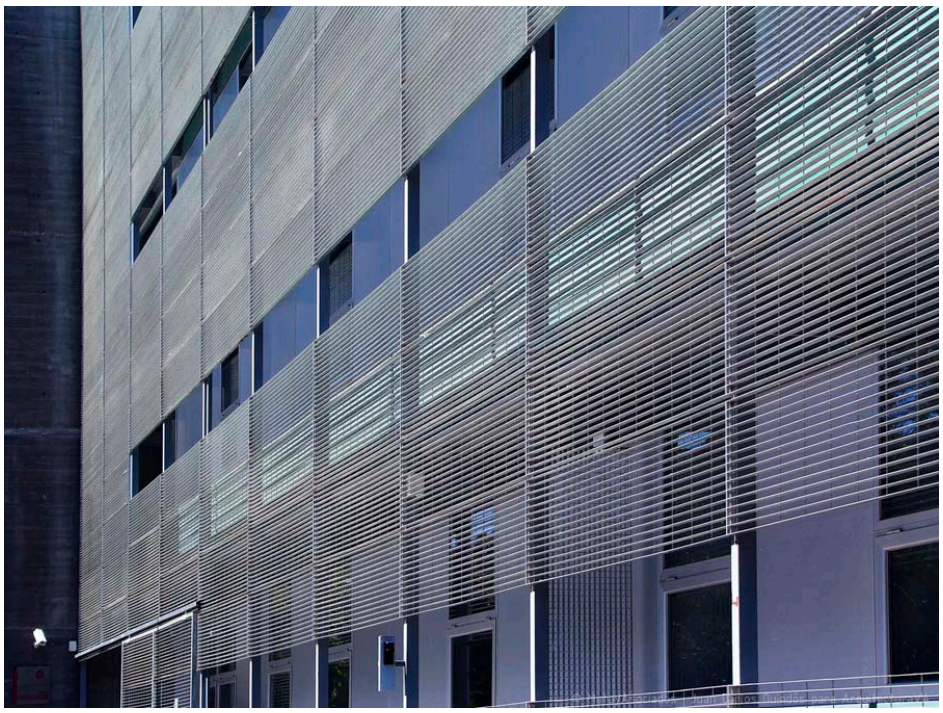
SCIENTIFIC REPORT 2018

Instituto de Biología y Genética Molecular (IBGM)



Universidad de Valladolid & CSIC

INTRODUCTION

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 Superior Council of Scientific Research (CSIC) founded in 1998.

The IBGM holds presently about 120 employees (about 40 from CSIC and 80 from UVa), including 10 CSIC staff researchers and 37 UVA Professors and Associate Professors, as well as predoctoral and postdoctoral researchers, technicians and administration and service personnel. The IBGM is presently organized into 21 research groups divided into 3 units devoted to:

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

The IBGM hosts 11 several Recognized Research Groups (GIR) of the UVa and 8 Units of Consolidated Research (UIC) of the Junta de Castilla y León.

What do we do?

The IBGM studies Cell and Molecular bases of the most important groups of diseases including cardiovascular and respiratory system diseases, the 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?

The IBGM produces some 40-60 scientific publications per year, the great majority in the first quartile, and some 15-20 publications in the first decile.

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 5-10 new PhD researchers each year.

The IBGM participates in a growing series of Cell Therapy and Regenerative Medicine Clinical Trials throughout Spain, 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.

How much does it cost and who pays for it?

IBGM researchers capture most of its funding on competitive basis amounting 1 - 1.5 M € / year on competitive research funds that contribute about € 250,000 in overheads to both institutions. These funds cover the expenses of the research projects including some 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 León, 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 building just behind of the Valladolid University Clinic Hospital

Scientific Publications

67 Scientific Publications Indexed in 2018

47 publications (70%) are first quartile (Q1) publications
20 publications (30%) are first decile (Q1 D1) publications

Total Impact Factor (TIF): 323

31 Publications (47%) with the main author belonging to IBGM
18 publications (26%) are International collaborations
28 publications (42%) are National collaborations
12 publications (18%) are Intramural collaborations

IBGM entrance hall

Cell and Molecular Physiology Unit

29 publications (44% of the total), 21 publications Q1 (72%), 9 publications Q1 D1 (31%), IFT 177. 13 articles (48%) with the main author of the IBGM, 11 international collaborations (38%), 9 national collaborations (31%) and 1 intramural collaboration (3%).

1. Rojo-Ruiz J, Rodríguez-Prados M, Delrio-Lorenzo A, **Alonso MT**, **García-Sancho J** (2018) Caffeine chelates calcium in the lumen of the endoplasmic reticulum. *Biochem J*. 2018 Nov 28; 475(22):3639-3649. doi: 10.1042/BCJ20180532. IF 3.620 /Q1.

2. García-Casas P, Arias-Del-Val J, Alvarez-Illera P, **Fonteriz RI**, **Montero M**, **Alvarez J** (2018) Inhibition of sarco-endoplasmic reticulum Ca^{2+} ATPase extends the lifespan in C. elegans worms. *Front Pharmacol*. 2018 Jun 25;9:669. doi: 10.3389/fphar.2018.00669. eCollection 2018. IF: 3.950 / Q1 D1.

3. **Núñez L**, Bird GS, Hernando-Pérez E, Pérez-Riesgo E, Putney JW, **Villalobos C** (2018) 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* Nov 16. pii: S0167-4889(18)30504-4. IF: 5.128 / Q1.

4. **Villalobos C**, Gutiérrez LG, Hernández-Morales M, del Bosque D, **Núñez L** (2018) Mitochondrial control of store-operated Ca^{2+} channels in cancer: pharmacological implications. *Pharmacol Res* 135, 136-143. IF: 4.897 / Q1 D1.

5. **Núñez L**, Calvo-Rodríguez M, Caballero E, García-Durillo M, **Villalobos C** (2018) Neurotoxic Ca^{2+} signalling induced by amyloid oligomers in aged hippocampal neurons in vitro. *Methods Mol Biol* 1779, 341-354. IF: 1.500 / Q2

6. Sanz-Blasco S, Calvo-Rodríguez M, Caballero E, García-Durillo M, **Núñez L**, **Villalobos C** (2018) Is it all said for NSAIDs in Alzheimer's disease? Role of mitochondrial calcium uptake. *Curr Alzheimer Res* 15, 1-7. IF: 3.145 / Q1

7. Humeau J, Bravo-San Pedro JM, **Núñez L**, **Villalobos C**, Kroemer G, Senovilla L (2018) Calcium signaling and cell cycle: progression or death. *Cell Calcium* 70, 3-15. IF: 3,707 / Q1

8. Cazaña-Pérez V, Cidad P, Donate-Correa J, Martín-Núñez E, **López-López JR**, **Pérez-García MT**, Giraldez T, Navarro-González JF, Alvarez de la Rosa D (2018) Phenotypic Modulation of Cultured Primary Human Aortic Vascular Smooth Muscle Cells by Uremic Serum. *Front Physiol*. 2018 Feb 12;9:89. doi: 10.3389/fphys.2018.00089. eCollection 2018. IF 3.660 / Q1

9. **López-López JR**, Cidad P, **Pérez-García MT** (2018) Kv channels and vascular smooth muscle cell proliferation. *Microcirculation*. 2018 Jan;25(1). doi: 10.1111/micc.12427. IF 2.83 / Q1

10. **Pérez-García MT**, Cidad P, **López-López JR** (2018) The secret life of ion channels: Kv1.3 potassium channels and proliferation. *Am J Physiol Cell Physiol*. 2018 Jan 1;314(1):C27-C42. doi: 10.1152/ajpcell.00136.2017. IF 3.454 / Q1

11. Olea E, Gonzalez-Obeso E, Agapito T, **Obeso A**, **Rigual R**, **Rocher A**, **Gomez-Niño A** (2018) Adrenal Medulla Chemo Sensitivity Does Not Compensate the Lack of Hypoxia Driven Carotid Body Chemo Reflex in Guinea Pigs. *Adv Exp Med Biol*. 2018;1071:167-174. doi: 10.1007/978-3-319-91137-3_21. IF 1.67 / Q2

12. Docio I, Olea E, Prieto-LLoret J, Gallego-Martin T, **Obeso A**, **Gomez-Niño A**, **Rocher A** (2018) Guinea Pig as a Model to Study the Carotid Body Mediated Chronic Intermittent Hypoxia Effects. *Front Physiol*. 2018 Jun 5;9:694. doi: 10.3389/fphys.2018.00694. eCollection 2018. IF 3.66 / Q1

13. Gomez-Niño A, Docio I, Prieto-Lloret J, **Simarro M**, **de la Fuente MA**, **Rocher A** (2018) Mitochondrial Complex I Dysfunction and Peripheral Chemoreflex Sensitivity in a FASTK-Deficient Mice Model. *Adv Exp Med Biol*. 2018;1071:51-59. doi: 10.1007/978-3-319-91137-3_6. IF 1.67 / Q2

14. Ribeiro MJ, Sacramento JF, Gallego-Martin T, Olea E, Melo BF, Guarino MP, Yubero S**, Obeso A,** Conde SV (2018) High fat diet blunts the effects of leptin on ventilation and on carotid body activity. *J Physiol*. 2018; 596(15):3187-3199. doi: 10.1113/JP275362. IF 3.44 / Q1

15. **Prieto-Lloret J,** Snetkov VA, Shaifta Y, Docio I, Connolly MJ, MacKay CE, Knock GA, Ward JPT, Aaronson PI (2018) Role of reactive oxygen species and sulfide-quinone oxoreductase in hydrogen sulfide-induced contraction of rat pulmonary arteries. *Am J Physiol Lung Cell Mol Physiol.* 2018 Apr 1;314(4):L670-L685. doi: 10.1152/ajplung.00283.2016. IF 4.22 / Q1 D1

16. Heikal L, Starr A, Hussein D, **Prieto-Lloret J**, Aaronson P, Dailey LA, Nandi M (2018) l-Phenylalanine Restores Vascular Function in Spontaneously Hypertensive Rats Through Activation of the GCH1-GFRP Complex. *JACC Basic Transl Sci*. 2018 May 30;3(3):366-377. doi: 10.1016/j.jacbts.2018.01.015. eCollection 2018. IF 2.32 / Q1

17. Sacramento JF, Chew DJ, Melo BF, Donegá M, Dopson W, Guarino MP, Robinson A, **Prieto-Lloret J**, Patel S, Holinski BJ, Ramnarain N, Pikov V, Famm K, Conde SV. Bioelectronic modulation of carotid sinus nerve activity in the rat: a potential therapeutic approach for type 2 diabetes. *Diabetologia*. 2018 Mar;61(3):700-710. doi: 10.1007/s00125-017-4533-7. IF 5.09 / Q1 D1

18. Porras G, Díaz-Marrero AR, de la Rosa JM, D'Croz L, de Pablo N, Perdomo G, **Cózar-Castellano, I,** Darias J, Cueto M (2018) Cembranoids from Eunicea sp enhance insulin-producing cells proliferation. Tetrahedron 74 (16): 2056-62. IF: 2.651 / Q2

19. Villa-Pérez P, Merino B, Fernández-Díaz CM, Cidad P, **Lobatón CD**, **Moreno A**, Muturi HT, Ghadieh HE, Najjar SM, Leissring MA, **Cózar-Castellano I**, Perdomo G (2018) Liver-specific ablation of insulin-degrading enzyme causes hepatic insulin resistance and glucose intolerance, without affecting insulin clearance in mice. *Metabolism*. 2018 Nov;88:1-11. doi: 10.1016/j.metabol.2018.08.001. IF: 5.36 / Q1 D1

20. Fernández-Díaz CM, Escobar-Curbelo L, López-Acosta JF, **Lobatón CD**, **Moreno A**, Sanz-Ortega J, Perdomo G, **Cózar-Castellano I** (2018) Insulin degrading enzyme is up-regulated in pancreatic β cells by insulin treatment. *Histol Histopathol*. 2018 Nov;33(11):1167-1180. doi: 10.14670/HH-11-997. IF 2.025 / Q2

21. Gallardo AB, Díaz-Marrero AR, de la Rosa JM, D'Croz L, Perdomo G, **Cózar-Castellano I**, Darias J, Cueto M (2018) Chloro-Furanocembranolides from Leptogorgia sp. Improve Pancreatic Beta-Cell Proliferation. *Mar Drugs*. 2018 Feb 2;16(2). pii: E49. doi: 10.3390/mQ1 D16020049. IF: 4.379 / Q1.

22. Contreras Muruaga MM, Reig G, Vivancos J, González A, Cardona P, Ramírez-Moreno JM, Martí-Fábregas J, Suárez Fernández C; en nombre de los investigadores del estudio ALADIN; Listado de investigadores del estudio ALADIN (2018) Factors associated with poor anticoagulation control with vitaminK antagonists among outpatients attended in Internal Medicine and Neurology. The ALADIN study. *Rev Clin Esp*. 2018 Oct;218(7):327-335. doi: 10.1016/j.rce.2018.04.020. IF 1.184 / Q2

23. Bang OY, Toyoda K, **Arenillas JF**, Liu L, Kim JS (2018) Intracranial Large Artery Disease of Non-Atherosclerotic Origin: Recent Progress and Clinical Implications. *J Stroke*. 2018 May;20(2):208-217. doi: 10.5853/jos.2018.00150. IF 3.52 / Q1

24. Ramos-Araque ME, Rodriguez C, Vecino R, Cortijo Garcia E, de Lera Alfonso M, Sanchez Barba M, Colàs-Campàs L, Purroy F, **Arenillas JF**, Almeida A, Delgado-Esteban M (2018) The Neuronal Ischemic Tolerance Is Conditioned by the Tp53 Arg72Pro Polymorphism. *Transl Stroke Res*. 2018 Apr 23. doi: 10.1007/s12975-018-0631-1. IF: 6.38 / Q1 D1

25. Masjuan J, Gállego J, Aguilera JM, **Arenillas JF**, Castellanos M, Díaz F, Portilla JC, Purroy F (2018) Use of cardiovascular polypills for the secondary prevention of cerebrovascular disease. *Neurologia*. 2018 Jan 8. pii: S0213-4853(17)30366-3. doi: 10.1016/j.nrl.2017.10.013. IF 0,53 / Q2

26. **Arenillas JF**, Cortijo E, García-Bermejo P, Levy EI, Jahan R, Liebeskind D, Goyal M, Saver JL, Albers GW (2018) Relative cerebral blood volume is associated with collateral status and infarct growth in stroke patients in SWIFT PRIME. *J Cereb Blood Flow Metab*. 2018 Oct;38(10):1839-1847. doi: 10.1177/0271678X17740293. IF. 5.070 / Q1 D1

27. Pagola J, Juega J, Francisco-Pascual J, Moya A, Sanchis M, Bustamante A, Penalba A, Usero M, Cortijo E, **Arenillas JF** et al. , CryptoAF investigators (2018) Yield of atrial fibrillation detection with Textile Wearable Holter from the acute phase of stroke: Pilot study of Crypto-AF registry. *Int J Cardiol*. 2018 Jan 15;251:45-50. doi: 10.1016/j.ijcard.2017.10.063. IF 4.034 / Q1

28. Román LS, Menon BK, Blasco J, (...**Arenillas JF**...), Keshvara R. Cunningham J (2018) Imaging features and safety and efficacy of endovascular stroke treatment: a meta-analysis of individual patient-level data. *The Lancet Neurol* 17(10), 895-904. IF. 9.390 / Q1 D1

29. Amarenco P et al. TIAregistry.org Investigators. Five-Year Risk of Stroke after TIA or Minor Ischemic Stroke. *N Engl J Med*. 2018 Jun 7;378(23):2182-2190. doi: 10.1056/NEJMoa1802712. IF. 79.258 / Q1 D1

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).

Research Highlights

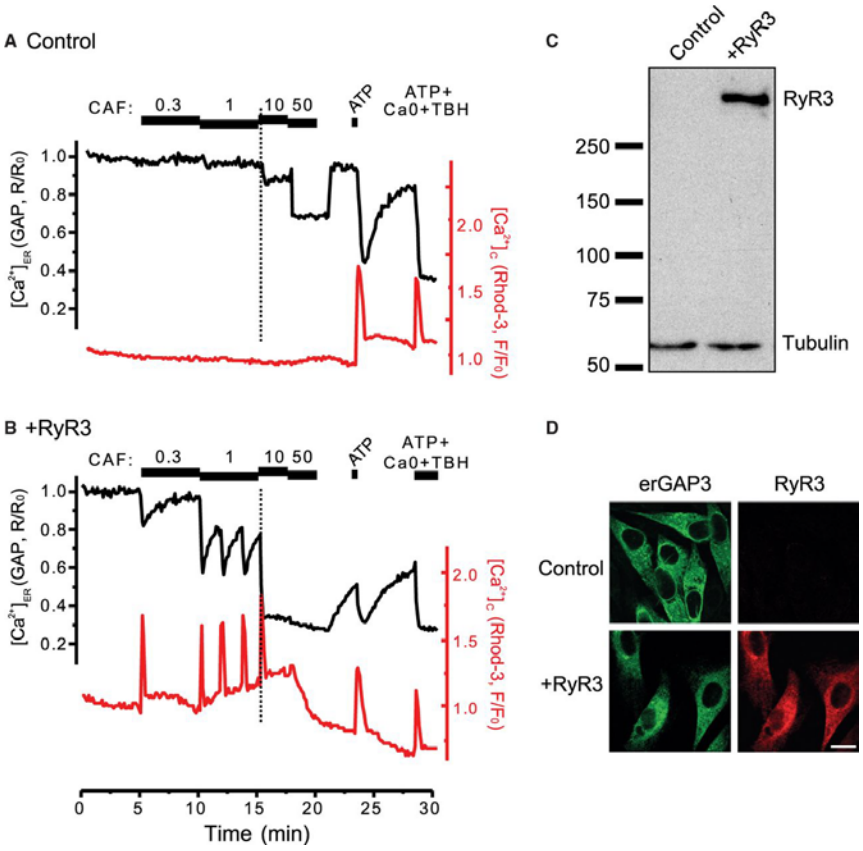
The research group founded by **Prof. J. García-Sancho** and headed also by **Prof. María Teresa Alonso** has extensive experience in the study of cellular activation phenomena, especially regarding the role of intracellular Ca^{2+} as second messenger. The work in this field began in 1984, after witnessing 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 2018

Rojo-Ruiz J, Rodríguez-Prados M, Delrio-Lorenzo A, **Alonso MT**, **García-Sancho J** (2018) Caffeine chelates calcium in the lumen of the endoplasmic reticulum. *Biochem J*. 2018 Nov 28;475(22):3639-3649. doi: 10.1042/BCJ20180532. IF 3.62 /Q1.



Comparison of the responses to caffeine in control (A) and RyR3-expressing HeLa cells (B).

Research Projects starting in 2018

Title: *Calcio y Función Celular*
Funding Agency: Plan Nacional I+D+I, Ministerio de Economía y Competitividad (BFU2017 83066-P)
From 2018 to 2021.
Funding: 363.000 €
Principal Investigator María T. Alonso & Javier García-Sancho

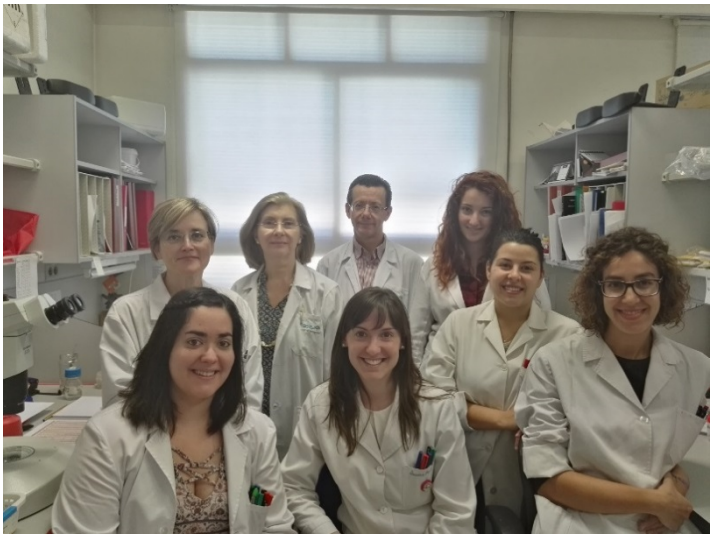
Cell and Molecular Physiology Unit

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

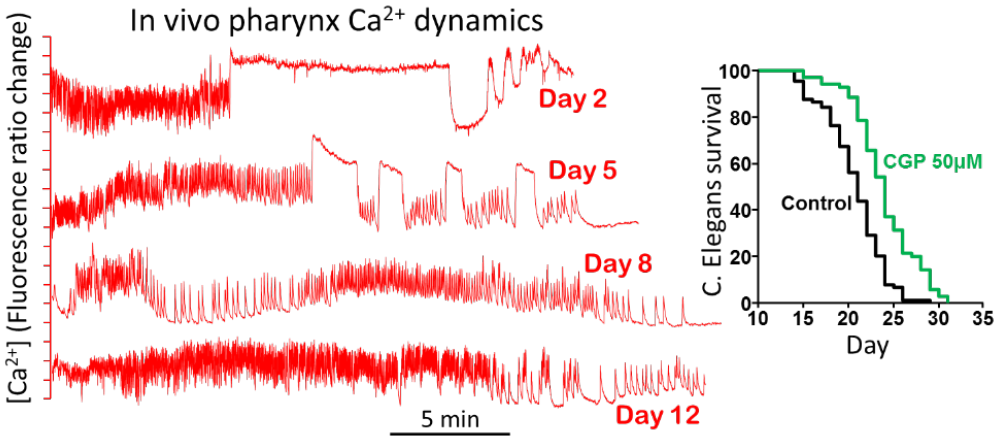


Research Highlights

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 2018

García-Casas P, Arias-Del-Val J, Alvarez-Illera P, **Fonteriz RI**, **Montero M**, **Alvarez J** (2018) Inhibition of sarco-endoplasmic reticulum Ca^{2+} ATPase extends the lifespan in C. elegans worms. *Front Pharmacol*. 2018 Jun 25;9:669. doi: 10.3389/fphar.2018.00669. eCollection 2018. IF: 3.950 / Q1 D1.

Research Projects starting in 2018

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

Doctoral Thesis in 2018

Title:	***Calcium dynamics in "Caenorhabditis elegans" pharynx***
Author:	Álvarez Illera, María Pilar
Director:	Montero Zoccola, María Teresa; Álvarez Martín, Javier; Fonteriz García, Rosalba
Year:	2018
Degree:	PhD in Biomedical Research, University of Valladolid

Tithel:	***Effects of AMP-activated kinase modulators on intracellular Ca^{2+} signalling and C. elegans lifespan***
Author:	Arias del Val, Jessica
Director:	Alvarez Martín, Javier; Fonteriz García, Inés; Montero Zoccola, María Teresa
Year:	2018
Degree:	PhD in Biomedical Research, University of Valladolid

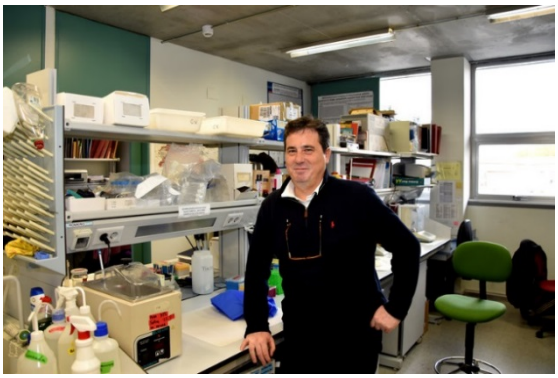
Cell and Molecular Physiology Unit

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), Agueda Prieto (Graduate candidate)



Research Highlights

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 2018

Núñez L, Bird GS, Hernando-Pérez E, Pérez-Riesgo E, Putney JW, **Villalobos C** (2018) 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* Nov 16. pii: S0167-4889(18)30504-4. IF: 5.128 / Q1.

Villalobos C, Gutiérrez LG, Hernández-Morales M, del Bosque D, **Núñez L** (2018) Mitochondrial control of store-operated Ca^{2+} channels in cancer: pharmacological implications. *Pharmacol Res* 135, 136-143. IF: 4.897 / Q1 D1.

Núñez L, Calvo-Rodríguez M, Caballero E, García-Durillo M, **Villalobos C** (2018) Neurotoxic Ca^{2+} signalling induced by amyloid oligomers in aged hippocampal neurons in vitro. *Methods Mol Biol* 1779, 341-354. IF: 1.500 / Q2

Sanz-Blasco S, Calvo-Rodríguez M, Caballero E, García-Durillo M, **Núñez L**, **Villalobos C** (2018) Is it all said for NSAIDs in Alzheimer's disease? Role of mitochondrial calcium uptake. *Curr Alzheimer Res* 15, 1-7. IF: 3.145 / Q1

Humeau J, Bravo-San Pedro JM, **Núñez L**, **Villalobos C**, Kroemer G, Senovilla L (2018) Calcium signaling and cell cycle: progression or death. *Cell Calcium* 70, 3-15. IF: 3.707 / Q1

Research Projects starting in 2018

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.

Communications to Scientific Meetings

Núñez L, Bird GS, Hernando-Pérez E, Pérez-Riesgo E, Birnbaumer L, Villalobos C and Putney JW. *Store-operated Ca^{2+} entry and Ca^{2+} responses to hypothalamic releasing hormones in anterior pituitary cells from Orai1 and heptaTRPC knockout mice*. XV International Meeting of the European Calcium Society (ECS2018). *Hamburg*, Germany. 9-13 September 2018.

Pérez-Riesgo E, Villalobos C. *Illuminating transcriptomics of Ca^{2+} remodeling in colorectal cancer*. XV International Meeting of The European Calcium Society (ECS2018). *Hamburg*, Germany. 9-13 September 2018.

Hernando-Pérez E, García-Durillo M, Villalobos C, Núñez L. *In vitro aging of rat hippocampal neurons is associated to changes in calcium responses to NMDA and expression of IP_3 receptor isoforms*. XXXIX Congreso de la Sociedad Española de Ciencias Fisiológicas (SECF). *Cádiz*, Spain. 18-21 September 2018. Oral Communication.

Pérez-Riesgo E, Villalobos. *Illuminating transcriptomics of Ca^{2+} remodeling in colorectal cancer*. XXXIX Congreso de la Sociedad Española de Ciencias Fisiológicas (SECF). *Cádiz*, Spain. 18-21 September 2018.

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

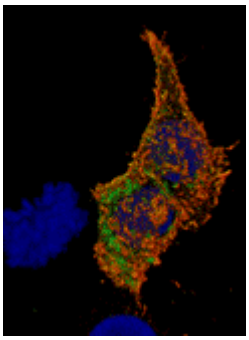
Research Highlights

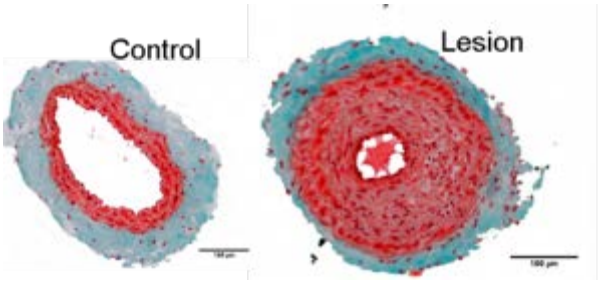
Characterization of the role of ion channels in vascular function, with special emphasis on essential hypertension and intimal hyperplasia.

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.





Publications in 2018

Cazaña-Pérez V, Cidad P, Donate-Correa J, Martín-Núñez E, **López-López JR**, **Pérez-García MT**, Giraldez T, Navarro-González JF, Alvarez de la Rosa D (2018) Phenotypic Modulation of Cultured Primary Human Aortic Vascular Smooth Muscle Cells by Uremic Serum. *Front Physiol*. 2018 Feb 12;9:89. doi: 10.3389/fphys.2018.00089. eCollection 2018. IF 3.66 / Q1

López-López JR, Cidad P, **Pérez-García MT** (2018) Kv channels and vascular smooth muscle cell proliferation. *Microcirculation*. 2018 Jan;25(1). doi: 10.1111/micc.12427. IF 2.83 / Q1

Pérez-García MT, Cidad P, **López-López JR** (2018) The secret life of ion channels: Kv1.3 potassium channels and proliferation. *Am J Physiol Cell Physiol*. 2018 Jan 1;314(1):C27-C42. doi: 10.1152/ajpcell.00136.2017. IF 3.454 / Q1

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, Mª Teresa Agapito.
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 2018

Olea E, Gonzalez-Obeso E, Agapito T, **Obeso A**, Rigual R, **Rocher A**, Gomez-Niño A (2018) Adrenal Medulla Chemo Sensitivity Does Not Compensate the Lack of Hypoxia Driven Carotid Body Chemo Reflex in Guinea Pigs. *Adv Exp Med Biol*. 2018;1071:167-174. doi: 10.1007/978-3-319-91137-3_21. IF 1,76 / Q2

Docio I, Olea E, Prieto-LLoret J, Gallego-Martin T, **Obeso A**, Gomez-Niño A, **Rocher A** (2018) Guinea Pig as a Model to Study the Carotid Body Mediated Chronic Intermittent Hypoxia Effects. *Front Physiol*. 2018 Jun 5;9:694. doi: 10.3389/fphys.2018.00694. eCollection 2018. IF 3,66 / Q1

Gomez-Niño A, Docio I, Prieto-Lloret J, **Simarro M**, **de la Fuente MA**, **Rocher A** (2018) Mitochondrial Complex I Dysfunction and Peripheral Chemoreflex Sensitivity in a FASTK-Deficient Mice Model. *Adv Exp Med Biol*. 2018;1071:51-59. doi: 10.1007/978-3-319-91137-3_6. IF 1,76 / Q2

Ribeiro MJ, Sacramento JF, Gallego-Martin T, Olea E, Melo BF, Guarino MP, Yubero S, **Obeso A**, Conde SV (2018) High fat diet blunts the effects of leptin on ventilation and on carotid body activity. *J Physiol*. 2018; 596(15):3187-3199. doi: 10.1113/JP275362. IF 4.54 / D1

Prieto-Lloret J, Snetkov VA, Shaifta Y, Docio I, Connolly MJ, MacKay CE, Knock GA, Ward JPT, Aaronson PI (2018) Role of reactive oxygen species and sulfide-quinone oxoreductase in hydrogen sulfide-induced contraction of rat pulmonary arteries. *Am J Physiol Lung Cell Mol Physiol.* 2018 Apr 1;314(4):L670-L685. doi: 10.1152/ajplung.00283.2016. IF 4,22 / D1

Heikal L, Starr A, Hussein D, **Prieto-Lloret J**, Aaronson P, Dailey LA, Nandi M (2018) l-Phenylalanine Restores Vascular Function in Spontaneously Hypertensive Rats Through Activation of the GCH1-GFRP Complex. *JACC Basic Transl Sci*. 2018 May 30;3(3):366-377. doi: 10.1016/j.jacbts.2018.01.015. eCollection 2018. IF 2,32 / Q1

Sacramento JF, Chew DJ, Melo BF, Donegá M, Dopson W, Guarino MP, Robinson A, **Prieto-Lloret J**, Patel S, Holinski BJ, Ramnarain N, Pikov V, Famm K, Conde SV (2018). Bioelectronic modulation of carotid sinus nerve activity in the rat: a potential therapeutic approach for type 2 diabetes. *Diabetologia*. Mar;61(3):700-710. doi: 10.1007/s00125-017-4533-7. IF 6.02 / D1

Research Projects starting in 2018

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

Teaching in 2018

Communications to Scientific Meetings in 2018

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 D. 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 2018

Porras G, Díaz-Marrero AR, de la Rosa JM, D'Croz L, de Pablo N, Perdomo G, **Cózar-Castellano, I,** Darias J, Cueto M (2018) Cembranoids from Eunicea sp enhance insulin-producing cells proliferation. Tetrahedron 74 (16): 2056-62. IF: 2.651 / Q2

Villa-Pérez P, Merino B, Fernández-Díaz CM, Cidad P, **Lobatón CD**, **Moreno A**, Muturi HT, Ghadieh HE, Najjar SM, Leissring MA, **Cózar-Castellano I**, Perdomo G (2018) Liver-specific ablation of insulin-degrading enzyme causes hepatic insulin resistance and glucose intolerance, without affecting insulin clearance in mice. *Metabolism*. 2018 Nov;88:1-11. doi: 10.1016/j.metabol.2018.08.001. IF: 5.36 / Q1 D1

Fernández-Díaz CM, Escobar-Curbelo L, López-Acosta JF, **Lobatón CD**, **Moreno A**, Sanz-Ortega J, Perdomo G, **Cózar-Castellano I** (2018) Insulin degrading enzyme is up-regulated in pancreatic β cells by insulin treatment. *Histol Histopathol*. 2018 Nov;33(11):1167-1180. doi: 10.14670/HH-11-997. IF 2.025 / Q2

Gallardo AB, Díaz-Marrero AR, de la Rosa JM, D'Croz L, Perdomo G, **Cózar-Castellano I**, Darias J, Cueto M (2018) Chloro-Furanocembranolides from Leptogorgia sp. Improve Pancreatic Beta-Cell Proliferation. *Mar Drugs*. 2018 Feb 2;16(2). pii: E49. doi: 10.3390/mQ1 D16020049. IF: 4.379 / Q1.

Research Projects starting in 2018

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

Doctoral Thesis in 2018

Título:	***Role Insulin-Degrading Enzyme (IDE) in Diabetes mellitus and Insuline resistance***
Author:	Pablo Villa Pérez
Directors:	Cózar Castellano, Irene; Perdomo Hernández, Germán; Domínguez Lobatón, Mª Carmen
Year:	2018
Area:	PhD in Biomedical Research

Cell and Molecular Physiology Unit

Neurovascular Pathology Group

Team

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

Postdocs: Jesús Agulla Freire

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:

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

Publications

Contreras Muruaga MM, Reig G, Vivancos J, González A, Cardona P, Ramírez-Moreno JM, Martí-Fábregas J, Suárez Fernández C; en nombre de los investigadores del estudio ALADIN; Listado de investigadores del estudio ALADIN (2018) Factors associated with poor anticoagulation control with vitaminK antagonists among outpatients attended in Internal Medicine and Neurology. The ALADIN study. *Rev Clin Esp*. 2018 Oct;218(7):327-335. doi: 10.1016/j.rce.2018.04.020. IF 1.184 / Q2

Bang OY, Toyoda K, **Arenillas JF**, Liu L, Kim JS (2018) Intracranial Large Artery Disease of Non-Atherosclerotic Origin: Recent Progress and Clinical Implications. *J Stroke*. 2018 May;20(2):208-217. doi: 10.5853/jos.2018.00150. IF 3.52 / Q1

Ramos-Araque ME, Rodriguez C, Vecino R, Cortijo Garcia E, de Lera Alfonso M, Sanchez Barba M, Colàs-Campàs L, Purroy F, **Arenillas JF**, Almeida A, Delgado-Esteban M (2018) The Neuronal Ischemic Tolerance Is Conditioned by the Tp53 Arg72Pro Polymorphism. *Transl Stroke Res*. 2018 Apr 23. doi: 10.1007/s12975-018-0631-1. IF: 6.38 / Q1 D1

Masjuan J, Gállego J, Aguilera JM, **Arenillas JF**, Castellanos M, Díaz F, Portilla JC, Purroy F (2018) Use of cardiovascular polypills for the secondary prevention of cerebrovascular disease. *Neurologia*. 2018 Jan 8. pii: S0213-4853(17)30366-3. doi: 10.1016/j.nrl.2017.10.013. IF 0.53 / Q2

Arenillas JF, Cortijo E, García-Bermejo P, Levy EI, Jahan R, Liebeskind D, Goyal M, Saver JL, Albers GW (2018) Relative cerebral blood volume is associated with collateral status and infarct growth in stroke patients in SWIFT PRIME. *J Cereb Blood Flow Metab*. 2018 Oct;38(10):1839-1847. doi: 10.1177/0271678X17740293. IF. 5.070 / Q1 D1

Pagola J, Juega J, Francisco-Pascual J, Moya A, Sanchis M, Bustamante A, Penalba A, Usero M, Cortijo E, **Arenillas JF**, Calleja AI, Sandin-Fuentes M, Rubio J, Mancha F, Escudero-Martinez I, Moniche F, de Torres R, Pérez-Sánchez S, González-Matos CE, Vega Á, Pedrote AA, Arana-Rueda E, Montaner J, Molina CA; CryptoAF investigators (2018) Yield of atrial fibrillation detection with Textile Wearable Holter from the acute phase of stroke: Pilot study of Crypto-AF registry. *Int J Cardiol*. 2018 Jan 15;251:45-50. doi: 10.1016/j.ijcard.2017.10.063. IF 4.034 / Q1

Román LS, Menon BK, Blasco J, (...), Keshvara R. Cunningham J (2018) Imaging features and safety and efficacy of endovascular stroke treatment: a meta-analysis of individual patient-level data. *The Lancet Neurol* 17(10), 895-904. IF. 9.390 / Q1 D1

Amarenco P et al., TIAregistry.org Investigators. Five-Year Risk of Stroke after TIA or Minor Ischemic Stroke. *N Engl J Med*. 2018 Jun 7;378(23):2182-2190. doi: 10.1056/NEJMoa1802712. IF. 79.258 / Q1 D1

Innate Immunity and Inflammation Unit

17 publications (26% of the total), 11Q1 (65%), 5Q1 D1 (29%), IFT 72. 7 articles (41%) with the main author of the IBGM. 2 international collaborations (12%), 10 national collaborations (59%), 7 intramural collaborations (41%).

1. **García-Rodríguez C**, Parra-Izquierdo I, Castaños-Mollor I, López J, San Román JA, **Sánchez Crespo M** (2018) Toll-Like Receptors, Inflammation, and Calcific Aortic Valve Disease. *Front Physiol*. 2018 Mar 12;9:201. doi: 10.3389/fphys.2018.00201. eCollection 2018. IF 3.66 / Q1

2. Parra-Izquierdo I, Castaños-Mollor I, López J, Gómez C, San Román JA, **Sánchez Crespo M**, **García-Rodríguez C** (2018) Calcification Induced by Type I Interferon in Human Aortic Valve Interstitial Cells Is Larger in Males and Blunted by a Janus Kinase Inhibitor. *Arterioscler Thromb Vasc Biol*. 2018 Sep;38(9):2148-2159. doi: 10.1161/ATVBAHA.118.311504. IF: 6.086 / Q1 D1

3. Herrero-Sánchez MC, Angomás EB, de Ramón C, **Tellería JJ**, Corchete LA, Alonso S, Ramos MDC, Peñarrubia MJ, Márquez S, Fernández N, García Frade LJ, **Sánchez Crespo M** (2018) Polymorphisms in receptors involved in opsonic and non-opsonic phagocytosis and the risk of infection in oncohematological patients. *Infect Immun*. 2018 Oct 1. pii: IAI.00709-18. doi: 10.1128/IAI.00709-18. IF: 3.256 / Q2

4. Vázquez P, Hernández-Sánchez C, Escalona-Garrido C, Pereira L, Contreras C, López M, **Balsinde J**, de Pablo F, Valverde ÁM (2018) Increased FGF21 in brown adipose tissue of tyrosine hydroxylase heterozygous mice: implications for cold adaptation. *J Lipid Res.* 2018 Dec;59(12):2308-2320. doi: 10.1194/jlr.M085209. IF 4.52 / Q1

5. Meana C, García-Rostán G, Peña L, Lordén G, Cubero Á, Orduña A, Győrffy B, **Balsinde J**, **Balboa MA** (2018) The phosphatidic acid phosphatase lipin-1 facilitates inflammation-driven colon carcinogenesis. *JCI Insight.* 2018 Sep 20;3(18). pii: 97506. doi: 10.1172/jci.insight.97506.

6. Rubio JM, Astudillo AM, Casas J, **Balboa MA**, **Balsinde J** (2018) Regulation of Phagocytosis in Macrophages by Membrane Ethanolamine Plasmalogens. *Front Immunol.* 2018 Jul 24;9:1723. doi: 10.3389/fimmu.2018.01723. eCollection 2018. IF 5.62 / Q1

7. Astudillo AM, **Balboa MA, Balsinde J** (2018) Selectivity of phospholipid hydrolysis by phospholipase A2 enzymes in activated cells leading to polyunsaturated fatty acid mobilization. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2018 Jul 17. pii: S1388-1981(18)30152-5. doi: 10.1016/j.bbalip.2018.07.002. IF 5.02 / Q1

8. Astudillo AM, Meana C, Guijas C, Pereira L, Lebrero P, **Balboa MA**, **Balsinde J** (2018) Occurrence and biological activity of palmitoleic acid isomers in phagocytic cells. *J Lipid Res*. 2018 Feb;59(2):237-249. doi: 10.1194/jlr.M079145. IF 4.52 / Q1

9. 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 (2018) 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. IF 4.36 / Q1 D1

10. Marín-Royo G, Gallardo I, Martínez-Martínez E, Gutiérrez B, Jurado-López R, López-Andrés N, Gutiérrez-Tenorio J, Rial E, Bartolomé MAV, **Nieto ML**, Cachofeiro V (2018) Inhibition of galectin-3 ameliorates the consequences of cardiac lipotoxicity in a rat model of diet-induced obesity. *Dis Model Mech*. 2018 Feb 5;11(2). pii: dmm032086. doi: 10.1242/dmm.032086. IF 4.28 / Q1 D1

11. Marín-Royo G, Martínez-Martínez E, Gutiérrez B, Jurado-López R, Gallardo I, Montero O, Bartolomé MV, San Román JA, Salaices M, **Nieto ML**, Cachofeiro V (2018) The impact of obesity in the cardiac lipidome and its consequences in the cardiac damage observed in obese rats. *Clin Investig Arterioscler*. 2018 Jan - Feb;30(1):10-20. doi: 10.1016/j.arteri.2017.07.004. IF 0.24 / Q3.

12. Núñez C, **Garrote JA**, **Arranz E**, Bilbao JR, Fernández Bañares F, Jiménez J, Perucho T, Ruiz Casares E, Sánchez-Valverde F, Serrano JI (2018) Recommendations to report and interpret HLA genetic findings in coeliac disease. *Rev Esp Enferm Dig*. 2018 Jul;110(7):458-461. doi: 10.17235/reed.2018.5269/2017. IF 0.7 / Q3

13. Ochoa JP et al. (2018) Formin Homology 2 Domain Containing 3 (FHOD3) Is a Genetic Basis for Hypertrophic Cardiomyopathy. *J Am Coll Cardiol.* 2018 Nov 13;72(20):2457-2467. doi: 10.1016/j.jacc.2018.10.001. IF 16.83 / Q1 D1

14. Cabanillas R et al. , (2018) Comprehensive genomic diagnosis of non-syndromic and syndromic hereditary hearing loss in Spanish patients. *BMC Med Genomics*. 2018 Jul 9;11(1):58. doi: 10.1186/s12920-018-0375-5. IF 3.41 / Q2

15. Olivares M, Benítez-Páez A, de Palma G, Capilla A, Nova E, Castillejo G, Varea V, Marcos A, **Garrote JA**, Polanco I, Donat E, Ribes-Koninckx C, Calvo C, Ortigosa L, Palau F, Sanz Y (2018) Increased prevalence of pathogenic bacteria in the gut microbiota of infants at risk of developing celiac disease: The PROFICEL study. *Gut Microbes*. 2018 Nov 2;9(6):551-558. doi: 10.1080/19490976.2018.1451276. IF 4.73 / Q1 D1

16. Casado-Medrano V, Baker MJ, Lopez-Haber C, Cooke M, Wang S, **Caloca MJ**, Kazanietz MG (2018) The role of Rac in tumor susceptibility and disease progression: from biochemistry to the clinic. *Biochem Soc Trans*. 2018 Aug 20;46(4):1003-1012. doi: 10.1042/BST20170519. IF 3.23 / Q2

17. Barrio-Real L, Lopez-Haber C, Casado-Medrano V, Goglia AG, Toettcher JE, **Caloca MJ**, Kazanietz MG (2018) P-Rex1 is dispensable for Erk activation and mitogenesis in breast cancer. *Oncotarget*. 2018 Jun 19;9(47):28612-28624. doi: 10.18632/oncotarget.25584. eCollection 2018 Jun 19. IF 4.65 / Q1

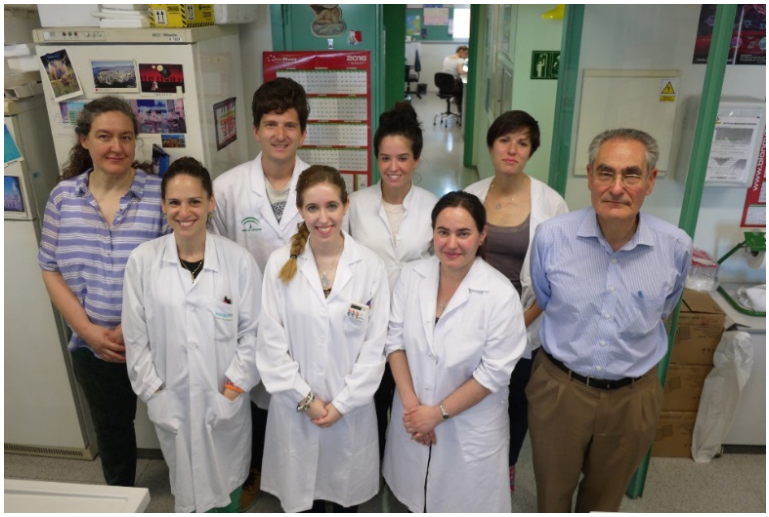
Innate Immunity and Inflammation Unit

Immune-mediated tissue injury and innate immunity Group

Team

Principal Investigators:
Mariano Sánchez Crespo (**CSIC**), mscres@ibgm.uva.es

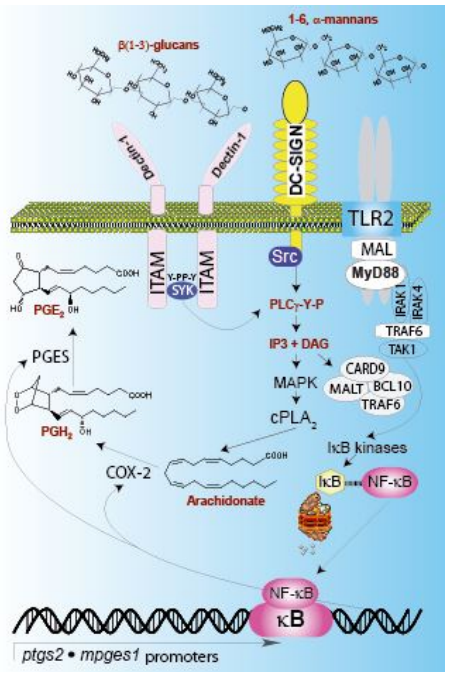
Scientific staff: Nieves Fernández
Postdocs: Carmen Herrero
Predocs: Cristina Martón, Cristina Mancebo, Saioa Márquez
Technicians: Sara Alonso



Sanchez Crespo Lab members

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 2018

Herrero-Sánchez MC, Angomás EB, de Ramón C, **Tellería JJ**, Corchete LA, Alonso S, Ramos MDC, Peñarrubia MJ, Márquez S, Fernández N, García Frade LJ, **Sánchez Crespo M** (2018) Polymorphisms in receptors involved in opsonic and non-opsonic phagocytosis and the risk of infection in oncohematological patients. *Infect Immun*. 2018 Oct 1. pii: IAI.00709-18. doi: 10.1128/IAI.00709-18. IF: 3.256 / Q2

García-Rodríguez C, Parra-Izquierdo I, Castaños-Mollor I, López J, San Román JA, **Sánchez Crespo M** (2018) Toll-Like Receptors, Inflammation, and Calcific Aortic Valve Disease. *Front Physiol*. 2018 Mar 12;9:201. doi: 10.3389/fphys.2018.00201. eCollection 2018. IF 3.66 / Q1

Parra-Izquierdo I, Castaños-Mollor I, López J, Gómez C, San Román JA, **Sánchez Crespo M**, **García-Rodríguez C** (2018) Calcification Induced by Type I Interferon in Human Aortic Valve Interstitial Cells Is Larger in Males and Blunted by a Janus Kinase Inhibitor. *Arterioscler Thromb Vasc Biol*. 2018 Sep;38(9):2148-2159. doi: 10.1161/ATVBAHA.118.311504. IF: 6.086 / Q1 D1

Research Projects starting in 2018

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 2019 to 2021.
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

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 2018

Vázquez P, Hernández-Sánchez C, Escalona-Garrido C, Pereira L, Contreras C, López M, **Balsinde J**, de Pablo F, Valverde ÁM (2018) Increased FGF21 in brown adipose tissue of tyrosine hydroxylase heterozygous mice: implications for cold adaptation. *J Lipid Res.* 2018 Dec;59(12):2308-2320. doi: 10.1194/jlr.M085209. IF 4.52 / Q1

Meana C, García-Rostán G, Peña L, Lordén G, Cubero Á, Orduña A, Győrffy B, **Balsinde J**, **Balboa MA** (2018) The phosphatidic acid phosphatase lipin-1 facilitates inflammation-driven colon carcinogenesis. *JCI Insight.* 2018 Sep 20;3(18). pii: 97506. doi: 10.1172/jci.insight.97506.

Rubio JM, Astudillo AM, Casas J, **Balboa MA**, **Balsinde J** (2018) Regulation of Phagocytosis in Macrophages by Membrane Ethanolamine Plasmalogens. *Front Immunol.* 2018 Jul 24;9:1723. doi: 10.3389/fimmu.2018.01723. eCollection 2018. IF 5.62 / Q1

Astudillo AM, **Balboa MA, Balsinde J** (2018) Selectivity of phospholipid hydrolysis by phospholipase A2 enzymes in activated cells leading to polyunsaturated fatty acid mobilization. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2018 Jul 17. pii: S1388-1981(18)30152-5. doi: 10.1016/j.bbalip.2018.07.002. IF 5.02 / Q1

Astudillo AM, Meana C, Guijas C, Pereira L, Lebrero P, **Balboa MA**, **Balsinde J** (2018) Occurrence and biological activity of palmitoleic acid isomers in phagocytic cells. *J Lipid Res*. 2018 Feb;59(2):237-249. doi: 10.1194/jlr.M079145. IF 4,52 / Q1

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

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 2018

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 (2018) 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. IF 4.36 / Q1 D1

Marín-Royo G, Gallardo I, Martínez-Martínez E, Gutiérrez B, Jurado-López R, López-Andrés N, Gutiérrez-Tenorio J, Rial E, Bartolomé MAV, **Nieto ML**, Cachofeiro V (2018) Inhibition of galectin-3 ameliorates the consequences of cardiac lipotoxicity in a rat model of diet-induced obesity. *Dis Model Mech*. 2018 Feb 5;11(2). pii: dmm032086. doi: 10.1242/dmm.032086. IF 4.28 / Q1 D1

Marín-Royo G, Martínez-Martínez E, Gutiérrez B, Jurado-López R, Gallardo I, Montero O, Bartolomé MV, San Román JA, Salaices M, **Nieto ML**, Cachofeiro V (2018) The impact of obesity in the cardiac lipidome and its consequences in the cardiac damage observed in obese rats. *Clin Investig Arterioscler*. 2018 Jan - Feb;30(1):10-20. doi: 10.1016/j.arteri.2017.07.004. IF 0.24 / Q3

Innate Immunity and Inflammation Unit

Lipid metabolism and Inflammation Group

Team

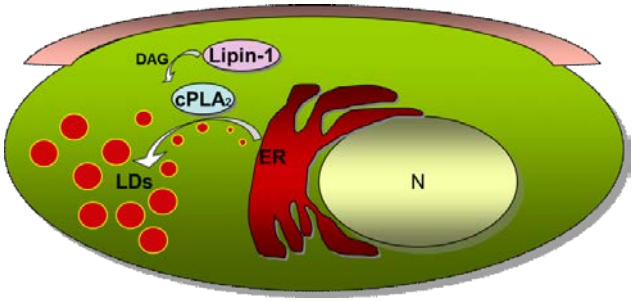
Principal Investigator:
Mª Angeles Balboa (**CSIC**), mbalboa@ibgm.uva.es

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 2018

Meana C, García-Rostán G, Peña L, Lordén G, Cubero Á, Orduña A, Győrffy B, **Balsinde J**, **Balboa MA** (2018) The phosphatidic acid phosphatase lipin-1 facilitates inflammation-driven colon carcinogenesis. *JCI Insight.* 2018 Sep 20;3(18). pii: 97506. doi: 10.1172/jci.insight.97506.

Rubio JM, Astudillo AM, Casas J, **Balboa MA**, **Balsinde J** (2018) Regulation of Phagocytosis in Macrophages by Membrane Ethanolamine Plasmalogens. *Front Immunol.* 2018 Jul 24;9:1723. doi: 10.3389/fimmu.2018.01723. eCollection 2018. IF 5.62 / Q1

Astudillo AM, **Balboa MA, Balsinde J** (2018) Selectivity of phospholipid hydrolysis by phospholipase A2 enzymes in activated cells leading to polyunsaturated fatty acid mobilization. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2018 Jul 17. pii: S1388-1981(18)30152-5. doi: 10.1016/j.bbalip.2018.07.002. IF 5.02 / Q1

Astudillo AM, Meana C, Guijas C, Pereira L, Lebrero P, **Balboa MA**, **Balsinde J** (2018) Occurrence and biological activity of palmitoleic acid isomers in phagocytic cells. *J Lipid Res*. 2018 Feb;59(2):237-249. doi: 10.1194/jlr.M079145. IF 4.52 / Q1

Innate Immunity and Inflammation Unit

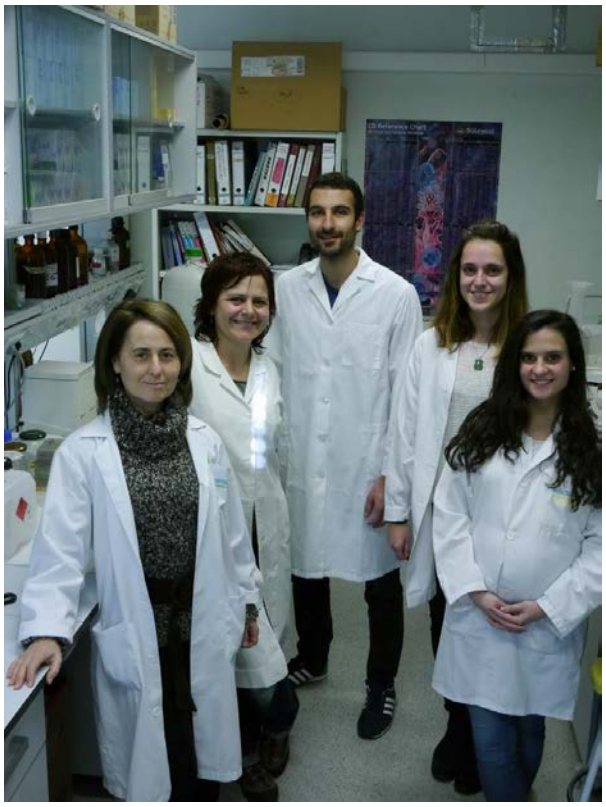
Toll Receptors and Inflammatory Diseases Group

Team

Principal Investigator:
Carmen García Rodríguez (**CSIC**), cgarcia@ibgm.uva.es

Predocs: Irene Castaños-Mollor, Ivan Parra-Izquierdo, Tania Sánchez-Bayuela
Technicians: Cristina Gómez

This team is member of CIBERCV

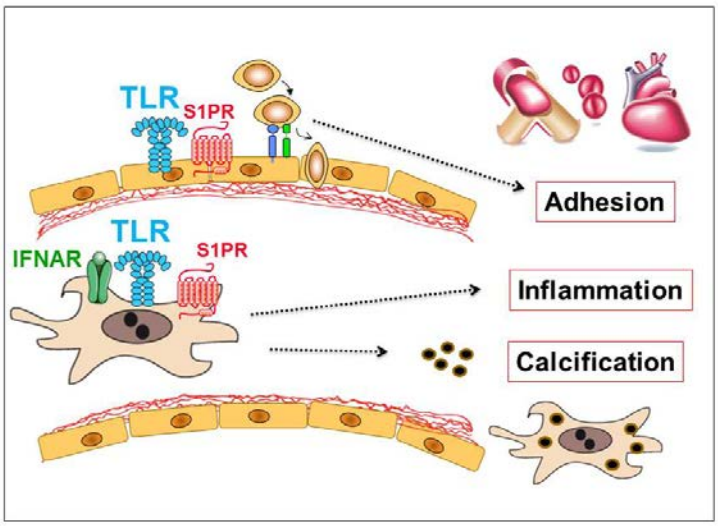


Carmen García group members

Research Highlights

The scientific interest of the group is to investigate the role of of innate immune receptors in the pathophysiology of inflammatory diseases using both basic and translational approaches, molecular biology and immunology techniques, as well as primary cultures of human cells. The Toll or TLR receptors, 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. The group belongs the CIBERCV (Cardiovascular Diseases) network, thus allowing the use of a translational approach to investigate the role of TLRs and other immunomodulators as interferons in the pathophysiology of cardiovascular diseases with an inflammatory component, i.e. atherosclerosis and calcified aortic stenosis. The ultimate goal is to design new therapeutic strategies for their treatment and / or prevention.



Publications in 2018

García-Rodríguez C, Parra-Izquierdo I, Castaños-Mollor I, López J, San Román JA, **Sánchez Crespo M** (2018) Toll-Like Receptors, Inflammation, and Calcific Aortic Valve Disease. *Front Physiol*. 2018 Mar 12;9:201. doi: 10.3389/fphys.2018.00201. eCollection 2018. IF 3.66 / Q1

Parra-Izquierdo I, Castaños-Mollor I, López J, Gómez C, San Román JA, **Sánchez Crespo M**, **García-Rodríguez C** (2018) Calcification Induced by Type I Interferon in Human Aortic Valve Interstitial Cells Is Larger in Males and Blunted by a Janus Kinase Inhibitor. *Arterioscler Thromb Vasc Biol*. 2018 Sep;38(9):2148-2159. doi: 10.1161/ATVBAHA.118.311504. IF: 6.086 / Q1 D1

Teaching in 2018

Teaching in the courses titled “Biomedical Applications of Molecular Biology” and “Immunity and Inflammation” at the Master of Biomedical Research by the University of Valladolid Medical School.

Others

- Carmen García is Member of the Academic Committee of the PhD in Biomedical Research University of Valladolid.
- Carmen García is co-organizer of the IBGM seminar cycle.
- Carmen García provided Informative talk at the Inaugural Conference of the PhD Program in Biomedical Research course 2018/2019 at the University of Valladolid. "The research career in the Superior Council of Scientific Research". November 12, 2018
- Carmen García Rodríguez participated in 3 visits of students to IBGM during 2018.

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

Yolanda Bayón and Andres Alonso Team

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.

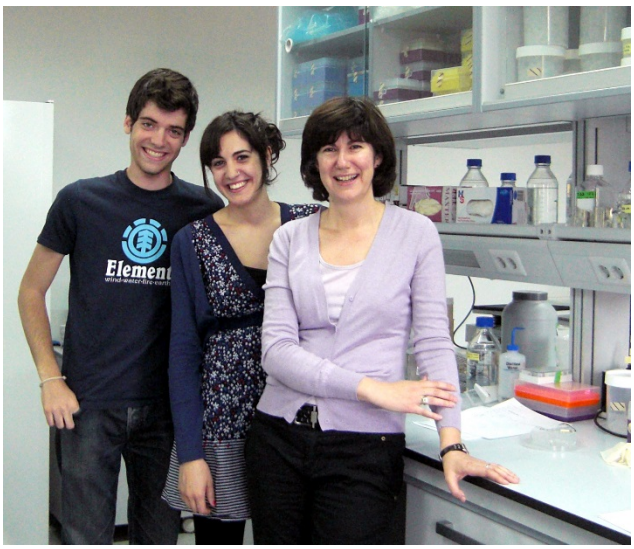
Disruption of normal protein phosphorylation levels in the proteins that participate in those signalling pathways may lead to diverse pathologies, such as autoimmune diseases or immunodeficiencies, either by increase or reduction of cell stimulation, respectively. In summary, on one hand we would like 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



Caloca Team

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 2018

Casado-Medrano V, Baker MJ, Lopez-Haber C, Cooke M, Wang S, **Caloca MJ**, Kazanietz MG (2018) The role of Rac in tumor susceptibility and disease progression: from biochemistry to the clinic. *Biochem Soc Trans*. 2018 Aug 20;46(4):1003-1012. doi: 10.1042/BST20170519. IF 3.23 / Q2

Barrio-Real L, Lopez-Haber C, Casado-Medrano V, Goglia AG, Toettcher JE, **Caloca MJ**, Kazanietz MG (2018) P-Rex1 is dispensable for Erk activation and mitogenesis in breast cancer. *Oncotarget*. 2018 Jun 19;9(47):28612-28624. doi: 10.18632/oncotarget.25584. eCollection 2018 Jun 19. IF 4.65 / Q1

Innate Immunity and Inflammation Unit

Allergy and Mucose Immunity Group

Team

Principal Investigators:
Eduardo Arranz (**UVA**), earranz@ibgm.uva.es
José Antonio Garrote (**UVA**)

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 and respiratory tract.
- Study of genetic anomalies that are reflected in diseases associated with the mucosa of the digestive, respiratory, colostrum, etc.
- 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.

Publications in 2018

Núñez C, **Garrote JA**, **Arranz E**, Bilbao JR, Fernández Bañares F, Jiménez J, Perucho T, Ruiz Casares E, Sánchez-Valverde F, Serrano JI (2018) Recommendations to report and interpret HLA genetic findings in coeliac disease. *Rev Esp Enferm Dig*. 2018 Jul;110(7):458-461. doi: 10.17235/reed.2018.5269/2017. IF 0.7 / Q3

Ochoa JP, Sabater-Molina M, García-Pinilla JM, Mogensen J, Restrepo-Córdoba A, Palomino-Doza J, Villacorta E, Martinez-Moreno M, Ramos-Maqueda J, Zorio E, Peña-Peña ML, García-Granja PE, Rodríguez-Palomares JF, Cárdenas-Reyes IJ, de la Torre-Carpente MM, Bautista-Pavés A, Akhtar MM, Cicerchia MN, Bilbao-Quesada R, Mogollón-Jimenez MV, Salazar-Mendiguchía J, Mesa Latorre JM, Arnaez B, Olavarri-Miguel I, Fuentes-Cañamero ME, Lamounier A Jr, Pérez Ruiz JM, Climent-Payá V, Pérez-Sanchez I, Trujillo-Quintero JP, Lopes LR, Repáraz-Andrade A, Marín-Iglesias R, Rodriguez-Vilela A, Sandín-Fuentes M, **Garrote JA**, Cortel-Fuster A, Lopez-Garrido M, Fontalba-Romero A, Ripoll-Vera T, Llano-Rivas I, Fernandez-Fernandez X, Isidoro-García M, Garcia-Giustiniani D, Barriales-Villa R, Ortiz-Genga M, García-Pavía P, Elliott PM, Gimeno JR, Monserrat L (2018) Formin Homology 2 Domain Containing 3 (FHOD3) Is a Genetic Basis for Hypertrophic Cardiomyopathy. *J Am Coll Cardiol.* 2018 Nov 13;72(20):2457-2467. doi: 10.1016/j.jacc.2018.10.001. IF 16.83 / Q1 D1

Cabanillas R, Diñeiro M, Cifuentes GA, Castillo D, Pruneda PC, Álvarez R, Sánchez-Durán N, Capín R, Plasencia A, Viejo-Díaz M, García-González N, Hernando I, Llorente JL, Repáraz-Andrade A, Torreira-Banzas C, Rosell J, Govea N, Gómez-Martínez JR, Núñez-Batalla F, **Garrote JA**, Mazón-Gutiérrez Á, Costales M, Isidoro-García M, García-Berrocal B, Ordóñez GR, Cadiñanos J (2018) Comprehensive genomic diagnosis of non-syndromic and syndromic hereditary hearing loss in Spanish patients. *BMC Med Genomics*. 2018 Jul 9;11(1):58. doi: 10.1186/s12920-018-0375-5. IF 3.41 / Q2

Olivares M, Benítez-Páez A, de Palma G, Capilla A, Nova E, Castillejo G, Varea V, Marcos A, **Garrote JA**, Polanco I, Donat E, Ribes-Koninckx C, Calvo C, Ortigosa L, Palau F, Sanz Y (2018) Increased prevalence of pathogenic bacteria in the gut microbiota of infants at risk of developing celiac disease: The PROFICEL study. *Gut Microbes*. 2018 Nov 2;9(6):551-558. doi: 10.1080/19490976.2018.1451276. IF 4.73 / Q1 D1

Polanco I, Montoro M, Fernández-Bañares F, **Arranz E**, Menchén LA, García Ruiz de Morales LJM, Arguelles F, Esteban B, Ortigosa L, Trujillo MM. Protocolo para el diagnóstico precoz de la enfermedad celiaca. Ministerio de Sanidad, Servicios Sociales e Igualdad. Servicio de Evaluación del Servicio Canario de la Salud (SESCS); 2018. Available in: http://portal.guiasalud.es/contenidos/iframes/documentos/opbe/2018-05/SESCS_2018_Protocolo_diag_precoz_EC.pdf

Teaching activities in 2018

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).

Invited speaker in meetings

E. Arranz. Title: Intestinal proteolisis of gluten peptides. In vitro effects in celular models Meeting: ESPHAN Masterclass on Celiac disease. Valencia, March 10th, 2018.

Other activities

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

Molecular Genetics of Disease Unit

21 publications (30% of the total), 14Q1 (70%), 6Q1 D1 (25%), IFT 74 11 articles (55%) with the main author of the IBGM. 4 international collaborations (20%), 9 national collaborations (45%) and 3 intramural collaborations (15%).

1. Calonge M, Pérez I, Galindo S, Nieto-Miguel T, López-Paniagua M, Fernández I, Alberca M, **García-Sancho J**, **Sánchez A**, Herreras JM (2018) A proof-of-concept clinical trial using mesenchymal stem cells for the treatment of corneal epithelial stem cell deficiency. *Transl Res*. 2018 Nov 22. pii: S1931-5244(18)30216-0. doi: 10.1016/j.trsl.2018.11.003. IF: 4.26 / Q1 D1

2. Barbado J, Tabera S, **Sánchez A**, **García-Sancho J** (2018) Therapeutic potential of allogeneic mesenchymal stromal cells transplantation for lupus nephritis. *Lupus*. 2018 Nov;27(13):2161-2165. doi: 10.1177/0961203318804922. IF 2.54 / Q2

3. Redondo LM, García V, Peral B, Verrier A, Becerra J, **Sánchez A**, **García-Sancho J** (2018) Repair of maxillary cystic bone defects with mesenchymal stem cells seeded on a cross-linked serum scaffold. *J Craniomaxillofac Surg*. 2018 Feb;46(2):222-229. doi: 10.1016/j.jcms.2017.11.004. IF 2.03 / Q1

4. **Duran Alonso MB**, Lopez Hernandez I, **de la Fuente MA**, **Garcia-Sancho J**, Giraldez F, **Schimmang T** (2018) Transcription factor induced conversion of human fibroblasts towards the hair cell lineage. *PLoS One*. 2018 Jul 6;13(7):e0200210. doi: 10.1371/journal.pone.0200210. eCollection 2018. IF. 3.01 / Q1 D1

5. Singer W, Manthey M, Panford-Walsh R, Matt L, Geisler HS, Passeri E, Baj G, Tongiorgi E, Leal G, Duarte CB, Salazar IL, Eckert P, Rohbock K, Hu J, Strotmann J, Ruth P, Zimmermann U, Rüttiger L, Ott T, **Schimmang T**, Knipper M (2018) BDNF-Live-Exon-Visualization (BLEV) Allows Differential Detection of BDNF Transcripts in vitro and in vivo. *Front Mol Neurosci*. 2018 Sep 27;11:325. doi: 10.3389/fnmol.2018.00325. eCollection 2018. IF 4.34 / Q1

6. Matt L, Eckert P, Panford-Walsh R, Geisler HS, Bausch AE, Manthey M, Müller NIC, Harasztosi C, Rohbock K, Ruth P, Friauf E, Ott T, Zimmermann U, Rüttiger L, **Schimmang T**, Knipper M, Singer W (2018) Visualizing BDNF Transcript Usage During Sound-Induced Memory Linked Plasticity. *Front Mol Neurosci*. 2018 Jul 31;11:260. doi: 10.3389/fnmol.2018.00260. eCollection 2018. IF 4.34 / Q1

7. Beer-Hammer S, Lee SC, Mauriac SA, Leiss V, Groh IAM, Novakovic A, Piekorz RP, Bucher K, Chen C, Ni K, Singer W, Harasztosi C, **Schimmang T**, Zimmermann U, Pfeffer K, Birnbaumer L, Forge A, Montcouquiol M, Knipper M, Nürnberg B, Rüttiger L (2018) Gαi Proteins are Indispensable for Hearing. *Cell Physiol Biochem*. 2018;47(4):1509-1532. doi: 10.1159/000490867. IF 4.83 / Q1

8. Pascua-Maestro R, Corraliza-Gomez M, Diez-Hermano S, Perez-Segurado C, **Ganfornina MD**, **Sanchez D** (2018) The MTT-formazan assay: Complementary technical approaches and in vivo validation in Drosophila larvae. *Acta Histochem.* 2018 Apr;120(3):179-186. doi: 10.1016/j.acthis.2018.01.006. IF 1.74 / Q2

9. García-Mateo N, Pascua-Maestro R, Pérez-Castellanos A, Lillo C, **Sanchez D**, **Ganfornina MD** (2018) Myelin extracellular leaflet compaction requires apolipoprotein D membrane management to optimize lysosomal-dependent recycling and glycocalyx removal. *Glia*. 2018 Mar;66(3):670-687. doi: 10.1002/glia.23274. IF. 6.00 / Q1 D1

10. Fraile-Bethencourt E, Valenzuela-Palomo A, Díez-Gómez B, Acedo A, **Velasco EA** (2018) Identification of Eight Spliceogenic Variants in BRCA2 Exon 16 by Minigene Assays. *Front Genet*. 2018 May 24;9:188. doi: 10.3389/fgene.2018.00188. eCollection 2018. IF 3.78 / Q1

11. Fraile-Bethencourt E, Valenzuela-Palomo A, Díez-Gómez B, **Infante M**, **Durán M**, Marcos G, Lastra E, Gómez-Barrero S, **Velasco EA** (2018) Genetic dissection of the BRCA2 promoter and transcriptional impact of DNA variants. *Breast Cancer Res Treat*. 2018 May 15. doi: 10.1007/s10549-018-4826-7. IF 3.73 / Q1

12. Villate O, Ibarluzea N, Fraile-Bethencourt E, Valenzuela A, **Velasco EA**, Grozeva D, Raymond FL, Botella MP, Tejada MI (2018) Functional Analyses of a Novel Splice Variant in the CHD7 Gene, Found by Next Generation Sequencing, Confirm Its Pathogenicity in a Spanish Patient and Diagnose Him with CHARGE Syndrome. *Front Genet*. 2018 Jan 26;9:7. doi: 10.3389/fgene.2018.00007. eCollection 2018. IF 3.78 / Q1

13. Montalban G, Fraile-Bethencourt E, López-Perolio I, Pérez-Segura P, **Infante M**, **Durán M**, Alonso-Cerezo MC, López-Fernández A, Diez O, de la Hoya M, **Velasco EA**, Gutiérrez-Enríquez S (2018) Characterization of spliceogenic variants located in regions linked to high levels of alternative splicing: BRCA2 c.7976+5G > T as a case study. *Hum Mutat*. 2018 Sep;39(9):1155-1160. doi: 10.1002/humu.23583. IF 4,52 / Q1

14. Velázquez C, Esteban-Cardeñosa EM, Lastra E, Abella LE, de la Cruz V, **Lobatón CD**, **Durán M**, I**nfante M** (2018) A PALB2 truncating mutation: Implication in cancer prevention and therapy of Hereditary Breast and Ovarian Cancer. *Breast*. 2018 Nov 29;43:91-96. doi: 10.1016/j.breast.2018.11.010, IF 3.00 / Q1 D1

15. Velázquez C, Esteban-Cardeñosa EM, Lastra E, Abella LE, de la Cruz V, **Lobatón CD**, **Durán M**, **Infante M** (2018) 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. IF 3.40 / Q2

16. Rebbeck TR…(Velazquez C).. et al. Mutational spectrum in a worldwide study of 29,700 families with BRCA1 or BRCA2 mutations. *Hum Mutat.* 2018 May;39(5):593-620. doi: 10.1002/humu.23406. IF 4,52 / Q1

17. García Del Río A, Delmiro A, Martín MA, Cantalapiedra R, Carretero R, Durántez C, Menegotto F, Morán M, Serrano-Lorenzo P, **De la Fuente MA**, Orduña A, **Simarro M** (2018) The Mitochondrial Isoform of FASTK Modulates Nonopsonic Phagocytosis of Bacteria by Macrophages via Regulation of Respiratory Complex I. *J Immunol*. 2018 Nov 15;201(10):2977-2985. doi: 10.4049/jimmunol.1701075. IF 4.539 / Q1

18. Elkhal A, Rodriguez Cetina Biefer H, **de la Fuente MA** (2018) Impact of Metabolism on Immune Responses. *J Immunol Res.* 2018 Jul 26;2018:5069316. doi: 10.1155/2018/5069316. eCollection 2018. IF 3.37 / Q2

19. Rodriguez Cetina Biefer H, Heinbokel T, Uehara H, Camacho V, Minami K, Nian Y, Koduru S, El Fatimy R, Ghiran I, Trachtenberg AJ, **de la Fuente MA**, Azuma H, Akbari O, Tullius SG, Vasudevan A, Elkhal A (2018). Mast cells regulate CD4(+) T-cell differentiation in the absence of antigen presentation. *J Allergy Clin Immunol*. 2018 Dec;142(6):1894-1908.e7. doi: 10.1016/j.jaci.2018.01.038. IF 6.94 / Q1 D1.

20. March GA, Gutiérrez MP, López I, Muñoz MF, Ortiz de Lejarazu R, **Simarro M**, Orduña A, Bratos MÁ. (2018) Epidemiological surveillance and wild-type MIC distribution of Legionella pneumophila in north-western Spain. 2003-2016. *Enferm Infecc Microbiol Clin*. 2018 Dec 24. pii: S0213-005X(18)30377-X. doi:10.1016/j.eimc.2018.11.006. IF 0.65 / Q4.

21. Cubero Á, Durántez C, Almaraz A, Fernández-Lago L, Gutiérrez MP, Castro MJ, Bratos MA, **Simarro M**, March GA, Orduña A. Usefulness of a single-assay chemiluminescence test (Tularaemia VIRCLIA IgG + IgM monotest) for the diagnosis of human tularemia. Comparison of five serological tests. *Eur J Clin Microbiol Infect Dis*. 2018 Apr;37(4):643-649. doi: 10.1007/s10096-017-3155-9. IF 2.88 / Q2

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

Cell Therapy Unit @ IBGM

Research Highlights

In 2007, IBGM Cell Production Unit was the first clean room launched 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 2018

Calonge M, Pérez I, Galindo S, Nieto-Miguel T, López-Paniagua M, Fernández I, Alberca M, **García-Sancho J**, **Sánchez A**, Herreras JM (2018) A proof-of-concept clinical trial using mesenchymal stem cells for the treatment of corneal epithelial stem cell deficiency. *Transl Res*. 2018 Nov 22. pii: S1931-5244(18)30216-0. doi: 10.1016/j.trsl.2018.11.003. IF: 4.26 / Q1 D1

Barbado J, Tabera S, **Sánchez A**, **García-Sancho J** (2018) Therapeutic potential of allogeneic mesenchymal stromal cells transplantation for lupus nephritis. *Lupus*. 2018 Nov;27(13):2161-2165. doi: 10.1177/0961203318804922. IF 2.54 / Q2

Redondo LM, García V, Peral B, Verrier A, Becerra J, **Sánchez A**, **García-Sancho J** (2018) Repair of maxillary cystic bone defects with mesenchymal stem cells seeded on a cross-linked serum scaffold. *J Craniomaxillofac Surg*. 2018 Feb;46(2):222-229. doi: 10.1016/j.jcms.2017.11.004. IF 2.03 / Q1

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

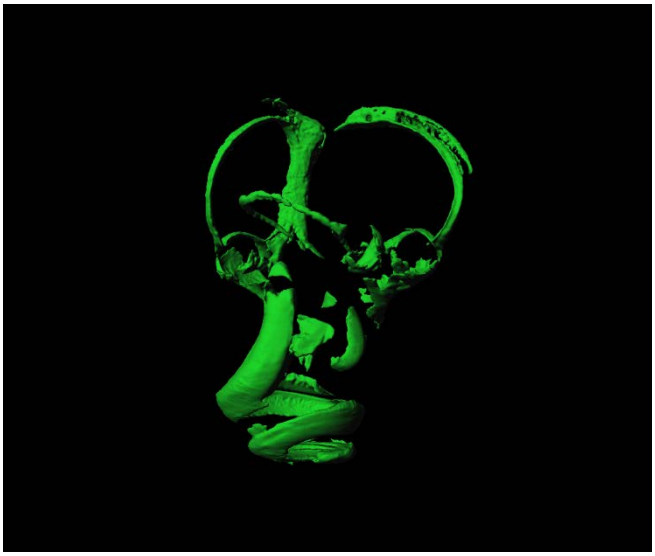
Molecular Genetics of Disease Unit

Inner Ear Development and Regeneration Group

Team

Principal Investigator:
Thomas Schimmang (**CSIC**), schimman@ibgm.uva.es

Postdoc: Beatriz Durán
Technician: Iris López Hernández



3D model of a mammalian cochlea

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 2018

Duran Alonso MB, Lopez Hernandez I, **de la Fuente MA**, **Garcia-Sancho J**, Giraldez F, **Schimmang T** (2018) Transcription factor induced conversion of human fibroblasts towards the hair cell lineage. *PLoS One*. 2018 Jul 6;13(7):e0200210. doi: 10.1371/journal.pone.0200210. eCollection 2018. IF. 3.01 / Q1 D1

Singer W, Manthey M, Panford-Walsh R, Matt L, Geisler HS, Passeri E, Baj G, Tongiorgi E, Leal G, Duarte CB, Salazar IL, Eckert P, Rohbock K, Hu J, Strotmann J, Ruth P, Zimmermann U, Rüttiger L, Ott T, **Schimmang T**, Knipper M (2018) BDNF-Live-Exon-Visualization (BLEV) Allows Differential Detection of BDNF Transcripts in vitro and in vivo. *Front Mol Neurosci*. 2018 Sep 27;11:325. doi: 10.3389/fnmol.2018.00325. eCollection 2018. IF 4.34 / Q1

Matt L, Eckert P, Panford-Walsh R, Geisler HS, Bausch AE, Manthey M, Müller NIC, Harasztosi C, Rohbock K, Ruth P, Friauf E, Ott T, Zimmermann U, Rüttiger L, **Schimmang T**, Knipper M, Singer W (2018) Visualizing BDNF Transcript Usage During Sound-Induced Memory Linked Plasticity. *Front Mol Neurosci*. 2018 Jul 31;11:260. doi: 10.3389/fnmol.2018.00260. eCollection 2018. IF 4.34 / Q1

Beer-Hammer S, Lee SC, Mauriac SA, Leiss V, Groh IAM, Novakovic A, Piekorz RP, Bucher K, Chen C, Ni K, Singer W, Harasztosi C, **Schimmang T**, Zimmermann U, Pfeffer K, Birnbaumer L, Forge A, Montcouquiol M, Knipper M, Nürnberg B, Rüttiger L (2018) Gαi Proteins are Indispensable for Hearing. *Cell Physiol Biochem*. 2018;47(4):1509-1532. doi: 10.1159/000490867. IF 4.83 / Q1

Molecular Genetics of Disease Unit

Nervous System Development & Degeneration Group

Team

Principal Investigators:
Mª Dolores Ganfornina (**UVA**), opabinia@ibgm.uva.es
Diego Sánchez (**UVA**), larazarill@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 2018

Pascua-Maestro R, Corraliza-Gomez M, Diez-Hermano S, Perez-Segurado C, **Ganfornina MD**, **Sanchez D** (2018) The MTT-formazan assay: Complementary technical approaches and in vivo validation in Drosophila larvae. *Acta Histochem.* 2018 Apr;120(3):179-186. doi: 10.1016/j.acthis.2018.01.006. IF 1.74 / Q2

García-Mateo N, Pascua-Maestro R, Pérez-Castellanos A, Lillo C, **Sanchez D**, **Ganfornina MD** (2018) Myelin extracellular leaflet compaction requires apolipoprotein D membrane management to optimize lysosomal-dependent recycling and glycocalyx removal. *Glia*. 2018 Mar;66(3):670-687. doi: 10.1002/glia.23274. IF. 6.00 / Q1 D1

Research Projects starting in 2018

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

Doctoral Thesis in 2018

Title	***Identification of a new mechanism for preserving lysosomal functional integrity upon oxidative stress***
Author:	Pascua Maestro, Raquel
Director:	Ganfornina Álvarez, María Dolores; Sánchez Romero, Diego
Year:	2018
Degree:	PhD in Biomedical Research by the University of Valladolid.

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”.

Diego Sánchez is “Director of the Research Support Facilities at the University of Valladolid.

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

Diego Sánchez contributed to the organization of “*Salamanca Pint of Science Festival*” in 2018.

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: Beatriz Díez

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 2018

Fraile-Bethencourt E, Valenzuela-Palomo A, Díez-Gómez B, Acedo A, **Velasco EA** (2018) Identification of Eight Spliceogenic Variants in BRCA2 Exon 16 by Minigene Assays. Front Genet. 2018 May 24;9:188. doi: 10.3389/fgene.2018.00188. eCollection 2018. IF 4.151 / Q1

Fraile-Bethencourt E, Valenzuela-Palomo A, Díez-Gómez B, Infante M, Durán M, Marcos G, Lastra E, Gómez-Barrero S, **Velasco EA** (2018) Genetic dissection of the BRCA2 promoter and transcriptional impact of DNA variants. Breast Cancer Res Treat. 2018 May 15. doi: 10.1007/s10549-018-4826-7. IF 3.626 / Q2

Villate O, Ibarluzea N, Fraile-Bethencourt E, Valenzuela A, **Velasco EA**, Grozeva D, Raymond FL, Botella MP, Tejada MI (2018) Functional Analyses of a Novel Splice Variant in the CHD7 Gene, Found by Next Generation Sequencing, Confirm Its Pathogenicity in a Spanish Patient and Diagnose Him with CHARGE Syndrome. Front Genet. 2018 Jan 26;9:7. doi: 10.3389/fgene.2018.00007. eCollection 2018. IF 4.151 / Q1

Montalban G, Fraile-Bethencourt E, López-Perolio I, Pérez-Segura P, Infante M, Durán M, Alonso-Cerezo MC, López-Fernández A, Diez O, de la Hoya M, **Velasco EA**, Gutiérrez-Enríquez S (2018) Characterization of spliceogenic variants located in regions linked to high levels of alternative splicing: BRCA2 c.7976+5G > T as a case study. Hum Mutat. 2018 Sep;39(9):1155-1160. doi: 10.1002/humu.23583. IF 5.36 / Q1

Research Projects starting in 2018

Title: S*plicing 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

This team also provides a service of minigenes (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 or take a look at: http://www.ibgm.med.uva.es/servicios/servicio-de-splicing-minigenes/

Technological support agreements in 2018

Title: Functional splicing assay of the IVS7-1G> A mutation of the GRN gene (Frontotemporal Dementia) and construction of ad hoc minigens.
Functional study of splicing of DNA variants from minigenes based on the pSAD vector for Dr. Ana Belén de la Hoz Rastrollo.
Technological contract associated with the patent P201231427 of my group
Date: 03/12/2018
Contracting entity: ASSOCIATION BIOCRUCES INSTITUTE OF SANITARY RESEARCH. HOSPITAL UNIVERSITARIO CRUCES, Barakaldo, Bizkaia. Amount: € 550
Researcher in charge: Eladio Andrés Velasco Sampedro

Title: Functional splicing assay of variant c.996 + 2_996 + 5del of the UGT1A1 gene (Gilbert's syndrome) and ad hoc minigen construction. Functional study of splicing of DNA variants from minigenes based on the pSAD vector for Dr. Linda Gaïlite.
Technological contract associated with the patent P201231427 of my group
Date: 10/30/2018
Contracting entity: Company SIA BioAVots and Riga Stradins University (Riga, Latvia). Amount: € 600
Researcher in charge: Eladio Andrés Velasco Sampedro

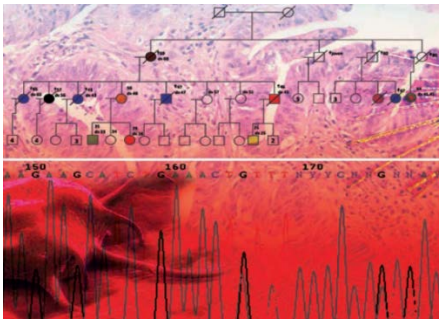
Molecular Genetics of Disease Unit

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



Mercedes Duran and Mar Infante Team

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 (germinally).

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 2018

Fraile-Bethencourt E, Valenzuela-Palomo A, Díez-Gómez B, **Infante M**, **Durán M**, Marcos G, Lastra E, Gómez-Barrero S, **Velasco EA** (2018) Genetic dissection of the BRCA2 promoter and transcriptional impact of DNA variants. *Breast Cancer Res Treat*. 2018 May 15. doi: 10.1007/s10549-018-4826-7. IF 3.73 / Q1

Montalban G, Fraile-Bethencourt E, López-Perolio I, Pérez-Segura P, **Infante M**, **Durán M**, Alonso-Cerezo MC, López-Fernández A, Diez O, de la Hoya M, **Velasco EA**, Gutiérrez-Enríquez S (2018) Characterization of spliceogenic variants located in regions linked to high levels of alternative splicing: BRCA2 c.7976+5G > T as a case study. *Hum Mutat*. 2018 Sep;39(9):1155-1160. doi: 10.1002/humu.23583. IF 4.52 / Q1

Velázquez C, Esteban-Cardeñosa EM, Lastra E, Abella LE, de la Cruz V, **Lobatón CD**, **Durán M**, I**nfante M** (2018) A PALB2 truncating mutation: Implication in cancer prevention and therapy of Hereditary Breast and Ovarian Cancer. *Breast*. 2018 Nov 29;43:91-96. doi: 10.1016/j.breast.2018.11.010, IF 3.00 / Q1 D1

Velázquez C, Esteban-Cardeñosa EM, Lastra E, Abella LE, de la Cruz V, **Lobatón CD**, **Durán M**, **Infante M** (2018) 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. IF 3.40 / Q2

Rebbeck TR, …(Velazquez C)... et al. Mutational spectrum in a worldwide study of 29,700 families with BRCA1 or BRCA2 mutations. *Hum Mutat.* 2018 May;39(5):593-620. doi: 10.1002/humu.23406. IF 4.52 / Q1

This team also provides a service of gene sequenciation

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.

Sequencing equipment at Hereditary Cancer Service

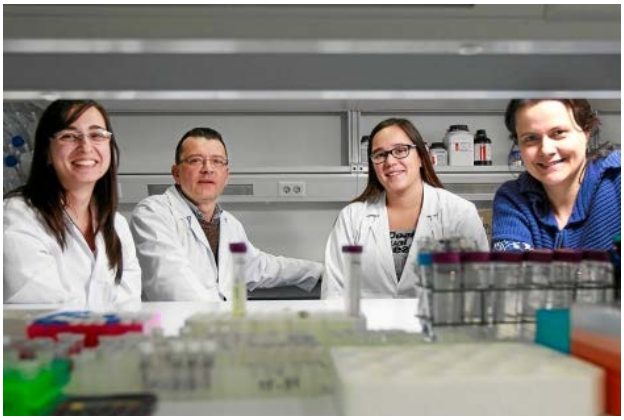
Molecular Genetics of Disease Unit

Directed Gene Therapy Group

Team

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

Scientific Staff: Juan José Tellería
Predocs: Dino J. Gobelli, Laura Pérez, Mª Alejandra Bernardi



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. For GT to occur, the vector must find the correct target on the chromosome and DNA recombination must occur between the homologous sequences that are present in the vector and the target gene. But compared to bacteria and yeast, homologous recombination in mammals is a very

inefficient process, with another one called non-homologous end joining (NHEJ) that induces repair between DNAs without homology to each other and that in humans is at least 1000 times more frequent than HR.

The objective of our line of work is the study of the experimental conditions that increase the frequency of GT in human cells by means of a) the assay of different donor vectors, b) the modification in the expression of key proteins in the repair of DNA lesions c) pretreatment with drugs that modify the mechanisms of DNA repair. The most effective methods will be applied to the correction of mutations and it will be studied how the function and capacity of differentiation of the cells subjected to the different treatments is affected.

Publications in 2018

García Del Río A, Delmiro A, Martín MA, Cantalapiedra R, Carretero R, Durántez C, Menegotto F, Morán M, Serrano-Lorenzo P, **De la Fuente MA**, Orduña A, **Simarro M** (2018) The Mitochondrial Isoform of FASTK Modulates Nonopsonic Phagocytosis of Bacteria by Macrophages via Regulation of Respiratory Complex I. *J Immunol*. 2018 Nov 15;201(10):2977-2985. doi: 10.4049/jimmunol.1701075. IF 4.539 / Q1

Elkhal A, Rodriguez Cetina Biefer H, **de la Fuente MA** (2018) Impact of Metabolism on Immune Responses. *J Immunol Res.* 2018 Jul 26;2018:5069316. doi: 10.1155/2018/5069316. eCollection 2018. IF 3.37 / Q2

Rodriguez Cetina Biefer H, Heinbokel T, Uehara H, Camacho V, Minami K, Nian Y, Koduru S, El Fatimy R, Ghiran I, Trachtenberg AJ, **de la Fuente MA**, Azuma H, Akbari O, Tullius SG, Vasudevan A, Elkhal A (2018). Mast cells regulate CD4(+) T-cell differentiation in the absence of antigen presentation. *J Allergy Clin Immunol*. 2018 Dec;142(6):1894-1908.e7. doi: 10.1016/j.jaci.2018.01.038. IF 6.94 / Q1 D1.

March GA, Gutiérrez MP, López I, Muñoz MF, Ortiz de Lejarazu R, **Simarro M**, Orduña A, Bratos MÁ. (2018) Epidemiological surveillance and wild-type MIC distribution of Legionella pneumophila in north-western Spain. 2003-2016. *Enferm Infecc Microbiol Clin*. 2018 Dec 24. pii: S0213-005X(18)30377-X. doi:10.1016/j.eimc.2018.11.006. IF 0.65 / Q4.

Cubero Á, Durántez C, Almaraz A, Fernández-Lago L, Gutiérrez MP, Castro MJ, Bratos MA, **Simarro M**, March GA, Orduña A. Usefulness of a single-assay chemiluminescence test (Tularaemia VIRCLIA IgG + IgM monotest) for the diagnosis of human tularemia. Comparison of five serological tests. *Eur J Clin Microbiol Infect Dis*. 2018 Apr;37(4):643-649. doi: 10.1007/s10096-017-3155-9. IF 2.88 / Q2

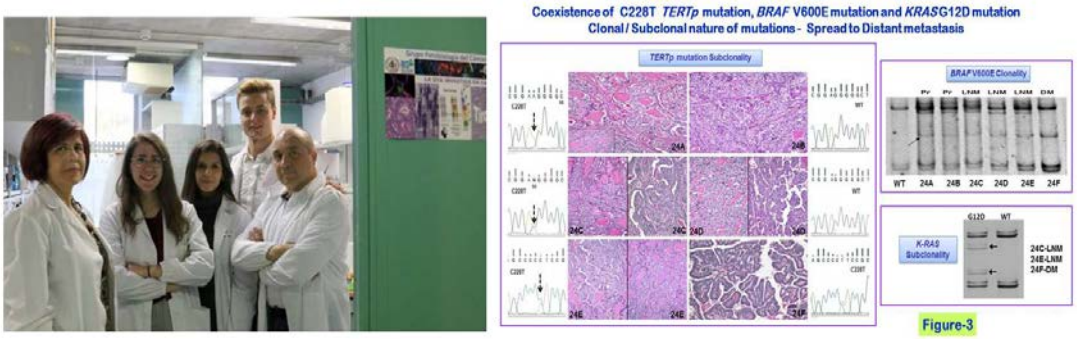
Molecular Genetics of Disease Unit

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



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 alterations are 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. It is important to trace the geography of clonal diversity or the subclonal architecture through treatment. To deliver curative therapies to cancer patients, will be essential to develop therapeutic algorithms that estimate inter-, and intra-tumoural heterogeneity and plasticity of cancer cells during tumor progression, influenced by the effects of treatments. Intra-tumoral heterogeneity is often a confounder in tumor evaluation for diagnosis and treatment.

Publications in 2018

Meana C, **García-Rostán G**, Peña L, Lordén G, Cubero Á, Orduña A, Győrffy B, **Balsinde J**, **Balboa MA** (2018) The phosphatidic acid phosphatase lipin-1 facilitates inflammation-driven colon carcinogenesis. *JCI Insight*. 2018 Sep 20;3(18). pii: 97506. doi: 10.1172/jci.insight.97506.

Research Projects funded in 2018

Title: Spatio-temporal Analysis of mutations underlying Sorafenib[Nexavar] response / resistance in advanced, metastatic, radioiodine resistant papillary thyroid carcinomas [CP-AMIR]. Ref.: GRS 1731/A/18
Funding Agency: Consejería de Sanidad – Junta de Castilla y León – Convocatoria proyectos de investigación en biomedicina, gestión sanitaria y atención sociosanitaria GRS 2019.
From 1st January 2019 to 31st December 2019.
Funding: 15.704€.
Principal Investigator: Joaquin Fra Rodríguez. Co-PI: 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

Master´s Degree Final Research Projects supervised and defended in 2018

Title: "Prevalence of *TERT* promoter mutations in Anaplastic Thyroid Carcinomas. Concurrent activation of TERT and MAPK signalling pathway."
Student: Mª Angeles Rodríguez García
Degree: MASTER IN BIOMEDICAL RESEARCH - VALLADOLID UNIVERSITY
Institution: Institute of Molecular Biology and Genetics (IBGM) – Valladolid University
Year: 2017-2018
Mark / Score: 7,95

Title: "Mutaciones en el factor de iniciación de la traducción protéica en eucariotas, EIF1AX, en carcinomas agresivos de tiroides"
Student: Sara Gil Bernabé
Degree: MASTER IN BIOMEDICAL RESEARCH - VALLADOLID UNIVERSITY
Institution: Institute of Molecular Biology and Genetics (IBGM) – Valladolid University
Year: 2017-2018
Mark / Score: 8,8

General Teaching in 2018:

Degree in Medicine University of Valladolid - Third year medical students: Classes of General and Special / Surgical Anatomic Pathology – "Structural and Functional Pathology" [220 h]

Master in Biomedical Research University of Valladolid [20 h]

Congresses, Workshops, Symposia, Conferences in 2018

Autors: N. Feás; M. Vega Herrero, E. Pérez Martín; G. García–Rostán
Title: "*Phylogenetic relationships between paired primary papillary thyroid carcinomas and distant metastasis: Intra-tumor molecular heterogeneity and clonal evolution".*
Type of presentation: Poster Ref. 240
Congress: 25th Biennial Congress of the European Association for Cancer Research (EACR).
Meeting Place: Amsterdam, Holland, 30th June–3th July, 2018
Publication: *ESMO Open*, vol.3, suppl. 2, 2018

RESEARCH SEMINARS @ IBGM in 2018

Jan 11, 2018. "*GAPs in insulin action*" by **Dr. Hadi Al-Hasani**. Universitat Dusseldorf, Germany. Invited by Dr. Dra. Irene Cózar

Feb 2, 2018. "*E152K STIM1 mutation deregulates Ca^{2+} signaling contributing to chronic pancreatitis*" by **Dr. Miguel Burgos**. Universidad de Castilla La Mancha, Spain. Invited by Dr. Carlos Villalobos

Feb 9, 2018. "*Mecanismos moleculares asociados con el envejecimiento vascular*" by **Dr. Ana Paula Dantas**. IDIBAPS, Barcelona, Spain. Invited by Prof. Mª Teresa Pérez-García.

March 16, 2018. "*Purinergic signalling in health and disease*" by **Dr. Carlos Matute**. Universidad del País Vasco, Spain. Invited by Dr. Diego Sánchez.

March 23, 2018. "*Especificidad y promiscuidad en la señalización por corticosteroides*" by **Dr. Diego Alvarez de la Rosa**. Universidad de la Laguna, Spain. Invited by Prof. Mª Teresa Pérez-García.

April 13, 2018. "*Papel clave del cuerpo carotideo en enfermedades con alteraciones autonómicas*" by **Dr. Rodrigo Iturriaga**. Pontificia Universidad Católica de Chile. Invited by Prof. Asunción Rocher.

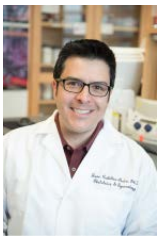
April 20, 2018. "*MicroRNA-dependent regulation of vascular smooth muscle function in health and disease*" by **Dr. Sebastian Albinsson**. Lund University, Sweden. Invited by Prof. Mª Teresa Pérez-García.

June 8, 2018. "*Molecular targets for enhancing pancreatic beta cell regeneration and survival*" by **Dr. Maureen Gannon**. Vanderbilt University, USA. Invited by Dr. Irene Cózar

June 12, "*New Biological Functions of Eicosanoids*" by **Dr. Lucia Faccioli**. University of Sao Paulo, Brasil. Invited by Dr. Mª Angeles Balboa

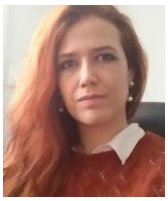
July 6, 2018. "*In vitro bioguided assays to detect anti-inflammatory phytochemicals*" by **Dr. Teresa Cruz**. University of Coimbra, Portugal. Invited by Dr. Carmen García-Rodríguez.

Sep 7, 2018. "*Is hydrogen sulfide the oxygen sensor in HPV*? By **Dr. Philip Aaronson**. King's College, London, UK.



Nov 15, 2018. "*Unfolding anti-cancer immunity: New roles for ER stress sensors in the tumor microenvironment*" by **Dr. Juan Rodrigo Cubillos**. Weill Cornell Medicine, NY, USA. Invited by Prof. Mariano Sánchez-Crespo.

Nov 22, 2018. "*Inmunovigilancia de las células cancerosas: El caso de las células poliploides*" by **Dr. Laura Senovilla**. INSERM, París, France. Invited by Dr. Lucía Núñez

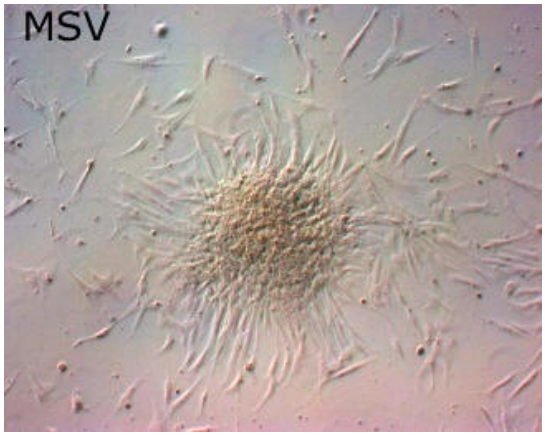


Dec 14, 2018. "*Papel de inervación somatosensorial en la inflamación pulmonar*" by **Dr. Ana I. Cáceres**. Duke University, NC, USA. Invited by Prof. Asunción Rocher.

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

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).

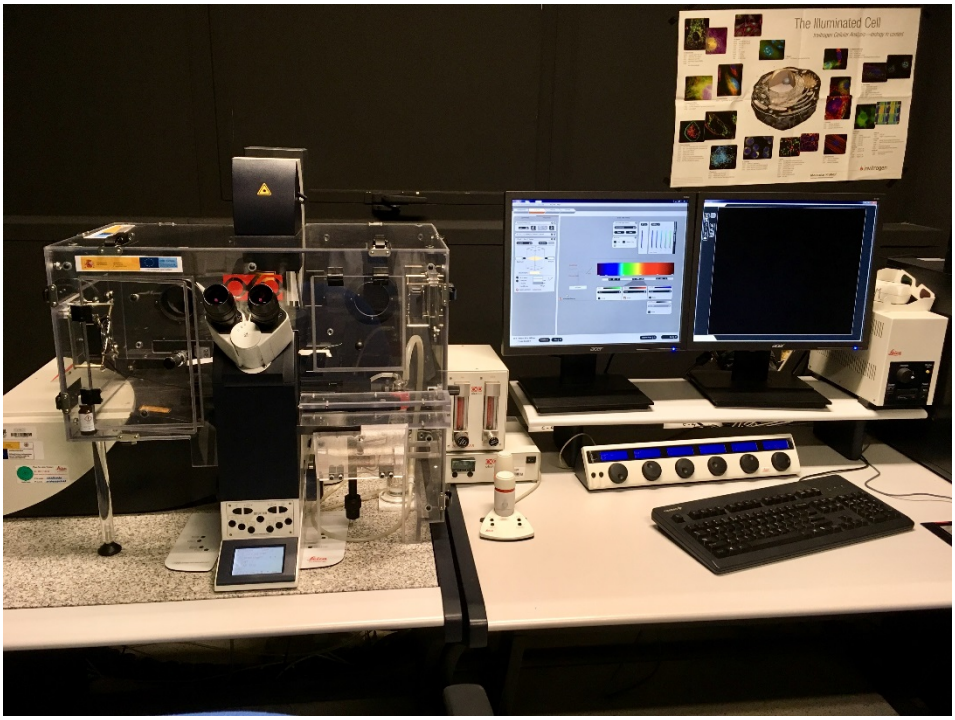
Equipment:

- 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).

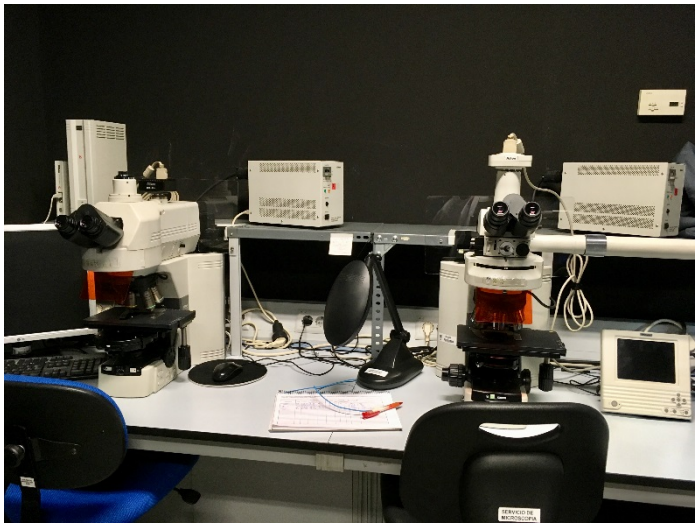
- NIKON Eclipse 90i Fluorescence Microscope, associated with CCD camera to take photographs NIKON brand, model DS-Ri1. Objectives: 4x, 10x, 20x, 40x, 60x and 100x (oil). Filters: UV-2A (Ex 330-380), B-2A (Ex 450-490) and G-2A (Ex 510-560).

- 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).



Confocal Microsopy @ IBGM

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.



SERVICES PROVIDED AT IBGM

Flow Cytometry and Cell Sorting Service @ IBGM

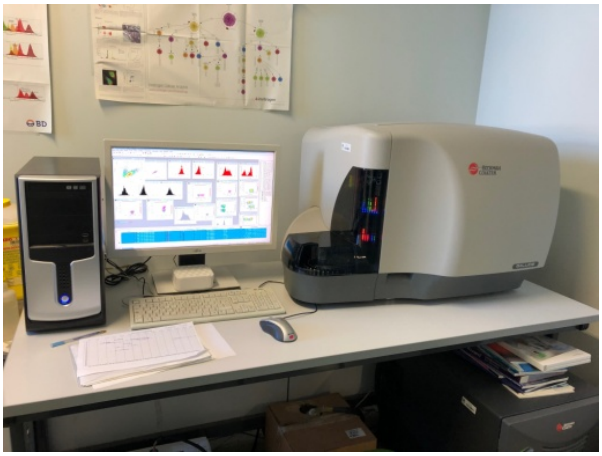
The IBGM's flow cytometry and Cell Sorting service has as its main function the support and technical advice in the field of cytometry to the institute and to any entity, whether public or private, that is interested in these services. To this end, it has two high-precision optical equipment: on the 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



NEWS IN PRESS

Nuevos pasos para obtener células humanas capaces de restaurar la audición. Científicos de Valladolid y Barcelona están intentando obtener, a partir de fibroblastos humanos, células humanas similares a las que se degeneran y originan la pérdida de audición, las células ciliadas. El trabajo se ha publicado en 'PLOS One'. http://www.dicyt.com/viewNews.php?newsId=39238

El IBGM de Valladolid, vanguardia en la lucha contra el Cáncer. El Norte de Castilla, 31 de octubre de 2018. https://www.elnortedecastilla.es/valladolid/valladolid-vanguardia-lucha-20181026095638-nt.html

En la senda del rescate de la audición (Diario de Valladolid, 11/09/2018) http://www.diariodevalladolid.es/noticias/innovadores/senda-rescate-audicion_128768.html

Una estrategia podría obtener células capaces de restaurar la audición (SINC 31/07/2018) https://www.agenciasinc.es/Noticias/Una-estrategia-podria-obtener-celulas-capaces-de-restaurar-la-audicion

Nuevos pasos para obtener células humanas capaces de restaurar la audición (NCYT, 27/07/2018) https://noticiasdelaciencia.com/art/29549/nuevos-pasos-para-obtener-celulas-humanas-capaces-de-restaurar-la-audicion

La Asociación Española Contra el Cáncer (AECC) de Valladolid entrega dos becas de investigación por 180.000 euros, una de ellas al Instituto de Biología y Genética Molecular (IBGM) de Valladolid. Norte de Castilla, 24 de abril de 2018. https://www.elnortedecastilla.es/valladolid/asociacion-cancer-valladolid-20180424133954-nt.html

El Centro en Red de Terapia Celular cumple una década con 40 proyectos de investigación y 10 millones invertidos (Salud a Diario, 25/04/2018) https://www.saludadiario.es/investigacion/centro-en-red-de-terapia-celular

Ensayan un tratamiento con células madre de las lesiones en los tendones (La Vanguardia 11/04/2018) https://www.lavanguardia.com/vida/20180411/442457893340/ensayan-un-tratamiento-con-celulas-madre-de-las-lesiones-en-los-tendones.html

Visita al IBGM de la presidenta del CSIC Rosa Ménendez (RTVE-CyL 06/04/2018. Min. 22.30) https://m.youtube.com/watch?list=PLEC9CEB536295FC7D&v=Ra34SV3Q1D1w4&feature=youtu.be

Un centenar de alumnos de Bachillerato asisten al UniStem Day en la Universidad de Valladolid (UVa, 16/03/2018) http://comunicacion.uva.es/export/sites/comunicacion/333d46c2-2926-11e8-9079-d59857eb090a/

Las chicas son científicas y guerreras (Blog CEIP San Gil, Cuéllar, 11/02/2018) http://bibliotecasangil.blogspot.com/2018/02/las-chicas-son-cientificas-y-guerreras.html

El colegio San Gil de Cuéllar acerca la labor científica de las mujeres (El Norte de Castilla, 07/02/2018) https://www.elnortedecastilla.es/segovia/colegio-cuellar-acerca-20180207114731-nt.html

Las mujeres investigadoras abren el CEIP San Gil el Ciclo del Día de la Niña y la Mujer en la Ciencia (Es Cuellar, 06/02/2018) http://escuellar.es/index.php/las-mujeres-investigadoras-abren-en-el-ceip-san-gil-el-ciclo-del-dia-de-nina-y-la-mujer-en-la-ciencia/

Secretaria de Estado de I+D+i defiende papel del mecenazgo junto a la "responsabilidad ineludible" de la Administración (20 minutos, 23/01/2018) https://www.20minutos.es/noticia/3241897/0/secretaria-estado-i-d-i-defiende-papel-mecenazgo-junto-responsabilidad-ineludible-administracion/

HIGH SCHOOL VISITS TO IBGM

IBGM members collaborate in many different actions intended to communicate research activities to the society. We are particularly proud of the visits paid by high school students from our city and region in which we try to implement love for science. Here is the list of high schools that visited us during 2018.

IES Zorrilla, Valladolid

IES Pinar de la Rubia, Valladolid

Centro Grial, Valladolid

IES Andrés Laguna, Laguna de Duero, Valladolid

IES Victorio Macho, Palencia

IES Diego de Praves, Valladolid

Colegio La Inmaculada-Maristas, Valladolid

IES Ramón y Cajal, Valladolid

IES Pardo de Tavera, Toro, Zamora

Colegio Ave María, Valladolid

Colegio la Inmaculada MSJO, Valladolid

IES Gregorio Fernández, Valladolid

IES González Allende, Toro, Zamora

Colegio San José, Valladolid

Colegio El Pilar, Valladolid

IES Fray Pedro de Urbina, Miranda de Ebro, Burgos

Centro Grial, Valladolid

IES Pardo de Tavera, Toro, Zamora

Colegio San Agustín, 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 2018 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 2018 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.