. 2019 Jul 11;25(39):9287-9294. doi: 10.1002/chem.201901372. D1 / IF: 4,77

17. Fernandez-Diaz CM, Merino B, Lopez-Acosta JF, Cidad P, **de la Fuente MA**, Lobaton CD, Moreno A, Leissring MA, Perdomo G, **Cozar-Castellano I** (2019) Pancreatic beta-cell-specific deletion of insulin-degrading enzyme leads to dysregulated insulin secretion and beta-cell functional immaturity. *Am J Physiol Endocrinol Metab*. 2019 Sep 3. doi: 10.1152/ajpendo.00040.2019. Q1 / IF: 3,89

18. Loera-Valencia R, Goikolea J, **Parrado-Fernandez C**, Merino-Serrais P, Maioli S (2019) Alterations in cholesterol metabolism as a risk factor for developing Alzheimer's disease: Potential novel targets for treatment. *J Steroid Biochem Mol Biol*. 2019 Jun;190:104-114. doi: 10.1016/j.jsbmb.2019.03.003. Q1 / IF: 3,73 / OPEN ACCESS

19. López-Gómez, J.J., Delgado-García, E., Coto-García, C., (...), **Arenillas-Lara, J.F.**, De Luis-Román, D.A. (2019). Influence of hyperglycemia associated with enteral nutrition on mortality in patients with stroke. *Nutrients* 11(5),996. D1 / IF: 4,51 /OPEN ACCESS



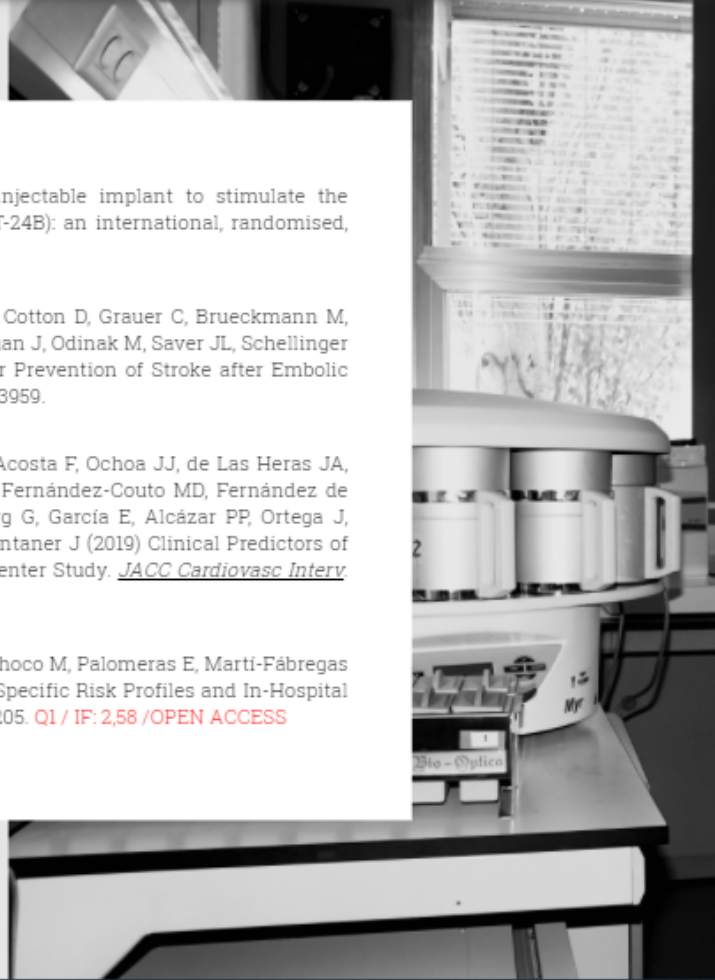
20. Ramos-Araque, M.E., Rodriguez, C., Vecino, R., (...Arenillas JF..), Almeida, A., Delgado-Esteban, M. (2019) The Neuronal Ischemic Tolerance Is Conditioned by the Tp53 Arg72Pro Polymorphism. *Translational Stroke Research* 10(2), pp. 204-215. D1 / IF: 4,87 /OPEN ACCESS

21. Lapresa, R., **Agulla, J.**, Sánchez-Morán, I., Bolaños, J.P., Almeida, A. (2019). Amyloid-ß promotes neurotoxicity by Cdk5-induced p53 stabilization. *Neuropharmacology* 146, pp. 19-27. D1 / IF: 4,42

22. Carrera C, Cullell N, Torres-Águila N, Muiño E, Bustamante A, Dávalos A, López-Cancio E, Ribó M, Molina CA, Giralt-Steinhauer E, Soriano-Tárraga C, Mola-Caminal M, Jiménez-Conde J, Roquer J, Vives-Bauza C, Navarro RD, Obach V, **Arenillas JF**, Segura T, Serrano-Heras G, Martí-Fàbregas J, Freijo M, Cabezas JA, Tatlisumak T, Heitsch L, Ibañez L, Cruchaga C, Lee JM, Strbian D, Montaner J, Fernández-Cadenas I; Spanish Stroke Genetic Consortium (2019) Validation of a clinical-genetics score to predict hemorrhagic transformations after rtPA. *Neurology*. 2019 Aug 27;93(9):e851-e863. doi: 10.1212/WNL.0000000000007997. Q1 / IF: 3,85

23. Amaro S, Renú A, Laredo C, Castellanos M, **Arenillas JF**, Llull L, Rudilloso S, Urra X, Obach V, Chamorro Á; on behalf of the URICO-ICTUS investigators (2019) Relevance of Collaterals for the Success of Neuroprotective Therapies in Acute Ischemic Stroke: Insights from the Randomized URICO-ICTUS Trial. *Cerebrovasc Dis*. 2019;47(3-4):171-177. doi: 10.1159/000500712. Q1 / IF: 2,58 /OPEN ACCESS

24. Campbell BCV, Ma H, Ringleb PA, Parsons MW, Churilov L, Bendszus M, Levi CR, Hsu C, Kleinig TJ, Fatar M, Leys D, Molina C, Wijeratne T, Curtze S, Dewey HM, Barber PA, Butcher KS, De Silva DA, Bladin CF, Yassi N, Pfaff JAR, Sharma G, Bivard A, Desmond PM, Schwab S, Schellinger PD, Yan B, Mitchell PJ, Serena J, Toni D, Thijs V, Hacke W, Davis SM, Donnan GA; EXTEND, ECASS-4, and EPITHET Investigators (2019) Extending thrombolysis to 4·5-9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data. *The Lancet*. 2019 Jul 13;394(10193):139-147. doi: 10.1016/S0140-6736(19)31053-0. D1 / IF: 10,28



25. Bornstein, N.M., Saver, J.L., Diener, H.C., (...Arenillas JF...), Zaidi, S., Devlin, T (2019). An injectable implant to stimulate the sphenopalatine ganglion for treatment of acute ischaemic stroke up to 24 h from onset (ImpACT-24B): an international, randomised, double-blind, sham-controlled, pivotal trial. *The Lancet* 394(10194), pp. 219-229. D1 / IF: 10,28

26. Diener HC, Sacco RL, Easton JD, Granger CB, Bernstein RA, Uchiyama S, Kreuzer J, Cronin L, Cotton D, Grauer C, Brueckmann M, Chernyatina M, Donnan G, Ferro JM, Grond M, Kallmünzer B, Krupinski J, Lee BC, Lemmens R, Masjuan J, Odinak M, Saver JL, Schellinger PD, Toni D, Toyoda K; RE-SPECT ESUS Steering Committee and Investigators (2019) Dabigatran for Prevention of Stroke after Embolic Stroke of Undetermined Source. *N Engl J Med*. 2019 May 16;380(20):1906-1917. doi: 10.1056/NEJMoa1813959.

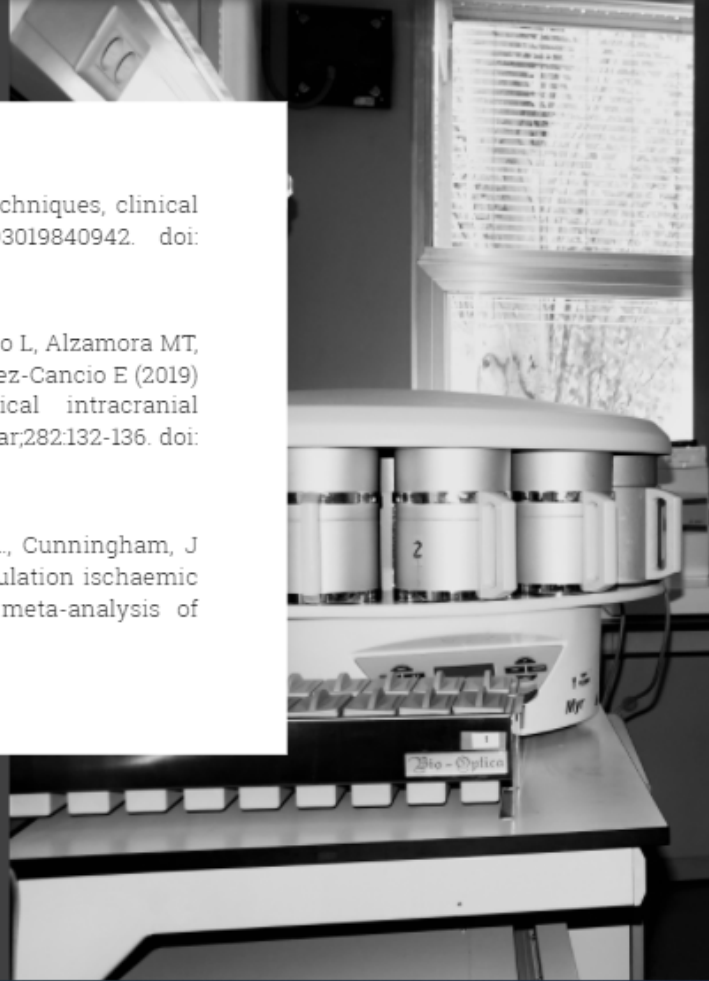
27. González García A, Moniche F, Escudero-Martínez I, Mancha F, Tomasello A, Ribó M, Delgado-Acosta F, Ochoa JJ, de Las Heras JA, López-Mesonero L, González-Delgado M, Murias E, Gil J, Gil R, Zamarro J, Parrilla G, Mosteiro S, Fernández-Couto MD, Fernández de Alarcón L, Ramírez-Moreno JM, Luna A, Gil A, González-Mandly A, Caniego JL, Zapata-Wainberg G, García E, Alcázar PP, Ortega J, Arenillas JF, Algaba P, Zapata-Arriaza E, Alcalde-López J, de Albóniga-Chindurza A, Cayuela A, Montaner J (2019) Clinical Predictors of Hyperperfusion Syndrome Following Carotid Stenting: Results From a National Prospective Multicenter Study. *JACC Cardiovasc Interv*. 2019 May 13;12(9):873-882. doi: 10.1016/j.jcin.2019.01.247. Q1 / IF: 3,31

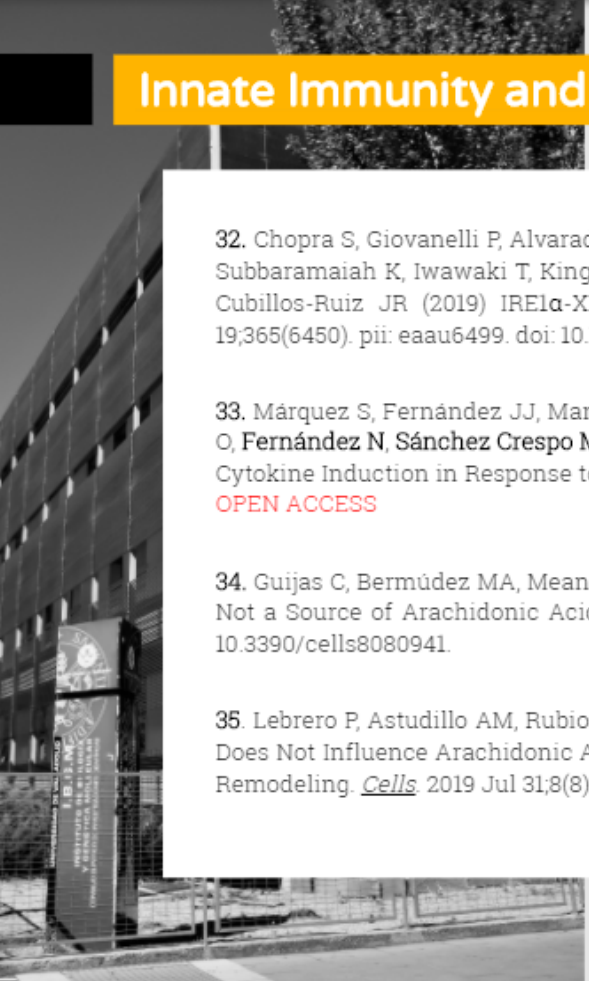
28. Purroy F, Vena A, Forné C, de Arce AM, Dávalos A, Fuentes B, Arenillas JF, Krupinski J, Gómez-Choco M, Palomeras E, Martí-Fábregas J, Castillo J, Ustrell X, Tejada J, Masjuan J, Garcés M, Benabdelhak I, Serena J (2019) Age- and Sex-Specific Risk Profiles and In-Hospital Mortality in 13,932 Spanish Stroke Patients. *Cerebrovasc Dis*. 2019;47(3-4):151-164. doi: 10.1159/000500205. Q1 / IF: 2,58 /OPEN ACCESS

29. **Arenillas JF**, Dieleman N, Bos D (2019) intracranial arterial wall imaging: Techniques, clinical applicability, and future perspectives. *Int J Stroke*. 2019 Apr 13:1747493019840942. doi: 10.1177/1747493019840942. Q2 / IF: 3,08

30. Planas-Ballvé A, Crespo AM, Aguilar LM, Hernández-Pérez M, Canento T, Dorado L, Alzamora MT, Torán P, Pera G, Muñoz-Ortiz L, **Arenillas JF**, Castañón M, Dávalos A, Millán M, López-Cancio E (2019) The Barcelona-Asymptomatic Intracranial Atherosclerosis study: Subclinical intracranial atherosclerosis as predictor of long-term vascular events. *Atherosclerosis*. 2019 Mar;282:132-136. doi: 10.1016/j.atherosclerosis.2019.01.022.

31. Campbell, B.C.V., Majoie, C.B.L.M., Albers, G.W., (...**Arenillas JF...**), Keshvara, R., Cunningham, J (2019) Penumbral imaging and functional outcome in patients with anterior circulation ischaemic stroke treated with endovascular thrombectomy versus medical therapy: a meta-analysis of individual patient-level data. *The Lancet Neurology* 18(1), pp. 46-55. D2 / IF: 8,81





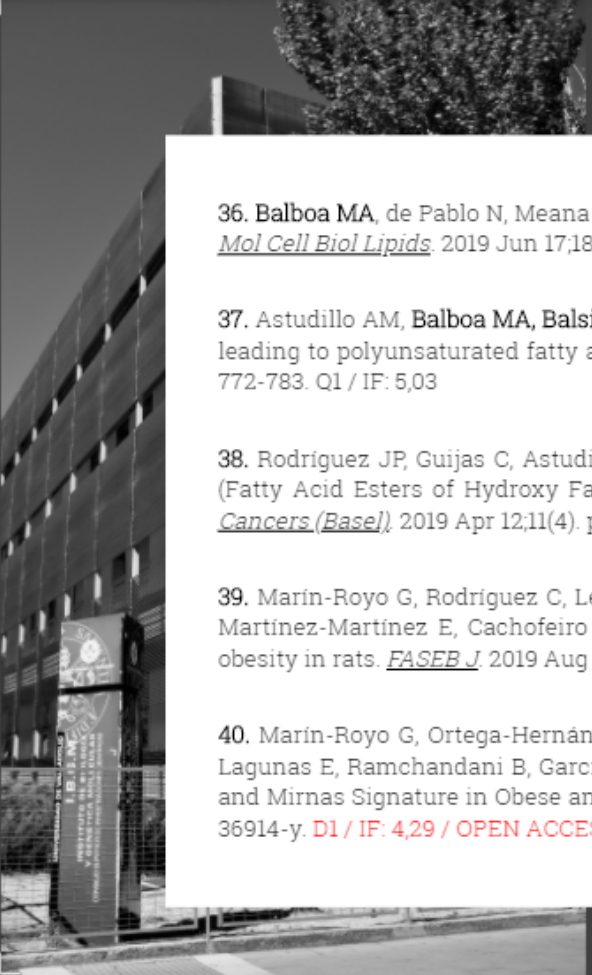
Innate Immunity and Inflammation Unit

32. Chopra S, Giovanelli P, Alvarado-Vazquez PA, Alonso S, Song M, Sandoval T, Chae CS, Tan C, Fonseca MM, Gutierrez S, Jimenez L, Subbaramaiah K, Iwawaki T, Kingsley PJ, Marnett LJ, Kossenkov AV, **Crespo M**, Dannenberg AJ, Glimcher LH, Romero-Sandoval EA, Cubillos-Ruiz JR (2019) IRE1α-XBP1 signaling in leukocytes controls prostaglandin biosynthesis and pain. *Science*. 2019 Jul 19;365(6450). pii: eaau6499. doi: 10.1126/science.aau6499. D1 / IF: 15,21

33. Márquez S, Fernández JJ, Mancebo C, Herrero-Sánchez C, Alonso S, Sandoval TA, Rodríguez Prados M, Cubillos-Ruiz JR, Montero O, **Fernández N**, **Sánchez Crespo M** (2019) Tricarboxylic Acid Cycle Activity and Remodeling of Glycerophosphocholine Lipids Support Cytokine Induction in Response to Fungal Patterns. *Cell Rep*. 2019 Apr 9;27(2):525-536.e4. doi: 10.1016/j.celrep.2019.03.033. D1 / IF: 8,04 / OPEN ACCESS

34. Guijas C, Bermúdez MA, Meana C, Astudillo AM, Pereira L, Fernández-Caballero L, **Balboa MA**, **Balsinde J** (2019) Neutral Lipids Are Not a Source of Arachidonic Acid for Lipid Mediator Signaling in Human Foamy Monocytes. *Cells*. 2019 Aug 20;8(8). pii: E941. doi: 10.3390/cells8080941.

35. Lebrero P, Astudillo AM, Rubio JM, Fernández-Caballero L, Kokotos G, **Balboa MA**, **Balsinde J** (2019) Cellular Plasmalogen Content Does Not Influence Arachidonic Acid Levels or Distribution in Macrophages: A Role for Cytosolic Phospholipase A2γ in Phospholipid Remodeling. *Cells*. 2019 Jul 31;8(8). pii: E799. doi: 10.3390/cells8080799.



36. Balboa MA, de Pablo N, Meana C, Balsinde J (2019) The role of lipins in innate immunity and inflammation. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2019 Jun 17;1864(10):1328-1337. doi: 10.1016/j.bbalip.2019.06.003. Q1 / IF: 5,03

37. Astudillo AM, Balboa MA, Balsinde J (2019) Selectivity of phospholipid hydrolysis by phospholipase A2 enzymes in activated cells leading to polyunsaturated fatty acid mobilization. *Biochimica et Biophysica Acta - Molecular and Cell Biology of Lipids* 1864(6), pp. 772-783. Q1 / IF: 5,03

38. Rodríguez JP, Guijas C, Astudillo AM, Rubio JM, Balboa MA, Balsinde J (2019) Sequestration of 9-Hydroxystearic Acid in FAHFA (Fatty Acid Esters of Hydroxy Fatty Acids) as a Protective Mechanism for Colon Carcinoma Cells to Avoid Apoptotic Cell Death. *Cancers (Basel)*. 2019 Apr 12;11(4). pii: E524. doi: 10.3390/cancers11040524. D1 / IF: 5,87 / OPEN ACCESS

39. Marín-Royo G, Rodríguez C, Le Pape A, Jurado-López R, Luaces M, Antequera A, Martínez-González J, Souza-Neto FV, Nieto ML, Martínez-Martínez E, Cachofeiro V (2019) The role of mitochondrial oxidative stress in the metabolic alterations in diet-induced obesity in rats. *FASEB J*. 2019 Aug 1:fj201900347RR. doi: 10.1096/fj.201900347RR. Q1 / IF: 4,32

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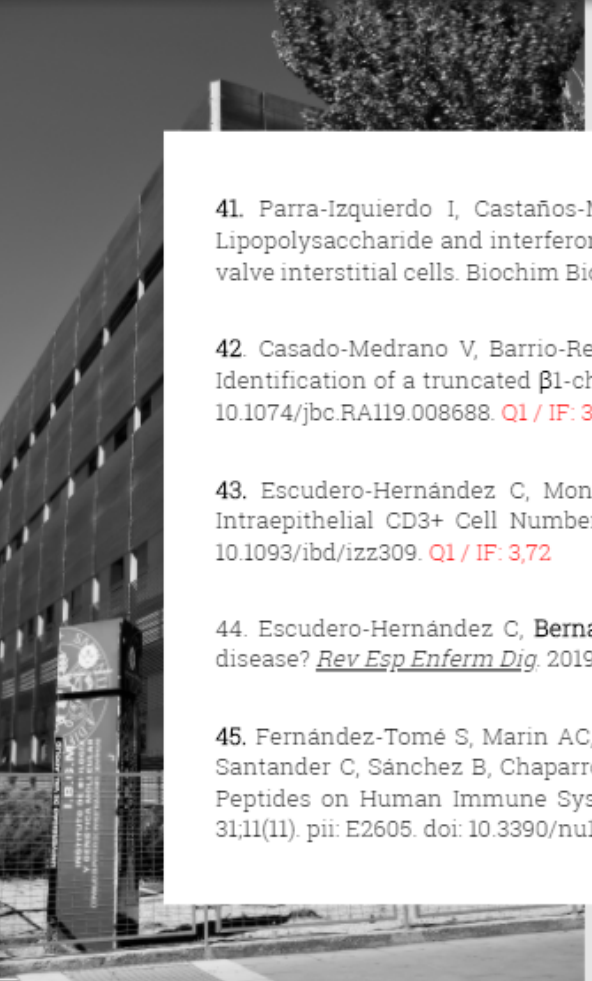

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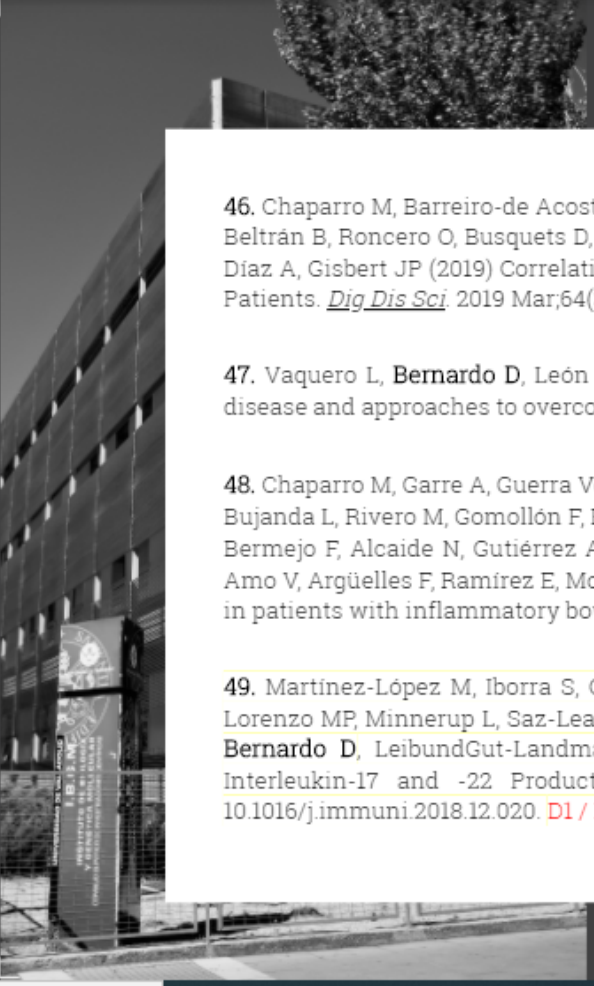

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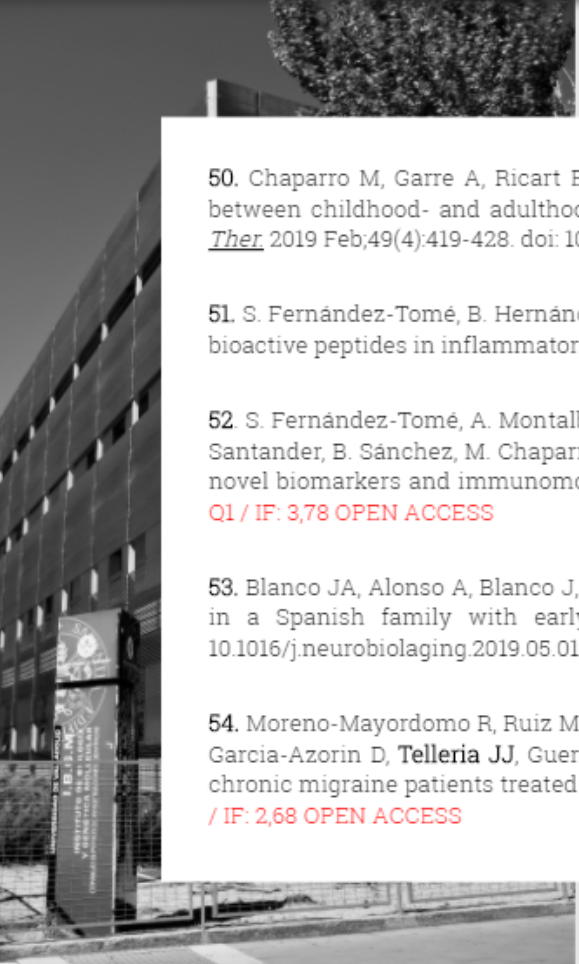
48. Chaparro M, Garre A, Guerra Veloz MF, Vázquez JM, De Castro ML, Leo E, Rodriguez E, Carbajo AY, Riestra S, Jiménez I, Calvet X, Bujanda L, Rivero M, Gomollón F, Benítez JM,
Bermejo F, Alcaide N, Gutiérrez A, Mañosa M, Iborra M, Lorente R, Rojas-Feria M, Barreiro-de Acosta M, Kolle L, Van Domselaar M, Amo V, Argüelles F, Ramírez E, Morell A, **Bernardo D**, Gisbert JP (2019) Effectiveness and safety of the switch from Remicade to CT-P13 in patients with inflammatory bowel disease. *J Crohns Colitis*. 2019 Apr 12. pii: jjz070. doi: 10.1093/ecco-jcc/jjz070. D1 / IF: 5,55

49. Martínez-López M, Iborra S, Conde-Garrosa R, Mastrangelo A, Danne C, Mann ER, Reid DM, Gaboriau-Routhiau V, Chaparro M, Lorenzo MP, Minnerup L, Saz-Leal P, Slack E, Kemp B, Gisbert JP, Dzionek A, Robinson MJ, Rupérez FJ, Cerf-Bensussan N, Brown GD, **Bernardo D**, LeibundGut-Landmann S, Sancho D (2019) Microbiota Sensing by Mincle-Syk Axis in Dendritic Cells Regulates Interleukin-17 and -22 Production and Promotes Intestinal Barrier Integrity. *Immunity*. 2019 Feb 19;50(2):446-461.e9. doi: 10.1016/j.immuni.2018.12.020. D1 / IF: 14,69 OPEN ACCESS



50. Chaparro M, Garre A, Ricart E, Iglesias-Flores E, Taxonera C, Domènech E, Gisbert JP; ENEIDA study group (2019) Differences between childhood- and adulthood-onset inflammatory bowel disease: the CAROUSEL study from GETECCU. *Aliment Pharmacol Ther.* 2019 Feb;49(4):419-428. doi: 10.1111/apt.15114. D1 / IF: 4,08

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Molecular Genetics of Disease Unit

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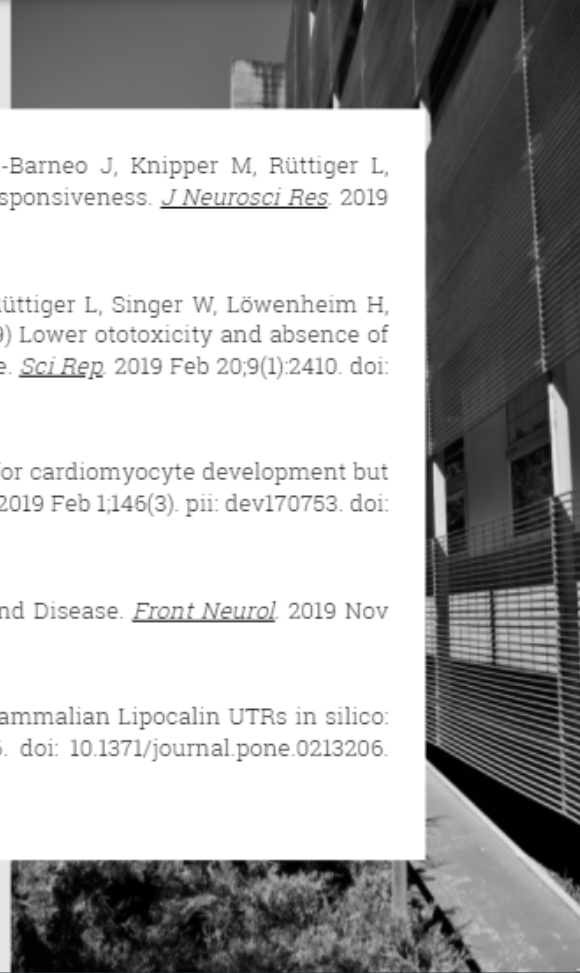

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69. Velázquez C, Esteban-Cardeñosa EM, Lastra E, Abella LE, de la Cruz V, **Lobatón CD**, **Durán M**, **Infante M** (2019) A PALB2 truncating mutation: Implication in cancer prevention and therapy of Hereditary Breast and Ovarian Cancer. *Breast*. 2019 Feb;43:91-96. doi: 10.1016/j.breast.2018.11.010. D1 / IF: 3,15

70. Velázquez C, Esteban-Cardeñosa EM, Lastra E, Abella LE, de la Cruz V, **Lobatón CD**, **Durán M**, **Infante M** (2019) Unraveling the molecular effect of a rare missense mutation in BRIP1 associated with inherited breast cancer. *Mol Carcinog*. 2019 Jan;58(1):156-160. doi: 10.1002/mc.22910. Q2 / IF: 3,43

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Cell and Molecular Physiology Unit
Calcium and Cell Function Group

Team

Principal Investigators:

María Teresa Alonso (UVA), talonso@ibgm.uva.es

Javier García-Sancho (UVA), jgsancho@ibgm.uva.es

Postdocs: Jonathan Rojo, Letizia Albarrán

Predocs: Alba del Río, Patricia Torres

Technicians: Jesús Fernández, Miriam García, Carla Rodríguez through the Cell Therapy Network (see Cell Therapy group).

The research group founded by Prof. J. GarcÃa-Sancho and headed also by Prof. MarÃa Teresa Alonso has extensive experience in the study of cellular activation phenomena, especially regarding the role of intracellular Ca^{2+} as second messenger. The work in this field began in 1984, after witnessing the birth of the first intracellular calcium indicator during a sabbatical stay in Cambridge. Aware of the potential of this new tool, we assembled and improved the technique in Valladolid, implementing in 1988, microfluorescence measurements and image analysis in living cells, with resolution at the individual cell level.

During the last 30 years the group has addressed issues related to the control by intracellular messengers of different functions, including the secretion by the beta cells of the pancreas, the anterior pituitary cells or chromaffin cells, various aspects of the physiology of blood cells and inflammation, the organization of spontaneous activity in neuronal circuits, the control of cell differentiation or the implications of Ca^{2+} in neuronal ischemic damage. Currently, our interest continues to focus mainly on Cell Activation, especially in the processes regulated by intracellular Ca^{2+} and in its action as a second messenger and in the biophysical mechanisms that contribute to its homeostasis.

During the last years, the group has been interested in the possibility of restoring the lost function in destructive or degenerative diseases through treatments of Cell Therapy. In close collaboration with hospital groups we have been involved in regeneration studies, both at a basic and clinical level, and we have promoted transversal collaboration between different groups and translational research through the Cell Therapy Network.

Publications in 2019

1. Etxaniz A, González-Bullón D, Martín C, **Alonso MT**, Ostolaza H (2019) Irreversible versus repairable membrane poration: differences in permeabilization elicited by Bordetella Adenylate Cyclase Toxin and its hemolysin domain in macrophages. FEBS J. 2019 Oct 24. doi: 10.1111/febs.15106.

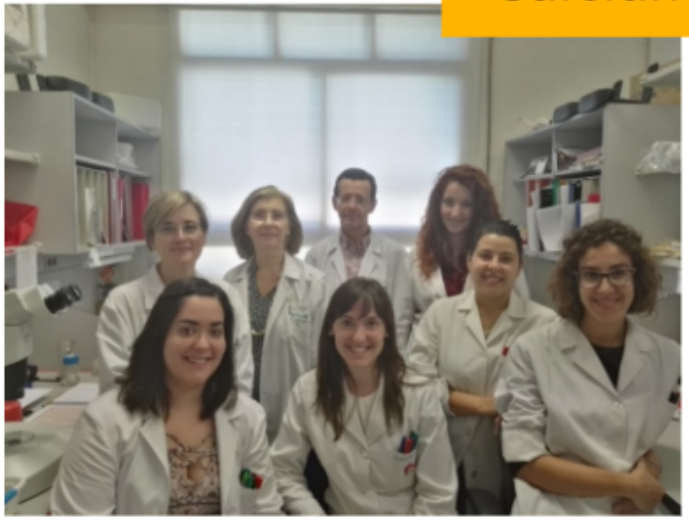
2. Rodas G, Soler R, Balius R, Alomar X, Peirau X, Alberca M, Sánchez A, **Sancho JG**, Rodellar C, Romero A, Masci L, Orozco L, Maffulli N (2019) Autologous bone marrow expanded mesenchymal stem cells in patellar tendinopathy: protocol for a phase I/II, single-centre, randomized with active control PRP, double-blinded clinical trial. *J Orthop Surg Res.* 2019 Dec 16;14(1):441. doi: 10.1186/s13018-019-1477-2.

3. Sánchez-Guijo F, García-Olmo D, Prósper F, Martínez S, Zapata A, Fernández-Avilés F, Toledo-Aral JJ, Torres M, Fariñas I, Badimón L, Labandeira-García JL, **García-Sancho J**, Moraleda JM; TerCel (2019) Spanish Cell Therapy Network (TerCel): 15 years of successful collaborative translational research. Cytotherapy 2019 Dec 19. pii: S1465-3249(19)30889-8. doi: 10.1016/j.jcyt.2019.11.001.

4. Calatayud C, Carola G, Fernández-Carasa I, Valtorta M, Jiménez-Delgado S, Díaz M, Soriano-Fradera J, Cappelletti G, **García-Sancho J**, Raya Á, Consiglio A (2019) CRISPR/Cas9-mediated generation of a tyrosine hydroxylase reporter iPSC line for live imaging and isolation of dopaminergic neurons. *Sci Rep.* 2019 May 2;9(1):6811. doi: 10.1038/s41598-019-43080-2.

5. Calonge M, Pérez I, Galindo S, Nieto-Miguel T, López-Paniagua M, Fernández I, Alberca M, **García-Sancho J**, Sánchez A, Herreras JM (2019) A proof-of-concept clinical trial using mesenchymal stem cells for the treatment of corneal epithelial stem cell deficiency. *Transl Res.* 2019 Apr;206:18-40. doi: 10.1016/j.trsl.2018.11.003. Epub 2018 Nov 22.

Cell and Molecular Physiology Unit
Calcium and Aging Group



Team

Principal Investigators:

Javier Alvarez (UVA), jalvarez@ibgm.uva.es

Mª Teresa Montero (UVA), mmontero@ibgm.uva.es

Scientific Staff: Rosalba I Fonteriz

Postdoc: Pilar García Illera

Predoc: Paloma García Casas

Our research team has a long experience of about 30 years working on intracellular Ca^{2+} homeostasis, with special emphasis on the dynamics of Ca^{2+} in subcellular organelles: mitochondria, endoplasmic reticulum and secretory vesicles. In recent years we have developed a system for *in-vivo* monitoring of $[Ca^{2+}]$ in the pharynx of *C. elegans* worms, and we have been able to obtain and give functional meaning to the dynamic records of $[Ca^{2+}]$ in cytosol and mitochondria of *C. elegans* pharynx throughout ageing, both in *C. elegans* wild type worms and in various mutants.

In addition, we are studying the effects of different modulators of Ca^{2+} fluxes on longevity in *C. elegans*. We have been able to verify that inhibitors of SERCA (the Ca^{2+} pump of the sarcoendoplasmic reticulum) such as thapsigargin and 2.5 benzohydroquinone (2.5-BHQ) produce significant increases in *C. elegans* half-life at intermediate doses (lower and higher doses produce fewer effects), which shows that submaximal inhibition of SERCA pumps has a pro-longevity effect.

This suggests that Ca^{2+} signaling plays an important role in the aging process and that it could be a novel and promising avenue of action on aging. Likewise, the inhibitor of the Na^{+}/Ca^{2+} mitochondrial exchanger CGP37157 at submaximal doses produces an important lengthening of the life of the worms. We are currently investigating the specific mechanism and routes involved in the increase in longevity induced by these compounds. Another important objective that we also have in progress is the study of the effect of these and other compounds in worms that are models of various neurodegenerative diseases, such as Alzheimer's, Parkinson's or Huntington's. In fact, the nematode *C. elegans* is increasingly being used as a model of multiple human diseases, by virtue of the surprising similitudes that exist between its genome and humans, which encompass up to 65% of the genes responsible for diseases. Our hope is that the modulators of Ca^{2+} fluxes will also be able to have a positive effect on these diseases which are especially frequent in old age.

Publications in 2019

1. García-Casas P, Arias-Del-Val J, Alvarez-Illera P, Wojnicz A, de Los Ríos C, Fonteriz RI, **Montero M**, **Alvarez J** (2019) The Neuroprotector Benzothiazepine CGP37157 Extends Lifespan in C. elegans Worms. *Front Aging Neurosci*. 2019 Jan 17;10:440. doi: 10.3389/fnagi.2018.00440. eCollection 2018.

2. Arias-Del-Val J, Santo-Domingo J, García-Casas P, Alvarez-Illera P, Núñez Galindo A, Wiederkehr A, Fonteriz RI, **Montero M**, **Alvarez J** (2019) Regulation of inositol 1,4,5-trisphosphate-induced Ca^{2+} release from the endoplasmic reticulum by AMP-activated kinase modulators. *Cell Calcium* 2019 Jan;77: 68-76. doi: 10.1016/j.ceca.2018.12.004.

Ongoing Projects

Title: *Papel de la señalización por Ca^{2+} en longevidad y neuroprotección en el modelo Caenorhabditis elegans.*
Funding Agency: Plan Nacional I+D+I, Ministerio de Economía y Competitividad (BFU2017-83509R)
From 2018 to 2021
Funding: 217.800 €
Principal Investigator: Javier Alvarez Martín, Mª Teresa Montero Zoccola

Title: *Longevidad, Neuroprotección y Señalización por Calcio*
Funding Agency: Junta de Castilla y León (VA011G18)
From 2018 to 2020
Funding: 12.000 €
Principal Investigator: Javier Alvarez Martín

Others (Seminars, Awards, Patents, Teaching...)

Cell and Molecular Physiology
Physiopathology of Intracellular Calcium Group

Team

Principal Investigators:

Carlos Villalobos (CSIC), carlosv@ibgm.uva.es
Lucía Núñez (UVA), nunezl@ibgm.uva.es

Postdocs: Sendoa Tajada

Predocs: Lucía G. Gutiérrez, Enrique Pérez Riesgo, Verónica Feijóo, Elena Hernando.

Technicians: David del Bosque

Students: Sara López (MS candidate), María Martín (Graduate candidate)

We study the role of intracellular calcium, mitochondria and the remodeling of calcium channels in cell death and proliferation as well as their possible contribution to the development of proliferative and neurodegenerative diseases such as cancer, excessive proliferation of smooth muscle cells vascular and Alzheimer's disease. On the other hand, we investigated the possible use of calcium channels as targets of new drugs for the treatment and / or prevention of previous diseases, especially the chemopreventive and neuroprotective mechanism of aspirin and various non-steroidal anti-inflammatory drugs. For this purpose, Cellular and Molecular Physiology methodologies are used, including cytosolic and subcellular calcium monitoring by means of fluorescence and bioluminescence imaging, ion channel registration through planar or automatic electrophysiology and other Molecular Biology methodologies including qRT-PCR, western blotting and siRNA.

Publications in 2019

1. Parys JB, Pereira CF, **Villalobos C** (2019) The Eighth ECS Workshop on "Calcium Signaling in Aging and Neurodegenerative Diseases". *Int J Mol Sci.* 2019 Dec 12;20(24). pii: E6263.

2. **Villalobos C**, Hernández-Morales M, Gutiérrez LG, **Núñez L** (2019) TRPC1 and Orai1 channels in colon cancer. *Cell Calcium* 81, 59–66. IF: 3.707 / Q1

3. **Núñez L**, Bird GS, Hernando-Pérez E, Pérez-Riesgo E, Putney JW, **Villalobos C** (2019) Store-operated Ca^{2+} entry and Ca^{2+} responses to hypothalamic-releasing hormones in anterior pituitary cells from Orai1 and heptaTRPC knockout mice. *Biochim Biophys Acta Mol Cel Res* 1866, 1124–1136.IF: 5.128 / Q1

4. Calvo-Rodriguez M, Hernando-Pérez E, **Núñez L**, **Villalobos C** (2019) Amyloid β oligomers increase ER-mitochondria Ca^{2+} cross talk in young hippocampal neurons and exacerbate aging-induced intracellular Ca^{2+} remodeling. *Front Cell Neurosci* 13:22. IF 4,3 / Q1

5. Gutiérrez LG, Hernández-Morales M, **Núñez L**, **Villalobos C** (2019) Inhibition of polyamine biosynthesis reverses Ca^{2+} channel remodeling in colon cancer cells. *Cancers* 2019 Jan 13;11(1). pii: E83. IF: 5.326 / D1

Starting and Ongoing Projects

Title: *Comprender y revertir el remodelado del calcio intracelular en cáncer y envejecimiento neuronal (CaRe).* Ref: RTI2018-099298-B-100
From 2019 - 2021
Funding: 121.000 €
Principal Investigator: Carlos Villalobos Jorge

Title: *Bases celulares y moleculares del envejecimiento neuronal y de la susceptibilidad asociada a las enfermedades neurodegenerativas* Ref. VA294P18
Funding Agency: Junta de Castilla y León, Consejería de Educación
From 2018 to 2020.
Funding: 120.000 €
Principal Investigator: Lucía Núñez Llorente

Teaching:

Carlos Villalobos has contributed to the teaching of the courses "Introduction of Biomedical Research" (30 h) and "Physiology of Transport" at the Master in Biomedical Research of the (4 h) University of Valladolid.
Lucía Núñez has contributed to the teaching of the courses of "Human Physiology" at the Degree in Medicine, Degree in Nutricion and Degree in Logopedics of the University of Valladolid. Total number of hours is 120 h.

Doctoral Thesis:

Lucía González Gutiérrez defended her thesis titled "*Calcium channel remodeling in colon cancer cells: implications for channel inactivation and reversal by polyamine synthesis inhibition*". Directors Carlos Villalobos and Lucía Núñez, IBGM/Facultad de Medicina, Universidad de Valladolid. She is now a Post-doctoral fellow at the laboratory of Prof. Juan A. Rosado, University of Extremadura, Cáceres, Spain.

Communications to Scientific Meetings

1. **Villalobos C**. *Store-operated channels in pituitary physiology*. RECI VII. Spanish Ion channel network meeting. Symposium on "Store-operated channels". May 2019. Cáceres, Spain. Symposia.

2. Gutiérrez LG, Hernández-Morales M, Núñez L, **Villalobos C**. Reversing Ca^{2+} channel remodeling in colon cancer cells by polyamine biosynthesis inhibition. 7th Meeting of the Spanish Ion Channel Network (RECI VII), *Cáceres*, Spain. May 15-17, 2019. Oral Communication.

3. Pérez-Riesgo E, **Villalobos C**. Illuminating transcriptomics analysis of calcium remodeling in colorectal cancer. 7th Meeting of the Spanish Ion Channel Network (RECI VII), *Cáceres*, Spain. May 15-17, 2019. Poster Communication.

4. Hernando-Pérez E, Calvo-Rodriguez M, García-Durillo M, **Villalobos C**, Nuñez L. Aging enhances expression of IP_3 receptors and ER-mitochondria colocalization leading to Ca^{2+} remodelling in rat hippocampal neurons. 7th Meeting of the Spanish Ion Channel Network (RECI VII), *Cáceres*, Spain. May 15-17, 2019. Poster Communication.

5. **Villalobos C**, Núñez L, Hernando-Pérez E, Calvo-Rodríguez M. Effects of amyloid β oligomers on Ca^{2+} remodeling in rat hippocampal neurons: from good to bad depending on age. AD/PD Meeting 2019. *Lisbon*, Portugal. March 2019. Póster Communication

Cell and Molecular Physiology Unit
Ion Channels and Vascular Physiopathology Group

Team

Principal Investigators:

Mª Teresa Pérez (UVA), tperez@ibgm.uva.es

José Ramón López López (UVA), jrlopez@ibgm.uva.es

Postdocs: Pilar Cidad

Predocs: Nuria Daghbouche, Lucía Alonso, Inés Alvarez, MaryCarmen Arévalo,
Sara Moreno.

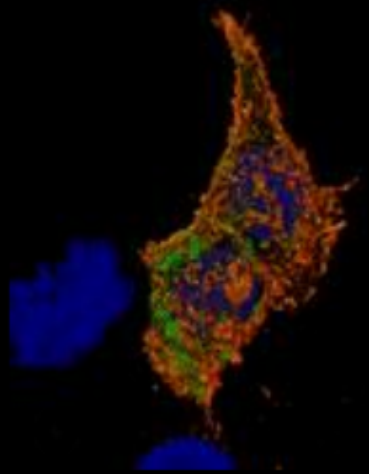
Technicians: Esperanza Alonso

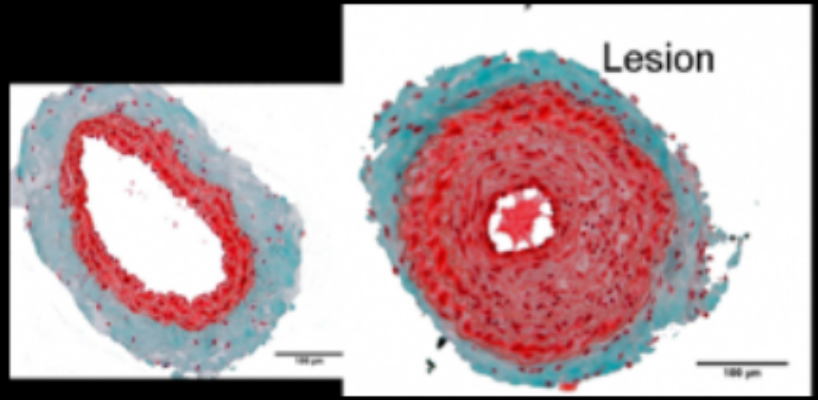
Resarch Highlights

Characterization of the role of ion channels in vascular function, with special emphasis on essential hypertension and intimal hyperplasia.

Essential hypertension. The increase in vascular tone during hypertension is a result of the change in the expression levels of different ion channels. We are currently involved in the molecular and functional characterization of various ion channels in vascular smooth muscle cells from different arterial beds in a hypertensive mouse model. With this characterization, we intend to clarify some of the mechanisms involved in the vascular hyperreactivity characteristic of hypertensive animals. In addition, we intend to find new therapeutic targets that allow the treatment of hypertension to be effectively addressed.

Intimal hyperplasia. Hyperplasia of the intima develops in response to noxious stimuli for the arterial wall (mechanical, chemical or immunological) and leads to a change in the vascular architecture due to thickening of the neointima. This thickening is the result of the proliferation and migration of vascular smooth muscle cells from the middle to the intimal arterial layer. We have recently characterized the change in the expression of ion channels associated with the phenotypic change of smooth muscle cells and we have identified Kv1.3 channels as modulating elements of the proliferative response. In the coming years, we propose to characterize the molecular mechanisms involved and explore the possibilities of using these channels as therapeutic targets in the treatment of intimal hyperplasia, one of the most important limiting factors for the long-term success of routine procedures in which an arterial bypass is performed.




Lesion

Publications in 2019

1. Arévalo-Martínez M, Cidad P, García-Mateo N, Moreno-Estar S, Serna J, Fernández M, Swärd K, **Simarro M, de la Fuente MA, López-López JR, Pérez-García MT** (2019) Myocardin-Dependent Kv1.5 Channel Expression Prevents Phenotypic Modulation of Human Vessels in Organ Culture. *Arterioscler Thromb Vasc Biol*. 2019 Dec;39(12):e273-e286. doi: 10.1161/ATVBAHA.119.313492

2. Alonso-Carbajo L, Alpizar YA, Startek JB, **López-López JR, Pérez-García MT**, Talavera K (2019) Activation of the cation channel TRPM3 in perivascular nerves induces vasodilation of resistance arteries. *J Mol Cell Cardiol*. 2019 Apr;129:219-230. doi: 10.1016/j.yjmcc.2019.03.003.

Doctoral Thesis

* **Lucía Alonso Carbajo**. "Functions of sensory TRP channels in vascular responses to chemical and thermal stimuli". PhD with International Mention and in codirection with KU Leuven University. Directors José Ramón López López and Mª Teresa Pérez García. IBGM/Facultad de Medicina, Universidad de Valladolid.

* **Inés Alvárez Miguel**. "Remodeling of vascular smooth muscle ion channels involved in purinergic signaling in essential hypertension" PhD with international mention. Directors José Ramón López López and Mª Teresa Pérez García. IBGM/Facultad de Medicina, Universidad de Valladolid.

Cell and Molecular Physiology Unit
Physiology and Physiopathology of O_2 Sensing Group

Team

Principal Investigators:
Asunción Rocher (UVA), rocher@ibgm.uva.es
Ana Obeso (UVA), aobeso@ibgm.uva.es

Scientists: Ricardo Rigual, Angela Gómez Niño.

Postdocs: Jesús Prieto-Lloret, Elena Olea Fraile, Elvira González Obeso

Predocs: Immaculada Docio.

Technicians: María Llanos, Ana Gordillo.

This team is member of CIBERES

Research Highlights

Our three main lines of research are as follows:

- Pathophysiological effects of Obstructive Sleep Apnea (OSA): multiparametric study in an animal model in Intermittent Chronic Hypoxia.
- Effects of Intermittent Chronic Hypoxia, as a model of OSA, on spontaneous tumorigenesis in a murine model.
- Characterization of Pulmonary Hypertension Associated with Chronic Hypoxia in a Rat Model: Hemodynamic Study and Vascular Characterization.

Publications in 2019

1. Sacramento JF, Olea E, Ribeiro MJ, **Prieto-Lloret J**, Melo BF, Gonzalez C, Martins FO, Monteiro EC, Conde SV (2019) Contribution of adenosine and ATP to the carotid body chemosensory activity in ageing. *J Physiol* 2019 Oct;597(19):4991-5008. doi: 10.1113/JP274179.

2. Gallego-Martin T, Prieto-Lloret J, Aaronson PI, **Rocher A, Obeso A** (2019) Hydroxycobalamin Reveals the Involvement of Hydrogen Sulfide in the Hypoxic Responses of Rat Carotid Body Chemoreceptor Cells. *Antioxidants (Basel).* 2019 Mar 13;8(3). pii: E62. doi: 10.3390/antiox8030062.

Doctoral Thesis

Inmaculada Docio Cuadrado. "Efectos inducidos por la hipoxia crónica intermitente en rata y cobaya como modelos animales de la apnea obstructiva del sueño". Directors Asunción Rocher and Jesús Prieto. IBGM/Facultad de Medicina, Universidad de Valladolid.

Ongoing Projects

Title: *Un nuevo efecto patológico de la hipoxia intermitente que ocurre en la apnea del sueño: tumorigénesis espontánea e implicaciones fisiopatológicas.*
Funding Agency: Junta de Castilla y León. Convocatoria de apoyo de los GIR a iniciar en 2018 (VA106G18)
From 2018 to 2020
Funding: 12.000 €
Principal Investigator: Ana Obeso

Others

Cell and Molecular Physiology
Diabetes and Pancreatic β Cell Group

Team

Principal Investigator:
Irene Cózar Castellano (UVA),
irene.cozar@ibgm.uva.es

Scientists: Mª Carmen Domínguez Lobatón, Alfredo Moreno

Postdocs: Beatriz Merino, Cristina Parrado

Predocs: Cristina Fernández Díaz, Carlos González Casimiro

Research Highlights

One of the characteristics common to the two most prevalent types of diabetes in the population (type 1-insulin dependent and type 2-insulin resistant) is the loss of functional beta-pancreatic mass (mass of insulin-producing cells). There is a loss of approximately 70-100% in type 1 diabetes and up to 65% in type 2 diabetes. Adult beta, pancreatic, rodent and human cells can be generated from the proliferation of beta-pancreatic cells Differentiated Therefore, the search for new therapeutic targets that preserve and / or induce the functional mass of beta-pancreatic cells is essential for the treatment of diabetes. It is also important to find new therapeutic targets involved in the production and secretion of insulin and glucagon, the main pancreatic hormones involved in the maintenance of glucose homeostasis. The main objective of our laboratory is: "Study of strategies for the maintenance of functional beta-pancreatic mass as therapy for diabetes". This is specified in three lines of action: Search for small molecules that induce regeneration / protection of the beta-pancreatic cell and improve its function, study of proteins involved in the function of beta- and alpha-pancreatic cells and study of the relationship of diabetes mellitus with neurodegenerative diseases.

Publications in 2019

1. Merino B, Fernández-Díaz CM, **Cózar-Castellano I**, Perdomo G (2019) Intestinal Fructose and Glucose Metabolism in Health and Disease. *Nutrients*. 2019 Dec 29;12(1). pii: E94. doi: 10.3390/nu12010094.

2. García-Calvo J, Torroba T, Brañas-Fresnillo V, Perdomo G, **Cózar-Castellano I**, Li YH, Legrand YM, Barboiu M (2019) Manipulation of Transmembrane Transport by Synthetic K+ Ionophore Depsipeptides and Its Implications in Glucose-Stimulated Insulin Secretion in β-Cells. *Chemistry*. 2019 Jul 11;25(39):9287-9294. doi: 10.1002/chem.201901372.

3. Fernandez-Diaz CM, Merino B, Lopez-Acosta JF, Cidad P, de la Fuente MA, Lobaton CD, Moreno A, Leissring MA, Perdomo G, **Cozar-Castellano I** (2019) Pancreatic beta-cell-specific deletion of insulin-degrading enzyme leads to dysregulated insulin secretion and beta-cell functional immaturity. *Am J Physiol Endocrinol Metab*. 2019 Sep 3. doi: 10.1152/ajpendo.00040.2019.

4. Loera-Valencia R, Goikolea J, **Parrado-Fernández C**, Merino-Serrais P, Maioli S (2019) Alterations in cholesterol metabolism as a risk factor for developing Alzheimer's disease: Potential novel targets for treatment. *J Steroid Biochem Mol Biol*. 2019 Jun;190:104-114. doi: 10.1016/j.jsbmb.2019.03.003. Epub 2019 Mar 13.

Ongoing Research Projects

Title: *Role of insulin-degrading enzyme (ide) in hepatic insulin resistance*
Funding Agency: *European Foundation for the Study of Diabetes from* Fundación general de la Universidad de Valladolid
Funding: 70.000 €
From 2018 to 2020
Principal Investigator: Irene Cózar Castellano

Doctoral Thesis in 2019

Cristina María Fernández Díaz. "Role of insulin-degrading enzyme (IDE) in pancreatic beta-cell function: relevance in health and diabetes mellitus". Director Irene Cózar. IBGM/Facultad de Medicina, Universidad de Valladolid.

Cell and Molecular Physiology Unit
Neurovascular Pathology Group

Team
Principal Investigator:
Juan F. Arenillas (UVA),
juanfrancisco.arenillas@uva.es

Research Highlights

The group's philosophy is to start from the clinical problem in order to obtain applied answers from basic research. In all of our strategic research lines we try to make a multi-modal approach to the problems, combining clinical information and biological samples with *in vitro* and *in vivo* experiments, with a key role in neuroimaging. We work with other groups at the University of Valladolid in the optimization and use of the RMa 9.4 T for experimental experiments in animal in vivo and postmortem. We strategically pursue advances in the field of molecular imaging applied to neurological diseases. The research activity of the GIPN is organized around four main strategic lines:

- Acute phase of the ischemic and hemorrhagic stroke. Brain reperfusion. Circulation collateral.
- Intracranial atherosclerosis and vascular cognitive deterioration.
- Neurorepair after stroke.
- Prevention: heart and brain.

Publications

1. Carrera C, Cullell N, Torres-Águila N, Muiño E, Bustamante A, Dávalos A, López-Cancio E, Ribó M, Molina CA, Giralt-Steinhauer E, Soriano-Tárraga C, Mola-Caminal M, Jiménez-Conde J, Roquer J, Vives-Bauza C, Navarro RD, Obach V, **Arenillas JF**, Segura T, Serrano-Heras G, Martí-Fàbregas J, Freijo M, Cabezas JA, Tatlisumak T, Heitsch L, Ibañez L, Cruchaga C, Lee JM, Strbian D, Montaner J, Fernández-Cadenas I; Spanish Stroke Genetic Consortium (2019) Validation of a clinical-genetics score to predict hemorrhagic transformations after rtPA. *Neurology*. 2019 Aug 27;93(9):e851-e863. doi: 10.1212/WNL.0000000000007997.

2. Amaro S, Renú A, Laredo C, Castellanos M, **Arenillas JF**, Llull L, Rudilloso S, Urra X, Obach V, Chamorro Á; on behalf of the URICO-ICTUS investigators (2019) Relevance of Collaterals for the Success of Neuroprotective Therapies in Acute Ischemic Stroke: Insights from the Randomized URICO-ICTUS Trial. *Cerebrovasc Dis*. 2019;47(3-4):171-177. doi: 10.1159/000500712. Epub 2019 Jun 4.

3. Campbell BCV, Ma H, Ringleb PA, Parsons MW, Churilov L, Bendszus M, Levi CR, Hsu C, Kleinig TJ, Fatar M, Leys D, Molina C, Wijeratne T, Curtze S, Dewey HM, Barber PA, Butcher KS, De Silva DA, Bladin CF, Yassi N, Pfaff JAR, Sharma G, Bivard A, Desmond PM, Schwab S, Schellinger PD, Yan B, Mitchell PJ, Serena J, Toni D, Thijs V, Hacke W, Davis SM, Donnan GA; EXTEND, ECASS-4, and EPITHET Investigators (2019) Extending thrombolysis to 4·5-9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data. *Lancet*. 2019 Jul 13;394(10193):139-147. doi: 10.1016/S0140-6736(19)31053-0. Epub 2019 May 22.

4. Diener HC, Sacco RL, Easton JD, Granger CB, Bernstein RA, Uchiyama S, Kreuzer J, Cronin L, Cotton D, Grauer C, Brueckmann M, Chernyatina M, Donnan G, Ferro JM, Grond M, Kallmünzer B, Krupinski J, Lee BC, Lemmens R, Masjuan J, Odinak M, Saver JL, Schellinger PD, Toni D, Toyoda K; RE-SPECT ESUS Steering Committee and Investigators (2019) Dabigatran for Prevention of Stroke after Embolic Stroke of Undetermined Source. *N Engl J Med*. 2019 May 16;380(20):1906-1917. doi: 10.1056/NEJMoa1813959.

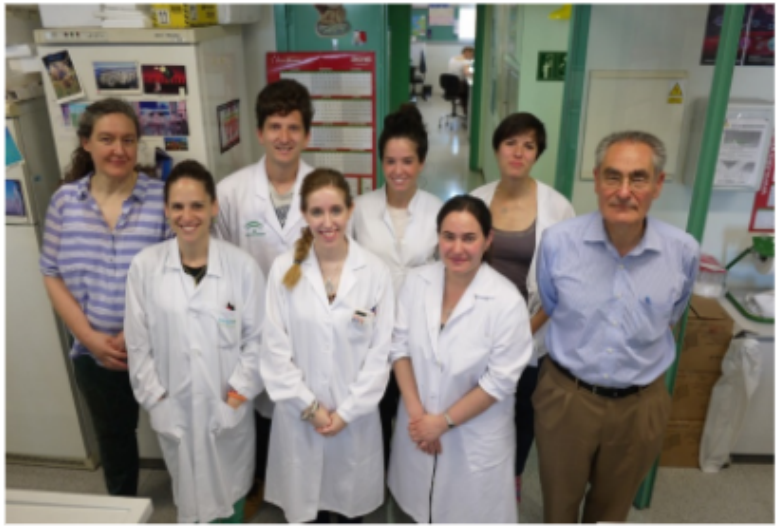
5. González García A, Moniche F, Escudero-Martínez I, Mancha F, Tomasello A, Ribó M, Delgado-Acosta F, Ochoa JJ, de Las Heras JA, López-Mesonero L, González-Delgado M, Murias E, Gil J, Gil R, Zamarro J, Parrilla G, Mosteiro S, Fernández-Couto MD, Fernández de Alarcón L, Ramírez-Moreno JM, Luna A, Gil A, González-Mandly A, Caniego JL, Zapata-Wainberg G, García E, Alcázar PP, Ortega J, **Arenillas JF**, Algaba P, Zapata-Arriaza E, Alcalde-López J, de Albóniga-Chindurza A, Cayuela A, Montaner J (2019) Clinical Predictors of Hyperperfusion Syndrome Following Carotid Stenting: Results From a National Prospective Multicenter Study. *JACC Cardiovasc Interv*. 2019 May 13;12(9):873-882. doi: 10.1016/j.jcin.2019.01.247.

6. Purroy F, Vena A, Forné C, de Arce AM, Dávalos A, Fuentes B, **Arenillas JF**, Krupinski J, Gómez-Choco M, Palomeras E, Martí-Fábregas J, Castillo J, Ustrell X, Tejada J, Masjuan J, Garcés M, Benabdelhak I, Serena J (2019) Age- and Sex-Specific Risk Profiles and In-Hospital Mortality in 13,932 Spanish Stroke Patients. *Cerebrovasc Dis*. 2019;47(3-4):151-164. doi: 10.1159/000500205.

7. **Arenillas JF**, Dieleman N, Bos D (2019) intracranial arterial wall imaging: Techniques, clinical applicability, and future perspectives. *Int J Stroke*. 2019 Apr 13:1747493019840942. doi: 10.1177/1747493019840942.

8. Planas-Ballvé A, Crespo AM, Aguilar LM, Hernández-Pérez M, Canento T, Dorado L, Alzamora MT, Torán P, Pera G, Muñoz-Ortiz L, **Arenillas JF**, Castañón M, Dávalos A, Millán M, López-Cancio E (2019) The Barcelona-Asymptomatic Intracranial Atherosclerosis study: Subclinical intracranial atherosclerosis as predictor of long-term vascular events. *Atherosclerosis*. 2019 Mar;282:132-136. doi: 10.1016/j.atherosclerosis.2019.01.022.

Innate Immunity and Inflammation Unit
Immune-mediated tissue injury and innate immunity Group



Team

Principal Investigators:

Mariano Sánchez Crespo (CSIC), mscres@ibgm.uva.es

Scientific staff: Nieves Fernández

Postdocs: Carmen Herrero

Predocs: Cristina Martón, Cristina Mancebo, Saioa Márquez

Technicians: Sara Alonso

Research Highlights

Our work covers the molecular mechanisms involved in the development of tissue damage by the immune mechanism and the characterization of the main chemical mediators that are generated after the occupation of the receptors for the molecular patterns associated with pathogens and the receptors for the Fc portion of the antibodies of the IgG class. The cooperation between these receptors explains the current models of functioning of the immune system, according to which sparingly soluble and particulate ligands are the triggers of the acute inflammatory reaction and the initiation of the adaptive response. These facts are extremely relevant to understanding the pathogenesis of autoimmune diseases and the defense against microbial invasion.

Publications in 2019

1. Chopra S, Giovanelli P, Alvarado-Vazquez PA, Alonso S, Song M, Sandoval T, Chae CS, Tan C, Fonseca MM, Gutierrez S, Jimenez L, Subbaramaiah K, Iwawaki T, Kingsley PJ, Marnett LJ, Kossenkov AV, **Crespo M**, Dannenberg AJ, Glimcher LH, Romero-Sandoval EA, Cubillos-Ruiz JR (2019) IRE1α-XBP1 signaling in leukocytes controls prostaglandin biosynthesis and pain. *Science*. 2019 Jul 19;365(6450). pii: eaau6499. doi: 10.1126/science.aau6499.

2. Márquez S, Fernández JJ, Mancebo C, Herrero-Sánchez C, Alonso S, Sandoval TA, Rodríguez Prados M, Cubillos-Ruiz JR, Montero O, **Fernández N**, **Sánchez Crespo M** (2019) Tricarboxylic Acid Cycle Activity and Remodeling of Glycerophosphocholine Lipids Support Cytokine Induction in Response to Fungal Patterns. *Cell Rep*. 2019 Apr 9;27(2):525-536.e4. doi: 10.1016/j.celrep.2019.03.033.

3. Parra-Izquierdo I, Castaños-Mollor I, López J, Gómez C, San Román JA, **Sánchez Crespo M**, **García-Rodríguez C** (2019) Lipopolysaccharide and interferon-γ team up to activate HIF-1α via STAT1 in normoxia and exhibit sex differences in human aortic valve interstitial cells. *Biochim Biophys Acta Mol Basis Dis*. 2019 Sep 1;1865(9):2168-2179. doi: 10.1016/j.bbadis.2019.04.014.

Doctoral Thesis

Saioa Marquez Piñeiro. "Regulación de la transcripción de citoquinas por la modulación del metabolismo energético y el estrés del retículo endoplasmático en células dendríticas". Directors Mariano Sanchez Crespo and Nieves Fernández. IBGM/Facultad de Medicina, Universidad de Valladolid.

Ongoing Research Projects

Title: *El eje metabolismo epigenoma en la polarización de la respuesta inmune.*
Funding Source: Plan Nacional I+D+I, Ministerio de Economía y Competitividad (SAF2017-83079-R)
From 2018 to 2020.
Funding: 121.000 €
Principal Investigator: Mariano Sánchez Crespo

Innate Immunity and Inflammation Unit
Bioactive Lipids and Lipidomics Group

Team
Principal Investigators:
Jesús Balsinde (CSIC), jbalsinde@ibgm.uva.es
Postdocs: Alma Astudillo
Predocs: Miguel Angel Bermúdez, Laura Pereira, Patricia Lebrero, Patricia Monge, Alvaro Garrido
Technicians: Montserrat Duque
This team is member of the Eicosanoid Research Division and CIBERDEM

The Eicosanoid Research Division
Valladolid

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Research Highlights

In our laboratory, we try to delineate the mechanisms through which certain lipids mediate inflammation and contribute to the pathogenesis of a variety of diseases. Monocytes and macrophages are cells of innate and adaptive immunity that participate and regulate inflammation by producing a series of modulators, such as cytokines, chemokines, and eicosanoids. Eicosanoids derive from the enzymatic oxygenation of arachidonic acid, a compound that is initially present as an esterified fatty acid in membrane phospholipids. This fatty acid is released from the membranes in situations of activation by several mechanisms, the most important of which is the involvement of phospholipases A2.

Publications in 2019

1. Guijas C, Bermúdez MA, Meana C, Astudillo AM, Pereira L, Fernández-Caballero L, **Balboa MA**, **Balsinde J** (2019) Neutral Lipids Are Not a Source of Arachidonic Acid for Lipid Mediator Signaling in Human Foamy Monocytes. *Cells*. 2019 Aug 20;8(8). pii: E941. doi: 10.3390/cells8080941.

2. Lebrero P, Astudillo AM, Rubio JM, Fernández-Caballero L, Kokotos G, **Balboa MA**, **Balsinde J** (2019) Cellular Plasmalogen Content Does Not Influence Arachidonic Acid Levels or Distribution in Macrophages: A Role for Cytosolic Phospholipase A2γ in Phospholipid Remodeling. *Cells*. 2019 Jul 31;8(8). pii: E799. doi: 10.3390/cells8080799.

3. **Balboa MA**, de Pablo N, Meana C, **Balsinde J** (2019) The role of lipins in innate immunity and inflammation. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2019 Jun 17;1864(10):1328-1337. doi: 10.1016/j.bbalip.2019.06.003.

4. Rodríguez JP, Guijas C, Astudillo AM, Rubio JM, **Balboa MA**, **Balsinde J** (2019) Sequestration of 9-Hydroxystearic Acid in FAHFA (Fatty Acid Esters of Hydroxy Fatty Acids) as a Protective Mechanism for Colon Carcinoma Cells to Avoid Apoptotic Cell Death. *Cancers (Basel)*. 2019 Apr 12;11(4). pii: E524. doi: 10.3390/cancers11040524.

Doctoral Thesis

- **Patricia Lebrero Fernández**. "Phospholipid arachidonic acid remodeling in macrophages: role of plasmalogen species". Directors Jesús Balsinde y María Angeles Balboa. IBGM/Facultad de Medicina, Universidad de Valladolid.
- **Nagore de Pablo Herranz**."Modulation of macrophage antiviral responses by lipin-2: type i interferon, inflammasome and cholesterol homeostasis". Directors Jesús Balsinde y María Angeles Balboa. IBGM/Facultad de Medicina, Universidad de Valladolid.
- **Miren Itziar San Juan García**. "Lipin-2 regulates palmitic acid-induced inflammasome nlrp3 activation in macrophages". Directors Jesús Balsinde y María Angeles Balboa. IBGM/Facultad de Medicina, Universidad de Valladolid.

Innate Immunity and Inflammation Unit
Inflammatory Degenerative Diseases Group

Team
Principal Investigators:
Mª Luisa Nieto (CSIC), mlnieto@ibgm.uva.es
Scientific staff: Marita Hernández
Postdocs: Yolanda Alvarez
Predocs: Isabel Gallardo, Beatriz Rosa, Inmaculada Simón
Technicians: Isabel Cabero
This team is member of CIBERCV

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Research Highlights

Our laboratory is interested in the signal transduction mechanisms regulating inflammatory and degenerative processes in cells of cardiovascular relevance. Our work focuses on the involvement of certain pro-inflammatory proteins such as tumor necrosis factor a (TNFa) or secreted phospholipase A2 (sPLA2) in the development of atherosclerotic lesions.

Our system model is the THP-1 monocytic cell line, in which we have described that both TNFa and sPLA2 are able to induce different actions, ranging from gene expression, cell differentiation, migration and apoptosis. Analyses of the signaling cascades triggered by these proteins include small molecular weight GTPase activation, MAPK activation, and PKB/Akt involvement. The correct definition of the steps implicated in generating biochemical signals will eventually allow us to assay different drugs.

We have already initiated studies with the anti-lipidemic drugs statins and 2-hydroxy-3-methyl-glutaryl-CoA inhibitors. We are also interested in defining the molecular basis of a process called astrogliosis, which occurs when astrocytes proliferate and change their shape in response to external aggression. These cells also release a variety of factors such as adhesion molecules, cytokines, and growth factors. These events may be of special relevance during ischemia. We work with glial cells and stimulate them with different agonists (thrombin, TNFa, sPLA2, lysophosphatidic acid). We are also interested in the possible interactions between these ligands at the level of receptor transactivation, cooperative signaling or desensitization.

Publications in 2019

1. Marín-Royo G, Rodríguez C, Le Pape A, Jurado-López R, Luaces M, Antequera A, Martínez-González J, Souza-Neto FV, **Nieto ML**, Martínez-Martínez E, Cachofeiro V (2019) The role of mitochondrial oxidative stress in the metabolic alterations in diet-induced obesity in rats. *FASEB J*. 2019 Aug 1:fj201900347RR. doi: 10.1096/fj.201900347RR.

2. Marín-Royo G, Ortega-Hernández A, Martínez-Martínez E, Jurado-López R, Luaces M, Islas F, Gómez-Garre D, Delgado-Valero B, Lagunas E, Ramchandani B, García-Bouza M, **Nieto ML**, Cachofeiro V (2019) The Impact of Cardiac Lipotoxicity on Cardiac Function and miRNAs Signature in Obese and Non-Obese Rats with Myocardial Infarction. *Sci Rep*. 2019 Jan 24;9(1):444. doi: 10.1038/s41598-018-36914-y.

Doctoral Thesis in 2019

- **Beatriz Rosa Gutiérrez Miranda.** "Propiedades terapéuticas de secoiridoides y triterpenos. Estudio en un modelo experimental de esclerosis múltiple". Director María Luisa Nieto. IBGM/Facultad de Medicina, Universidad de Valladolid.
- **Isabel Gallardo Romero**. "Potencial terapéutico de antioxidantes sintéticos y naturales en la prevención de alteraciones asociadas a la miocarditis: estudio en un modelo de miocarditis autoinmune experimental". Director María Luisa Nieto, IBGM/Facultad de Medicina, Universidad de Valladolid.

Innate Immunity and Inflammation Unit
Lipid metabolism and Inflammation Group

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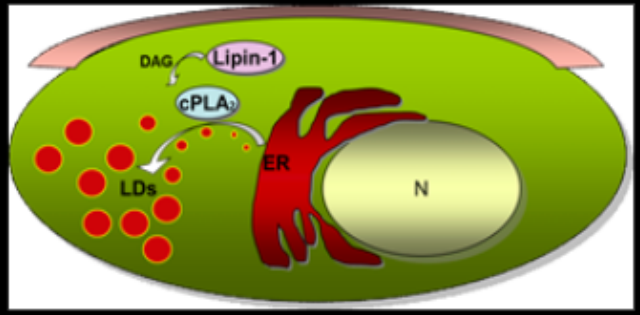
Team
Principal Investigator:
Mª Angeles Balboa (CSIC), mbalboa@ibgm.uva.es
Postdocs: Clara Meana, Javier Casas
Predocs: Lidia Fernández-Caballero, Miren Itziar, Nagore de Pablo
This team is member of the Eicosanoid Research Division and CIBERDEM

Research Highlights

Our previous investigations have indicated that in promonocitic human cells the inhibition of lipin activity produces a profound deregulation of the lipid metabolism of these cells, decreasing the synthesis of phospholipids and triglycerides, and even reaching apoptosis through the mitochondrial pathway. Also, it has been found that lipin could be related to the activation and expression of important enzymes of the biosynthetic pathway of proinflammatory lipid mediators. For example, the induction of cyclooxygenase 2 (COX-2), an enzyme that metabolizes AA to prostaglandins, is blocked by inhibitors that decrease lipin activity. In certain cellular systems, the DAG generated by lipin facilitates the interaction of the cytosolic phospholipase A2 of the IVA group (cPLA2) with its substrates, producing the release of arachidonic acid from membrane phospholipids. Recently, we have observed that in human macrophages, lipin-1 is located on the surface of cellular TAG storage organelles known as lipid droplets (lipid droplets).

Other gene expression experiments by "arrays" analysis show that lipin 1 regulates the expression of multiple genes in mouse peritoneal macrophages after activation with lipopolysaccharide (LPS) from the bacterial wall of E. coli. These genes include inducible nitric oxide synthase (iNOS), which has an important role in the elimination of invading microorganisms, and IL-23, a proinflammatory interleukin that maintains Th17 responses, important in the elimination of pathogens and in autoimmunity.



We plan to:

1) define which metabolites produced or eliminated by the action of lipin control the generation of proinflammatory factors in macrophages, how they do it and what is the impact of all this in murine models of inflammation.

2) define the role of lipin in the macrophage activation by fatty acids in the diet, dissecting the signal transduction pathways involved.

3)define the role of lipin in the generation and maintenance of lipid droplets, cellular organelles where lipids are stored and which seem to play an important role in the inflammatory response of macrophages, and finally.

4) define the lipidomic impact of the absence of lipins in macrophages during inflammatory processes.

Publications in 2019

1. Guijas C, Bermúdez MA, Meana C, Astudillo AM, Pereira L, Fernández-Caballero L, **Balboa MA**, **Balsinde J** (2019) Neutral Lipids Are Not a Source of Arachidonic Acid for Lipid Mediator Signaling in Human Foamy Monocytes. *Cells*. 2019 Aug 20;8(8). pii: E941. doi: 10.3390/cells8080941.

2. Lebrero P, Astudillo AM, Rubio JM, Fernández-Caballero L, Kokotos G, **Balboa MA**, **Balsinde J** (2019) Cellular Plasmalogen Content Does Not Influence Arachidonic Acid Levels or Distribution in Macrophages: A Role for Cytosolic Phospholipase A2γ in Phospholipid Remodeling. *Cells*. 2019 Jul 31;8(8). pii: E799. doi: 10.3390/cells8080799.

3. **Balboa MA**, de Pablo N, Meana C, **Balsinde J** (2019) The role of lipins in innate immunity and inflammation. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2019 Jun 17;1864(10):1328-1337. doi: 10.1016/j.bbalip.2019.06.003.

4. Rodríguez JP, Guijas C, Astudillo AM, Rubio JM, **Balboa MA**, **Balsinde J** (2019) Sequestration of 9-Hydroxystearic Acid in FAHFA (Fatty Acid Esters of Hydroxy Fatty Acids) as a Protective Mechanism for Colon Carcinoma Cells to Avoid Apoptotic Cell Death. *Cancers (Basel)*. 2019 Apr 12;11(4). pii: E524. doi: 10.3390/cancers11040524.

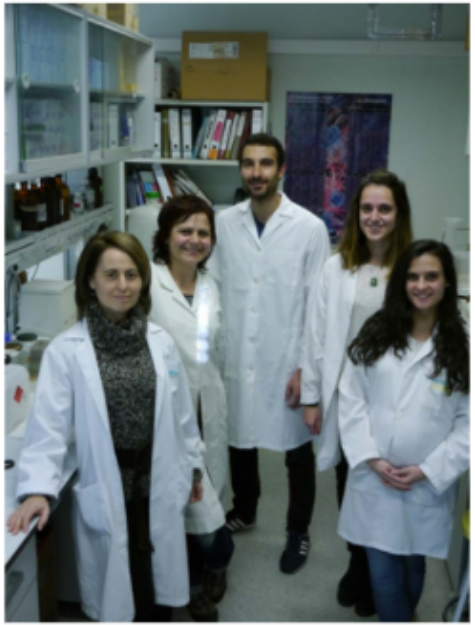
Doctoral Thesis

- **Patricia Lebrero Fernández**. "Phospholipid arachidonic acid remodeling in macrophages: role of plasmalogen species". Directors Jesús Balsinde y María Angeles Balboa. IBGM/Facultad de Medicina, Universidad de Valladolid.

- **Nagore de Pablo Herranz**."Modulation of macrophage antiviral responses by lipin-2: type i interferon, inflammasome and cholesterol homeostasis". Directors Jesús Balsinde y María Angeles Balboa. IBGM/Facultad de Medicina, Universidad de Valladolid.

- **Miren Itziar San Juan García**. "Lipin-2 regulates palmitic acid-induced inflammasome nlrp3 activation in macrophages". Directors Jesús Balsinde y María Angeles Balboa. IBGM/Facultad de Medicina, Universidad de Valladolid.

Innate Immunity and Inflammation Unit
Toll-Like Receptors & Inflammatory Diseases Group



Team

Principal Investigator:

Carmen García Rodríguez (CSIC),

cgarcia@ibgm.uva.es

Predocs: Irene Castaños-Mollor, Iván Parra-Izquierdo, Tania Sánchez-Bayuela

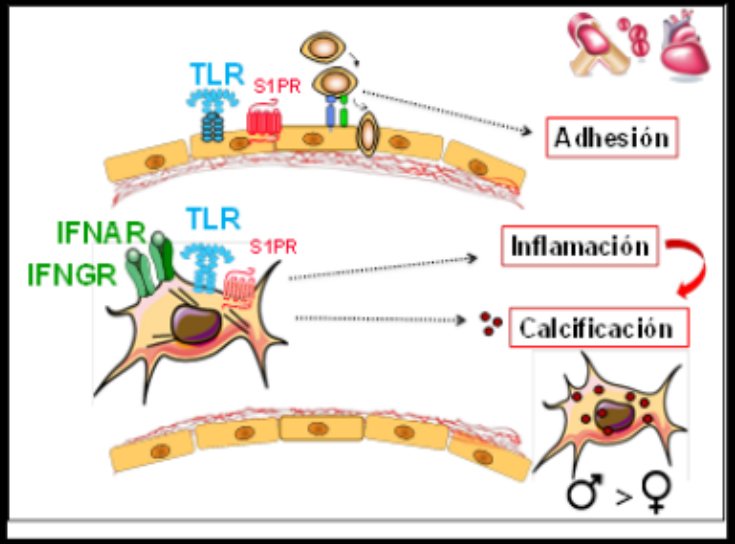
Technicians: Cristina Gómez

This team is member of the CIBERCV network

cibercv isciii

Research Highlights

The scientific interest of the group is focused on the role of of innate immune receptors in the pathophysiology of inflammatory diseases. For this purpose, basic and translational approaches, molecular biology and immunology techniques, as well as primary cultures of human cells are used. The Toll-like receptors or TLRs, whose discoverers received the Nobel Prize in Physiology and Medicine in 2011, act as sentinels of the immune system against pathogens as well as endogenous molecules from tissue damage, thus activating defense mechanisms and inflammation. Notably, inflammation is estimated to be present in about two thirds of the diseases. Our focus is to investigate the role of TLRs and other immunomodulators as interferons in the initial phases of the pathogeny of cardiovascular diseases with an inflammatory component, i.e. calcified aortic stenosis and atherosclerosis. Additionally, our interest is to elucidate the sex-specific mechanisms underlying gender differences in cardiovascular diseases. The ultimate goal is to design new therapeutic strategies for their treatment and / or prevention.



Publications in 2019

1. Parra-Izquierdo I, Castaños-Mollor I, López J, Gómez C, San Román JA, **Sánchez Crespo M, García-Rodríguez C** (2019) Lipopolysaccharide and interferon-γ team up to activate HIF-1α via STAT1 in normoxia and exhibit sex differences in human aortic valve interstitial cells. *Biochim Biophys Acta Mol Basis Dis*. 2019 Sep 1;1865(9):2168-2179. doi: 10.1016/j.bbadis.2019.04.014.

Doctoral Thesis in 2019

"Effects of interferons and their interactions with other ligands in human aortic valve cells" Director Carmen García Rodríguez. (PhD with International mention. PhD Supervisor Mª Carmen García Rodríguez. IBGM/Facultad de Medicina, Universidad de Valladolid.

Teaching

Master of Biomedical Research, University of Valladolid. "Biomedical Applications of Molecular Biology" and "Immunity and Inflammation" courses.

Others

- Invited Conference in 2019: "Daños colaterales en el corazón y diferencias según el sexo".Instituto de Innovación e Investigación Biomédica, Universidad de Cádiz.
- Guided visits to IBGM for high-school students (participation in 4 visits).
- Carmen García is Member of the Academic Committee of the PhD in Biomedical Research from the University of Valladolid.
- Carmen García is co-organizer of the "IBGM seminars" cycle.

Innate Immunity and Inflammation Unit
Tyrosine Phosphatases in the Immune System

Team

Principal Investigators:

Andrés Alonso (CSIC), andres@ibgm.uva.es

Yolanda Bayón (UVA), ybayon@ibgm.uva.es

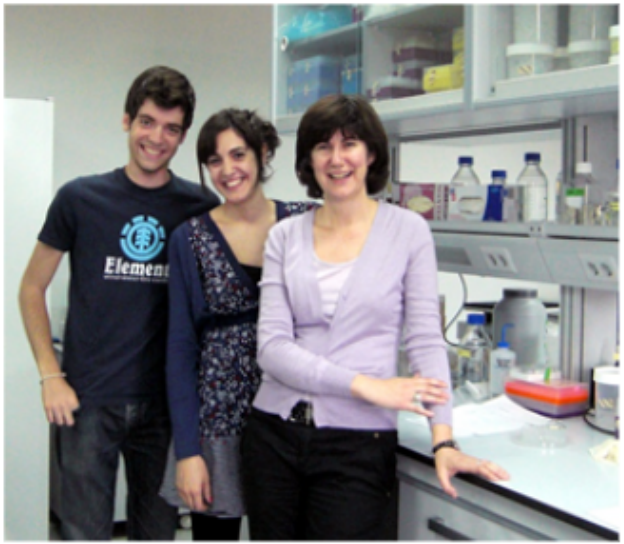
Research Highlights

Reversible protein tyrosine phosphorylation is a key mechanism that regulates the vast majority of cellular processes, from gene expression to cell cycle, and is controlled by two types of enzymes with opposing actions, kinases and phosphatases. Although during the last decades there has been a great advance in the knowledge of kinases, phosphatases are much less known. In this sense, recently it has described that the human genome contains 107 tyrosine phosphatases, a few of them are not characterized yet.

Our lab is interested in studying the function played by phosphatases in the immune response against pathogens. Antigen binding to TCR (T-cell receptor), BCR (B-cell receptor) and FcR (Fc receptor) receptors in the immune cells activates signalling pathways that are initiated by phosphorylation of proteins on tyrosine residues.

Disruption of normal protein phosphorylation levels in the proteins that participate in those signalling pathways may lead to diverse pathologies, such as autoimmune diseases or immunodeficiencies, either by increase or reduction of cell stimulation, respectively. In summary, on one hand we would like to determine the proteins that are phosphorylated on tyrosine in the immune cells activated by antigens, and on the other hand to determine the phosphatases that are involved in their regulation and mainly which is the physiological function of these phosphatases in the immune system. In particular, our attention is focus in a group of tyrosine phosphatases called dual specificity phosphatases, among which we are studying the role that plays VHR (VH1 related) in T cells stimulated through the TCR.

Innate Immunity and Inflammation Unit
Rho GTPases and Lipid Signaling Group



Team

Principal Investigators:

Mª José Caloca (CSIC),

mjcaloca@ibgm.uva.es

Research Highlights

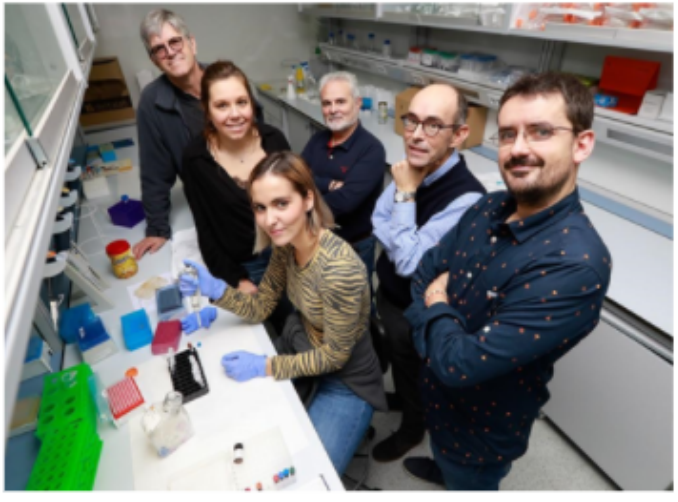
In our laboratory we are studying a family of GAP proteins, chimerins. The chimerin family consists of four members: chimerins α1-, α2-, β1- and β2-chimaerin. These proteins have a characteristic structure with a C1 domain that binds DAG and phorbol esters, a GAP domain that specifically inactivates the GTPase Rac, and an N-terminal SH2 domain, only present in the isoforms α2- and β2-chimaerin. These unique characteristics of the chimerins place them as key molecules that connect the signaling by DAG with the activation of Rac. Our laboratory uses biochemical techniques, cell biology, genetics and animal models to analyze the regulation of these proteins, determine the signaling pathways in which they participate and determine their function in cell biology and pathophysiology.

Publications in 2019

1. Casado-Medrano V, Barrio-Real L, Gutiérrez-Miranda L, González-Sarmiento R, Velasco EA, Kazanietz MG, **Caloca MJ** (2019) Identification of a truncated β1-chimaerin variant that inactivates nuclear Rac1. *J Biol Chem*. 2019 Dec 22. pii: jbc.RA119.008688. doi: 10.1074/jbc.RA119.008688.

2. Fraile-Bethencourt E, Valenzuela-Palomo A, Díez-Gómez B, **Caloca MJ**, Gómez-Barrero S, **Velasco EA** (2019) Minigene Splicing Assays Identify 12 Spliceogenic Variants of BRCA2 Exons 14 and 15. *Front Genet*. 2019 May 28;10:503. doi: 10.3389/fgene.2019.00503. eCollection 2019.

Innate Immunity and Inflammation Unit
Allergy and Mucose Immunity Group/ Mucosal Immunology and Alergy



Team

Principal Investigators:

Eduardo Arranz (UVa), earranz@uva.es
David Bernardo (UVa), d.bernardo.ordiz@gmail.com
José Antonio Garrote (UVa), joseantonio.garrote@uva.es
Luis Fernández Salazar (UVa) luisfernsal@gmail.com

PhD students: Aida Fiz López, Elisa Arribas Rodríguez
MsC students: Angel de Prado
Undergrad students: Carlota Rivera Bengoa

Research Highlights

Our main goas are as follows:

- Study of the mechanisms of the normal and pathological immune response in the mucous membranes of the digestive tract.
- Study of immune abnormalities that are reflected in diseases associated with the gastrointestinal mucosa including coeliac disease and inflammatory bowel disease.
- Immunological diagnosis of diseases that have their origin in abnormalities of the mucosal immune system, or affect the functionality of said system.
- Development of new therapies based on immunomodulation, and evaluation of vaccine strategies to improve the efficacy and route of administration.
- Unravelling the ontogeny, phenotype and function of mucosal dendritic cell and macrophage subsets and their circulating precursors in health and under inflammatory conditions.

Publications in 2019

1. Escudero-Hernández C, Montalvillo E, Antolín B, **Bernardo D, Garrote JA, Arranz E,** Fernández-Salazar L (2019) Different Intraepithelial CD3+ Cell Numbers in Crohn's Disease and Ulcerative Colitis. *Inflamm Bowel Dis*. 2019 Dec 28. pii: izz309. doi: 10.1093/ibd/izz309.

2. Escudero-Hernández C, **Bernardo D, Arranz E, Garrote JA** (2019) Is celiac disease really associated with inflammatory bowel disease? *Rev Esp Enferm Dig*. 2019 Dec 13;112. doi: 10.17235/reed.2019.6779/2019.

3. Fernández-Tomé S, Marin AC, Ortega Moreno L, Baldan-Martin M, Mora-Gutiérrez I, Lanas-Gimeno A, Moreno-Monteagudo JA, Santander C, Sánchez B, Chaparro M, Gisbert JP, **Bernardo D** (2019) Immunomodulatory Effect of Gut Microbiota-Derived Bioactive Peptides on Human Immune System from Healthy Controls and Patients with Inflammatory Bowel Disease. *Nutrients*. 2019 Oct 31;11(11). pii: E2605. doi: 10.3390/nu11112605.

4. S. Fernández-Tomé, B. Hernández-Ledesma, M. Chaparro, P. Indiano-Romacho, J.P. Gisbert, **D. Bernardo.** Role of food proteins and bioactive peptides in inflammatory bowel disease. *Trends in Food Science and Technology*. 2019. 88:194-206.

5. S. Fernández-Tomé, A. Montalbán-Arques, A. Díaz-Guerra, J.M. Galvan-Román, A.C. Marín, I. Mora-Gutiérrez, L. Ortega-Moreno, C. Santander, B. Sánchez, M. Chaparro, J.P. Gisbert, **D. Bernardo**. Peptides encrypted in the human intestinal microbial-exoproteome as novel biomarkers and immunomodulatory compounds in the gastrointestinal tract . *Journal of Functional Foods*. 2019. 52. 459-468.

6. Chaparro M, Barreiro-de Acosta M, Echarri A, Almendros R, Barrio J, Llao J, Gomollón F, Vera M, Cabriada JL, Guardiola J, Guerra I, Beltrán B, Roncero O, Busquets D, Taxonera C, Calvet X, Ferreiro-Iglesias R, Ollero Pena V, **Bernardo D**, Donday MG, Garre A, Godino A, Díaz A, Gisbert JP (2019) Correlation Between Anti-TNF Serum Levels and Endoscopic Inflammation in Inflammatory Bowel Disease Patients. *Dig Dis Sci*. 2019 Mar;64(3):846-854. doi: 10.1007/s10620-018-5362-3.

7. Vaquero L, **Bernardo D**, León F, Rodríguez-Martín L, Alvarez-Cuenllas B, Vivas S (2019) Challenges to drug discovery for celiac disease and approaches to overcome them. *Expert Opin Drug Discov*. 2019 Jul 16:1-12. doi: 10.1080/17460441.2019.1642321.

8. Chaparro M, Garre A, Guerra Veloz MF, Vázquez JM, De Castro ML, Leo E, Rodriguez E, Carbajo AY, Riestra S, Jiménez I, Calvet X, Bujanda L, Rivero M, Gomollón F, Benítez JM, Bermejo F, Alcaide N, Gutiérrez A, Mañosa M, Iborra M, Lorente R, Rojas-Feria M, Barreiro-de Acosta M, Kolle L, Van Domselaar M, Amo V, Argüelles F, Ramírez E, Morell A, **Bernardo D**, Gisbert JP (2019) Effectiveness and safety of the switch from Remicade to CT-P13 in patients with inflammatory bowel disease. *J Crohns Colitis*. 2019 Apr 12. pii: jjz070. doi: 10.1093/ecco-jcc/jjz070.

9. Martínez-López M, Iborra S, Conde-Garrosa R, Mastrangelo A, Danne C, Mann ER, Reid DM, Gaboriau-Routhiau V, Chaparro M, Lorenzo MP, Minnerup L, Saz-Leal P, Slack E, Kemp B, Gisbert JP, Dzionek A, Robinson MJ, Rupérez FJ, Cerf-Bensussan N, Brown GD, **Bernardo D**, LeibundGut-Landmann S, Sancho D (2019) Microbiota Sensing by Mincle-Syk Axis in Dendritic Cells Regulates Interleukin-17 and -22 Production and Promotes Intestinal Barrier Integrity. *Immunity*. 2019 Feb 19;50(2):446-461.e9. doi: 10.1016/j.immuni.2018.12.020.

Projects in 2019

- Pfizer (54211793). Immunomodulatory effect of tofacitinib on human intestinal dendritic cell subsets from patients with ulcerative colitis. 2020-2021. 28,750€. PI David Bernardo, Collaborators: Eduardo Arranz, José A. Garrote, Luis Fernández Salazar

- IV Beca GETECCU-MSD. Implicación funcional de las sub-poblaciones de células dendríticas en la patogénesis de la enfermedad de Crohn. 2020-2021. 12,000€. PI David Bernardo, Collaborators: Eduardo Arranz, José A. Garrote, Luis Fernández Salazar

- Diputación General de Aragón (LMP226_18). Characterization of the effect of bioactive compounds secreted by the intestinal microbiota in the maturation and function of hepatocytes derived from hESC/hiPSC: a new hepatic signaling pathway? 76,000€. Research Colaborator: David Bernard

- Aspire Pfizer (53589311).Predictive biomarkers for response to JAK-inhibitors and biologic therapies in ulcerative colitis by a multi-omic approach. 220,927,28$. PI David Bernardo

- Gerencia Regional de Salud de Castilla y León (1973/A/19). Reclutamiento de los monocitos circulantes y su posterior condicionamiento hacia macrófagos en la mucosa de los pacientes con enfermedad celiaca. 14,760€. PI: Luis Fernández Salazar; Research collaborators: David Bernardo, Collaborators: Eduardo Arranz, José A. Garrote

Teaching activities:

• Degree of Medicine University of Valladolid. Subjects Human Inmunology (2th year) and Immunopatology & allergy (5th year. E. Arranz: coordinator); Clinical Biochemistry & Molecular Pathology (5th year).

• Degree of Human Nutrition & Dietetics University of Valladolid. Subjects: Biology (1st year) and Nutrition & Immune System (4th year).

• Degree of Nursing University of Valladolid. Subject: Immunology in Nursing (3th year).

• Master in Biomedical Research University of Valladolid. Subjects Basis of Immunology (E. Arranz: coordinator), and Inmunity & Inflammation: role in physiology and pathology (E. Arranz: coordinator).

Teaching activities:

• Degree of Medicine University of Valladolid. Subjects Human Inmunology (2th year) and Immunopatology & allergy (5th year. E. Arranz: coordinator); Clinical Biochemistry & Molecular Pathology (5th year).

• Degree of Human Nutrition & Dietetics University of Valladolid. Subjects: Biology (1st year) and Nutrition & Immune System (4th year).

• Degree of Nursing University of Valladolid. Subject: Immunology in Nursing (3th year).

• Master in Biomedical Research University of Valladolid. Subjects Basis of Immunology (E. Arranz: coordinator), and Inmunity & Inflammation: role in physiology and pathology (E. Arranz: coordinator).

Other activities:

E. Arranz. Head of the Department of Pediatrics, Immunology, Gynecology-Obstetrics, Nutrition-Bromatology, Psychiatry & History of Science.

Molecular Genetics of Disease Unit
Cell Therapy Group

Team

Principal Investigators:

Ana Sánchez (UVA), asanchez@ibgm.uva.es
Javier García-Sancho (UVA), jgsancho@ibgm.uva.es

Postdocs: Mercedes Alberca, Verónica García, Margarita González-Vallinas

Predocs: Africa Cubero

Technicians: Jesús Fernández, Ana Amigo, Sandra Güemes, Berta Santa Úrsula, Vanesa de Santiago, Victoria Sáez, Juan Marcos García, Inés Bonilla, Raquel Díaz, Cristina Martón

Administration: Virginia Gordillo

This team is of member of the Cell Therapy Network

This team founded the spin off company Citospin

TerCel | isciii Red de Terapia Celular

Citospin

Research Highlights

In 2007, IBGM Cell Production Unit was the first clean roomlaunched in our country promoted by the public sector to support the clinical trials of the national health system. Since then, the Cell Production Unit of the IBGM (UPC-IBGM) has trained technicians, product and quality managers which now constitute a team of 17 people. In 2010, new larger facilities were built, thus allowing the participation of the UPC-IBGM in several cell therapy clinical trials aimed at testing its regenerative capability in the treatment of various pathologies: cardiac (myocardial infarction), osteoarticular diseases (lumbar degenerative disc disease, articular gonarthrosis), ophthalmological (repair of the damaged ocular surface), autoimmune disorders (lupus), with very promising results that led to the publication of several scientific articles. In 2011 Dra. Ana Sánchez and Dr. García-Sancho founded the spin-off company Citospin that provides GMP-compliant products for human cell therapy. In 2017 we were granted the European project "Respine" in Horizon 2020 call, with 9 partners belonging to 5 different countries. The UPC-IBGM will manufacture allogeneic bone marrow stem cells for a clinical trial in 8 hospitals of the EU. The study aims to improve symptoms and life quality of patients with low back pain caused by disc degeneration.

Publications in 2019

1. Cipriani F, Ariño Palao B, Gonzalez de Torre I, Vega Castrillo A, Aguado Hernández HJ, Alonso Rodrigo M, Àlvarez Barcia AJ, **Sanchez A**, García Diaz V, Lopez Peña M, Rodriguez-Cabello JC (2019) An elastin-like recombinamer-based bioactive hydrogel embedded with mesenchymal stromal cells as an injectable scaffold for osteochondral repair. *Regen Biomater*. 2019 Dec;6(6):335-347. doi: 10.1093/rb/rbz023.

2. Rodas G, Soler R, Balius R, Alomar X, Peirau X, Alberca M, **Sánchez A**, **Sancho JG**, Rodellar C, Romero A, Masci L, Orozco L, Maffulli N (2019) Autologous bone marrow expanded mesenchymal stem cells in patellar tendinopathy: protocol for a phase I/II, single-centre, randomized with active control PRP, double-blinded clinical trial. *J Orthop Surg Res*. 2019 Dec 16;14(1):441. doi: 10.1186/s13018-019-1477-2.

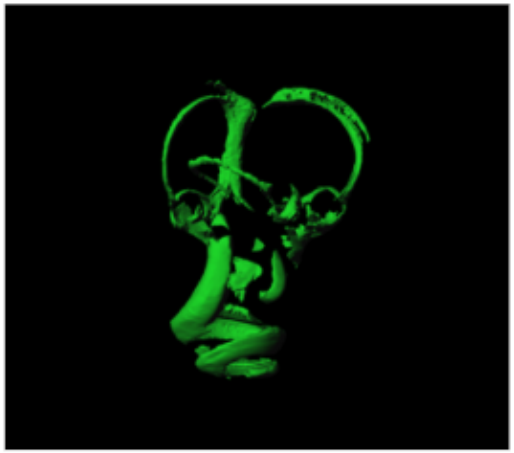
3. Sánchez-Guijo F, García-Olmo D, Prósper F, Martínez S, Zapata A, Fernández-Avilés F, Toledo-Aral JJ, Torres M, Fariñas I, Badimón L, Labandeira-García JL, **García-Sancho J**, Moraleda JM; TerCel (2019) Spanish Cell Therapy Network (TerCel): 15 years of successful collaborative translational research. Cytotherapy 2019 Dec 19. pii: S1465-3249(19)30889-8. doi: 10.1016/j.jcyt.2019.11.001.

4. Calatayud C, Carola G, Fernández-Carasa I, Valtorta M, Jiménez-Delgado S, Díaz M, Soriano-Fradera J, Cappelletti G, **García-Sancho J**, Raya Á, Consiglio A (2019) CRISPR/Cas9-mediated generation of a tyrosine hydroxylase reporter iPSC line for live imaging and isolation of dopaminergic neurons. *Sci Rep*. 2019 May 2;9(1):6811. doi: 10.1038/s41598-019-43080-2.

5. Calonge M, Pérez I, Galindo S, Nieto-Miguel T, López-Paniagua M, Fernández I, Alberca M, **García-Sancho J**, **Sánchez A**, Herreras JM (2019) A proof-of-concept clinical trial using mesenchymal stem cells for the treatment of corneal epithelial stem cell deficiency. *Transl Res*. 2019 Apr;206:18-40. doi: 10.1016/j.trsl.2018.11.003. Epub 2018 Nov 22.

This team also provides a service of Cell Therapy through the spin off company Citospin

Molecular Genetics of Disease Unit
Inner Ear Development and Regeneration Group



3D model of a mammalian cochlea

Team
Principal Investigator:
Thomas Schimmang (CSIC),
schimman@ibgm.uva.es
Postdoc: Beatriz Durán
Technician: Iris López Hernández

Research Highlights

The loss of hearing is one of the main defects that affects especially the populations of industrialized countries. It can be caused by exposure to noise, direct damage or genetically inherited with 1 in 1000 affected newborns. However, especially in industrialized countries, exposure to medications (eg aminoglycosides for the treatment of severe infections) and the increasing number of individuals with advanced age has resulted in an increase in chronic hearing loss. The loss of the quality of life in the affected people and the associated costs for the diagnosis and treatment of patients is a considerable social and economic burden for our societies. Our interest focuses on various physiological aspects of the auditory organ such as its development and innervation, pathophysiological processes involved in the injury and degeneration of auditory neurons and hair cells and gene transfer in the inner ear.

At the molecular level we have concentrated on neurotrophins and their receptors, fibroblast growth factors (FGFs) and different transcription factors (myc, otx2, meis2). The functional analysis of these genes is carried out in vivo by transgenic mice. These experiments are complemented by in vitro studies using cultures of hair cells and auditory neurons. We performed both gain-of-function experiments (viral expression, transgenic mice) and loss of function (knock-out mice). We have recently introduced new lines of research that are dedicated to designing protocols to cure hearing loss through cell or gene therapy.

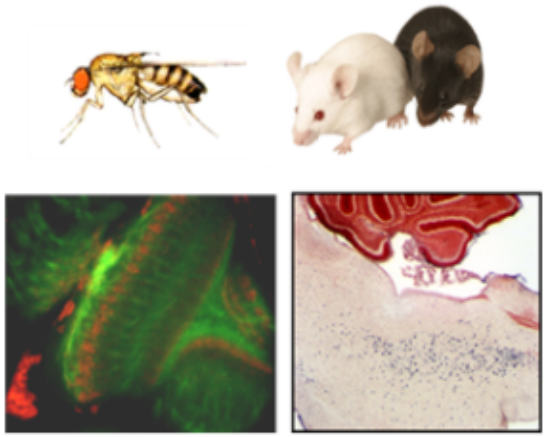
Publications in 2019

1. Harasztosi C, Wolter S, Gutsche K, Durán-Alonso MB, López-Hernández I, Pascual A, López-Barneo J, Knipper M, Rüttiger L, **Schimmang T** (2019) Differential deletion of GDNF in the auditory system leads to altered sound responsiveness. *J Neurosci Res*. 2019 Oct 30. doi: 10.1002/jnr.24544.

2. Ishikawa M, García-Mateo N, **Čusak A**, López-Hernández I, Fernández-Martínez M, Müller M, Rüttiger L, Singer W, Löwenheim H, Kosec G, Fujs **Š**, Martínez-Martínez L, **Schimmang T**, Petković **H**, Knipper M, Durán-Alonso MB (2019) Lower ototoxicity and absence of hidden hearing loss point to gentamicin C1a and apramycin as promising antibiotics for clinical use. *Sci Rep*. 2019 Feb 20;9(1):2410. doi: 10.1038/s41598-019-38634-3.

3. Muñoz-Martín N, Sierra R, **Schimmang T**, Villa Del Campo C, Torres M (2019) Myc is dispensable for cardiomyocyte development but rescues Mycn-deficient hearts through functional replacement and cell competition. *Development*. 2019 Feb 1;146(3). pii: dev170753. doi: 10.1242/dev.170753.

Molecular Genetics of Disease Unit
Nervous System Development & Degeneration Group



Team

Principal Investigators:

Mª Dolores Ganfornina (UVa),
opabinia@ibgm.uva.es

Diego Sánchez (UVa),
lazarill@ibgm.uva.es

Predocs: Miriam Corraliza

Technicians: Cándido Pérez, Teresa Bermejo, Elisa Arribas

Research Highlights

The objective of our laboratory is to understand the mechanisms that underlie the development of the NERVOUS SYSTEM, understanding DEVELOPMENT, as the complete process during the life of an organism: from embryonic development to aging. We are also interested in NEURODEGENERATION processes. Our research work has focused on the analysis of a specific family of proteins, LIPOCALINES, and members of this family that are expressed in the nervous system at key moments of DEVELOPMENT. These proteins, named for their well-preserved three-dimensional cup-shaped structure that unites mostly hydrophobic ligands, constitutes a very diverse family present in all realms of life.

Among them is the lipocalin LAZARILLO (Laz) and its relatives (the homologous gene in vertebrates is called APOLIPOPROTEIN D, ApoD), which play important roles both in early development and during physiological aging and neurodegeneration: axonal growth, modulation of the length of life and neuroprotection are some of its known functions. We are currently trying to identify and analyze all aspects of the Laz / ApoD physiology that are related to the development of the nervous system as well as its normal or pathological aging.

Publications in 2019

1. Corraliza-Gomez M, **Sanchez D, Ganfornina MD** (2019) Lipid-Binding Proteins in Brain Health and Disease. *Front Neurol*. 2019 Nov 7;10:1152. doi: 10.3389/fneur.2019.01152.

2. Mejias A, Diez-Hermano S, **Ganfornina MD**, Gutierrez G, **Sanchez D** (2019) Characterization of mammalian Lipocalin UTRs in silico: Predictions for their role in post-transcriptional regulation. *PLoS One*. 2019 Mar 6;14(3):e0213206. doi: 10.1371/journal.pone.0213206. eCollection 2019.

3. Pascua-Maestro R, González E, Lillo C, **Ganfornina MD**, Falcón-Pérez JM, **Sanchez D** (2019) Extracellular Vesicles Secreted by Astroglial Cells Transport Apolipoprotein D to Neurons and Mediate Neuronal Survival Upon Oxidative Stress. *Front Cell Neurosci*. 2019 Jan 10;12:526. doi: 10.3389/fncel.2018.00526. eCollection 2018.

Ongoing Research Projects

Title: *Papel de la enzima degradadora de insulina en el comportamiento de la microglía durante la enfermedad de Alzheimer en el contexto metabólico de diabetes mellitus tipo* Funding Agency: Junta de Castilla y León. Convocatoria de apoyo de los GIR a iniciar en 2018 (VA086G18)
From 2018 to 2020
Funding: 12.000 euros
Principal Investigator: María Dolores Ganfornina

Others

Profs. L. Ganfornina and D. Sánchez contribute to teaching in the Degree in Medicine of the University of Valladolid courses on "Human Physiology", "Advanced Neuroscience" and "Biomedical Research" in addition to the Master in Biomedical Research: Course on "Data analysis".

Lola Ganfornina is Academic Secretary of Department of Biochemistry, Molecular Biology and Physiology, Valladolid University School of Medicine.

Molecular Genetics of Disease Unit
Splicing and Susceptibility to Cancer Group

Team
Principal Investigator:
Eladio Velasco (CSIC),
eavelsam@ibgm.uva.es
Predocs: Eugenia Fraile, Alberto Valenzuela, Lara Sanoguera
Technicians: Alicia García

Research Highlights

Our interest is focused on Hereditary Breast and Ovarian Cancer (HBOC) syndrome that is characterized by a high genetic heterogeneity and whose predisposing spectrum has not been elucidated yet. So far there have been identified inactivating mutations in at least 25 responsible genes, including BRCA1, BRCA2, TP53 (Li-Fraumeni disease), STK11 (Peutz-Jeghers syndrome), PTEN (Cowden syndrome), CDH1, PALB2, ATM, CHEK2, BARD1, Abraxas, XRCC2, MUTY, BRIP1, RAD50, RAD51C, RAD51D and NBS1 (Nielsen et al 2016). Most of them are involved in the DNA repair pathway in order to keep the genomic integrity. The two principal genes, BRCA1 and BRCA2, account for only 16% of familial breast cancer risk, whereas the rest of the genes and SNPs (GWAS studies) contribute up to 50% of the familial risk.

Genetic testing of BRCA1 and BRCA2 provides essential information for the clinical management of HBOC families since it allows the detection of asymptomatic mutation carriers and facilitates preventive decision-making. On the other hand, 15-20% of patients carry a BRCA1/2 DNA variant of unknown clinical significance (VUS) since it is not known whether they are neutral or disease-causing, hampering genetic diagnostic and, therefore, disease prevention. Pathogenic mutations are often predicted on the basis of their impact on protein function but other gene expression steps, such as transcription and splicing, may be disrupted by DNA variants and involved in a disease.

Publications in 2019

1. Fraile-Bethencourt E, Valenzuela-Palomo A, Díez-Gómez B, **Caloca MJ**, Gómez-Barrero S, **Velasco EA** (2019) Minigene Splicing Assays Identify 12 Spliceogenic Variants of BRCA2 Exons 14 and 15. *Front Genet*. 2019 May 28;10:503. doi: 10.3389/fgene.2019.00503. eCollection 2019.

2. Lopez-Perolio I, Leman R, Behar R, Lattimore V, Pearson JF, Castéra L, Martins A, Vaur D, Goardon N, Davy G, Garre P, García-Barberán V, Llovet P, Pérez-Segura P, Díaz-Rubio E, Caldés T, Hruska KS, Hsuan V, Wu S, Pesaran T, Karam R, Vallon-Christersson J, Borg A, Investigators K, Valenzuela-Palomo A, **Velasco EA**, Southey M, Vreeswijk MPG, Devilee P, Kvist A, Spurdle AB, Walker LC, Krieger S, de la Hoya M (2019) Alternative splicing and ACMG-AMP-2015-based classification of PALB2 genetic variants: an ENIGMA report. *J Med Genet*. 2019 Jul;56(7):453-460. doi: 10.1136/jmedgenet-2018-105834.

3. Fraile-Bethencourt E, Valenzuela-Palomo A, Díez-Gómez B, Goina E, Acedo A, Buratti E, **Velasco EA** (2019) Mis-splicing in breast cancer: identification of pathogenic BRCA2 variants by systematic minigene assays. *J Pathol*. 2019 Aug;248(4):409-420. doi: 10.1002/path.5268.

4. Pérez-Alonso M, Briongos LS, Ruiz-Mambrilla M, **Velasco EA**, Olmos JM, de Luis D, Dueñas-Laita A, Pérez-Castrillón JL (2019) Association Between Bat Vitamin D Receptor 3' Haplotypes and Vitamin D Levels at Baseline and a Lower Response After Increased Vitamin D Supplementation and Exposure to Sunlight. *Int J Vitam Nutr Res*. 2019 Feb 21:1-5. doi: 10.1024/0300-9831/a000534.

Doctoral Thesis

Mª Eugenia Fraile Bethencourt. "Transcripción y splicing de brca2 y su relación con la susceptibilidad a cáncer de mama y ovario hereditario" Director Eladio Velasco. IBGM/Facultad de Medicina, Universidad de Valladolid. Postdoctoral fellow at University of Oregon (USA).

Ongoing Research Projects

Title: *Splicing aberrante en cáncer de mama hereditario. Análisis funcional de genes de susceptibilidad mediante minigenes híbridos*. Ref. PI17/00227
Funding Agency: Ministerio de Economía y Competitividad, Instituto de Salud Carlos III
From 2018 to 2020.
Funding: 99.220 €.
Principal Investigator: Eladio Velasco Sampedro

Title; *Desregulación del splicing en cáncer de mama hereditario. Análisis funcional de genes de susceptibilidad mediante minigenes híbridos*. Ref. CSI242P18
Funding Agency: Junta de Castilla y León, Consejería de Educación
From 2019 to 2021.
Funding: 120.000 €.
Principal Investigator: Eladio Velasco Sampedro

Title; *Breast Cancer Risk after Diagnostic Gene Sequencing (BRIDGES)*. Ref. 634935
Funding Agency: European Commission
From 2015 to 2021.
Funding: 75.000 €.
Principal Investigator: Eladio Velasco Sampedro

This team also provides a minigene service (Minigene Facility)

A high proportion of pathogenic variants in disease-responsible genes disrupts pre-mRNA processing or splicing (Lopez-Bigas et al 2005). Direct analysis of RNA from a patient would the most reliable method of establishing with certainty whether a particular DNA substitution affects splicing but patient RNA is not always available and often difficult to obtain. Splicing reporter plasmids are useful alternative tools to study the impact of a variant on splicing. The Splicing and cancer susceptibility group of the IBGM (CSIC, PI Eladio A. Velasco) designed and patented the splicing reporter plasmid pSAD. This has been used for the development of this line of research through the construction of a wide battery of minigenes from breast cancer susceptibility genes (*BRCA1, BRCA2, CHEK2, PALB2, ATM, RAD51C, RAD51D*). In 2013, there has been developed an external facility of minigenes with the goal of providing support in the functional study of candidate splicing variants of other disease-responsible genes.

These tests facilitate the clinical interpretation of variants and decision-making concerning preventive and/or therapeutic measures. Since then, there have been signed technological support agreements with different public institutions and private companies for minigene construction and variant assays of the following genes: *MLH1* (Lynch syndrome), *COL1A1* (Osteogenesis Imperfecta), *SERPINA1* (α1-antitrypsin deficiency), *CHD7* (Charge syndrome, Intellectual disability), *GRN* (Frontotemporal Dementia) y *UGT1A1* (Gilbert and Crigler-Najjar syndromes).

For further information, please contact Dr. Eladio Velasco at eavelsam@ibgm.uva.es take a look at: http://www.ibgm.med.uva.es/servicios/servicio-de-splicing-minigenes/

Technological support agreements

1. Name of the project: Construction of an ad hoc minigene of the TRPM4 gene in the pSAD vector. Splicing functional assay of TRPM4 variant c.25-1G>T for Dr. Hemminki and Dr. Bandapalli
Degree of contribution: Scientific coordinator
Name principal investigator (PI, Co-PI....): (IP) Eladio A. Velasco Sampedro
Participating entity/entities: German Cancer Research Center (DKFZ), Heidelberg, Germany. Instituto de Biología y Genética Molecular (CSIC-UVa)
Start date: 09/04/2019. **Duration:** 3 months
Total amount: 600 €

2. **Name of the project:** SPLICING FUNCTIONAL STUDY OF DNA VARIANTS IN PSAD-DERIVED MINIGENES. BASIC FUNCTIONAL ASSAYS (WILD TYPE AND MUTANT MINIGENES). INSERTION OF EXON I
Degree of contribution: Scientific coordinator
Name principal investigator (PI, Co-PI....): (IP) Eladio A. Velasco Sampedro
Participating entity/entities: Riga Stradins University (Latvia). Instituto de Biología y Genética Molecular (CSIC-UVa);
Start date: 18/03/2019 **Duration:** 3 months
Total amount: 400 €

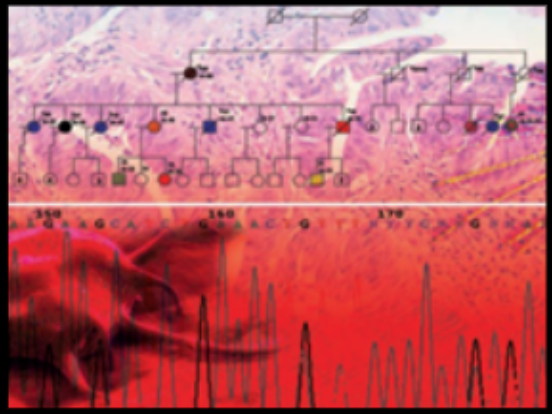
3. **Name of the project:** Splicing Functional Assay of variant c.996+2_996+5del of the UGT1A1 gene (Crigler-Najjar Syndrome) and construction of a custom minigene for Dr. Linda Gaïlite
Degree of contribution: Scientific coordinator
Name principal investigator (PI, Co-PI....): (IP) Eladio A. Velasco Sampedro
Participating entity/entities: Instituto de Biología y Genética Molecular (CSIC-UVa); Riga Stradins University (Latvia)
City funding entity: Latvia
Start date: 30/10/2018 **Duration:** 3 months
Total amount: 600 €

Molecular Genetics of Disease Unit
Molecular Genetics of Inherited Cancer Group

Team
Principal Investigator:
Mercedes Durán (UVA), merche@ibgm.uva.es
Mar Infante (UVA), minfante@ibgm.uva.es
Scientific Staff: Carmen D. Lobatón (UVA)
Predocs: Carolina Velázquez
Technicians: Lara Hernández, Noemí Martínez

Research Highlights

Cancer, understood as an uncontrolled cell growth that can invade other tissues, is nowadays one of the main public health problems worldwide due to its incidence, prevalence and mortality. It is estimated that one in three men and one in four women will be diagnosed with cancer throughout their lives. In addition, although much progress has been made towards reducing the incidence, mortality rates and improving patient survival, cancer is still responsible for more deaths than cardiovascular diseases in people under 85 years of age.



Most patients who develop some type of cancer do so sporadically, that is, there is no family or hereditary risk of suffering from the disease. In these cases the disease appears frequently at advanced ages and as a consequence of the accumulation of genetic alterations produced throughout the life of the individual. However, there is a small percentage of patients suffering from a hereditary cancerous syndrome (between 5 and 10%), which is identified based on their personal or family history, and which is due to genetic susceptibility factors that the patient carries. individual from his birth.

Advances in the knowledge of the genetic basis of diseases currently allow carrying out a prevention aimed at avoiding them or at least minimizing their consequences. The identification of individuals and families with an increased risk of developing cancer allows, in addition to an individualized assessment of the risk of developing the disease, recommend adequate prevention and early diagnosis strategies in each case.

Our team provides a diagnosis service of hereditary breast and colon cancer risk susceptibility to about half of Castilla y León population. In addition, we follow two research lines:

- Breast cancer: analysis of genes of low penetrance, study of founder mutations, breast cancer in males, evaluation of mutations of variants of uncertain significance. New mutation detection techniques. Massive sequencing

Colon cancer: tumor DNA analysis: mutations in BRAF, promoter methylation, study of microsatellite instability, mutations in KRAS. Study of type X and Lynch-like colorectal cancer. Attenuated polyposis. Genotype-phenotype relationship.

Publications in 2019

1. Velázquez C, Esteban-Cardeñosa EM, Lastra E, Abella LE, de la Cruz V, Lobatón CD, **Durán M**, **Infante M** (2019) A PALB2 truncating mutation: Implication in cancer prevention and therapy of Hereditary Breast and Ovarian Cancer. *Breast*. 2019 Feb;43:91-96. doi: 10.1016/j.breast.2018.11.010.

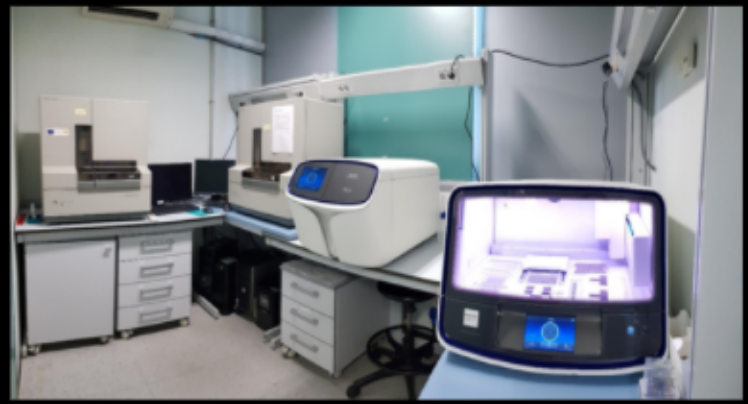
2. Velázquez C, Esteban-Cardeñosa EM, Lastra E, Abella LE, de la Cruz V, Lobatón CD, **Durán M**, **Infante M** (2019) Unraveling the molecular effect of a rare missense mutation in BRIP1 associated with inherited breast cancer. *Mol Carcinog*. 2019 Jan;58(1):156-160. doi: 10.1002/mc.22910.

Doctoral Thesis in 2019

Carolina Velázquez Pérez. "Detección, análisis y clasificación de variantes genéticas en el diagnóstico molecular del cáncer hereditario". Directors Mercedes Durán, Mar Infante and Carmen Domínguez. IBGM/Facultad de Medicina, Universidad de Valladolid.

This team also provides a service of gene sequencing:

SANGER sequencing for detection of point mutations in ABI3130XL automatic bioanalyzer.
Detection of genomic rearrangements using Multiplex Ligation-dependent Probe Amplification (MLPA) technique and automatic sequencer analysis.
Massive NGS sequencing, genetic panels using the Ion S5 platform + ThermoFisher Chef.



Molecular Genetics of Disease Unit
Directed Gene Therapy Group

Team

Principal Investigators:

Miguel Angel de la Fuente (UVA),
mafuente@ibgm.uva.es
María Simarro (UVA),
msimarrogrande@ibgm.uva.es

Investigator: Juan José Tellería

Predocs: Dino Joaquín Gobelli, Julia Serna Pérez, Carlos Durántez

Research Highlights

Most current gene therapy strategies and related clinical trials use vectors that are randomly integrated into the host genome. An important disadvantage is the variability in the site and frequency of integration of the transgene: several copies can be integrated, which can cause cell death or mutagenesis, leading to malignant transformation of the treated cell. In addition, the stability and expression of the transgene are unpredictable.

An ideal method of gene therapy should achieve replacement of the mutated gene with a normal one at the corresponding locus without the possibility of errors and thus avoiding random insertion. This is known as directed gene manipulation (gene targeting, GT), which occurs through the process of homologous recombination (homologous recombination, HR), thanks to which the transgene recombines with its natural locus in the host's genome ensuring the correct transcription.

We have developed great experience in molecular biology, and also in the production and use of viral vectors (lentivirus and AAV virus). The use of the CRISPR / Cas9 system for gene editing has allowed us to develop several cellular models of human disease, including the generation of human cell lines that do not express some of the proteins of the FASTK family (Fas-activated serine / threonine kinase) of mitochondrial proteins. We identified the family integrated by FASTK (the founding member) and its homologs FASTKD1-5 seven years ago and since then, we have made relevant contributions to understanding their functions. The study of their mechanisms of action represents the main objective of our first line of research. They are RNA binding proteins that act as post-transcriptional regulators of mitochondrial gene expression. All members of the family are architecturally related, but each of them has a different function in the regulation of mitochondrial RNA biology. Our studies have focused so far on two members of the family: FASTK and FASTKD3. Our second line of research has been initiated very recently and it is focused on the development of new vectors for the expression of chimeric antigen (CAR) receptors in T cells in combination with the editing of certain genes with the aim of generating "therapeutic" and "universal" allogeneic T lymphocytes that improve their anti-tumor effectiveness.

Publications in 2019

1. Arévalo-Martínez M, Cidad P, García-Mateo N, Moreno-Estar S, Serna J, Fernández M, Swärd K, **Simarro M**, **de la Fuente MA**, **López-López JR**, **Pérez-García MT** (2019) Myocardin-Dependent Kv1.5 Channel Expression Prevents Phenotypic Modulation of Human Vessels in Organ Culture. *Arterioscler Thromb Vasc Biol*. 2019 Dec;39(12):e273-e286. doi: 10.1161/ATVBAHA.119.313492

2. March GA, Gutiérrez MP, López I, Muñoz MF, Ortiz de Lejarazu R, **Simarro M**, Orduña A, Bratos MÁ (2019) Epidemiological surveillance and wild-type MIC distribution of Legionella pneumophila in north-western Spain. 2003-2016. Enferm Infecc Microbiol Clin. 2019 Oct;37(8):514-520. doi: 10.1016/j.eimc.2018.11.006. Epub 2018 Dec 24.

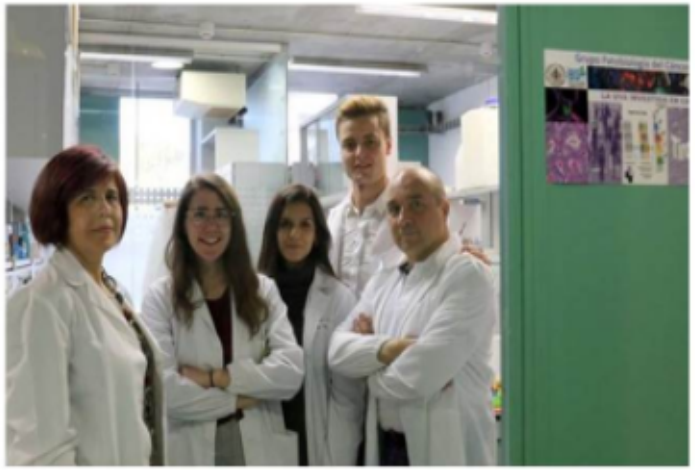
Doctoral Thesis in 2019

Ana García del Río "Papel de la isoforma mitocondrial de fastk en la modulación de la fagocitosis no opsónica de bacterias por los macrófagos". Directors María Simarro y Miguel Angel de la Fuente. IBGM/Facultad de Medicina, Universidad de Valladolid.

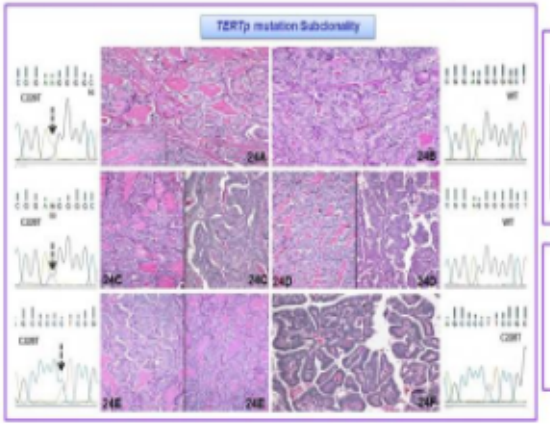
Carlos Durántez Fernández. "Desarrollo y utilidad de las técnicas de ELISA y quimioluminiscencia para el diagnóstico de la tularemia humana". Director María Simarro. Facultad de Medicina, Universidad de Valladolid.

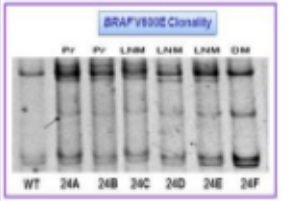
Molecular Genetics of Disease Unit
Pathobiology of Cancer: Inter-, Intra-tumoral Heterogeneity and Molecular Targets

Team
Principal Investigator:
Ginesa García-Rostán (UVA), ginesarostan@ibgm.uva.es
Associate Researcher: Joaquín Fra Rodríguez
Predocs: Noa Feás, Elena Pérez, Sara Gil
Students: José Javier Estébanez, Miriam Mayal



Coexistence of C228T *TERTp* mutation, *BRAF* V600E mutation and *KRAS*G12D mutation
Clonal / Subclonal nature of mutations - Spread to Distant metastasis





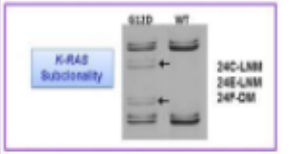


Figure-3

Research Highlights

We pursue developing an integrated research at the interface between cancer genetics / genomics, cellular biology, molecular pathology and clinical management of cancer patients.

As the name of the group reveals, **the main scientific query that drives our research is how molecular alterationsare passed along the different components of a tumor and how that influences on heterogeneity and plasticity of tumor cells.** We want to comprehend how mutations arise in cancer cells and how they segregate in cancer cell subpopulations through space and time.

Tumor heterogeneity is a pivotal condition in our understanding of tumor development and evolution. The analysis of individual cancer genomes has shown not only a puzzling inter-tumor heterogeneity, with limited somatic alterations shared between identical tumor histotypes, but also a complicated intra-tumor heterogeneity, affecting individual tumor areas within a particular tumor biopsy and biopsies of the same tumor separated in space and time.

Sequential analysis of tumors during disease course (primary tumor, recurrences and metastases during follow-up) has unveil that intra-tumoral heterogeneity also evolves during disease course.
Tumor cells devise strategies to bypass the effect of small molecule cancer drugs. The selective pressure induced by targeted therapies directed against tumor cells bearing a particular mutation can result in the dominance of a minoritary sub-clon present in the tumor, which harbours molecular alterations resistant to the given drug or in the acquisition of additional driver mutations or molecular aberrations in the targeted clone or in new tumor subclones refractory to the inhibitor, that in either case raise the activity of alternate signaling pathways that rescue tumor growth and metastasis.
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Title: “Molecular Pathobiology of Cancer”.
Intramural Research Project of IBGM with funds from Consejería de Sanidad – Junta de Castilla y León
From 1st January 2019 to 31st December 2019.
Funding: 5.000 €.
Principal Investigator:Ginesa García-Rostán

Title: “THYROID CANCER”. Ref.: 060/157341
Funding Agency: “Philanthropy / Patronage”.
Management Entity: Fundación General de la Universidad de Valladolid (FUNGE)
From open indefinitely
Funding: 30.000 €.
Principal Investigator:Ginesa García-Rostán

General Teaching in 2019:

Degree in Medicine University of Valladolid - Third year medical students: Classes of General and Special / Surgical Anatomic Pathology – "Structural and Functional Basis of Pathology" – "Molecular Pathology" [240 h]

Ginesa García Rostan is the coordinator of Anatomical and Surgical Pathology at the School of Medicine of Valladolid University.

Congresses, Workshops, Symposia, Conferences in 2019

Author(s):S. Gil-Bernabe, N. Feas Rodríguez, M. Vega Herrero, JJ. Estébanez García, D. Soto de Prado, J. Fra Rodríguez, G. García-Rostán.
Title: Spatiotemporal intratumor genetic heterogeneity and clonal evolution in PTCs and paired DM.
TYPE OF PRESENTATION:Poster – Oral Discussion Ref. 1864
CONGRESS: 44TH CONGRESS OF THE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY (ESMO)
PUBLICATION:*Annals of Oncology*.
Volume: 30, Suppl, 5, pp:757-757Published:October2019DOI:
https://doi.org/10.1093/annonc/mdz267.002
https://doi.org/10.1093/annonc/mdz267.002
IMPACT FACTOR – JCR - 2019: 14.196
MEETING PLACE: Barcelona, Spain.
YEAR:September 27 – October 1,2019.

Author(s):S. Gil-Bernabe, N. Feas Rodríguez, M. Vega Herrero, JJ.Estébanez García, G. García-Rostán.

Title: Spatio-temporal genetic heterogeneity and clonal evolution in advanced papillary thyroid carcinomas and matched distant metastases.

TYPE OF PRESENTATION: Poster Ref. 2770 - Session Expression Profiling & Biomarkers of Tumor Progression and Metastasis

CONGRESS:110TH ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH (AACR). PUBLICATION:*Cancer Research*.

Volume: 79(13), Suppl.,Published:July2019DOI: 10.1158/1538-7445.SABCS18-2770

https://cancerres.aacrjournals.org/content/79/13_Supplement/2770

IMPACT FACTOR – JCR - 2019: 8.378

MEETING PLACE: Atlanta, Georgia.

YEAR:March 29 - April 3, 2019.

AUTHORS:S. Gil-Bernabe, N. Feas Rodríguez, M. Vega Herrero, JJ. Estébanez García, J. Fra, G. García-Rostán.
TITLE: "Dissection of spatio-temporal dynamic changes in subclonal mutational architecture in primary papillary thyroid carcinomas and matching distant metastases."
TYPE OF PRESENTATION: Oral – Platform – 219 – Immunohistochemistry and Molecular Pathology Session [24-5-2019].
CONGRESS: XXIX NATIONAL CONGRESS OF THE SPANISH PATHOLOGY SOCIETY and IAP
PUBLICATION: Platform Congress Proceedings.
https://www.seap2019granada.es/Com_Granada.pdf
MEETING PLACE: Granada. Spain.
YEAR: May 22-24, 2019.

SCIENTIFIC SEMINARS @IBGM in 2019

In 2019, we celebrated 39 scientific seminars at IBGM including 23 presentations by national and international researchers from outside the center, 3 researchers at IBGM and 13 presentations by IBGM PhD candidates. The list of seminars is as follows:

January 18, 2019. "*LRH-1/NR5A2 connecting immune and islet cells in reverting autoimmune Diabetes*" by **Dr. Benoit Gauthier**. Centro Andaluz de Medicina Regenerativa (CABIMER), Univ. Sevilla/CSIC, Spain. Invited by Dr Irene Cózar.

January 25, 2019 "Reprogramación Metabólica en Células Dendríticas y su Implicación en la Inducción de Citoquinas en Respuesta a Patrones Fúngicos" by PhD candidate **Cristina Mancebo**. Laboratory of Dr. Mariano Sánchez-Crespo and Nieves Fernández at IBGM (UVA/CSIC).

January 25, 2019. "*Transcripción y splicing de BRCA2 y su relación con la susceptibilidad a Cáncer de Mama y Ovario Hereditario*" PhD candidate **Mª Eugenia Fraile Bethencourt**. Laboratory of Dr. Eladio Velasco at IBGM (UVA/CSIC).

February 1st, 2019. "*Papel de la lipina-2 en la activación del inflamasoma NLRP3 en respuesta a ácido palmítico en macrófagos*" by PhD candidate **Miren Itziar Sanjuan García**. Laboratory of Dr. M. Angeles Balboa at IBGM (UVA/CSIC).

February 1st, 2019. "Protease-sensitive Elastin-like recombinamers-based hydrogels able to stimulate angiogenesis" by PhD candidate **Tatjana Flora**. Laboratory of Dr.Juan Carlos Rodríguez Cabello and I. González, Bioforge, University of Valladolid.

February 8, 2019. "*Microbiota: A key orchestrator of immunometabolic diseases*" by **Dr. José Moisés Laparra**, Llopis Fundación IMDEA Alimentación. Invited by Dr. María Angeles Balboa

February 15, 2019. "*Identificación de nuevos mediadores lipídicos en inflamación y enfermedades metabólicas*" **Dra. Alma Astudillo**. Laboratory of Dr. Jesus Balsinde at IBGM (UVA/CSIC).

February 22, 2019. "*The mysterious Ca^{2+} activated Cl^- channel TMEM16A in the vascular wall*" by **Dr Christian Aalkajaer**, Aarhus University, Denmark. Invited by Dr. Teresa Pérez García.

March 8, 2019. "*Pancreatic beta cell adaptation to diet and age: When Myc is just not enough*" by **Dr. Adolfo García Ocaña**, Mount Sinai Hospital, New York, NY, USA. Invited by Dr. Irene Cózar.

March 13, 2019. "*Regulatory T cell Immunotherapy in Organ Transplantation*" by **Dr. Laura Contreras**, Dana Farber Cancer Center, Harvard University, MS USA. Meeting with PhD candidates: "The hidden benefits of a PhD: Identify, Develop, and Communicate your transferable skills".

March 15, 2019. "*Cellular stress resilience in brain disorders*" by **Dr. Claudia Pereira**, Coimbra University, Portugal. Invited by Dr Carlos Villalobos. Includes a meeting with PhD candidates.

March 22, 2019. "*The LDLR related protein 1 (LRP1) regulates pulmonary function: Tales of airway epithelium and alveolar type 2 cells*" by **Dr. Itsaso García Arcos**. State University of New York (SUNY), NY, USA.

March 29, 2019. "*Metabolismo energético y regulación transcripcional en células dendríticas*" by PhD candidate **Saioa Márquez Piñeiro**. Laboratory of Dr Mariano Sánchez Crespo and Nieves Fernández at IBGM, UVA/CSIC.

March 29, 2019. "*Effects of immune mediators on human aortic valve cells*" by PhD candidate **Iván Parra Izquierdo**. Laboratory of Dr Carmen García at IBGM, UVA/CSIC.

April 5, 2019. "*Mitochondrial signal transduction in pancreatic beta-cells*" by **Dr Jaime SantoDomingo,** Nestlé Institute of Health Sciences, Lausanne, Switzerland. Includes a meeting with PhD candidates. Invited by Dr. Javier Alvarez.

April 10, 2019. "*Cancer and pH: the voltage activated H+ channel (HVCN1) as a potential target in neoplastic disease*" by **Dr Verónica Milesi**, Universidad Nacional de La Plata- CONICET, Argentina. Invited by Dr Teresa Pérez García.

April 12, 2019. "*Modelos preclínicos de enfermedad cardiovascular para el desarrollo de nuevas estrategias terapéuticas: Limitaciones y oportunidades*" by **Dr. Mercè Roqué**, IDIBAPS, Univ Barcelona/CSIC, Spain. Invited by Dr. Teresa Pérez García. Includes a meeting with PhD candidates.

April 26, 2019. "*Pathophysiology of cold-activated TRP channels*" by **Dr. Felix Viana**, Instituto de Neurociencias de Alicante, Universidad Miguel Hernández/CSIC, Spain. Invited by Dr. Teresa Pérez García. Includes a meeting with PhD candidates.

May 9, 2019. "Manejo de colonias transgénicas" by **Dr. Ernesto de la Cueva**, Instituto Príncipe Felipe, Valencia, Spain. Invited by Angel José Alvarez Barcia.

May 17, 2019. "*Lipin-2 regulates inflammasome activation in response to viral RNA in macrophages*" by PhD candidate **Nagore De Pablo Herranz**. Laboratory of Dr. M. Angeles Balboa at IBGM (UVA/CSIC).

June 7, 2019. "*Human intestinal dendritic cell and macrophage subsets in health and inflammatory bowel disease*" by new IBGM Ramon y Cajal researcher **Dr. David Bernardo**. IBGM (UVA/CSIC).

July 17, 2019. "*Insulin-degrading enzyme (IDE): la paradoja de la diabetes mellitus*" by new IBGM Principal Investigator **Dr. Germán Perdomo.** University of Burgos (pending incorporation to IBGM/CSIC)

July 25, 2019. "*New regulators of autophagy in pancreatic beta-cells*" by **Dr. Safia Costes** Institute for Functional Genomics, Montpellier, France. Invited by Dr Irene Cózar.

October 25, 2019. "*In vivo Ca^{2+} imaging reveals correlation between sarcoplasmic reticulum Ca^{2+} content and sarcopenia in aging flies*" by PhD candidate **Alba del Río Lorenzo**. Laboratory of Drs Javier García-Sancho and María Teresa Alonso at IBGM (UVA/CSIC).

November 13, 2019. "*Loss of Hepatic CEACAM1 links Impairment of Insulin Clearance to NASH*" by **Dr. Sonia Najjar**, University of Ohio. Invited by Dr. Irene Cózar.

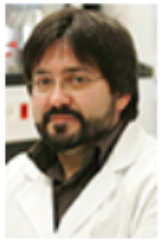
November 15, 2019. "*Not just corpse removal: how microglial phagocytosis maintains brain tissue homeostasis*" by **Dr. Amanda Sierra**, Achucarro Basque Center for Neuroscience, Spain. Invited by Dr. Diego Sánchez.

November 22, 2019. "*Envejecimiento y señalización por calcio en el modelo Caenorhabditis elegans*" by PhD candidate **Paloma García Casas**. Laboratory of Drs. Javier Alvarez, Mayte Montero and Rosalba Fonteriz at IBGM (UVA/CSIC).

November 29, 2019. "*El complejo Integrador, un regulador de la transcripción génica*" by **Dr. Juan Cabello**, Center for Biomedical Research of La Rioja (CIBIR), Spain. Invited by Dr. Rosalba Fonteriz.

December 13, 2019. "*Mechanisms of muscle wasting in chronic respiratory diseases: potential for future research*" by **Dr. Esther Barreiro**, Hospital del Mar-IMIM, Spain. Invited by Dr. Ana Obeso.

December 20, 2019. IV Seminar Series "Vuelve a casa por Navidad" Presentations by former PhD candidates presently working abroad as postdoctoral fellows **Dr. Alberto Rico**, Centro Investigaciones Médicas Avanzadas (CIMA), Universidad de Navarra, Spain.



Dr. Alberto Rico, Centro Investigaciones Médicas Avanzadas (CIMA), Universidad de Navarra, Spain.

Dr. Sergio de la Fuente, Center for Translational Medicine, Department of Medicine, Thomas Jefferson University, Philadelphia, PA, USA.

Dr. Alberto Acedo. Biome Makers SL. Valladolid, Spain and San Francisco, USA.

SERVICES PROVIDED AT IBGM

Cell Therapy Unit @ IBGM / Spin Off Company CITOSPIN

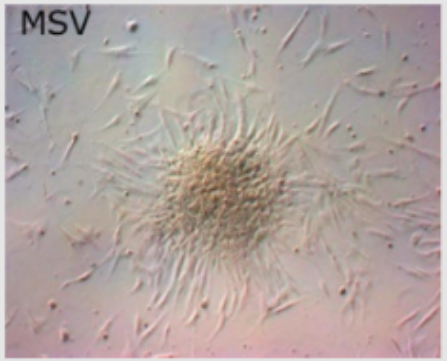
Citospin manufactures GMP-compliant products for human cell therapy. Our catalog includes Valladolid bone marrow mesenchymal stem cells* (MSV®), limbal stem cells, fat mesenchymal stem cells, skin equivalents, fibroblasts and chondrocytes and tissue engineering in a propietary scaffold with different cell types. Applications include Intervertebral disc disease, Knee osteoarthritis, Maxillary bone cysts refilling, Chronic ischemic cardiopathy, Corneal lesions, Diabetic ulcers and Venous ulcers

For further information, please visit:
http://www.citospin.com/

For contact:

CITOSPIN, S.L.
Unidad de Producción Celular
Edificio I+D, Paseo de Belén, 11
Campus Miguel Delibes
47011 Valladolid
N.I.F.: B-47673538

e-mail: citospin@citospin.com



SERVICES PROVIDED AT IBGM

Microscopy Unit @ IBGM

The Microscopy Service of IBGM is located on the second floor of the IBGM building, Laboratory D6. The Service's Research Manager is **Dr. María A. Balboa** mbalboa@ibgm.uva.es, and the technicians in charge of its use are **Cristina Sánchez** crissv@ibgm.uva.es and **Yolanda Noriega** ynoriega@ibgm.uva.es.

The Microscopy Service provides its services to all IBGM personnel, as well as any person outside the IBGM who needs to use it, both from the University of Valladolid, as well as from any public or private entity. To make any query or suggestion related to the Microscopy service, you just have to contact by email to the previous contacts, or by phone at 983 18 48 26 (Microscopy service).

Equipment:

- Leica TCS SP5 Confocal Microscope, with Resonant Scanner, White Laser (470 nm - 670 nm), 5 Argon laser lines, and a 405 line. Objectives: 10x, 20x, 40x (oil) and 63x (oil).

- Confocal microscope BioRad laser scannig system Radiance 2100, equipped with three laser lines Ar (457,476, 488, 514 nm), HeNe (543 nm) and Red Diode (637 nm) with microscope model NIKON Eclipse TE2000-U, with stage motorized Objectives: 10x, 20x, 40x, and 60x (oil).

- NIKON Eclipse 90i Fluorescence Microscope, associated with CCD camera to take photographs NIKON brand, model DS-Ri1. Objectives: 4x, 10x, 20x, 40x, 60x and 100x (oil). Filters: UV-2A (Ex 330-380), B-2A (Ex 450-490) and G-2A (Ex 510-560).

- NIKON Eclipse 80i fluorescence microscope. Referred to as Fluorescence Microscope B. Objectives: 1x, 2x, 4x, 10x, 20x, 40x, 60x (oil). Filters: UV-2A (Ex 330-380) and B-2A (Ex 450-490).

SERVICES PROVIDED AT IBGM

Flow Cytometry and Cell Sorting Service @ IBGM

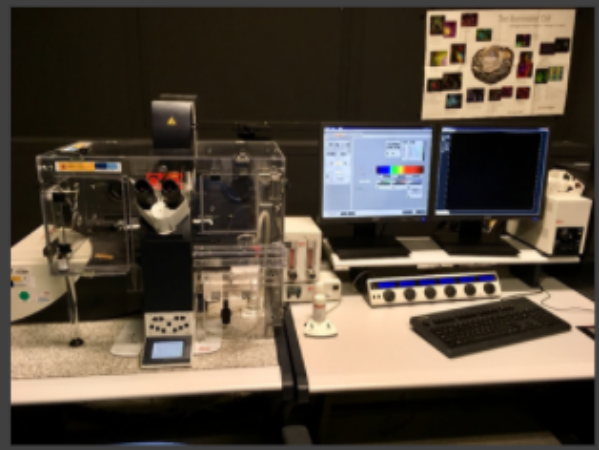
The IBGM's flow cytometry and Cell Sorting service has as its main function the support and technical advice in the field of cytometry to the institute and to any entity, whether public or private, that is interested in these services. To this end, it has two high-precision optical equipment: on the one hand, the Gallios analytical cytometer from Beckman Coulter, which gives information on the size, complexity and up to 10 colors of fluorescence, and on the other hand, the Facs Aria cell separator by Beckton Dickinson, which It gives information on the size, complexity and 9 fluorescence colors, and that can also separate up to 4 cell populations at the same time, allowing studies of specific populations and even single cell.

The service also has a unique cytometry data analysis software called Kaluza software.

The diversity of studies of these teams is very broad, since it offers a study of individualized particles ranging from immunophenotyping, reporter proteins or apoptosis and necrosis, to the cell cycle, ROS studies, proliferation or phagocytosis.

Not only eukaryotic cells, but also bacteria, viruses and even nanoparticles.
The scientific coordinator of the service is **Dr. María Luisa Nieto** mlnieto@ibgm.uva.es
The technical manager of the service is **Álvaro Martín** amartinm@ibgm.uva.es

Currently, the Leica TCS SP5 confocal microscope is the equipment that is open for external use, but any of the other equipment could also be used, if someone had that need. To use the Confocal Microscope, it is only necessary to make a previous reservation in the Intranet of the IBGM in the section Reservations - Microscopy - Confocal Leica SP5 (in the case that is a person of the center), or an email is sent to any of the members of the Microscopy Service, to specify the date and time at which the service will take place. The user will bring their samples already assembled, although the technician will advise you as far as possible based on the needs of the first one. In this case, it is the technician who manages the equipment and the user will only look for the field / image that he wants to obtain.



NEWS IN PRESS

https://www.eldiadevalladolid.com/noticia/Z213FDEF7-F5AE-3893-ABCE585B2A52269F/El-IBGM-estudia-la-enfermedad-de-Crohn-y-la-colitis-ulcerosa

http://www.icalnews.com/Mostrar.cfm/noticias/1/revista/science/hace/eco/investigacion/internacional/participa/uva/nuevos/tratamientos/dolor/463018

http://www.dicyt.com/noticias/una-puerta-al-diseno-de-nuevos-tratamientos-contra-el-dolor-no-adictivos

https://www.rtvcyl.es/noticia/460CFB16-984F-9A3C-BD2D5B096D4610AF/20190224//consiguen/detectar/dos/genes/aumentan/85/riesgo/padecer/cancer/mama

https://www.eldiadevalladolid.com/noticia/z67cde86c-0bb1-90ad-62abb58cf03508ce/science-publica-una-investigacion-del-ibgm-de-valladolid

Una puerta al diseño de nuevos tratamientos contra el dolor no adictivos: Investigadores del IBGM participan el descubrimiento de un mecanismo molecular que interviene en la producción de prostaglandina, moléculas implicadas en la percepción del dolor. El trabajo se ha publicado hoy en '*Science*'.

El Norte de Castilla:

Un nuevo análisis genético de la Universidad de Valladolid permite alertar a diez familias de un cáncer hereditario.
Más información en:

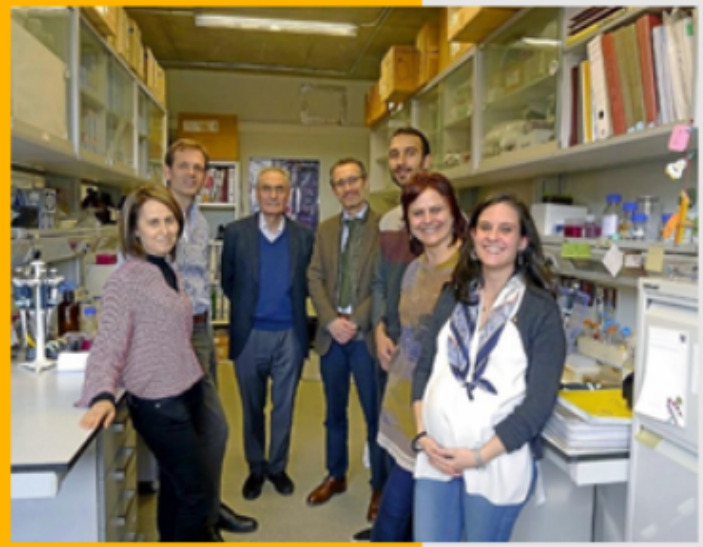
https://www.elnortedecastilla.es/valladolid/nuevo-analisis-genetico-20191104164551-nt.html

Diario de Valladolid:

La terapia que abre los caminos al corazón. Investigadores del IBGM descubren una potencial diana terapéutica para tratar la estenosis aórtica degenerativa calcificada / Estudian la aplicación de un fármaco para la cura de esta enfermedad cuya única opción es la cirugía.

Más información en el siguiente link:

http://www.diariodevalladolid.es/noticias/innovadores/terapia-abre-caminos-corazon_153903.html



HIGH SCHOOL VISITS TO IBGM

2018-2019

- Colegio Jesús y María, Valladolid
- Colegio Safa-Grial, Valladolid
- IES Pinar de la Rubia, Valladolid
- IES Camino de Santiago, Burgos
- IES Andrés Laguna, Segovia
- Colegio La Inmaculada, Valladolid
- Centro López Vicuña, Palencia
- IES Jiménez Lozano, Valladolid
- IES Eulogio Florentino Sanz, Arévalo, Avila.
- Colegio Ave María, Valladolid
- IES Señorío de Guardo, Guardo, Palencia
- IES Diego de Praves, Valladolid
- IES Montes Obarenes, Miranda de Ebro, Burgos
- IES Galileo, Valladolid
- IES Gregorio Fernández, Valladolid

IBGM members collaborate in many different actions intended to communicate research activities to the society. We are particularly proud of the visits of high school students from our City and Community in which we try to implement love for science. Here is the list of high schools that visited us during 2019.

2019-2020

- IES Hipólito Ruiz López, Belorado, ValladolidBurgos
- Colegio Peñalba, Simancas, Valladolid
- Colegio Safa-Grial, Valladolid
- Colegio San José, Valladolid
- IES Diego de Praves, Valladolid
- Colegio San Agustín, Valladolid
- Colegio Nuestra Señora del Pilar, Valladolid
- Colegio Ave María, Valladolid

PROGRAMAS PARA CONOCER EL MUNDO LABORAL

- Programa "WORKDAY", Colegio La Immaculada, Valladolid
- Programa "Conociendo el mundo laboral", IES Ribera de Castilla, Valladolid
- Programa "Colegas por un día", IES Condesa Eylo, Valladolid

EDUCATIONAL/TRAINING PROGRAM AT IBGM

Training for Undergraduate and Graduate Students. IBGM members collaborate with the formative activity of different Universities through Curricular and Extra-curricular practices between June-September. In 2019 we have received students from the University of Salamanca and other universities.

Training for Technicians: IBGM members collaborate in the Training program for students in Anatomical Pathology and Clinical and Biomedical Laboratory. It is organized through agreements with institutions that provide secondary education for laboratory technicians in Valladolid.In 2019 we received students from two schools:

IES Ramón y Cajal. Especialidad Anatomía Patológica
Centro Grial. Especialidad Laboratorio Clínico y Biomédico

Stay at IBGM of Students that achieved to the finals of the Spanish Biology Olympiads.


IBGM
INSTITUTO DE BIOLOGÍA
Y GENÉTICA MOLECULAR