Maria Mittelbrunn, PhD Group Leader (2015-Present)

Date and place of birth 29/12/1977, Madrid, Spain e-mail: mmittelbrunn@cbm.csic.es

Working Address: Centro de Biología Molecular Severo Ochoa, Nicolás Cabrera, 1, Madrid

Researcher identifier(s): Researcher ID: I-5882-2015 Orcid: orcid.org/0000-0003-3487-8762

MAIN DISCOVERIES AS PRINCIPAL INVESTIGATOR

- o **Desynchronizing the Age of the Immune System** from the rest of the tissues. As in many other cells and tissues, cells of the immune system present mitochondrial decline with age. To investigate the consequences of the aging of the immune system, we have induced age-associated mitochondrial dysfunction prematurely in T cell. Targeting mitochondrial function in T cells recapitulates metabolic, phenotypic and functional features of aged T cells, including *susceptibility to infections, cancer and premature inflammaging* (Science, 2020).
- o Premature T cell ageing drives systemic multi-tissue ageing. We found that inducing age-associated mitochondrial decline in T lymphocytes, does not only cause T cell senescence, but actually causes a general, body-wide deterioration of health with multiple aging-related features, including metabolic, musculoskeletal, cardiovascular and cognitive alterations, altogether resulting in premature death. Thus, premature aging of T lymphocytes may be 'contagious', driving a generalized acceleration of aging throughout multiple organ systems (Science, 2020). Our results place the metabolism of T cells at the crossroad between inflammation, senescence and aging, highlighting that immunometabolism can be a therapeutic target to delay aging.
- o Mechanism underlying aging driven by T cells. We have contributed to decode the molecular mechanisms by which T cells contribute to inflammaging and age-related diseases. (a) *Th1-Cytokines induce senescence*: Age-associated mitochondrial decline in T cells promotes the acquisition of a Th1 phenotype, characterized by secreting TNF and IFNγ, accelerating inflammaging. This inflammaging promotes paracrine senescence in multiple tissues. (b) *Loss of Self-tolerance*. Senescent T cells indiscriminately destroy cells in the tissues, highlighting the importance of immune tolerance mechanisms. (c) *Defective senescence-surveillance* Dysfunctional T cells lose their ability to effectively clear senescent cells from tissues. (d) *Altered gut microbiota*. A decline in T cell function in the gut mucosa can compromise intestinal barrier integrity, favoring gut dysbiosis, bacteria translocation and inflammaging. (Cell Metabolism 2021; Nature Rev Immunol, 2022; *Annual Rev Immunol*, 2024)
- o NAD precursors to delay Age-Associated Multimorbidity, Aortic Aneurysm and Dissections Metabolic reprogramming of the immune cells has been implicated in many age-associated diseases. NAD precursor are able to attenuate this metabolic rewiring and delay the onset of age related multimorbidity (EMBO Mol Med, 2023). In addition, this metabolic reprograming occurs in vascular cells during aortic aneurysm. Treatment with NAD precursor prevent and reverse aortic aneurysm and prevent sudden death Circulation, 2021; Atherosclerosis, Thrombosis Vascular Biology, 2022)
- o Exosomes as vehicles for cell to cell communication: Her research was pioneer in the field of cellular communication through exosomes (**Nature Commun**, 2011, within the 1% of the most cited articles; **Nature Rev Mol Cell Biol**, 2012), the identification of the mechanism that controls the loading of miRNAs in exosomes (**Nature Commun**, 2013).

OVERARCHING GOALS

Driven by our previous work, we are investigating how the time-dependent deterioration of the immune system might contribute to systemic senescence as well as to the general aging process. Would the rejuvenation of the immune system compartment suffice to delay organismal aging or at least some of its manifestations? An affirmative response to this question might have vast consequence for opening new strategies to improve healthy aging.

• EDUCATION

May 2006 PhD degree; Thesis "Adhesion receptors at immune synapses and their relevance in the Immune Response" Grade: "Cum Laude" by unanimity. Extraordinary Award Universidad Autónoma de Madrid. Advisor: Prof. Francisco Sánchez-Madrid, Hospital de la Princesa, Madrid

July 2000 BSc degree Biochemistry and Molecular Biology. Universidad Autónoma de Madrid (Spain)

• CURRENT POSITION(S)

Position	Head of Immunometabolism & Inflammation Lab , Tenured Researcher CSIC			
Initial date	March 2017			
Institution	Consejo Superior de Investigaciones Científicas			
Department/Center	Centro de Biología Molecular Severo Ochoa (CSIC-UAM)			
City, Country	Madrid, Spain	Teleph. number	+34911964528	

Position	Visiting Professor		
Initial date	March 2024		
Institution	Columbia University		
Department/Center	Center of Human Longevity and Center of Translational		
Department/Center	Immunology (CCTI), Dept. Medicine		
City, Country	New York, US	Email mm6603@cumc.columbia.edu	

• PREVIOUS POSITIONS

2015-2021	Group Leader at Cellular Homeostasis lab at Hospital 12 de Octubre (Madrid)
2013-2014	Visiting Researcher, Biochemistry Dept the Universidad de Oviedo (Oviedo, Spain)
2007-2013	Postdoctoral Researcher at National Center of Cardiovascular Research (Madrid, Spain)
2007	Postdoctoral Visiting Researcher at Immunity and Cancer, Institut Curie (Paris, France)
2000-2006	Predoctoral Fellowship at Immunology Department, Hospital de la Princesa (Madrid, Spain)

• FELLOWSHIPS AND AWARDS

2023	FRACE-Royal Academy of Science Award for women reserarchers.
2022	Banco Sabadell Award in Biomedicine
2021	Tenured Scientist Spanish National Research Council.
2019	PINP- Best Article Award of the Year at Centro de Biologia Molecular (CBMSO)
2015	L'Oréal - UNESCO Women for Science Award
2015-2021	Miguel Servet Program for Junior group leaders from Health Ministry-Spain
2007-2012	Sara Borrell Postdoctoral Fellowship (Health Ministry)
2006	Doctoral Thesis Award at Fundación Investigación Biomédica del Hospital de la Princesa
2006	Extraordinary Prize to Doctoral Thesis. Universidad Autónoma de Madrid.
2000-2004	FPU fellowship from the Education Ministry

• SUPERVISION OF GRADUATE STUDENTS AND POSTDOCTORAL FELLOWS.

2016-today Supervision of 4 completed (Sobresaliente "*Cum-Laude*") and 4 ongoing PhD theses. Supervisor of 7 Master student and 5 Grade Students. Current supervision of 4 postdoctoral fellows.

• TEACHING ACTIVITIES

2017-2021 **Associate Professor** at the Universidad Autónoma de Madrid. **Lecturer in Bioenergetics for Biochemistry Degree**

2020-2024 Professor at **Technical Innovation in Immuno-Oncology by CIVIS**, a European Civic University formed by the alliance of eight leading research higher education institutions across Europe (https://civis.eu/)

2018-2020 Lecturer at Master in Molecular and Cellular Integrative Biology at Universidad Internacional Menéndez Pelayo Madrid (UIMP)

2017-today Lecturer at Translational Medicine Master at Universidad Complutense de Madrid (UCM)

2014-today Member of the Thesis Board of more than 20 PhD candidates for different European Universities

2012-today Lecturer at Master Molecular Biomedicine at Universidad Autónoma de Madrid (UAM)

ORGANISATION OF SCIENTIFIC MEETINGS

2024 *Co-organiser* of an EMBO Meeting Developmental Circuits of Aging, Nice, France

2015 *Co-organiser* of the International ISEV Seminar "EV Associated RNA: What is the Purpose?" (Sept 24-25, 2015, Utrecht, The Netherlands)

2015 Scientific Committee for 1st Iberian Meeting on Extracellular vesicles (Sept 30, Porto, Portugal)

2013 *Course co-organiser* Universidad Internacional Menéndez Pelayo. "Extracellular vesicles; implications in biomedicine" (Sept 18-20, 2013, Valencia, Spain)

2012 *Organizing Committee* of the 1st GEIVEX Symposium (Nov 8-9, 2012, Segovia, Spain)

REVIEWING AND MENTORSHIP ACTIVITIES

- Mentor enrolled in Spanish Mentorship program CRECE (https://cre.org.es/crece/), a network of mentors and mentees that participate in a personalized mentoring platform, aimed at helping researchers returned from abroad or on the way to return to Spain
- Scientific Advisor for National Research Council (AEI, ISCIII)
- Panel Advisory Board for Ramon y Cajal (2017, 2019), Juan de la Cierva (2019) for National Research Council (AEI)
- Scientific Advisor for International Research Agencies :
 - French National Research Agency (ANR)
 - Medical Research Council UK (MRC)
 - Israel Science Foundation (ISF)
 - German-Isrelí Foundation for Scientific Research (GIF)
 - National Science Center Poland (OPUS)
 - Czech Science Foundation
 - Human Frontier Science Program (HFSP)
 - Biotechnology and Biological Sciences Research Council, UK (BBSRC)
 - Swiss National Science Fundation (SNSF)
- o Peer reviewing activity for international journals including: Science, Nature, Nature Medicine, Nature Aging, Nature Neuroscience, Cell Metabolism, Science Advances, Aging Cell, Nature Communications, Scientific Reports, Frontiers in Neuroscience, Clinical and Experimental Medicine, Journal of Extracellular Vesicles, Cell Death and Disease, Leukemia, Trends Parasitology, The International Journal of Biochemistry & Cell Biology and Frontiers in Immunology, FASEB Journal

• MEMBERSHIPS OF SCIENTIFIC SOCIETIES

Founding Member of Senescel, Spanish Group of Research on Senescence https://senescel.org

New Generation of Scientific Leaders by Fundacion Ciencias de la Salud,

2022 Diploma from **Real Academia de Medicina de España** and the Institute 'Teofilo Henando'

2020-today President Scientific Advisor Board of Spanish patient association Alstrom Syndrome

2019-today Scientific Advisory Board Fundación Gadea Ciencia https://gadeaciencia.org

2015-today Member of the Spanish Society of Molecular Biology

Founding Member of GEIVEX, Spanish Group of Research on Exosomes http://geivex.org/

2012 Member of the *COST* European Network on Microvesicles & Exosomes in Health and Disease

2012 Member of the International Society of Extracellular Vesicles

• BIBLIOMETRICS INDICATORS

BIBLIOMETRIC INDICA	ATORS
Number of citations	17.800
H-index	48
Number of articles	65

GRANTS AS PRINCIPAL INVESTIGATOR

Grant	Source	Amount (Euros)	Period	Principal Investigator
Exosomes in cardioprotection	ISCIII	€121.000	2015-2017	M. Mittelbrunn
Mitochondria deficiency in Systemic Inflammation	LOREAL	€15.000	2016	M. Mittelbrunn
Immunometabolism and its implications in Cardiovascular diseases and Aging	ISCIII	€157.602	2017-2020	M. Mittelbrunn
EndoMitTalk: Endolysosomal-Mitochondria Crosstalk in Cell and Organism Homeostasis	ERC Starting Grant	€1.498.000	2017-2022	M.Mittelbrunn
Cellular metabolism to prevent Cardiovascular Diseases and Age-related Multimorbidity	ISCIII	€147.620	2020-2022	M.Mittelbrunn
Nutri-SI-ON: Nutritional strategies to reactivate deteriorated Immune System as a result of Age, Obesity or Chemotherapy	CAM	€617.000	2021-2024	A. Ramirez/ M. Mittelbrunn /
Let T Be: Letting up Senescence by T cells	ERC Consolidator Grant	€2.000.000	2022-2027	M. Mittelbrunn
GutToBrain: Age-associated T cells in Gut-Brain Axis	AEI Plan Nacional	€455.000	2024-2026	M. Mittelbrunn
Ener-LIGHT : Energizing the failing heart	AEI ERA4Health	€200.000	2024-2026	Abdellatif

• REPRESENTATIVE PUBLICATIONS (Highly Cited Article)

- 1. Soto-Heredero G, Gómez de Las Heras MM, Escrig-Larena JI, <u>Mittelbrunn M.</u> Extremely Differentiated T Cell Subsets Contribute to Tissue Deterioration During Aging *Annu Rev Immunol*. 2023 Apr 26;41:181-205.
- 2. Gómez de Las Heras MM, <u>Mittelbrunn M</u>. Old T cells pollute with mito-litter *Nat Aging*. 2023 May;3(5):475-476.
- 3. Escrig-Larena JI, Delgado-Pulido S, <u>Mittelbrunn M</u>. Mitochondria during T cell aging. *Semin Immunol*. 2023 Sep;69:101808. doi: 10.1016/j.smim.2023.101808.
- 4. Gabande-Rodriguez, Pfeiffer & Mittelbrunn, M. Immuno(T)herapy for Age related Diseases *EMBO Mol Med* 2023 Jan 11;15(1):e16301
- 5. Oller, J... & Mittelbrunn, M. Rewiring Vascular Metabolism Prevents Sudden Death due to Aortic Ruptures-Brief Report Arterioscler Thromb *Vasc Biol*. 2022 ;42(4):462-469

- 6. Carrasco, E. ... & Mittelbrunn, M. The role of T cells in Age-related diseases *Nature Rev. Immunology* 2022 22(2):97-111
- 7. Mittelbrunn, M & Kroemer G. Hallmarks of T cell Aging. *Nature Immunology*. 2021 22 (6), 687-698
- 8. Oller, J.; Gabandé-Rodríguez, E.; ... & <u>Mittelbrunn, M.</u> Extracellular Tuning of Mitochondrial Respiration Leads to Aortic Aneurysm. *Circulation* 2021 143 (21), 2091-2109
- Soto-Heredero, G.; Desdín-Micó, G. & <u>Mittelbrunn</u>, M. Mitochondrial Dysfunction Defines T Cell Exhaustion. *Cell Metabolism*. 2021, 33 (3), 470–472
- 10. Navarro, M. N.; Gómez de Las Heras, M. M. & <u>Mittelbrunn, M.</u> NAD+ Metabolism in the Immune Response, Autoimmunity and Inflammageing. *Br. J. Pharmacol.* 2021.
- 11. Desdín-Micó, G.; Soto-Heredero, G.; ... & <u>Mittelbrunn, M</u>. T Cells with Dysfunctional Mitochondria Induce Multimorbidity and Premature Senescence. *Science* 2020, *368* (6497)
- 12. Soto-Heredero, MM Gomez de las Heras, & Mittelbrunn, M. Glycolysis—a key player in the inflammatory response. *The FEBS journal* 2020 287 (16), 3350-3369
- 13. Baixauli, F.; ... & Mittelbrunn, M. Mitochondrial Respiration Controls Lysosomal Function during Inflammatory T Cell Responses. *Cell Metabolism* 2015, *22* (3), 485–498.
- 14. Villarroya-Beltri, C.; Gutiérrez-Vázquez C Mittelbrunn, M* & Sánchez-Madrid, F* (*cosenior). Sumoylated hnRNPA2B1 controls the sorting of miRNAs into exosomes through binding to specific motifs. *Nature Commun*. 2013;4:2980 **
- 15. Villarroya-Beltri, C.; Baixauli, F.; Sánchez-Madrid, F.; & Mittelbrunn, M. Sorting It out: Regulation of Exosome Loading. *Semin. Cancer Biol.* 2014, *28*, 3–13.
- 16. <u>Mittelbrunn, M.</u>; & Sánchez-Madrid, F. Intercellular communication: diverse structures for exchange of genetic information. *Nature Rev. Molecular Cell Biology*. 2011, 2, 282
- 17. Baixauli, F.; López-Otín, C. & <u>Mittelbrunn, M</u>. Exosomes and Autophagy: Coordinated Mechanisms for the Maintenance of Cellular Fitness. *Front. Immunol.* 2014, *5*, 403.
- 18. Mittelbrunn, M.; Gutiérrez-Vázquez, C.; Villarroya-Beltri, C.; González, S.; Sánchez-Cabo, F.; González, M. Á.; Bernad, A.; Sánchez-Madrid, F. Unidirectional Transfer of MicroRNA-Loaded Exosomes from T Cells to Antigen-Presenting Cells. Nature Commun. 2011, 2, 282
- 19. <u>Mittelbrunn M</u>, Ana Molina, María M Escribese ... & Francisco Sánchez-Madrid. VLA-4 integrin concentrates at the peripheral supramolecular activation complex of the immune synapse and drives T helper 1 responses **Proc. Natl Acad Sci U S A** 2004;101(30):11058-63.
- 20. <u>Mittelbrunn, M, Martinez del Hoyo G, & Sánchez-Madrid, F. Imaging of plasmacytoid dendritic cell interactions with T cells. **Blood** 2009 13(1):75-84</u>

PATENTS

2020-2021 Granted to participate in *Healthstart2020* training program for Creation and Management of Health Startups http://www.madrimasd.org/healthstart/projects

2020 Co-inventor of a patent (P202030906, Spain) that protects the *use of mitochondrial boosting strategies in genetic Aortic aneurysm* (Patent presented to Spanish Patent Office).

- Participated in an International Patent Publication WO 2014/049125, which was filed in *the United States* on March 27, 2015 and assigned Serial No. 14/431,955 entitled "*Nucleotide Sequence Motifs Directing Nucleic Acid Location to Extracellular Vesicles*"
- 2004 Co-inventor of a patent that protects the use of drugs that modulates the *acetylation/deacetylation of microtubules for the regulation of the immune response* (P200400107, Spain).

2001-2004 Collaboration with IFC Cantabria (2001-2004) to set up a procedure for the identification of *photoprotective compounds in modulating immune response*. The findings have been protected with a patent (P2009304289, Spain)

• INVITED LECTURES

More than 60 invited talks and lectures to international Conferences, Research Centers and Universities. Selection of invited lectures during the last years:

- 2024 Invited Speaker *Nature Conference* "Mitochondria and Immunity", Beijing, China
- 2024 Invited Speaker *Cell Symposia*: "Multifaceted Mitochondria", Sitges, Spain
- 2024 30th European Cell Death Organization Conference Cell Death at the Crossroads of Neurodegeneration and Cancer, Luxemburg
- 2024 Invited Speaker Congreso de la Sociedad Española de Geriatría y Gerontología, Malaga
- 2024 *Gordon Research Conference*, "Immune System: Molecular and Cellular Pathways in Organismal Health and Disease", Maine, US
- 2024 Invited Talk at *Annual Harvard/Paul F. Glenn Symposium on Aging,* Harvard University, US
- 2024 Invited Speaker FOCIS Annual Meeting, San Francisco, California US
- 2024 Invited Speaker Lymphocyte Antigen Receptor, Siena, Italy
- 2024 Flagship Lecture BioTechMed-Graz Faculty Club, Graz, Austria
- 2024 Invited Lecture, Day of Immunology 2024 organize by International Union of Immunological Societies and The European Federation of Immunological Societies (EFIS)
- 2024 Invited Lecture, Inaugural Annual Workshop from the Aging Program of Gene Lay Institute of Immunology and Inflammation, **Harvard Medical School**, Boston, US
- 2024 Invited Lecture, Institute Principe Felipe, Valencia, Spain
- 2024 Invited Lecture, Institute for Research in Biomedicine (IRB), Bellinzona, Switzerland
- 2024 Invited Lecture Josep Carreras Lecture in Barcelona, Spain
- 2024 Invited Speaker Keystone Symposia on Mitochondrial Signaling and Disease, Canada
- 2024 Invited Speaker Midwinter Conference Advances In Immunobiology, Seefeld, Austria
- 2024 Josep Carreras Invited Lectures, Spain
- 2024 Invited Lecture for PhD program in Immunobiology, Cell Biology and Biochemistry, IRB Bellinzona, Switzerland
- 2024 Flagship Lecture at our BioTechMed-Graz Faculty Club, Graz, Austria
- 2024 Inaugural Workshop Aging Program of the Gene Lay Institute of Immunology and Inflammation, Harvard Medical School, US
- 2024 Co-organizer at EMBO Meeting Developmental Circuits of Aging, Nice, France
- 2024 Invited Speaker at Sociedad Española de Gerontologia, Malaga
- 2024 Invited Speaker at Instituto Principe Felipe, Valencia
- 2024 Invited Speaker Keystone Symposia on Mitochondrial Signaling and Disease, Canada
- 2023 Invited Speaker *Gordon Conference*, Biology of Aging, Castildefells,, Spain
- 2023 Invited Speaker *Keystone Symposia* on Neuroimmune Interactions: From Basic Mechanisms to Novel Therapeutic Directions, Canada
- 2023 Invited Speaker Annual Meeting Societate Portuguesa de Immunologia, Aviro, Portugal
- 2023 Invited Lecture, Idival, Santander
- 2023 Invited Lecture Padua University, Italy
- 2023 Invited Lecture 6th Course on Immunity and Cancer Immunotherapy, Marsella, France
- 2023 Invited Speaker at SPI Meeting, Aveiro Portugal
- 2023 Invited Lecture Spring School Skin Homeostasis and Inflammation, Hornbæk, Denmark

- 2023 Invited Speaker at EuroMit, Bologna, Italy
- 2023 Molecular Medicine Invited Lecture at UMCG Seminar Series University of Groningen, Netherlands
- 2023 **NIH WORKSHOP** Advances in Aging, Immunity and Chronic Inflammatory Diseases, Rockville, MD, USA
- 2023 Invited Speaker *Keystone Symposia* on Neuroimmune Interactions: From Basic Mechanisms to Novel Therapeutic Directions, Canada
- 2023 Invited Speaker Cologne Spring Meeting, Cell Death and Mitochondrial Signaling in Health and Disease", Germany
- 2022 Invited Talk Precision Medicine & Chronic Diseases, University of Glasgow, UK
- 2022 **Keynote Speaker**, Young Research Symposium, Inst Maimónides de Investigación Biomédica de Córdoba
- 2022 Keynote Speaker Conference Spanish Society Biomedical Applications of Nanomaterials
- 2022 Invited Talk Cardiopulmonary Institute Goethe University Frankfurt, Germany
- 2022 Invited Speaker "Aging & Metabolism", A Coruña, Spain
- 2022 Invited Talk, Research Institute for *Biomedical Aging*, Innsbruck, Austria
- 2022 Invited Speaker EMBO Workshop "Energy balance in metabolic disorders", Malaga,
- 2022 Invited Speaker EMBO/FEBS Course "Mitochondria in life, death and disease" Montenegro
- 2022 Invited Speaker FEBS Workshop "Ageing and Regeneration", July, 2022, Mutters, Austria
- 2022 Keynote Speaker Conference on Biomedical Applications of Nanomaterials, Spain
- 2021 Invited Speaker *Gordon Research Conference Biology of Aging*, Barcelona , Spain
- 2021 Keynote Speaker 1st Birmingham Inflammation, Repair and Ageing Conference, UK
- 2021 Invited Talk Cambridge Immunology Network, Cambridge University, UK
- 2021 Invited Talk The Kennedy Strategy Session : *Inflamm-ageing*. Kennedy Institute of Rheumatology, UK
- 2021 Invited Seminar Molecular metabolism, *Karolinska Institutet*, Sweden
- 2021 Invited Speaker Joint Meeting *Mitochondria & Aging,* Lisbon, Portugal
- 2021 Invited Speaker **Pathogen Immunity and Signalling**, Saint-Malo, Brittany, France
- 2021 Invited Speaker 6th European Congress of Immunology, Belgrade, Serbia
- 2021 Invited Speaker *The Immune System: in sickness and in health* Josep Carreras Leukaemia Research Institute, Barcelona, Spain
- 2021 Invited Speaker Federation of Clinical Immunology Societies FOCIS, Belgrado
- 2021 Invited Speaker Spanish Society of Cellular Biology, Madrid, Spain
- 2021 Invited Talk Institute of Genetics and Molecular Medicine, *University of Edinburg*, UK
- 2021 Invited Speaker Spanish Society Longevity Medicine SEMAL, Madrid, Spain
- 2021 Invited Speaker Mitochondria and Metabolism in Health and Disease, *Cold Spring Harbor Asia*, Suzhou, China
- 2021 Invited Talk Humanitas Seminar Series, Rozzano, Italy
- 2021 Invited Talk The William Harvey Research Institute, Queen Mary University of London,
- 2021 Invited Talk Cardiff School of Medicine, UK

• Contracts, technological or transfer merits

2020-2022 Granted to participate in *Healthstart2020* training program for Creation and Management of Health Startups http://www.madrimasd.org/healthstart/projects

2021Co-inventor of a patent (P202030906, Spain) that protects the *use of mitochondrial boosting strategies in genetic Aortic aneurysm* (Patent presented to Spanish Patent Office).

2016Participated in an International Patent Publication WO 2014/049125, which was filed in *the United States* on March 27, 2015 and assigned Serial No. 14/431,955 entitled "*Nucleotide Sequence Motifs Directing Nucleic Acid Location to Extracellular Vesicles*"

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2001-2005 Collaboration with IFC Cantabria (2001-2004) to set up a procedure for the identification of *photoprotective compounds in modulating immune response.* The findings have been protected with a patent (P2009304289, Spain)