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DIRECTOR'S FOREWORD

The Institute of Advanced Chemistry of Catalonia (IQAC) is one of the research centers of the Consejo Superior de Investigaciones Científicas (CSIC). The Institute is located in Barcelona and it was created to do research of excellence focused on basic chemical sciences, but also addressed to solve specific problems of our society by using tools from the chemistry-biology interface, theoretical chemistry, chemical and biomolecular nanotechnology and sustainable chemistry. In particular, the identification of niches where our expertise can make important contributions is systematically pursued. Equally important to all of us is to be in a permanent attitude to transfer our knowledge and technology results to the industrial sector.

The present Report covers the biennium 2014-2015 giving account of our research activity and of the main results obtained during this period.

These two years have been characterized by the continuation of a long period of economic crisis that affected the amount of funds coming from both the public and industrials sectors to support the research activity all over the country.

The lack of funding has changed the long term expectations as well as reduced the amount of people in the institute, but it did not affect seriously the scientific output of the institute; on the contrary, scientists stepped up with a higher level of dedication to achieve excellent results.

During 2014-2015 the Institute has achieved the highest number of publications (more than 160 per year) as well as the highest average impact factor (4.4) with 5 papers published in Nature publishing group journals and 10 papers published in journals with an impact factor higher than 10. This represents a clear increase in the number of articles published in the highest impact journals compared with the last biennial report.

In addition to the information given here, we invite you to navigate our website (www.iqac.csic.es). There, you will find additional information about the research problems that we face and their results and perspectives. The web page contains also details about the facilities and methodologies that we can offer to the scientific community, both from the public and the private domains, to complement or improve their own projects, or those that can be put in the frame of a joint initiative. In this sense, the research groups and technical services from our Institute will be wide open to attend your inquiries and to offer their best efforts to find adequate responses to your needs, based on their background and expertise.

Ramon Eritja
Director of IQAC

STRUCTURE AND GENERAL RESULTS

HISTORY

The Institute was created in 2007 to better accommodate the interests of scientists of the Chemistry areas working at the "Center of Investigation and Development" (CID) and to provide a greater external projection of the activities of these scientists within the frame of the Spanish Research Council (CSIC). In spite of its recent creation, the Institute inherits the long and fruitful research tradition in Organic Chemistry initiated by Prof. José Pascual Vila since 1940. After finalizing his activity in the University, in 1967 Prof. Pascual Vila moved with his co-workers of CSIC into the Institute of Organic Chemistry of Barcelona in CID. At the same time, CSIC scientists working on Chemical Technology, such as those related to the textile and leather fields, were also incorporated into CID. During many years the CID has been the referent of the CSIC Chemistry in Catalonia and of the organic and bioorganic chemistry research in our community. Many graduate students and post-docs formed in this Center have moved to relevant positions in academic institutions (Universities, CSIC) and in private sector. In 1996, a joined action of the bioorganic, theoretical and technological groups together with those working in chemical issues related to the environment, led to the creation of the Institute of Chemical and Environmental Research "Josep Pascual Vila" (IIQAB). During the ten-year period of IIQAB, research groups have adapted their objectives to the new demands of society and new groups have also been generated. From these efforts, the Biological Chemistry, Theoretical and Computational Chemistry, Sustainable Chemistry and selected items of Chemical Technology have been reinforced. Concomitantly, potent groups working on Chemical and Biomolecular Nanotechnology have emerged or have been incorporated into IQAC. Actually, this set of scientific interests, in which the apparent heterogeneity of the active research areas is clearly compensated by the wide opportunities of their mutual interaction, justifies the creation of IQAC as a solid and modern Institute that looks at the future leaning on two pillars: the enthusiasm and expertise of its personnel and the robustness of the Chemistry tradition in our Centre.

Although its creation was in 2007, the research groups incorporated into IQAC have a recognized international prestige in their research fields. Among others, it should be highlighted the design, synthesis and evaluation of molecules of therapeutic, pharmacological or biological interest, the chemistry and applications of surfactants, the study of hormones and enzymatic transformations in insects, the development of environmentally friendly technologies, the treatment of industrial waste, the research in peptides and proteins, the theoretical study in electronic structure, or the application of nanotechnological approaches to the understanding of nanoscale systems and the development of novel nanomaterials and nanodevices, such as bioanalytical tools based on the combination of tailored bioreceptors, new nucleic acid derivatives and well-defined nanostructures and advanced materials.

In addition, our Institute has a set of scientific and technical facilities that offer services to the IQAC research groups as well as to groups or companies from elsewhere: Thermal Analysis and Calorimetry, Magnetic Resonance (NMR and EPR), Organic Microanalysis, Synthesis of High-Added Value Molecules, X-Ray Dispersion at Small Angle (SAXS-WAXS), Characterization of Colloidal Dispersions, Service of Dermocosmetic Assesment, Custom Antibody Service (CAbS), Biodegradation and Aquatic Toxicity, Proteomics and Technology transfer.

INSTITUTE BOARD MEMBERS

Ramon Eritja Casadellà
Director

Ramon Pons Pons
Deputy Director

Joan Ricard Ibáñez Villar
Head of Administration

Jesús Joglar Tamargo / Jordi Bujons Vilas
Department of Biological Chemistry and Molecular Modelling

Amadeu Llebaria Soldevila
Department of Biomedicinal Chemistry

Jordi Esquena Moret
Department of Chemical and Biomolecular Nanotechnology

Maria Teresa García Ramon
Department of Chemical and Surfactants Technology

Jaume Caelles Balcells
Personnel Representative

Avencia Diez Ortego
Personnel Representative

Meritxell Martí Gelabert
Personnel Representative

Josep Carilla Auguet / Maite Vila
Invited Services Representative

ADMINISTRATION

Director:
Ramon Eritja Casadellà

Deputy Director:
Ramon Pons Pons

Head of Administration:
Joan Ricard Ibáñez Villar

Secretaries:
Lídia Beltran Fabregat
Leonor Moliner Ferrer

«AD HONOREM» MEMBERS

Jaume Cot Cosp

DEPARTMENTS AND RESEARCH GROUPS

Department of Biological Chemistry and Molecular Modelling

- Nutraceuticals and Free Radicals
- Biotransformation and Bioactive Molecules
- Supramolecular Chemistry
- Ecological Chemistry
- Theoretical and Computational Chemistry
- Bioorganic Chemistry

Department of Biomedicinal Chemistry

- Research Unit on BioActive Molecules
- Synthesis and Biomedical Applications of Peptides
- Unit of Glycoconjugate Chemistry
- Chemical Biology
- Medicinal Chemistry

Department of Chemical and Biomolecular Nanotechnology

- Nanobiotechnology for Diagnostics
- Nucleic Acids Chemistry
- Colloid and Interfacial Chemistry
- Surface Chemistry
- Cell Therapy

Department of Chemical and Surfactants Technology

- Development of Non-contaminant industrial processes
- Statistical Modelling and Fibre Physics
- Plasma Chemistry
- Biocompatible Surfactants
- Environmental Chemistry of Surfactants and Ionic Liquids
- Physical Chemistry of Surfactant Systems
- Textile and Cosmetic Innovations
- Biophysics of Lipids and Interphases

Collaborative Leave at University of Regensburg

- David Diaz Diaz

SPIN-OFF Activities

- Bicosome, S.L.

IQAC FACILITIES AND TECHNOLOGY TRANSFER

- Custom Antibody Service (CAbS)
- Characterization of Colloidal Dispersions Service
- Microanalysis Service
- Biodegradation and Aquatic Toxicity Service
- Infrared and UV-visible Spectroscopy Service
- Service of Dermocosmetic Assessment
- SAXS-WAXS Service
- Synthesis of High Added Value Molecules Service
- Proteomics Service
- Nuclear Magnetic Resonance Spectroscopy Facility
- Electronic Paramagnetic Resonance (EPR Unit)
- Thermal Analysis and Calorimetry Service
- Lipidomics Core Facility
- Technology Transfer
- Cell Culture Service

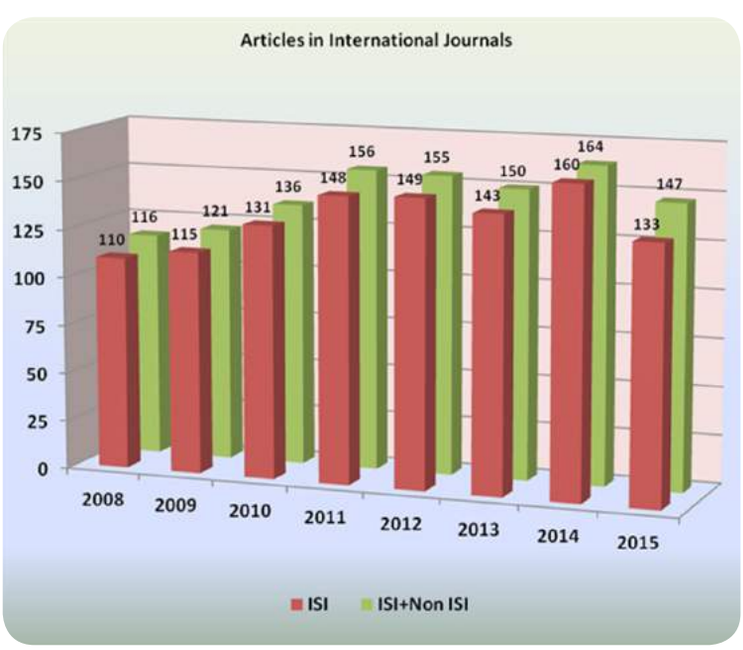
NUMERICAL SUMMARIES

PERSONNEL	Staff	Technicians	Postdocs	Ph. D. Students + undergrads
BCMM	14	3	16	17
BMC	9	2	6	34
CBN	6	4	24	30
CST	12	6	12	16
Services	3	2	2	2
TOTAL	44	17	60	99

SCIENTIFIC OUTPUT	ISI Journals	Non-ISI int	Non-ISI nat	Book ch.
BCMM	93	0	2	5
BMC	57	0	0	3
CBN	108	0	0	4
CST	67	3	4	5
TOTAL	**335**	3	6	17

ACADEMIC OUTPUT	PhD Thesis	Courses	Conferences
BCMM	15	6	11
BMC	4	1	7
CBN	7	17	10
CST	3	11	1
TOTAL	29	35	28

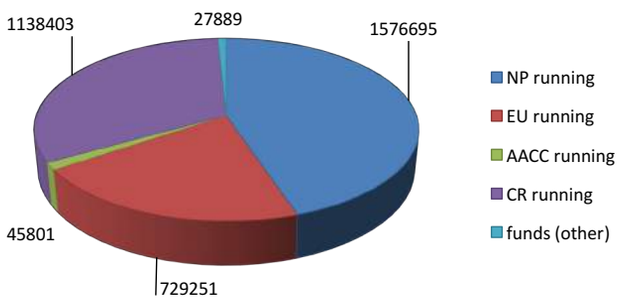
EVOLUTION OF THE NUMBER OF ARTICLES IN THE PAST EIGHT YEARS



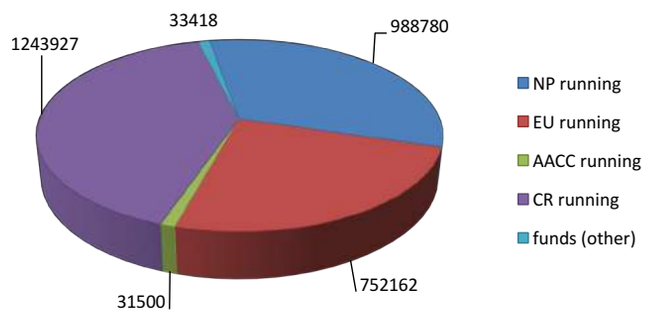
COMPETITIVE FUNDS

PROJECTS	2014	budget	2015	budget
NP running	43	1576695	29	988780
EU running	10	729251	11	752162
AACC running	3	45801	3	31500
CR running	27	1138403	33	1243927
Funds (other)	5	27889	5	33418
TOTAL		**3518039**		**3049787**
NP: National Project; EU: European Union; AACC: Autonomous Community; CR: Contracted Research				

BUDGET IN 2014

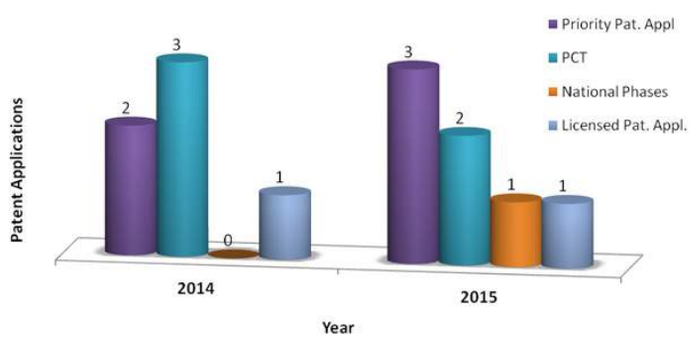


BUDGET IN 2015

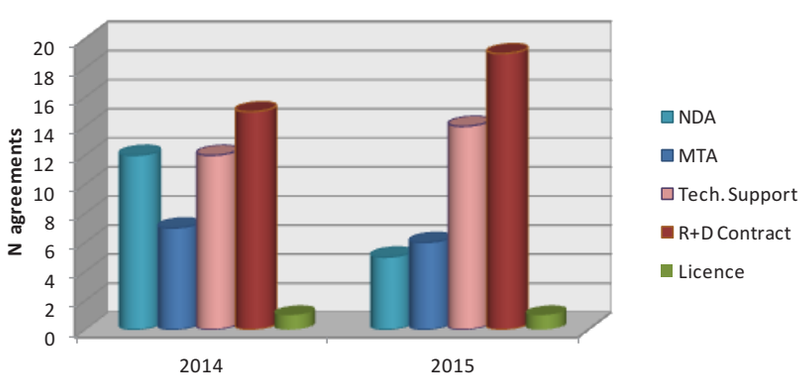


TECHNOLOGICAL OUTPUT	2014	2015	Total
Priority Patent Appl.	2	3	5
PCT	3	2	5
National Phases	0	1	1
Licensed Patents	1	1	2

PATENTS 2014-2015



KNOWLEDGE TRANSFER ACTIVITY



PARTNERSHIPS AND INSTITUTIONAL AGREEMENTS

Four groups of IQAC belongs to the Biomedical Research Networking center in Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN). This network is one of nine CIBER consortia in Spain, created under the leadership of the Carlos III Health Institute (ISCIII) to promote research excellence and build a critical mass of researchers in the field of Biomedicine and Health Sciences. The research programs of the CIBER-BBN are: Bioengineering and biomedical imaging, Biomaterials and tissue engineering and Nanomedicine, with the Centre's research aimed at developing both systems for prevention, diagnosis and monitoring and related technologies for specific treatments such as Regenerative Medicine and Nanotherapies.

Two groups of IQAC constitute the colloidal and interfacial chemistry unit (QCI) in the TECNIO network. TECNIO is the umbrella brand for Catalan Technology Centres and University Research Groups dedicated to industrial research and technology transfer. TECNIO offers access to cutting edge R&D capabilities: key technologies and knowledge for improving industrial competitive position, providing a wide range of support services for technological innovation, selected under rigorous quality criteria.

At the end of 2015, two more of IQAC have been accepted in the TECNIO network: the Custom Antibody Service (CAbS) and the Synthesis of High Added Value Molecules Service. Congratulations for the new additions.

2015. The Custom Antibody Service (CAbS) and the Characterization of Colloidal Dispersions Service (QCI) now forms part of the Singular Scientific and Technological Infrastructures (ICTS) along with the other services provided by CIBER-BBN and in collaboration with the Jesus Uson Centre for Minimally Invasive Surgery (CCMIJU). This infrastructure called NANBIOSIS is orientated towards medical applications and hopes to give a complete service and easy access through its unique window that includes the design and production of nanomaterials and biomaterials, their characterization or the characterization of tissues, medical devices or systems from a physical, chemical, functional, toxicological or biological view including pre-clinical validation. These services are located in Barcelona, Madrid, Zaragoza, Badajoz, Caceres, Valencia and Alava

2014-2015. Bilateral agreement between l'IQAC-CSIC and the University de Regensburg to support the incorporation of IQAC researcher Dr. David Díaz at the University de Regensburg. Dr. Díaz was appointed as DFG Heisenberg Professor (W2 professor).

2014-2015. Collaborative agreement between IQAC and Canigó Highschool (Col.legi Canigó, Barcelona) to develop motivation and interest for chemistry to highschool students by the perfromance of prcatical works at the IQAC laboratories.

2014-2015. Bilateral agreement between IQAC-CSIC and with Max Planck Gesellschaft zur foerderung der wissenschaften e.v. to create a Max Planck Associate Group directed by Dr. Gemma Triola at the IQAC.

2014-2015. Cooperation Agreement between the "Comité Español de Detergencia, Tensioactivos y Afines" (CED), in Barcelona and IQAC in order to enhance collaboration between industry and academic research in the surfactants field.

NEW INSTRUMENTATION

2015. Remodelation of the 500 MHz NMR instrument. The 500 MHz NMR instrument has been updated. A new Bruker AvaceIII HD console and a new Bruker Cryoprobe have been acquired to increase the sensitivity and the experimental capacities of the 500 NMR.

AWARDS, CERTIFICATIONS, SPIN-OFFS

2014-2015. Consolidation of BICOSOME S.L., an spin-off of CSIC Fundación founded by several researchers of the Dpt of Chemical and Surfactants Technology

2014. Dr. David Díaz Díaz has received in Japan the Young Investigator Award sponsored by Sumitomo

Bakelite Co. Ltd. during the 22nd Polymer Networks Group Meeting (PNG) and the 10th Gel Symposium in Tokyo in November 10, 2014.

2014, Young Investigator Award, Polymer Networks & Gels (Japan) given to David Díaz.

2014, David Díaz Díaz was selected as Editor-in-Chief "Gels" (Switzerland)

2015. Best Poster Award given to Marta Broto for her "Competitive Barcode Assay for Detection of Small Analytes at the 11th Workshop on Biosensors & Bioanalytical Microtechniques in Environmental, Food and Clinical Analysis in Regensburg, Germany.

2015. "Travel Award for Outstanding Contribution" at the Gordon Research Conference 2015, Barrier function of mammalian skin for presenting the work entitled "Mimiking Lamellar Bodies but Up-To-Down: A Repairing Strategy of the Stratum Corneum Lipid Structure" coauthored by V. Moner, E. Fernández, G. Rodríguez, M.Cócera, L. Barbosa-Barros, A. de la Maza, O. López and presented by Verónica Moner from the Biophysics of Lipids and Interphases group.

G. Triola. Best poster Award. VI Spanish Drug Discovery Network Meeting, Madrid, November 2014. Poster: Small-molecule inhibition of the KRas-PDEd interaction impairs oncogenic K-Ras signaling.

2015. Prize FUNDE for an excelent scientific career given to Conxita Solans given at Lleida on November 20, 2015.

2015. A research article published by a collaborative effort of the 3 CIBER-BBN groups (R. Eritja, J.L. Pedraz, E. Fernández) in Journal of Controlled Released 174, 24-36 (2014) was selected for a price given by the Spanish Society of Industrial Pharmacy and Galenics (SEFIG). The price was awarded in Barcelona on the 26/02/2015 at the XII SEFIG meeting.

The Service of Dermocosmetic Assesment (SED) obtained a Quality System of Managment in accordance with the UNE-EN-ISO 9001:2008 certified by AENOR with the reference ER-0430/2012.

2014 and 2015, Dr. Juan Pablo Salvador participated in the VALORTEC programme and competition organized by ACCIÓ which helps investigators to apply their knowledge towards the development of services or products with the possibility of commercialisation. Dr. Salvador presented his project "Oral Anticoagulants Diagnosis Kit" in the category of a Commercial Plan for a Technology and was selected as finalist. The VALORTEC programme included training sessions with important marketing and business companies such the EAE Business School, whose aim was to teach the participants the art of negotiation and product promotion

2015. The Ph. D. student of the Supramolecular Chemistry group Joan Atcher was selected to attend the 65th Nobel Prize Lindau Meeting.

2015. The article in Angew. Chem. 2015, 54, 3013-3017, from Biotransformation and Bioactive Molecules group, has been referenced by Synfacts: Biocatalytic Synthesis of Amino Acids Bearing α-Quaternary Stereocenters. Synfacts 2015; 11(5): 0550.

Novartis Chemistry Lectureship 2014-2015: R. Sarpong, A. Doyle, M. S. Sigman, F. Glorius, D. Trauner, and K. R. Liedl / Karl Heinz Beckurts Prize: A. Marx / Polymer Networks Group Young Investigator Award: D. Díaz Díaz, J. Groll, F. H. Schacher, and S. Seiffert.

"Young Career Focus: Professor David Díaz Díaz (University of Regensburg, Germany)". SYNFORM, 2014/10; Synstories A139-A140 (DOI: 10.1055/s-0034-1379038).

ORGANIZATION OF SCIENTIFIC MEETINGS

R. Eritja, A. Aviñó, C. Fàbrega. Organization of the congress "X Meeting on Nucleic Acids and Nucleosides (X-RANN), Barcelona, 29-30/06/2015. 70 attendees.

C. Solans, J. Esquena. Organization of Jornada QCI (IQAC-CSIC) "Innovar per Resoldre Reptes en la Formulació de Productes", Barcelona (Spain), 3/11/2015.

PARTICIPATION IN COMMITTEES

2014-2015. Dr. Angel Messeguer was selected to be a member of the Institut de Estudis Catalans as well as delegate at the Calatan Society of Chemistry.

2014. Dr. Marco was a member of the Scientific Committee for the XI Monographic Conference of the Spanish Society of Medicinal Chemistry.

2014-2015. Dr. Angel Messeguer member of the CSIC Council ("Consejo Científico Asesor del CSIC").

2015-2016. Dr. Angel Messeguer was a member of the Programme "Amgen Experiencia" (2015-2016).

2014. Dr. Angel Messeguer was a member of the Organising Committee of the 2014 Felix Serratosa Lecture.

2015. Dr. Angel Messeguer was chairman of the Spanish-Italian Congress of Medicinal Chemistry (SIMCC-2015), July 2015.

2014-2015. O. López. Spanish delegate in ESUO (European Synchrotron User Organization)

INVITED ORAL COMMUNICATIONS

C. Solans. Invited speaker at UK Colloids 2014. Design of nano-emulsions with controlled size by low energy methods. London (England), 6th July to 9th July 2014.

R. Eritja. Invited speaker at the NanoSpain 2014, Madrid, 11-13 March 2014.

A. Llebaria. Photoswitchable ligands to control GPCR activity "GPCRs, from physiology to drugs" 3rd Annual Congress of the CNRS GDR-3545. Montpellier (France) October 20-22, 2014.

R. Eritja. Selected Oral Communication at the XXI Round Table on Nucleosides, Nucleotides and Nucleic Acids (IRT 2014), Poznan, Poland, 24-28 August 2014

A. Llebaria. Optical Control of metabotropic glutamate receptor with photoswitchable drugs. Invited lecture. 8th International Meeting on Metabotropic Glutamate Receptors. Taormina (Italy) September 28th – October 3rd, 2014

R. Eritja. Keynote speaker at NanoBio&Med 2014 Conference, Barcelona (Spain), 18-21 November 2014.

P. Marco. Keynote speaker at NanoBio&Med 2014 Conference, Barcelona (Spain), 18-21 November 2014.

P. Marco. Invited lecturer at PACIFICHEM 2015 International Chemical Congress on Pacific Basin Societies hosted in Hawaii, USA

R. Eritja. Invited speaker at the meeting "Advances in Chemistry of Life Sciences, II Ed." Napoli (Italy). 30 March 2015.

R. Eritja. Conference on the Nobel Price of Chemistry 2015 organized by the Catalan Society of Chemistry. 16 December 2015.

G. Triola. Spanish Italian Medicinal Chemistry Congress (SIMCC2015), Barcelona July 2015. Selected talk: Small-molecule inhibition of the KRas-PDEd interaction impairs oncogenic K-Ras signaling.

A. Llebaria. Aminocyclitol glycolipid mimetics are potent activators of NKT cells and immune response. 250th AMERICAN CHEMICAL SOCIETY NATIONAL MEETING . Abstracts of Papers, 250th ACS National Meeting & Exposition, Boston, MA, United States, August 16-20, 2015 (2015), CARB-43.

INVITED CONFERENCES OR LECTURES

A. Messeguer. Sailing on the CombiChem boat: ups and downs". Lecture presented at the Department of Organic Chemistry of the University of Barcelona . October 2014.

R. Eritja. "Desarrollo de ácidos nucleicos modificados para la inhibición de la expresión génica". Research Seminars IOBA, Institute of Applied Ophtalmobiology University of Valladolid, 15 January 2014.

R. Eritja. "DNA bidimensional architectures, the role of nucleic acids chemistry in the game". Invited conference at the IX Workshop. Doctorate in Chemistry, Biochemistry and Ecology of Plant Protection Products and Xenobiotics. Milan (Italy), 27-28 January 2014.

A. Messeguer. "Hi haurà química entre nosaltres". Opening Lecture of the Science Week at the University of Vic. November, 2014.

A. Messeguer. "La Química Biológica y su potencial en el mundo de la salud humana". Lecture presented at the "Residencia de Estudiantes de la Delegación del CSIC" November 2014.

A. Llebaria. Drug-like photoswitchable allosteric ligands for optical control of GPCRs

CISBIO BIOASSAYS (Host E.Trinquet). Codolet (France). November 14th, 2014

J. Solà. A short walk through supramolecular chemistry. Centro Singular de Investigación en Química Biológica y Materiales Moleculares (CIQUS), Santiago de Compostela, 2014.

I. Alfonso. Química bio-inspirada con pseudopéptidos: de la simplicidad a los sistemas complejos. XVIII SEMANA CIENTÍFICA ANTONIO GONZALEZ, Instituto Universitario de Química Bio-Orgánica Antonio González, Universidad de la Laguna, Tenerife, 2014.

D. Díaz. ERC-Grantees Conference 2014. Frontiers in Chemistry - The Basis for Advanced Materials, Berlin, Germany, 28-29 August, 2014

J. Solà. Peptides in supramolecular chemistry: transfer of chiral information and molecular recognition. Universitat Jaume I, Castelló de la Plana, 2015.

I. Alfonso. Pseudopéptidos en custodia compartida. Jornada de celebración del 60 cumpleaños del profesor Santiago V. Luis, Universitat Jaume I, Catselló, 2015.

I. Alfonso. Química Supramolecular Bioinspirada con pseudopéptidos: jaulas y quimiotecas dinámicas. Centro de Química Orgánica "Lora-Tamayo", CSIC, Madrid, 2015.

I. Alfonso. Bioinspired Supramolecular Chemistry with Pseudopeptides: Molecular Cages and Dynamic Combinatorial Libraries. Ben Gurion University, Be'er Sheva, Israel, 2015.

A. Llebaria. Drug-like photoswitchable allosteric ligands for precise control of GPCRs with light. Monash Institute of Pharmaceutical Sciences (MIPS), MONASH UNIVERSITY (Host:Bernard Flynn). Melbourne (Australia); November 23, 2015.

G. Arsequell. Estrategias farmacológicas actuales en la enfermedad de Alzheimer. Lugar: Instituto de Neurociencias de Castilla y León (Universidad de Salamanca). Seminars INCyL. Febrruary 2015

A. Llebaria. Drug-like photoswitchable allosteric ligands for precise control of GPCRs with light. CIB-CSIC (Host:FJ Cañada). Madrid, October 8th, 2015.

O. López. Bicosome: New lipid technology for skin treatment. "Center for Dermal Research Seminar Series", in New Jersey Center for Biomaterials, Rutgers University. New Jersey, USA.

A. Llebaria. Allosteric ligands for in vivo control of metabotropic glutamate receptors with light. Instituto Cajal CSIC (Host:Gertrudis Perea). Madrid,December 4th, 2015

D. Díaz. Freie Universität Berlin, Germany, 2015

D. Díaz. Ulm University, Germany, 2015

D. Díaz. University of Montpellier, ICGM MACS, ED and IBMM, France, 2015

D. Díaz. University of Florence, Italy, 2015

D. Diaz. 1st iPUR Symposium, 2015. Santiago de Chile, Chile, 21-22 September, 2015

D. Diaz. GDCh-Wissenschaftsforum Chemie, Chemie 2015. Dresden, Germany, 30.8-2 October, 2015

D. Diaz. 2015 MDPI Editors-in-Chief Confeence. 12-30 June, 2015

G. Triola. Spanish Italian Medicinal Chemistry Congress (SIMCC2015), Barcelona July 2015. Selected talk: Small-molecule inhibition of the KRas-PDEd interaction impairs oncogenic K-Ras signaling.

COURSES ORGANIZED BY IQAC

María José Bleda, Albert Manich. Introducción al diseño de experimentos. Cursos de Formación (CSIC), 2014 and 2015.

María José Bleda, Albert Manich Introducción al diseño de experimentos aplicado en la química. Cursos de Formación (CSIC), 2014 and 2015.

Isabel Haro. Coordinator of the Course: "Curso Experimental en Química Biológica, Ambiental y Tecnologías relacionadas" (Postgrado y Especialización del CSIC). 2014-2015.

OUTREACH ACTIVITIES ORGANIZED AT IQAC

IV Workshop CBN'14 ((Departament of Chemical and Biomolecular de Nanotecnology). 16 October 2014. Invited speakers:

1) Dr. Manuel Merlos. Director of Pharmacology. Drug Discovery & Preclinical Development. Laboratorios Esteve. Antagonistes sigma, una nova diana en el tractament del dolor.

2) Dr. Carlos Rodriguez-Abreu. International Iberian Nanotechnology Laboratory (INL), Braga, Portugal. Design and formulation of colloidal magnetic nanocomposites toward theranostic applications.

3) Dra. Gemma Triola. IQAC-CSIC. Lipid-protein interactions: an attractive target for drug discovery.

2014-2015. Participation of IQAC researchers in the Science week with 4-5 conferences to the general public related with the activities of the institute.

2014-2015. Participation of IQAC researchers in updating information directed to highschool teachers with 3 conferences related with the activities of the institute.

V Workshop CBN'15 (Departament of Chemical and Biomolecular de Nanotecnology). 15 October 2015. Invited speakers

Dr. Ramon Crehuet. What are Intrinsically Disordered Proteins and why are they challenging

Dr. Rafael Muñoz-Espí. Colloids, Polymers, and Inorganics: A Ménage à Trois in Nanoparticle Synthesis

Dr. Salvador Borrós. Challenges in the development of a technological base Start Up. The example of Sagetis Biotech.

2014. Organization of the 18th Conference dedicated to the memory of Dr. FÈLIX SERRATOSA.

PH. D. THESIS

2014

30/01/2014

Péptidos derivados del GB virus C como potenciales inhibidores del virus de la inmunodeficiencia humana tipo 1

Ramona Galatola

Faculty of Pharmacy. University of Barcelona

Supervisors: I. Haro, M.J. Gomara

30/01/2014

Study of relevant factors in the treatment of effluents by fungi for the degradation of emerging contaminants

Marina Badia Fabregat

Autonomous University of Barcelona

Supervisor: Glòria Caminal

30/01/2014

Iminociclitoles como inhibidores de glicosidasas y su posible aplicación como coadyuvantes en el tratamiento de trastornos metabólicos

Livia Gómez

Faculty of Pharmacy. University of Barcelona

Supervisor: P. Clapés

21/03/2014

Textiles funcionales obtenidos a partir de la incorporación de nanopartículas poliméricas

Silvia Vílchez Maldonado

Faculty of Physics. University of Barcelona

Supervisors: G. Calderó, R. Molina

10/07/2014

Formulación y caracterización de emulsiones altamente concentradas de betún en agua

María Martínez Rodríguez

Faculty of Chemistry. University of Barcelona.

Supervisor: J. Esquena

25/07/2014

Chemoenzymatic Synthesis of Carbohydrates and Derivatives with Engineered D-Fructose-6-Phosphate Aldolase

Anna Szekrényi

Faculty of Pharmacy. University of Barcelona

Supervisors: P. Clapés, J. Bujons, J. Joglar

18/11/2014

Estudis de l'expressió i secreció de proteïnes recombinants (agarasa i lacasa) en una soca SipY- de Streptomyces lividans

Marcel·la Vidal Gabarró

Autonomous University of Barcelona
Supervisor: G. Caminal

25/11/2014

Studies on the chemical modulation of neuroprotective agents related to cr-6 addressed to improve the delivery through the blood-brain barrier

Laura Vázquez Jiménez

Faculty of Chemistry. University of Barcelona

Supervisors: A. Messeguer, C. Jimeno

09/12/2014

Protein flexibility: from local to global motions. A computational study

Melchor Sánchez Martínez

Faculty of Chemistry. University of Barcelona

Supervisor: R. Crehuet

2015

21/01/2015

Estudio del efecto de los ácidos grasos poliinsaturados, polifenoles e iminociclitoles sobre marcadores relacionados con el síndrome metabólico

Eunice María Molinar Toribio

Faculty of Chemistry, University of Barcelona.

Supervisor: Josep Luis Torres

21/01/2015

Development of multifunctional polymeric nanoparticles by nano-emulsion templating as adavanced nanocarriers targeting the blood-brain barrier.

Cristina Fornaguera

Faculty of Chemistry. University of Barcelona

Supervisors: C. Solans / G. Calderó / M. J. García Celma

23/01/2015

Nuevas aplicaciones de la L-Serina hidroximetiltransferasa y la benzaldehído liasa en síntesis orgánica

Karel Hernández Sánchez
Faculty of Pharmacy. University of Barcelona

Supervisor: P. Clapés, J. Bujons

14/05/2015

Síntesi quimioenzimàtica d'iminociclitols mitjançant aldolases natives i modificades genèticament

Anna Soler Casaponsa

Faculty of Chemistry. University of Barcelona

Supervisors: P. Clapés, J. Joglar

16/04/2015

Formación y propiedades de espumas macroporosas de quitosano obtenidas a partir de emulsiones altamente concentradas

Jonathan Miras Hernández

Faculty of Chemistry. University of Barcelona.

Supervisors: S. Vílchez and J. Esquena

19/05/2015

Estudio de emulsiones altamente concentradas de tipo w/o: relación entre tamaño de gota y propiedades

Mª Carmen Lendínez Gris

Faculty of Chemistry. University of Barcelona

Supervisers: C. Solans, A. Manich

19/05/2015

Desenvolupament d'antagonistes de feromones sexuals per a un control biorracional de plagues d'insectes. Síntesi i activitat

Marc Puigmartí Borrell

Faculty of Chemistry, University of Barcelona

Supervisors: A. Guerrero, M. P. Bosch

22/06/2015

Estrategias analíticas basadas en el diseño de inmunoreactivos con selectividad de clase para el control de residuos de quinolona en leche

Daniel González Pinacho

Faculty of Chemistry. Universidad de Barcelona,

Supervisors: P. Marco, F. Sánchez Baeza, A. Montaña

1/07/2015

hAGT inhibitors as chemotherapy enhancers

Maria Tintoré

Faculty of Pharmacy. University of Barcelona.

Supervisors: R. Eritja, C. Fàbrega

10/07/2015

New insights into sphingolipid metabolism and functions by using chemical tools

Francesca Cingolani

Faculty of Biology, University of Barcelona

Supervisor: J. Casas

28/07/2015

Disulfide-based dynamic combinatorial libraries of macrocyclic pseudopeptides as bio-inspired complex chemical systems

Joan Atcher Ubiergo

Faculty of Chemistry. University of Bareclona.

Supervisor: Ignacio Alfonso

24/11/2015

Polyene sphingolipids with latent fluorescence: new tools to study the biophysical properties of cellular membranes

Ingrid Nieves Calatrava

Faculty of Pharmacy, University of Barcelona

Supervisors: J. L. Abad, A. Delgado

4/12/2015

Antioxidantes y nanoestructuras lipídicas para prevenir el daño solar en tejidos lipoqueratínicos

Estibalitz Fernández Pinto

Faculty of Chemistry. University of Barcelona

Supervisor: O. López

5/12/2015

Silvia Pittolo

Development of light-modulated allosteric ligands for remote, non-invasive control of neuronal receptors

Faculty of Chemistry. University of Barcelona.

Supervisors: Pau Gorostiza (IBEC); Amadeu Llebaria (IQAC-CSIC)

11/12/2015

Modulation of RNAi pathway by chemically modified siRNA molecules

Adele Alagia

Faculty of Chemistry. University of Barcelona

Supervisors: R. Eritja, M. Terrazas

17/12/2015

Enzymatic resistant glucuronoconjugated metabolites of testosterone: from their synthesis to their evaluation as alternative markers in doping control

Aristotelis Kotronoulas

Faculty of Chemistry. University of Barcelona

Supervisors: Jesús Joglar, Oscar Pozo

18/12/2015

Diseño y síntesis de nanosistemas derivatizados con péptidos y su aplicación en biomedicina

Aimee Vasconcelos Pacheco

Faculty of Pharmacy. University of Barcelona
Supervisors: I. Haro

PATENT APPLICATIONS

2014

PCT/ES2014/070161. Haptenos y conjugados derivados de piocianina, anticuerpos de los mismos, y método inmunoquímico para la detección de infecciones provocadas por Pseudomonas aeruginosa. 2014 PCT application.

Mª Pilar Marco

Priority date:

Applicant: Consejo Superior de Investigaciones Científicas (CSIC)

WO2014027053 (A1). Benzimidazoles for the treatment of cancer

Waldmann H., Triola G., Wittinghofer A., Bastiaens P., Vartak N., Papke B., Zimmermann G., Shehab I., Schultz-Fademrecht C., Koch U.

Priority date:

Applicant: Max Planck Gesellschaft zur foerderung der wissenschaften e.v

Sensor higrométrico basado en un material colagénico.

Spanish Patent: ES201431019. Date 7/07/2014

PCT: PCT/ES2015/070479

2015

EP15382470. Antiviral agents comprising an oligonucleotides-lipids conjugates forming G-Quadruplex

Lyonnais, S., Eritja, R., Grijalvo, S., Sanchez-Palomino, S., Alvarez, C., Meyerhans, A., Martínez Vesga, J., Fleta, E., Díez Antón, H.M., Koutsoudakis, G., Mirambeau, G.

European Patent aplication EP15382470,

Priority date 28/09/2015

Applicant: Instituto de Investigaciones Biomédicas Agust Pi i Sunyer (IDIBAPS), Institució Catalana de Recerca i Estudis Avançats (ICREA), Universidad Pompeu Fabra, Consejo Superior de Investigaciones Científicas (CSIC), Centro de Investigación Biomédica en Red en Bioengenieria, Biomateriales y Nanomedicina (CIBER-BBN).

Compuestos y sus usos como haptenos para la detección S. aureus.

Pilar Marco

Nº sol: P201530780

Priority date: 3/06/2015

Applicant: Consejo Superior de Investigaciones Científicas (CSIC), Centro de Investigación Biomédica en Red en Bioengenieria, Biomateriales y Nanomedicina (CIBER-BBN).

A. Llebaria. Glutamate receptor photomodulators. PCT/ES2014/070635

Allowance as United States Patent (US 9.012.405 B2) and as European Patent (EP 2161284) of the invention: "citrullinated fibrin-filaggrin chimeric polypeptide capable of detecting the antibodies generated in Rheumatoid Arthitis" on 21/4/2015 and 8/8/2014, respectively

R. Pons. Material compuesto adsorbente que comprende metales nobles y un polímero tensioactivo, procedimiento de síntesis y su utilización para la desulfuración de fluidos. PCT/ES2014/070504. ES201330939, Licensed on 21/01/2014.

Tensiactivos catiónicos derivados del aminoácido histidina

Lourdes Pérez, Aurora Pinazo

P201530919

Priority date 26/06/2015

Applicant: Consejo Superior de Investigaciones Científicas (CSIC).

Amidas de acidos grasos para la prevención y/o tratamiento de la esteatohepatitis

Jesús Joglar

PCT/ES2015/070848

Bicelas encapsuladas en liposomas y su aplicacion en sistemas diluidos

(WO2011107643) PCT/ES2011/070128

De la maza A, López O, Rodríguez G, Rubio L, Barbosa L, Soria G., Planas AM, Cócera M.

Patente transferida en 2012 a las empresas SmartNano S.L. y Labiana S.L

LICENSED PATENTS

2014

Material compuesto adsorbente que comprende metales nobles y un polímero tensioactivo, procedimiento de síntesis y su utilización para la desulfuración de fluidos. ES201330939. Fecha licencia: 21/01/2014.

2015

Agonists of neurotrophin receptors and their use as medicaments.

Investigador Principal: Àngel Messeguer

Nº sol: US13/223,166

COURSES

Mª Pilar Marco. European Master in Quality in Analytical Laboratories (EMQAL). Erasmus Mundum Programme Immunoassays (5hours). University of Barcelona, 2014.

Mª Pilar Marco. Course "Técnicas de Inmunodiagnóstico" organized by the "Asociación Española de Técnicos de Laboratorio (AETEL)" directed towards "Técnicos Superiores en Laboratorio de Diagnóstico Clínico y Técnicos Superiores en Anatomía Patológica y Citología". Nuevas perspectivas nano biotecnológicas (1 hour). XXVII Congreso Nacional AETEL, Cordoba, 2014.

Lourdes Pérez. Fenómenos Interfaciales en la explotación de yacimientos petrolíferos. Junio 2014.

Conxita Solans. "Nano-emulsification", COST Action CM1101 Training School. Delft (Netherlands) 17 April 2014.

Conxita Solans, Jordi Esquena, Lourdes Pérez. "Fenómenos Interfaciales en yacimientos petrolíferos", for Petróleos de Venezuela, S.A. (PDVSA) company staff. Barcelona (Spain), 4-10 June 2014.

Conxita Solans, Jordi Esquena. "Tensioactivos, Emulsiones, Microemulsiones y Dispersiones de Nanopartículas" for Tekniker Company staff. Eibar (Gipuzkoa, Spain) 15-16 July 2014.

Albert Manich. Estadística aplicada a la preformulación y formulación de medicamentos. Especialización en Farmacia Industrial y Galénica. University of Barcelona. 2014 and 2015.

Conxita Solans. "Nano-emulsiones: Formación por métodos de baja energía y propiedades" and "Aplicaciones de las nano-emulsiones como plantillas para la preparación de nanopartículas", Cátedra Neal R. Amundson. Universidad de Guadalajara (México), October 2^{on} and 3rd 2014.

Conxita Solans. "Nano-emulsiones y su caracterización", PhD Program in Nanoscience and Nanotechnology. "Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional" (México), 8th October to 9th October 2014.

Josep M Anglada. "Introducció al Python per a científics" Course in the Institute of Sciences of Education of the University of Barcelona. 2014 and 2015.

Jordi Esquena. BIBAFOODS First Annual School: Getting your concepts right and how to turn a scientific idea into a successful start-up company. "Formation, characterization and stability of emulsions". University of Coimbra (Portugal), 9th January to 15th January 2015.

Jordi Esquena. BIBAFOODS Second Annual School: Colloidal Carriers for Enzymes and How to Turn a Scientific Idea into a Successful Start-up Company. "Design, properties and applications of porous materials obtained in highly concentrated emulsions". Universidad de Alcalá (Alcalá de Henares, Madrid). 17th November to 20th November 2015.

R. Pons. X-ray scattering as a tool for characterization in the nanometric domain In BIBAFOODS Second Annual School Program . Alcalá de Henares 15/11/2015.

Conxita Solans, Jordi Esquena. Practical tutorials of the "Máster en Cosmética y Dermofarmacia" in collaboration with "Centro de Estudios Superiores de la Industria Farmacéutica". Barcelona (Spain), Two editions: June-July 2014 and June-July 2015.

Ramon Eritja. Genetic and cellular basis of biotechnology. Master of Biotechnology. University of Barcelona, 2014 -2015.

Ramon Eritja. Biomolecular Nanoscience. 4th Year of the Graduate studies of Nanotechnology. Autonomous University of Barcelona, 2014 -2015.

Mª Pilar Marco. International Course on Antimicrobial Strategies in Sepsis (ICASIS 2015). Nanotechnology (1 hour). Sitges, Barcelona, 2015.

J.-Pablo Salvador Vico. GLOBAQUA: Short course on rapid screening of aquatic organic pollution and toxicity using bioassays and biosensors. Immunochemical

determination of environment pollutants in sea water (11/2 hours). IDAEA-CSIC, Barcelona, 2015.

Albert Manich. Planificación y Diseño de Experimentos. Curso de Especialización (Laboratorios SALVAT), 2015.

Albert Manich. Planificación y Diseño de Experimentos. Curso de Especialización (KERN Pharma), 2015.

Albert Manich. Sistemas y Equipos de Medida en Análisis Térmico. Máster en Industria Alimentaria y Bioprocesos (UPC), 2015.

Ramon Eritja and Carme Fàbrega. II Summer School on Molecular and Cellular Integrative Biology. Synthetic Biology and Biological Systems Engineering. IUMP., Santander (Spain), July 2015.

Conxita Solans. "Formación de emulsiones utilizando métodos de baja energía"and "Importancia de las emulsiones en la industria alimentaria y farmacológica". Universidad de la Frontera (UFRO, Chile) 19th October to 23rd October 2015.

Ignacio Alfonso. Dynamic NMR & Chemical Exchange. XI Manuel Rico NMR School, (Eds: López-Ortiz, F.; Parella, T.), NMR Advanced Course organized by GERMN, 2015.

Amadeu Llebaria. Enciende la luz y apaga el dolor: Optogenética y Optofarmacología
CURSO: Las Fronteras del Dolor. Facultad de Ciencias de la Salud. Universidad Rey Juan Carlos, Alcorcón, Madrid, Spain. 29 June to 3 July, 2015.

PARTICIPATION IN GENERAL PUBLIC EVENTS/ FERIAS

Jordi Esquena. Participation to the "IV Fòrum del Parc Científic i Tecnològic de la Universitat de Girona: marketplace tecnològic de Girona", Fabruary 6th 2014.

Jordi Esquena. Participation to the Brokerage Event Alimentaria 2014, ACC1Ó (Generalitat de Catalunya), EEN y Cambra de Comercio de Barcelona, Barcelona Barcelona (Spain), 1st April to 2April 2014.

Jordi Esquena. Participation to the "Festa de la ciència, tecnologia i innovació 2014", Institut de Cultura de Barcelona. Barcelona (Spain), June 15th 2014.

Jordi Esquena. Participation to Brokerage Event Expoquimia 2014, ACC1Ó (Generalitat de Catalunya) and EEN. Barcelona (Spain), October 2nd 2014.

PARTICIPATION IN INTERNATIONAL GRADUATE EXCHANGE PROGRAMMES.

Erasmus Mobility Programme. Coordination by Dr. Maria Teresa García. Traineeship: Olga Kaczerewska. Adam Mickiewicz University.

UNIPHARMA/ Leonardo da Vinci Italian-Spanish bilateral exchanges. Coordination by Dr. Amadeu Llebaria. 2014-2015.

École National Superièure de Chimie de Lille. Université Chimie de Lille. Exchange Programme, 2014-2015.

MEDIA COVERAGE

Multimedia presentation of the results obtained by the European project SEA-on-a-CHIP in the TVE programme "Fabrica de Ideas" to discuss our participation in this multidisciplinary project, the object of which is to create an autonomous device for the detection of contaminants in sea water. Our group will provide the immunoreagents that will detect contaminants of interest such as pesticides or algal toxins ".

30/07/2014. Press release on the article published in Proc. Nat. Acad. Sci. USA, , 111(32), 11618-11623, 2014., by J. M. Anglada, M. Martins-Costa, M. F. Ruiz-López, J. S. Francisco. Comments in several newspapers such as La Vanguardia, ABC, El dia, Canarias7, La Razón and commented in Radio Aragon.

10/07/2014. Press release on the Max Planck Associate Group supervised by Dr. Gemma Triola published on R + D CSIC.

23/09/2015. Press release on the article published on Nature Chemistry 7, 724–729 2015 by A. Szekrenyi, X. Darrabou, T. Parella, J. Joglar, J. Bujons, P. Clapés published on R + D CSIC.

2014. Special issue of the journal Natural Product Communications dedicated to Dr. Josep Coll on his 70th anniversary.

2

DEPARTMENT OF BIOLOGICAL CHEMISTRY AND MOLECULAR MODELLING

DEPARTMENT OF BIOLOGICAL CHEMISTRY AND MOLECULAR MODELLING

Heads: Jesús Joglar Tamargo (until Aug. 2015)
Jordi Bujons Vilàs (from Sept. 2015)

Research interests of this Department are focused on:

- Molecules of biological and biomedical interest. Isolation, design, synthesis, biosynthesis, and activity evaluation of drugs, insect pheromones, secondary metabolites, enzymatic inhibitors, biocatalysts, functional food ingredients and antioxidants.
- Molecular recognition of ions and molecules of biological interest.
- Asymmetric organocatalysis.
- Study of non covalent interactions. Modelling of enzymatic catalysis mechanisms.
- Modification of the activity and selectivity of biocatalysts by means of genetic engineering and computational methods. Investigation on carboligases in Systems Biocatalysis for asymmetric carbon-carbon bond formation.
- Biorational control of pests. Characterization of insect proteins by means of proteomic and molecular biology techniques.
- Persistent organic free radicals as biochemical sensors. Mechanisms of action of antioxidant protectors.
- Study of the electronic structure and reactivity of molecules by means of theoretical chemistry computational techniques. Computational elucidation of reaction mechanisms of interest in atmospheric chemistry. New theoretical methods for exploring potential energy surfaces.

RESEARCH GROUPS

- Nutraceuticals and Free Radicals
- Biotransformation and Bioactive Molecules
- Supramolecular Chemistry
- Ecological Chemistry
- Theoretical and Computational Chemistry
- Bioorganic Chemistry

NUTRACEUTICALS AND FREE RADICALS

Research at NFR involves the thorough evaluation of potentially new disease preventing and health promoting agents such as nutraceuticals or functional food components. The nutraceuticals (e.g. antioxidant polyphenols, omega-3 polyunsaturated fatty acids, iminosugars) are natural products obtained by either from agricultural and fishery by-products or by environmentally friendly biosynthetic procedures. The biological activities tested on the nutraceuticals are related to oxidative stress, which is a major damaging process, mediated by free radicals and occurring in many disorders (metabolic syndrome, cardiovascular disease, type 2 diabetes, cancer, Alzheimer, Parkinson). The study of free radicals, their reactivity, their use as probes for antioxidant activity and their control or elimination by natural nutraceuticals is a central focus of our research. Recently, we have focused on *in vivo* studies with rats models of the metabolic syndrome and tested combinations of nutraceuticals with complementary activities. The antioxidant activity is measured by Electron Paramagnetic Resonance spectroscopy with the spin trapping and radical scavenging methodology.

STAFF

LUIS JULIÀ BARGÈS, GROUP LEADER
JOSEP LLUÍS TORRES SIMON
LLUÍS FAJARÍ AGUDO

PH. D.

SARA RAMOS ROMERO

PH. D. STUDENTS

EUNICE MOLINAR TORIBIO
MERCÈ HEREU PLANAS

ARTICLES

Bicelles and bicosomes as free radical scavengers in the skin

Fernández, E.; Fajarí, L.; Rodríguez, G.; López-Iglesias, C.; Cócera, M.; Barbosa-Barros, L.; De La Maza, A.; López, O.

RSC Adv., 4, 53109-53121, **2014**.

Cardiovascular disease-related parameters and oxidative stress in SHROB rats, a model for metabolic syndrome

Molinar-Toribio, E.; Pérez-Jiménez, J.; Ramos-Romero, S.; Lluís, L.; Sánchez-Martos, V.; Taltavull, N.; Romeu, M.; Pazos, M.; Méndez, L.; Miranda, A.; Cascante, M.; Medina, I.; Torres, J.L.

PLoS ONE, 9, **2014.**

Charge transfer states in stable neutral and oxidized radical adducts from carbazole derivatives

Fajarí, L.; Papoular, R.; Reig, M.; Brillas, E.; Jorda, J.L.; Vallcorba, O.; Rius, J.; Velasco, D.; Juliá, L.

J. Org. Chem., 79, 1771-1779, **2014.**

Effect of d -fagomine on excreted enterobacteria and weight gain in rats fed a high-fat high-sucrose diet

Ramos-Romero, S.; Molinar-Toribio, E.; Gómez, L.; Pérez-Jiménez, J.; Casado, M.; Clapés, P.; Piña, B.; Torres, J.L.

Obesity, 22, 976-979, **2014**.

Radical scavenging of white tea and its flavonoid constituents by electron paramagnetic resonance (EPR) spectroscopy

Azman, N.A.M.; Peiró, S.; Fajarí, L.; Julià, L.; Almajano, M.P.

J. Agricul. Food Chem.., 62, 5743-5748, **2014.**

Eicosapentaenoic acid/docosahexaenoic acid 1:1 ratio improves histological alterations in obese rats with metabolic syndrome

Taltavull, N.; Muñoz-Cortés, M.; Lluís, L.; Jové, M.; Fortuño, A.; Molinar-Toribio, E.; Torres, J.L.; Pazos, M.; Medina, I.; Nogués, M.R.

Lipids Health Disease, 13, 31, **2014**.

Identification of phenolic compounds by HPLC-ESI-MS/MS and antioxidant activity from Chilean propolis

Castro, C.; Mura, F.; Valenzuela, G.; Figueroa, C.; Salinas, R.; Zuñiga, M.C.; Torres, J.L.; Fuguet, E.; Delporte, C.

Food Research Int., 64, 873-879, **2014.**

Identification of polyphenols from antiviral Chamaecrista nictitans extract using high-resolution LC-ESI-MS/MS.

Mateos-Martín, M.L.; Fuguet, E.; Jiménez-Ardón, A.; Herrero-Uribe, L.; Tamayo-Castillo, G.; Torres, J.L.

Anal. Bioanal. Chem., 406, 5501-5506, **2014**.

Protein carbonylation associated to high-fat, high-sucrose diet and its metabolic effects

Mendez, L., Pazos, M., Molinar-Toribio, E., Sanchez-Martos, V., Gallardo, J. M., Nogues, R., Torres, J. L.; Medina, I.

J. Nutritional Biochem., 25, 1243-1253, **2014**.

Resveratrol and EGCG bind directly and distinctively to miR-33a and miR-122 and modulate divergently their levels in hepatic cells

Baselga-Escudero, L.; Blade, C.; Ribas-Latre, A.; Casanova, E.; Suárez, M.; Torres, J.L.; Salvadó, M.J.; Arola, L.; Arola-Arnal, A.

Nucleic Acids Res., 42, 882-892, **2014**.

Targets of protein carbonylation in spontaneously hypertensive obese Koletsky rats and healthy Wistar counterparts: A potential role on metabolic disorders

Méndez, L.; Pazos, M.; Giralt, M.; Nogués, M.R.; Pérez-Jiménez, J.; Torres, J.L.; Gallardo, J.M.; Medina, I.

J. Proteomics, 106, 246-259, **2014**.

Fluorescent polyene ceramide analogues as membrane probes

Nieves, I.; Artetxe, I.; Abad, J.L.; Alonso, A.; Busto, J.V.; Fajarí, L.; Montes, L.R.; Sot, J.; Delgado, A.; Goñi, F.M.

Langmuir, 31, 2484-2492, **2015**.

Effect of n-3 PUFA supplementation at different EPA:DHA ratios on the spontaneously hypertensive obese rat model of the metabolic syndrome

Molinar-Toribio, E.; Pérez-Jiménez, J.; Ramos-Romero, S.; Romeu, M.; Giralt, M.; Taltavull, N.; Muñoz-Cortes, M.; Jáuregui, O.; Méndez, L.; Medina, I.; Torres, J.L.

Brit. J. Nutrition, 113, 878-887, **2015**.

Effects of food processing on polyphenol contents: A systematic analysis using phenol-explorer data

Rothwell, J.A.; Medina-Remón, A.; Pérez-Jiménez, J.; Neveu, V.; Knaze, V.; Slimani, N.; Scalbert, A.

Mol. Nutrition Food Res., 59, 160-170, **2015**.

Identification of esterified oleanolic acid in Cestrum parqui leaves and its apoptotic induction on HT-29 cell line.

H. Chenni, M.A. Mahjoub, F. Estévez, M. Cascante, J.L. Torres, K. M. Ali, D. Ghosh, M.M. Travelsi

J. Med. Pharm. Innov. 2(7), 63-68, **2015**.

Apoptosis Induction by Cestrum parqui L'Hér. leaves on HL-60 Cell Line: Identification of Active Phytomolecules.

H. Chenni, J.L. Torres, F. Estévez, K. M. Ali, D. Ghosh, M.M. Travelsi

Int. J. Cancer Stud. Res. S1:001, 1-8, **2015**.

D-Fagomine attenuates metabolic alterations induced by a high-energy-dense diet in rats.

E. Molinar-Toribio, J. Pérez-Jiménez, S. Ramos-Romero, L. Gómez, N. Taltavull, M. R. Nogués, A. Adeva, O. Jáuregui, J. Joglar, P. Clapés, J. L. Torres

Food Funct. 6, 2614-2619, **2015**.

The effect of Convolvulus arvensis dried extract as a potential antioxidant in food models.

N.A.M. Azman, M.G. Gallego, L. Julià, Ll. Fajarí, M.P. Almajano

Antioxidants, 4, 170-184, **2015**.

Copper(II) complexes of macrocyclic and open-chain pseudopeptidic ligands: synthesis, characterization and interaction with dicarboxylates

E. Faggi, R. Gavara, M. Bolte, Ll. Fajarí, L. Juliá, L. Rodriguez, I. Alfonso

Dalton Trans. 44, 12700-12710, **2015**.

RESEARCH PROJECTS

Desarrollo aplicaciones de análogos de azucares: D-fagomina. Estudios de actividad, eficacia y toxicidad en su uso como nuevo ingrediente nutricional para la prevención de sobrepeso y resistencia a enfermedades.

Nacional, IPT-2011-0828-900000

2011-2014

Effect of marine omega 3 PUFA and iminosugars to avert metabolic disorders derived of hypercaloric diets: role of lipid mediators and fagomine.

Ref: AGL2013-49079-C2-2-R

Entidad financiadora: Ministerio de Economía y Competitividad, Programa de I+D+i orientada a los Retos de la Sociedad.

Entidades participantes: CSIC (IQAC-IIM), Universitat Rovira i Virgili

Duración: 2014-2017

Investigador principal: **Dr. Josep Lluís Torres**.

Grup de Bioquímica Integrativa.

Ref: 2014SGR1017

Entidad financiadora: Agència de Gestió d'Ajuts Universitaris i de Recerca. Generalitat de Catalunya.

Entidades participantes: UB-CSIC

Duración: 2014-2016

Investigador principal: **Dra Marta Cascante**.

Señalizacion errónea del consumo de frutas y patogénesis de la obesidad. Circadian rythms, photoperiod, phenolic compounds, obesity, fruits seasonality.

Ref: AGL2013-49500-EXP

Entidad financiadora: Ministerio de Economía y Competitividad, Programa de I+D+i, EXPLORA.

Entidades participantes: Universitat Rovira i Virgili, CSIC (IQAC)

Duración: 2014-2016

Investigador principal: **Dra. M. Cinta Bladé**

Estudio de moléculas orgánicas semiconductoras con propiedades ópticas, electrónicas, magnéticas y su aplicación en materiales líquido-cristalinos mecano-luminiscentes

Ref: CTQ2012-36074

Entidad financiadora: Dirección General de Investigación Científica y Técnica,

Ministerio de Economía y Competitividad

Duración: 2013-2015

Investigador principal: **Dolores Velasco Castrillo**

RESEARCH HIGHLIGHTS

D-Fagomine attenuates metabolic alterations induced by a high-energy-dense diet in rats.

Diabetes and obesity are two modern worldwide epidemics that may be caused, at least in part, by bad nutritional habits such as an excessive intake of saturated fats and refined sugars . D-Fagomine is a natural iminosugar that counteracts the short-term effects of a high-energy-dense diet on body weight, fasting blood glucose levels and the proportion of gut Enterobacteriales. This suggests that supplementation with D-fagomine may delay the onset of metabolic alterations. We evaluated the effects of D-fagomine dietary supplementation on relevant metabolic hormones and lipid peroxidation. Adult Sprague–Dawley rats were fed a high-fat high-sucrose diet supplemented or not with D-fagomine (0.065% w/w) for 9 weeks. Weight gain, plasma triglycerides, glucose, insulin, glucagon, ghrelin, leptin, and urine F2-isoprostanes were evaluated. D-Fagomine attenuated the changes induced by the high-energy-dense

diet in triglycerides and all the hormones tested. These results suggest that D-fagomine may help to avert the complications associated with unhealthy eating by counteracting the effects of high-energy-dense diets during the early stages of the development of metabolic disorders that may lead to type 2 diabetes.

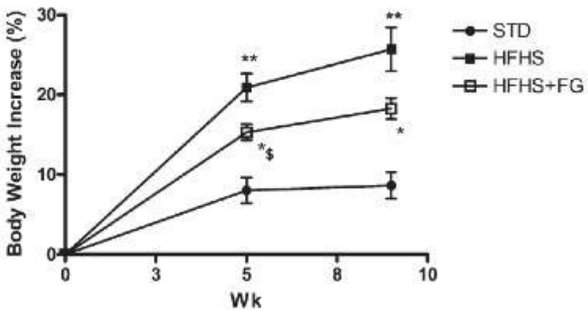
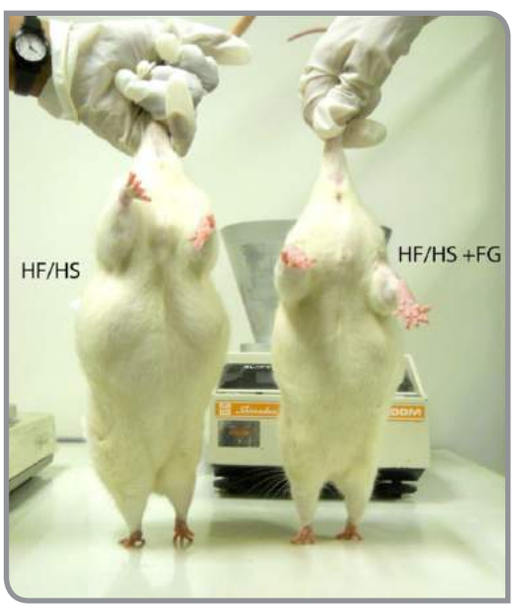
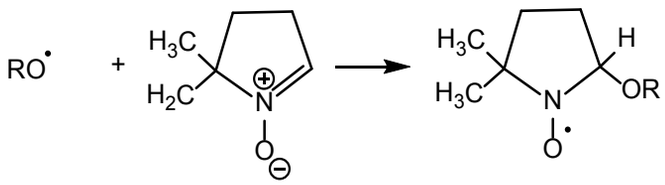


Fig. 1 Body weight gain in rats fed a standard (STD, ●), high-fat high-sucrose (HFHS, ■), or high-fat high-sucrose with D-fagomine (HFHS + FG, □) diet for 9 weeks. Data are presented as means with their standard errors. Comparisons were performed using the Kruskal–Wallis and Mann–Whitney *U* tests. $^{*}P < 0.05$ *vs.* STD group, $^{**}P < 0.001$ *vs.* STD group, $^{\$}P < 0.05$ *vs.* HFHS group.



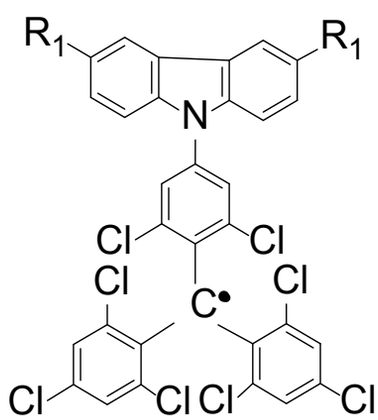
Antioxidant properties of natural plant extracts

We have carried out research work related to the antioxidant properties of natural plant extracts. In this context, we have studied the radical scavenging activity of white tea against the reactive oxygen species such as hydroxyl radical and methoxyl radical. This work has been done with the electron paramagnetic resonance (EPR) through the spin trapping technique. A very unstable transient radical reacts with a spin trap, a nitrone or a nitroso compound, to form a much more stable radical adduct detected by epr.



Stable radical adducts as molecular electronic devices

Another of our targets is to develop new stable organic radical adducts possessing dipolar structure from tris(2,4,6-trichlorophenyl)methyl radical as the electron-acceptor open-shell moiety, and derivatives of carbazole as the electron donor moiety. All of them show significant physical and electrochemical properties, in addition to the intrinsic magnetic character.



BIOTRANSFORMATION AND BIOACTIVE MOLECULES

The research is focused on the design, production and evaluation of biocatalysts, biologically active molecules and metabolites. Biocatalysis has the potential to access to stereochemical complex molecules that are not produced easily by conventional organic synthesis, and that are particularly appropriate for obtaining new type of structures (i.e. generate molecular diversity) accessible for investigations in drug discovery. Fundamental components of the biocatalysis are the enzymes. The utilization of enzymes to catalyze reactions on a plethora of non-natural substrates is the core principle for a growing sustainable bioproduction industry. The research includes identification of new enzymes, creation of tailor-made enzymes using structure-guided protein design, computational models for ligand-protein interaction as a way to redesign biocatalysts and biologically active molecules

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ARTICLES

Apaf-1 inhibitors protect from unwanted cell death in In vivo models of kidney ischemia and chemotherapy induced ototoxicity

Orzáez, M.; Sancho, M.; Marchán, S.; Mondragón, L.; Montava, R.; Valero, J.G.; Landeta, O.; Basañez, G.; Carbajo, R.J.; Pineda-Lucena, A.; Bujons, J.; Moure, A.; Messeguer, A.; Lagunas, C.; Herrero, C.; Pérez-Payá, E.

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Aldolase-catalyzed synthesis of conformationally constrained iminocyclitols: Preparation of polyhydroxylated benzopyrrolizidines and cyclohexapyrrolizidines

Laborda, P.; Sayago, F.J.; Cativiela, C.; Parella, T.; Joglar, J.; Clapés, P.

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Castañar, L.; Roldán, R.; Clapés, P.; Virgili, A.; Parella, T.

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Engineered L-Serine hydroxymethyltransferase from *Streptococcus thermophilus* for the synthesis of alpha,alpha-dialkyl-alpha-amino acids.

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Degradation of pharmaceuticals from membrane biological reactor sludge with *Trametes versicolor*

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BOOK CHAPTERS

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RESEARCH PROJECTS

Sustainable industrial processes based on a C-C bond-forming enzyme platform

European Union Framewok Programme Horizon 2020: Carbazymes-635595

2015 - 2019

Rediseño de carboligasas para la formación asimétrica de enlaces carbono-carbono: hacia la síntesis one-pot multietapa de compuestos polioxigenados

Nacional, CTQ2012-31605

2013-2015

Synthesis of recently reported phase II metabolites for their inclusion in routine doping control

Internacional, WADA-12A130P

2013-2014

Tecnología de microrreactores para reacciones enzimáticas de formación de enlaces carbono-carbono. ERA-Industrial BIOTECH

Nacional, ERA-IB-PIM2010EEI-00607

2011-2014

Nuevas alternativas para la producción microbiana de enzimas y síntesis multienzimática estereoselectiva

Nacional MICINN CTQ 2011-28398-C02-01

2012-2014

Expanding the industrial use of Robust Oxidative Biocatalysts for the conversion and production of alcohols (ROBOX)

Horizon 2020 : H2020-LEIT-BIO-2014-1. TOPIC: BIOTEC-3-2014

2015-2019

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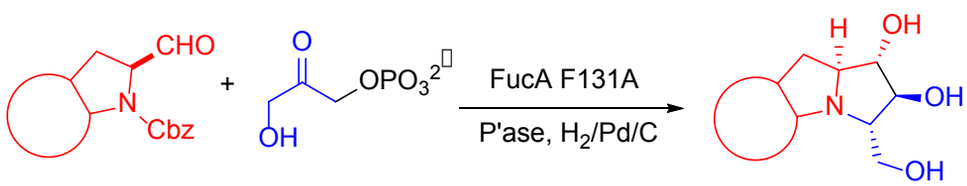
2014-2016.

RESEARCH HIGHLIGHTS

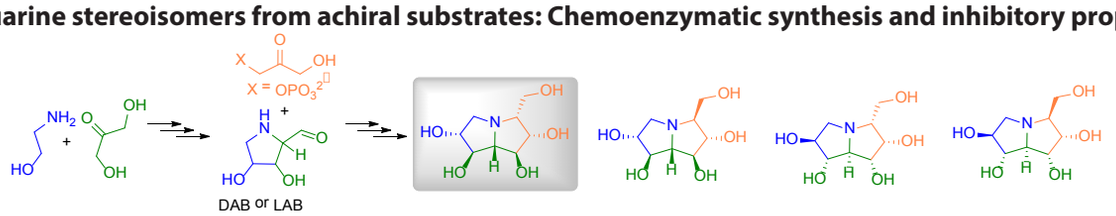
Synthesis of biologically relevant compounds

- **Aldolase-catalyzed synthesis of conformationally constrained iminocyclitols: Preparation of polyhydroxylated benzopyrrolizidines and cyclohexapyrrolizidines.**



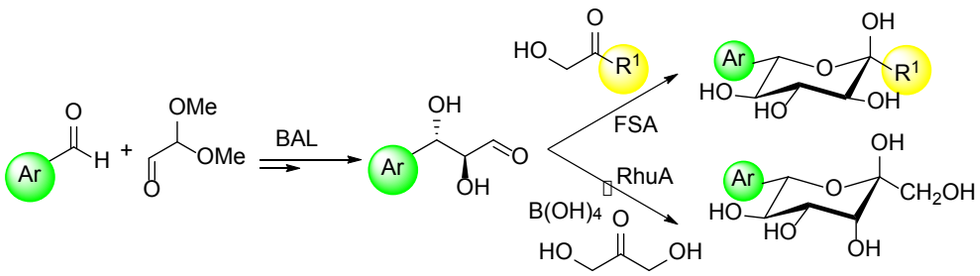
We developed a chemo-enzymatic synthesis of new polyhydroxylated benzopyrrolizidines and cyclohexapyrrolizidines, consisting of L-fuculose-1-phosphate aldolase variant F131A-catalyzed aldol addition of dihydroxyacetone phosphate to *rac*-*N*-benzyloxycarbonylindoline-2-carbaldehyde, (2*S**,3a*S**,7a*S**)- and (2*S**,3a*R**,7a*R**)-*N*-benzyloxycarbonyloctahydroindole-2-carbaldehydes and subsequent one-step catalytic deprotection-reductive amination.

- **Casuarine stereoisomers from achiral substrates: Chemoenzymatic synthesis and inhibitory properties.**



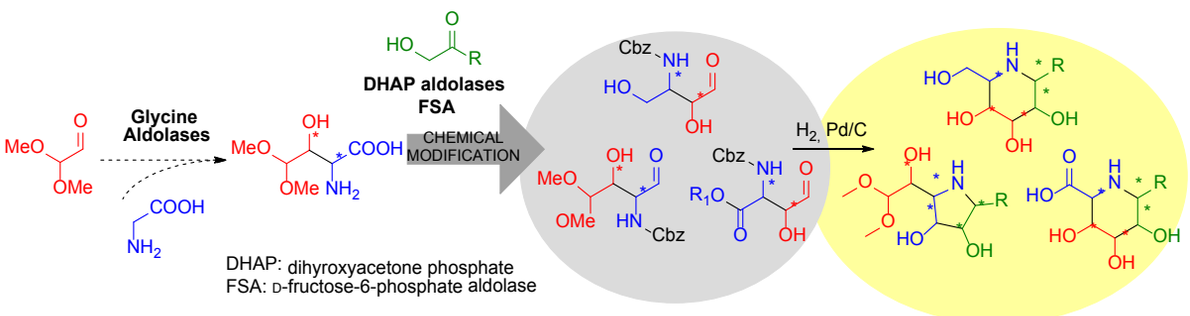
Four uncovered casuarine stereoisomers were obtained by a chemo-enzymatic strategy consisting of two key enzymatic steps. First, 1,4-dideoxy-1,4-imino-D-arabinitol (DAB) and its enantiomer (LAB) were obtained from dihydroxyacetone and aminoethanol using D-fructose-6-phosphate aldolase and l-rhamnulose-1-phosphate aldolase, respectively. Second, L-fuculose-1-phosphate aldolase F131A variant catalyzed aldol addition of dihydroxyacetone phosphate to aldehyde derivatives of DAB and LAB. The new *ent*-3-epicasuarine (highlighted) was a strong inhibitor of α-D-glucosidase from rice and of rat intestinal sucrase.

- **Expedient synthesis of C-aryl carbohydrates by consecutive biocatalytic benzoin and aldol reactions.**



Installation of aromatic residues connected by C-C bond into the non-reducing end of carbohydrates is highly significant for the development of innovative structures with improved binding affinity and selectivity (e.g. *C*-aril-sLex). An asymmetric "*de novo*" route to new aryl carbohydrate derivatives was developed. First, the benzoin reaction of aromatic aldehydes to dimethoxyacetaldehyde catalyzed by benzaldehyde lyase from *Pseudomonas f.* (BAL). Then, the α-hydroxy ketones formed were reduced using $NaBH_4$ yielding the *anti* diol. After acetal hydrolysis the aldol addition of dihydroxyacetone, hydroxyacetone or glycolaldehyde catalyzed by stereocomplementary FSA and RhuA aldolases was performed. In this way, *C*6-aryl-L-sorbose, -L-fructose, -L-tagatose and C5-aryl-L-xylose, derivatives were prepared.

- **Sequential biocatalytic aldol reactions in multistep asymmetric synthesis: Pipecolic acid, piperidine and pyrrolidine (homo)iminocyclitol derivatives from achiral building blocks**

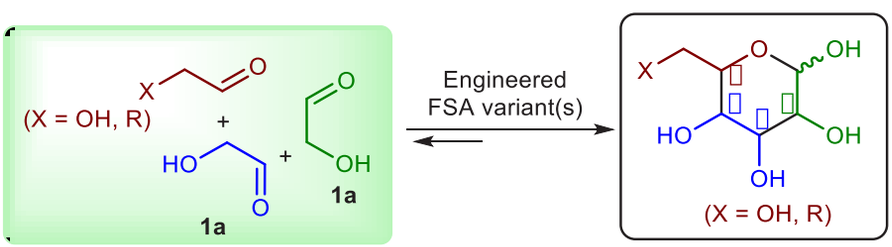


Combining glycine-dependent aldolases and both D-fructose-6-phosphate aldolase (FSA) and dihydroxyacetone phosphate (DHAP)-dependent aldolases a multistep chemo-enzymatic synthesis for stereodiverse polyhydroxypipecolic acid analogues, homoiminocyclitols and polyhydroxylated piperidine and pyrrolidine derivatives was developed. The methodology allowed preparing known and innovative imine derived molecules with a great structural diversity from simple achiral substrates. The reported strategy thus designed creates up to five new stereogenic centers in three steps, four of them being controlled in two enzymatic reactions. This was possible by taking the full advantage of using aldolases in a multistep approach by virtue of their stereocomplementarity, stereoselectivity and broad substrate tolerance.

BIOCATALYST REDESIGN

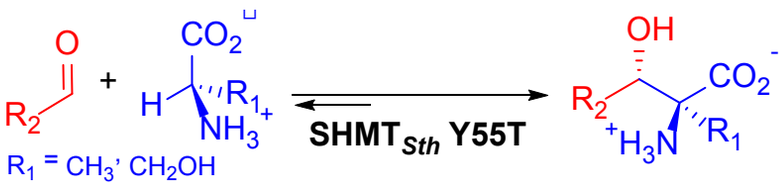
Synthesis of biologically relevant compounds

- **Asymmetric assembly of aldose carbohydrates from formaldehyde and glycolaldehyde by tandem biocatalytic aldol reactions.**



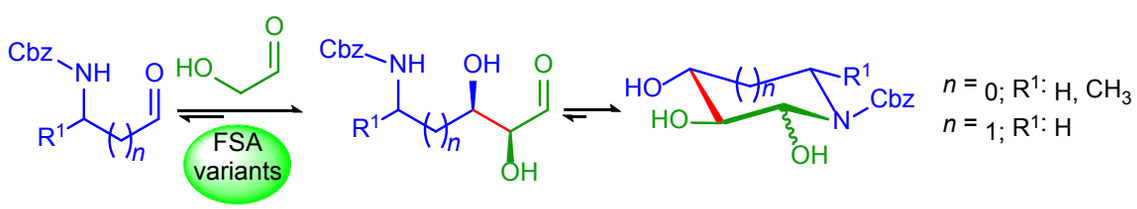
The preparation of multifunctional chiral molecules can be greatly simplified by adopting a route via sequential catalytic assembly of achiral building blocks. The catalytic aldol assembly of prebiotic compounds into carbohydrates is an as-yet unmet challenge. We use engineered D-fructose-6-phosphate aldolase from *E. coli* to prepare a series of three- to six-carbon aldoses by sequential one-pot additions of glycolaldehyde. Notably, the pertinent selection of the aldolase variant provides control of the sugar size. The stereochemical outcome of the addition was also altered to allow the synthesis of L-glucose and related derivatives. Such engineered biocatalysts may offer new routes for the straightforward synthesis of natural molecules and their analogues, which circumvent the intricate enzymatic pathways forged by evolution.

- **Engineered L-Serine hydroxymethyltransferase from *Streptococcus thermophilus* for the synthesis of α,α-dialkyl-α-amino acids.**



α,α-Disubstituted-α-amino acids are central to biotechnological and biomedical chemical processes on their own sake and as substructures of biologically active molecules for diverse biomedical applications. Structurally, these compounds contain a quaternary stereocenter, which is particularly challenging for stereoselective synthesis. The pyridoxal-5′-phosphate (PLP)-dependent L-serine hydroxymethyltransferase from *Streptococcus thermophilus* ($SHMT_{Sth}$; EC 2.1.2.1) was engineered to achieve the stereoselective synthesis of a broad structural variety of α,α-dialkyl-α-amino acids. This was accomplished by the formation of quaternary stereocenters through aldol addition of the amino acids D-Ala and D-Ser to a wide acceptor scope catalyzed by the minimalist $SHMT_{Sth}$ Y55T variant overcoming the limitation of the native enzyme for Gly.

- **Structure-guided engineering of D-fructose-6-phosphate aldolase for improved acceptor tolerance in biocatalytic aldol additions.**



A combination of a structure-guided program of saturation, site directed mutagenesis and computational modeling was applied to construct a set of FSA variants that improved the catalytic efficiency towards glycolaldehyde dimerization up to 1800-fold. The new FSA variants were applied as highly efficient catalysts for cross-aldol additions of glycolaldehyde to *N*-Cbz-aminoaldehydes, furnishing between 80-98% aldol adduct under optimized reactions conditions. These results attest to the exceptional malleability of the active site of FSA, which can be remodeled to tolerate a wide spectrum of donor and acceptor substrates with high efficiency and selectivity.

SUPRAMOLECULAR CHEMISTRY

Supramolecular chemistry is the "chemistry beyond the molecule" and deals with the interactions between chemical species in an ordered and hierarchical way, leading to the formation of well-defined supramolecules. We mainly work in the fields of molecular recognition, programmed folding and self-assembling processes, using a large variety of experimental and theoretical approaches. The discovery, preparation and study of new synthetic receptors for biologically interesting molecules and ions (especially anions) are our main activities. We also use supramolecular approaches to synthetic procedures, such as templated synthesis, dynamic combinatorial chemistry and constitutional dynamic chemistry. Additionally, we collaborate with several groups (both at IQAC and outside) to study biomolecular and biomimetic systems from a supramolecular point of view.

STAFF

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ARTICLES

Bioinspired chemistry based on minimalistic pseudopeptides

Luis, S.V.; Alfonso, I.

Acc. Chem. Res., 47, 112-124, **2014.**

Chiral imidazolium receptors for citrate and malate: The importance of the preorganization

Faggi, E.; Porcar, R.; Bolte, M.; Luis, S.V.; García-Verdugo, E.; Alfonso, I.

J. Org. Chem., 79, 9141-9149, **2014.**

Constitutional self-selection from dynamic combinatorial libraries in aqueous solution through supramolecular interactions

Solà, J.; Lafuente, M.; Atcher, J.; Alfonso, I.

Chem. Comm., 50, 4564-4566, **2014.**

Pseudopeptidic cages as receptors for N-protected dipeptides

Faggi, E.; Moure, A.; Bolte, M.; Vicent, C.; Luis, S.V.; Alfonso, I.

J. Org. Chem., 79, 4590-4601, **2014.**

Tight and selective caging of chloride ions by a pseudopeptidic host

Martí, I.; Bolte, M.; Burguete, M.I.; Vicent, C.; Alfonso, I.; Luis, S.V.

Chemistry Eur. J., 20, 7458-7464, **2014.**

Hafnia-Silica Cryogels: Solvent-Assisted Textural and Catalytic Control in the Citronellal Cyclization

Jimeno, C., Miras, J., Esquena, J.

ChemCatChem, 6, 2626-2633, **2014.**

Synthesis and characterization of 6β-hydroxyandrosterone and 6β-hydroxyetiocholanolone conjugated with glucuronic acid

Kotronoulas, A.; Fabregat, A.; Alfonso, I.; Parella, T.; Segura, J.; Ventura, R.; Joglar, J.; Pozo, O.J.

Drug Testing Anal., 7, 247-252, **2015.**

A quantitative 1H NMR approach for evaluating the metabolic response of Saccharomyces cerevisiae to mild heat stress

Puig-Castellví, F.; Alfonso, I.; Piña, B.; Tauler, R.

Metabolomics, 11, 1612- 1625, **2015.**

Copper(ii) complexes of macrocyclic and open-chain pseudopeptidic ligands: synthesis, characterization and interaction with dicarboxylates

Faggi, E.; Gavara, R.; Bolte, M.; Fajarí, L.; Juliá, L.; Rodríguez, L.; Alfonso, I.

Dalton Transactions, 44, 12700-12710, **2015.**

Highly stable oil-in-water emulsions with a gemini amphiphilic pseudopeptide

Lotfallah, A.H.; Burguete, M.I.; Alfonso, I.; Luis, S.V.

RSC Adv., 5, 36890-36893, **2015.**

Intramolecular hydrogen bonding guides a cationic amphiphilic organocatalyst to highly stereoselective aldol reactions in water

Valdivielso, A.M.; Catot, A.; Alfonso, I.; Jimeno, C.

RSC Adv., 5, 62331-62335, **2015.**

Salt-induced adaptation of a dynamic combinatorial library of pseudopeptidic macrocycles: Unraveling the electrostatic effects in mixed aqueous media

Atcher, J.; Moure, A.; Bujons, J.; Alfonso, I.

Chemistry Eur. J., 21, 6869-6878, **2015.**

Efficient synthesis of conformationally restricted apoptosis inhibitors bearing a triazole moiety

Corredor, M.; Garrido, M.; Bujons, J.; Orzáez, M.; Pérez--Payá, E.; Alfonso, I.; Messeguer, A.

Chemistry Eur. J., 21, 14122-14128, **2015.**

Dynamic assembly of a zinc-templated bifunctional organocatalyst in the presence of water for the asymmetric aldol reaction

Serra-Pont, A.; Alfonso, I.; Jimeno, C.; Solà, J.

Chem. Comm., 51, 17386-17389, **2015.**

Adaptive correction from virtually complex dynamic libraries: the role of non-covalent interactions in structural selection and folding

Lafuente, M.; Atcher, J.; Solà, J.; Alfonso, I.

Chem. Eur. J., 21, 17002-17009, **2015.**

Conformational promiscuity in triazolamers derived from quaternary amino acids mimics peptide behaviour

Solà, J.; Bolte, M.; Alfonso, I.

Org. Biomol. Chem., 13, 10797-10801, **2015.**

Restringint l'espai conformacional: pèptids helicoidals per la transmissió de quiralitat a distància (Constraining conformational space: helical peptides as conveyors of stereochemical informacion)

Solà, J

Revista de la Societat Catalana de Química., 14, 7-15, **2015.**

Stereoselective recognition of the Ac-Glu-Tyr-OH dipeptide by pseudopeptidic cages

Faggi, E.; Vicent, C.; Luis, S. V.; Alfonso, I.

Org. Biomol. Chem., 13, 11721-11731, **2015.**

RESEARCH PROJECTS

Moléculas pseudopeptídicas: sistemas complejos de receptor-huésped, auto-ensamblaje y química constitucional dinámica

Nacional, CTQ2012-38543-C03-03

2013-2015

Aproximaciones no convencionales a la catálisis asimétrica: de nanomateriales inorgánicos a enzimas artificiales

Nacional, CTQ2012-38594-C02-02

2013-2015

Dynamic constitutional chemistry for the preparation of receptors for anions of biological interest

CCEE, 321659

2012-2016

Catálisis biomimética dirigida entrópicamente

Nacional, CTQ2011-14528-E

2011-2014

Emergence and Evolution of Complex Chemical Systems (SYSCHEM)

Unión Europea, Cost Action CM 1304

2013-2017

Prolonged inhibition of semaphorin3a pathway via a bio-degradable implant towards a better therapy for visual sensory impairments (VISION)

Unión Europea, C-HEALTH/1444

2012-2015

CHEMometric and High-Throughput Omics Analytical Methods for Assessment of Global Change Effects on Environmental and Biological Systems (CHEMAGEB)

Unión Europea, ERC-AdG 320327 (Romà Tauler, IDAEA)

2013-2017

RESEARCH HIGHLIGHTS

The Supramolecular Chemistry group has successfully advanced in the different research lines related to Supramolecular Chemistry and Catalysis:

1) Supramolecular Chemistry studies. We have advanced in the field of ***molecular recognition***, working with pseudopeptidic hosts. Thus, we prepared large pseudopeptidic cages for the stereoselective molecular recognition of the Ac-Glu-Tyr-OH dipeptide in aqueous acetonitrile. We used the corresponding cages derived from Ser or Thr amino acids as hosts, and the four possible stereoisomers of the dipeptide as the guests. The binding phenomena both in the solution state (NMR) and also in the gas phase (ESI-MS) were studied. Overall, we observed similar stereoselective trends with the different techniques, which allowed us to propose a mode of binding (Figure 1A, *J. Org. Chem*., 79, 4590-4601, **2014** and *Org. Biomol. Chem*., 13, 11721-11731, **2015**).

We have also used macrocyclic and open-chain pseudopeptidic receptors for the preparation of metal complexes with one or two Cu(II) centers, being characterized by different experimental techniques (UV-vis spectroscopy, ESI-MS, NMR, EPR; FT-IR, X-Ray diffraction of single crystals). The complexes thus obtained were used as metalloreceptors of biologically relevant dicarboxylates, like malate, aspartate and glutamate (Figure 1B, *Dalton Transactions*, 44, 12700-12710, **2015**).

The syntheses and study of peptidomimetic species with a ***programmed folding***, the so-called foldamers, has been also accomplished. We have efficiently prepared triazolamers (oligomers where the amide bond has been replaced by a triazole) derived from quaternary amino acids, which mimic the conformational promiscuity of peptides both in solution and in the solid state (Figure 1C, *Org. Biomol. Chem*., 13, 10797-10801, **2015**).

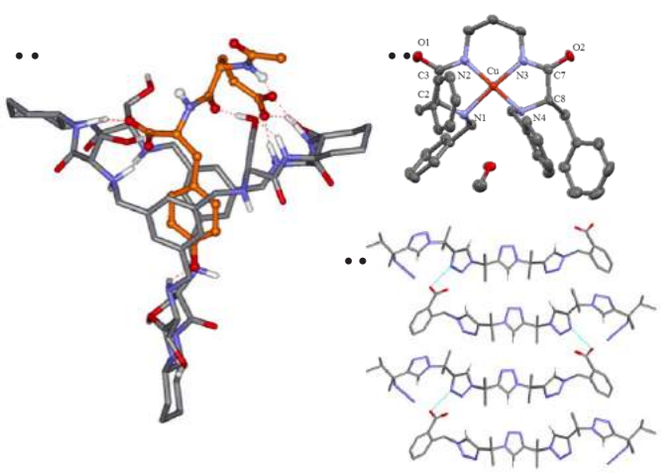

Figura 1

The research line dealing with the ***Dynamic Combinatorial Chemistry*** (DCC) studies also rendered fruitful results in this period of time. We have described the preparation and full description of a complex dynamic library of pseudopeptidic disulfide macrocycles bearing residues with different polarity and charged side chains (both positive and negative at the working pH). The library thus formed was able to respond to a simple though biologically relevant stimulus: the increase of salt concentration. The careful analysis of the evolution of the library and the dynamic deconvolution of the mixtures allowed understanding the driving force for the adaptive process. The whole system can be described by their corresponding exchange equilibrium constants and its knowledge permitted the design of tailored dynamic systems with either competitive of cooperative relationships between the members of the network (Figure 2A, *HOT paper* in *Chemistry Eur. J.*, 21, 6869-6878, **2015**).

Also within the field of DCC, we have studied the effect of mixing building blocks (BBs) with different valence in a disulfide-based dynamic library of pseudopeptides. Thus, we discovered that the mixture of bipodal and tripodal building blocks can generate a very complex mixture of species with different topology. The presence of a specific monopodal BB (cysteine) surprisingly simplified the library, rendering a virtually single species formed by the combination of the three BBs in a very stable molecule. The mechanism for the formation of this species has been carefully studied, showing the typical ***error correction pathway***. Moreover, the selected species has been fully characterized and the source for the observed selectivity studied by a combination of structural studies and a battery of control experiments. Overall, we concluded that the selection process occurred by the non-covalent interaction of the pendant cysteine with the macrocyclic pseudopeptide moiety. These interactions are polar in nature (H-bonding and salt-bridges) and are only possible with the zwitterionic form of the amino acid and in a folded conformation, a very remarkable result for a simple pseudopeptidic species in aqueous solution at a pH close to neutrality (Figure 2B, *Chem. Comm.*, 50, 4564-4566, **2014** and *Chem. Eur. J.*, 21, 17002-17009, **2015**).

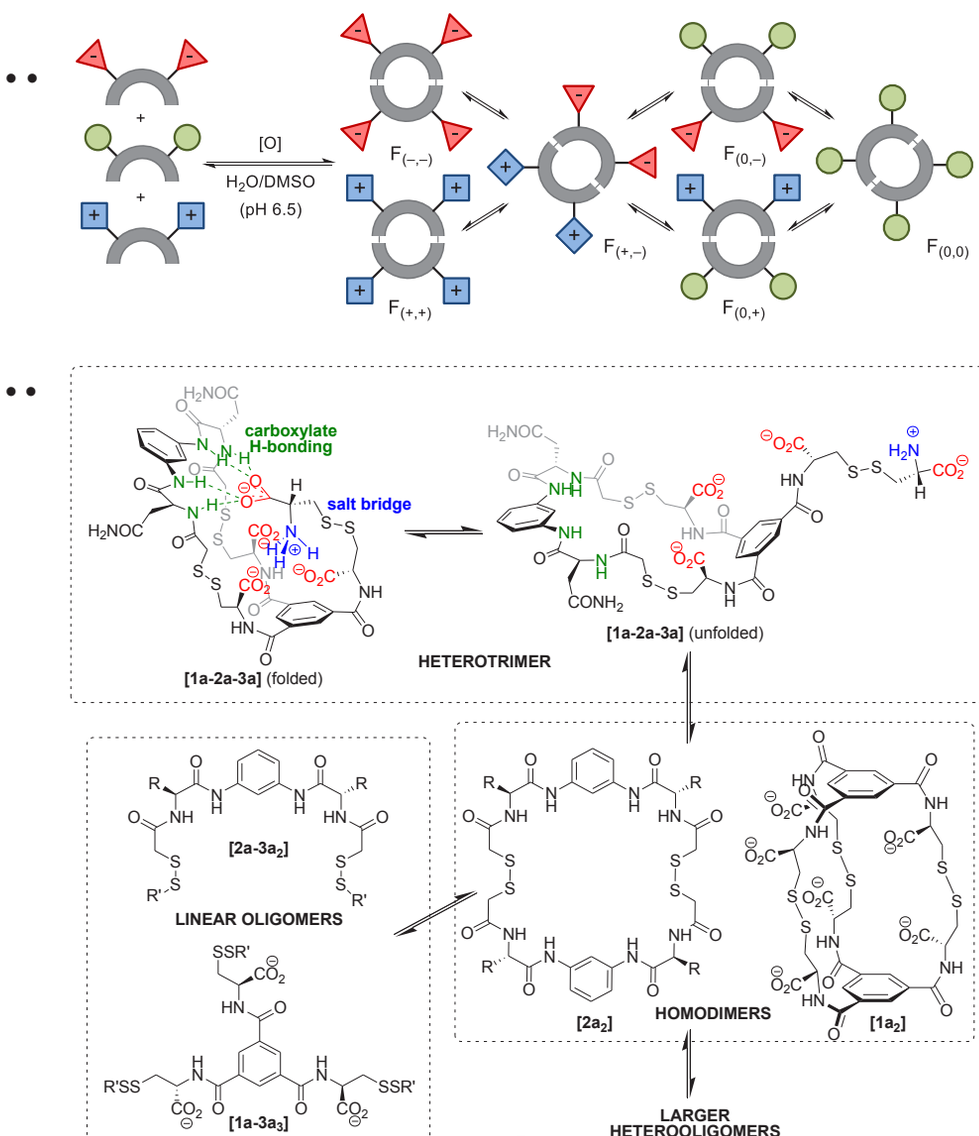

Figura 2

2) Catalysis studies: Our group has also advanced in the field of catalysis, by applying ***supramolecular concepts to the development of new organocatalytic species***. In a recent work, we have designed a novel amphiphilic guanidine organocatalyst, efficient for asymmetric aldol reactions of ketones in water at neutral pH. The reaction presented a clear substrate dependence depicting a free energy linear correlation with ee. The catalytic system is a self-assembled emulsion where an intramolecular hydrogen bonding in the acylguanidine moiety was identified as the key structural motif. Therefore the success of the system is due to a delicate combination of intermolecular (hydrophobic) and intramolecular (H-bonds) non-covalent interactions (Figure 3A, *RSC Adv*., 5, 62331-62335, **2015**).

We have also used the ***DCC concept for the discovery of new catalytic systems***. Thus, a bifunctional organocatalytic system consisting of simple pyridine ligands containing separate catalytic functionalities (prolinamide and thiourea) was assembled using ZnCl2. This novel metal-templated catalyst furnished high yields and stereoselectivities towards the aldol reaction. In our dynamic mixture of metal complexes, the addition of controlled amounts of water turned out to be crucial to dissolve the system and achieve optimal results. The importance of this work is that, to our knowledge, this is the first example of a metal templated organocatalyst of this type furnishing high yields and stereoselectivities for a variety of substrates in the aldol reaction. The potential applications of this type of catalysis are huge, ranging from the fast generation and screening of tailor-made asymmetric catalysts for particular substrates to the mechanistic understanding of the separate catalytic functions and comparison with biological systems (Figure 3B, *Chem. Comm.*, 51, 17386-17389, **2015**).

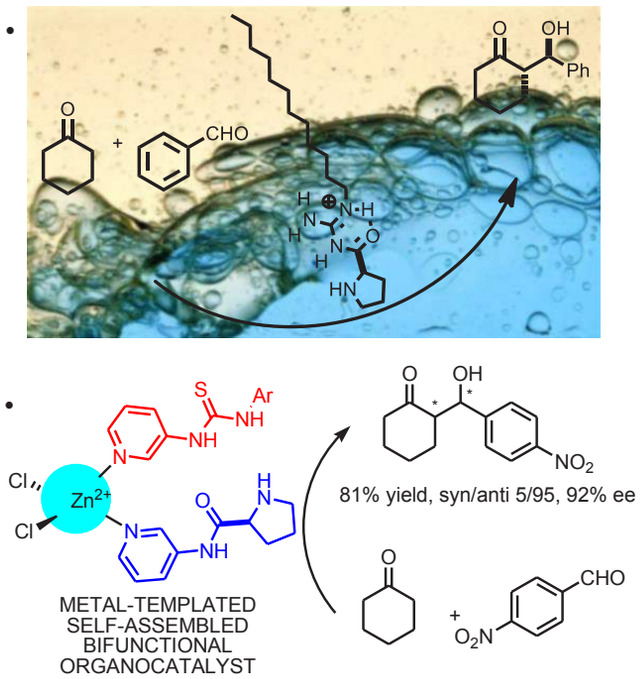

Figura 3

ECOLOGICAL CHEMISTRY GROUP

Our group deals with different aspects related with new insect pheromones, from structural characterization and synthesis of pheromones and analogues to determination of their attractant activity in the laboratory by electrophysiological techniques (electroantennogram and coupled gas chromatography-electroantennogram) and behavioral bioassays, as well as in the field. In addition, we are also involved in the development of new alternative, biorational and non-contaminant methods of pest control, based on inhibition of the enzymes responsible for the degradation of pheromone molecules at the insect's antennae.

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DAVID PÉREZ FITÉ
JUDIT ALTARRIBA FATSINI

ARTICLES

Cuticular and internal chemical composition of biting midges *Culicoides* spp. (Diptera: Ceratopogonidae), potential vectors of viral diseases

González, M.; López, S.; Rosell, G.; Goldarazena, A.; Guerrero, A.

Natural Product Comm., 9, 1103-1108, **2014.**

EAG responses increase of *Spodoptera littoralis* antennae after a single pheromone pulse

Quero, C.; Vidal, B.; Guerrero, A.

Natural Product Comm., 9, 1099-1101, **2014.**

Semiochemical and natural product-based approaches to control *Spodoptera* spp. (Lepidoptera: Noctuidae)

Guerrero, A.; Malo, E.A.; Coll, J.; Quero, C.

J. Pest Sci., 87, 231-247, **2014.**

Laboratory and field evaluations of chemical and plant-derived potential repellents against *Culicoides* biting midges in northern Spain

González, M.; Venter, G.J.; López, S.; Iturrondobeitia, J.C.; Goldarazena, A.

Med. Vet. Entomol., 28, 421-431, **2014.**

Caracterización y actividad de un posible componente de la feromona sexual de la langosta mediterránea *Dociostaurus maroccanus*

Fürstenau, B.; Muñoz, L.; Coca-Abia, M.; Rosell, G.; Guerrero A.; Quero, C.

Phytoma 264, 32-39, **2014**.

Aggressive mimicry coexists with mutualism in an aphid

Salazar, A.; Fürstenau, B.; Quero, C.; Pérez-Hidalgo, N.; Carazo, P.; Font, E.; Martínez-Torres, D.

Proc. Nat. Acad. Sci. USA, 112, 1101-1106, **2015.**

An improved and convenient new synthesis of the pheromone components of the tomato leafminer *Tuta absoluta*

Puigmartí, M.; Bosch, M.P.; Guerrero, A.

Synthesis, 47, 961-968, **2015.**

Biosynthetic infochemical communication

Olsson, S.B.; Challiss, R.A.J.; Cole, M.; Gardeniers, J.G.E.; Gardner, J.W.; Guerrero, A.; Hansson, B.S.; Pearce, T.C.

Bioinsp. Biomim., 10, 043001, **2015.**

Field trapping of the flathead oak borer *Coroebus undatus* (Coleoptera: Buprestidae) with different traps and volatile lures

Fürstenau, B.; Quero, C.; Riba, J.M.; Rosell, G.; Guerrero, A.

Insect Sci., 22, 139-149, **2015.**

Identification and characterization of a fatty acyl reductase from a *Spodoptera littoralis* female gland involved in pheromone biosynthesis

Carot-Sans, G.; Muñoz, L.; Piulachs, M.D.; Guerrero, A.; Rosell, G.

Insect Mol. Biol., 24, 82-92, **2015.**

New selective A_{2A} agonists and A_3 antagonists for human adenosine receptors: synthesis, biological activity and molecular docking studies

Rodríguez, A.; Guerrero, A.; Gutierrez-de-Terán, H.; Rodríguez, D.; Brea, J.; Loza, M.I.; Rosell, G.; Pilar Bosch, M.

Med. Chem. Commun., 6, 1178-1185, **2015.**

RESEARCH PROJECTS

Aproximación hacia un control de plagas de insectos de interés económico mediante disrupción de la comunicación química entre sexos

Nacional, AGL2012-39869-C02-01

2013-2015

Ayudas para apoyar las actividades de los grupos de investigación para el año 2009. Nombre del grupo: Unitat d'Ecologia Quimica (UCE)

Generalitat de Catalunya, 2009SGR871

2014-2016

Desarrollo y aplicación de compuestos atrayentes para el control biorracional de *Coroebus undatus* Fabricius

Junta de Andalucía, Proyectos de Investigación de Excelencia, RNM-7729

2013-2017

Obtención de atrayente para el control de moscas de la fruta de la especie *Bactrocera oleae* y de la especie *Rhagoletis cerasi*

Sociedad Española de Desarrollos Químicos (SEDQ), S.A.

2013-2016

Suministrament d'atraients d'aplicació a trampes pel control de *Coroebus undatus*

Generalitat de Catalunya

2014-2015

RESEARCH HIGHLIGHTS

Characterization of a fatty acyl reductase involved in the pheromone biosynthesis of *Spodoptera littoralis*

Fatty acyl-CoA reductases (FARs), the enzymes that catalyze reduction of a fatty acyl-CoA to the corresponding alcohol in insect biosynthesis, are postulated to play an important role in determining the proportion of each component in the pheromone blend. For the first time, we have isolated and characterized from the Egyptian cotton leaf worm *Spodoptera littoralis* (Lepidoptera: Noctuidae) a FAR cDNA (Slit-FAR1), which appeared to be expressed only in the pheromone gland and was undetectable in other female tissues such as fat body, ovaries, wings, legs or thorax. The encoded protein has been successfully expressed in a recombinant system, and the recombinant enzyme is able to produce the intermediate fatty acid alcohols of the pheromone biosynthesis of *S. littoralis* from the corresponding acyl-CoA precursors. The kinetic parameters K_m and V_{max}, which have been calculated for each acyl-CoA phero-

mone precursor, suggest that in *S. littoralis* pheromone biosynthesis other biosynthetic enzymes (desaturases, acetyl transferase,…) should also contribute to the final ratio of components of the pheromone blend. In a phylogenetic analysis, Slit-FAR1 appeared grouped in a cluster of other FARs involved in the pheromone biosynthesis of other insects with little or no-specificity for the natural pheromone precursors (Figure 1) (*Insect Mol. Biol*., 2015**)**.

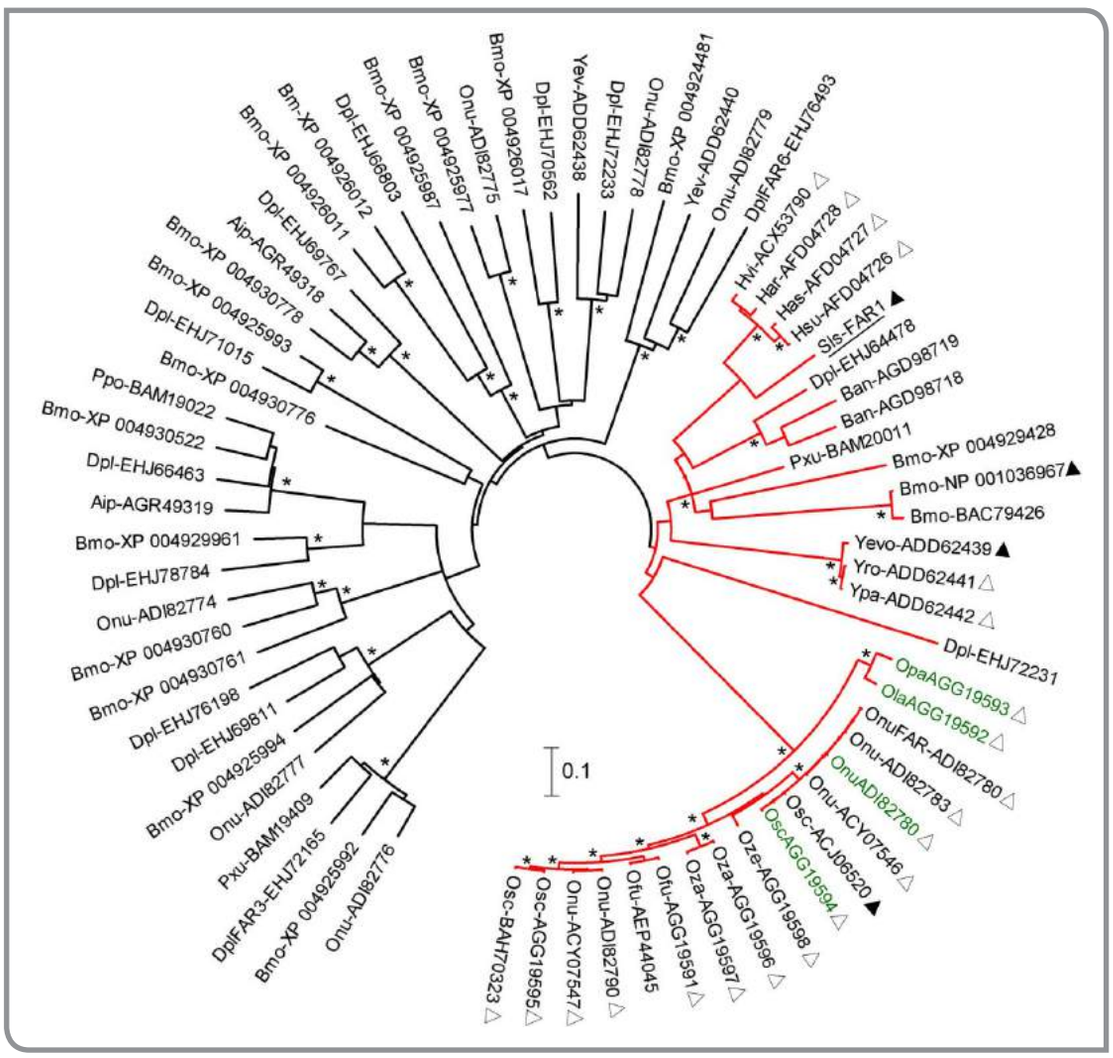

Figure 1. Phylogenetic analysis of lepidoptera FARs. Branches corresponding to the group of Slit-FAR1 (underlined) are in red. Functionally verified proteins are marked with a triangle (full triangle indicate also proven pheromone gland specificity) and FARs with substrate specificity are in green. Asterisks indicate a bootstrap value ≥ 90%.

Trapping of *Coroebus undatus*, an important pest of the cork oak

The cork oak *Quercus suber* is a valuable endemic plant of the western Mediterranean Basin producing annually ca. 340.000 tons of cork worth about 1.500 million US dollars. The most important use of cork is as stopper for premium wines with a production of approximately 13.000 million stoppers per year. The flathead oak borer *Coroebus undatus* (Coleoptera: Buprestidae) is one of the primary pests of the cork oak in the Mediterranean region causing great economic losses to the cork industry. Very little is known about its biology and behavior and, so far, no control measures have been established against this pest. In a 3-year field study aimed to develop an efficient trapping method for monitoring *C. undatus* population, we have found that purple-colored prism traps baited with a mixture of green leaf volatiles (GLVs) from the host (Figure 2) is the most effective combination to catch *C. undatus* adults (solely females) compared to other trap and lure types tested. Wavelength and reflectance measurements revealed that purple traps exhibit reflectance peak values similar to those found in the abdominal and elytral cuticle of both sexes, suggesting the involvement of visual cues for mate location in this species. Our data are the first to demonstrate captures of adults of the genus *Coroebus* by an attractant-based trapping method (*Insect Sci*., 2015**)**.

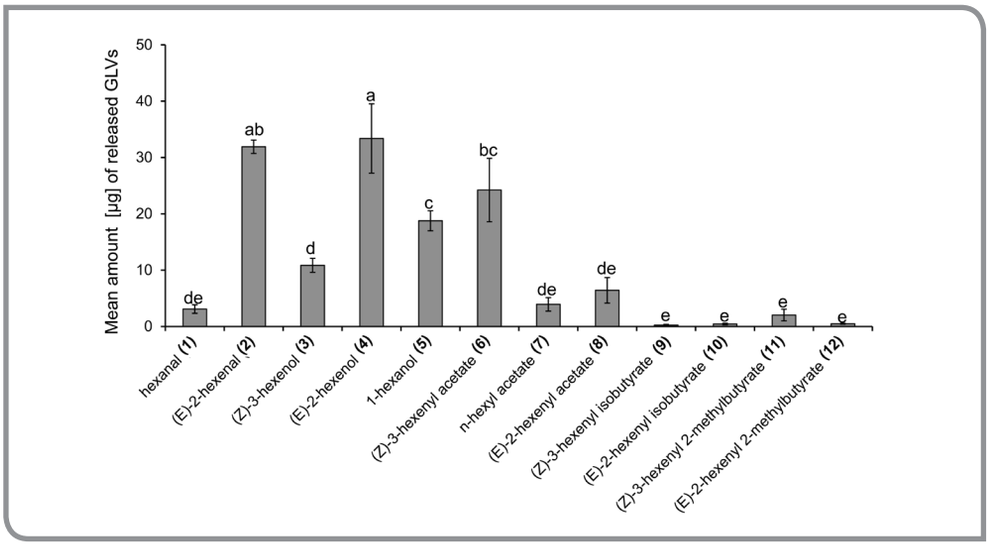

Figure 2. Mean amount (±SE) of GLVs identified from headspace volatiles released by freshly cut Q. suber branches and collected during 24 h.

This work represents an authentic breakthrough since it is the first time that formulations prepared in our laboratory have been used in the last few years by Forestal Catalana, a public company of the Generalitat de Catalunya, to control this pest in an environmentally friendly approach. In addition, similar formulations adsorbed in specific low-release dispensers prepared by SEDQ, S.A. have been used in Andalucia for the same purpose within the context of the project "Desarrollo y aplicación de compuestos atrayentes para el control biorracional de *Coroebus undatus* Fabricius**"** as Research project of Excellence by Junta de Andalucía.

New synthesis of the pheromone of the tomato pest *Tuta absoluta*

The tomato leafminer *Tuta absoluta* is one of the most devastating pests of tomato in South America, many European countries, North Africa and the Middle East. The female produces a pheromone (Figure 3) that has been used in monitoring and control of the pest. One of the main drawbacks of the pheromone is its high cost, particularly that of the triene, which limits its production and utilization in large scale. We have accomplished an improved new synthesis of both components of the pheromone **1, 2** in high overall yields (30% for the major compound and 23% for the minor component) and stereoselectivity (E,Z,Z 97% for the major and E,Z 99% for the minor). The new approaches compare favorably with others previously reported (*Synthesis*, 2015).

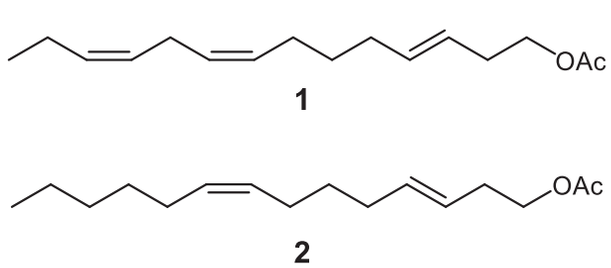

Figure 3. Structures of the major (**1**) and minor (**2**) components of the pheromone of *Tuta absoluta*

THEORETICAL AND COMPUTATIONAL CHEMISTRY

The Theoretical and Computational Chemistry Group (QTC) studies the structure and reactivity of molecules using the computational methods of Theoretical Chemistry. Special interest is devoted to two main areas:

- Oxidation reactions playing an important role in atmospheric and environmental chemistry, as well as in biological systems
- Protein dynamics, with special interest in enzyme catalysis, thermostability, and Intrinsically Disordered Proteins.

STAFF

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PH. D. STUDENTS

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SUSANA BARRERA VILARMAU

ARTICLES

Unexpected Reactivity of Amidogen Radical in the Gas Phase Degradation of Nitric Acid.

Josep M Anglada, Santiago Olivella, Albert Solé

J. Am. Chem. Soc**., 136,** 6834-6837, **2014**

DOI: 10.1021/ja501967x

Effect of the Meso-Substituent in the Huckel-to-Mobius Topological Switches.

E. Marcos, J.M. Anglada, M Torrent-Sucarrat

REF. REVISTA: J. Org. Chem., ***79,*** 5036-5046, **2014**

DOI: 10.1021/jo500569p

Mechanistic Studies on the Intramolecular Cyclization of O-Tosyl Phytosphingosines to Jaspines.

R. Crehuet, D. Mormeneo, J.M. Anglada, A. Delgado.

Nat. Prod. Commun., **9,** 1087-1090, **2014**.

Spectroscopic signatures of ozone at the air-water interface and photochemistry implications.

J.M. Anglada, M. Martins-Costa, M.F. Ruiz-López, J.S. Francisco.

Proc. Natl. Acad. Sci.., **111,** 11618-11693 **2014**.

DOI: 10.1073/pnas.1411727111

Atmospheric formation of the NO_3 radical from gas-phase reaction of HNO_3 acid with the NH_2 radical: proton-coupled electron-transfer versus hydrogen atom transfer mechanisms.

Josep M Anglada, Santiago Olivella, Albert Solé.

Phys. Chem. Chem. Phys., **16,** 19437-19445, **2014.**

DOI:10.1039/c4cp02792b.

Application of the Maximum Entropy Principle to Determine Ensembles of Intrinsically Disordered Proteins from Residual Dipolar Couplings

Sanchez-Martinez, M.; Crehuet, R..

Phys. Chem. Chem. Phys., 16, 26030–26039, **2014**.

Interconnection of Reactive Oxygen Species Chemistry across the Interfaces of Atmospheric, Environmental, and Biological Processes.

Josep M. Anglada, Marilia Martins-Costa, Joseph S. Francisco, and Manuel F. Ruiz-López.

Acc. Chem. Res., **48**, 575-583, **2015**.
DOI: 10.1021/ar500412p

Structure of hydrogen tetroxide in gas phase and in aqueous environments: relationship to the hydroperoxyl radical self-reaction.

M.T.C. Martins-Costa, J. M. Anglada, and M. F. Ruiz-López.

Struct. Chem.
DOI: 10.1007/s11224-015-0717-2.

Enzymatic Minimum Free Energy Path Calculations Using Swarms of Trajectories.

Sanchez-Martinez, M.; Field, M.; Crehuet, R.

J. Phys. Chem. B, 119, 1103–1113, **2015**.

Mechanism of the Glycosidic Bond Cleavage of Mismatched Thymine in Human Thymine DNA Glycosylase Revealed by Classical Molecular Dynamics and Quantum Mechanical/Molecular Mechanical Calculations.

Kanaan, N.; Crehuet, R.; Imhof, P.
J. Phys. Chem. B, 119, 12365–12380, **2015**.

BOOK CHAPTERS

Interplay between Enzyme Function and Protein Dynamics: A Multiscale Approach to the Study of the NAG Kinase Family and Two Class II Aldolases.

Marcos, E.; Sanchez-Martinez, M.; Crehuet, R.

Computational Approaches to Protein Dyanmics; Fuxreiter, M., Ed.; CRC Press, 2015; pp. 127–149.

PROJECTS AND CONTRACTS

Descripción de proteínas intrínsecamente desordenadas mediante la integración de datos de RMN y SAXS a simulaciones coarse grained

Nacional, CTQ2012-33324
24.570 euros
2013-2015

Estudio teórico de reacciones de oxidación iniciadas por HO, O3 y NO3

Nacional, CTQ2011-27812
72.600 euros
2010-2014

Especies Reactivas de Oxígeno: De la fase gas a la interfase aire-agua y la disolución acuosa.

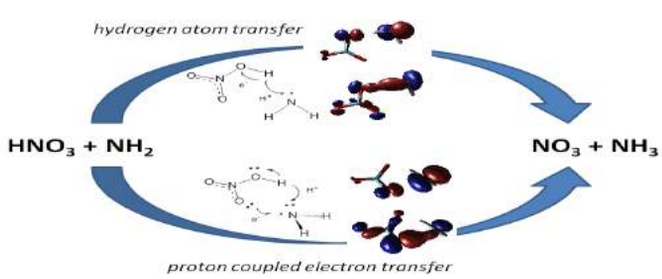
Nacional: CTQ2014-59768-P
2015-2017

RESEARCH HIGHLIGHTS

Ammonia and nitric acid contribute to the formation of a new atmospheric *catalytic cycle*

Ammonia (NH_3) and nitric acid (HNO_3) are among the most important species in the Earth's atmosphere and play an important role in the atmospheric gas phase, in heterogeneous chemistry and in the formation of aerosols.

Along with this investigation we have disclosed that amidogen radical can also oxidize nitric acid, in a process that takes place through a proton coupled electron transfer mechanism. The results of our calculations suggest that in those atmospheric conditions where the concentration of ammonia is greater than the concentration of nitric acid, hydroxyl radical should preferentially oxidize ammonia, and the formed amidogen radical contributes to the atmospheric degradation of nitric acid. Our findings also allow us to propose a new atmospheric catalytic-like cycle in which ammonia is oxidized by OH radical to form NH_2, radical and then amidogen radical further reacts with nitric acid yielding nitrate radical and regenerating ammonia. (J. Am. Chem. Soc., **2014**, ***136***, 6834-6837; Phys. Chem. Chem. Phys., **2014**, ***16***, 19437-19445

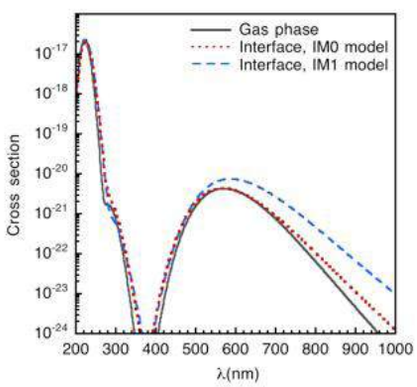


Ozone photochemistry at the air-water interface enhances the formation of hydroxyl radicals.

Ozone plays a dual role in the atmosphere. In the stratosphere it prevents harmful UV radiation from reaching the Earth's surface, thus protecting living organism, but in the troposphere act as a pollutant.

The photochemistry of ozone is an important source of hydroxyl radicals, which are key to the chemistry of the atmosphere. Ozone exhibits an affinity for the air-water interface, which modifies its UV-Vis spectra and photolytic rate constants. This modification, combined with the potential contribution of the O3 + hν ⟶ O(3P) + O2(X3Σg-) photolytic channel at the interface, leads to an enhancement of the OH radical formation rate by almost four orders of magnitude. These results suggest that clouds can influence the overall oxidizing capacity of the troposphere on a global scale by stimulating the production of OH radicals through ozone photolysis at the air-water interface. (Proc. Natl. Acad. Sci.., 2014, 111, 11618-11693.)

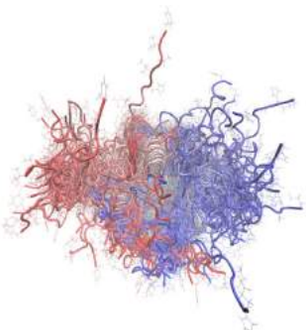
Interconnection of Reactive Oxygen Species Chemistry across the Interfaces of Atmospheric, Environmental, and Biological Processes



Oxidation reactions are among the most fundamental processes in nature and are related to reactive oxygen species (ROS) such as ozone, hydrogen peroxide and hydrogen polyoxides, as well as the associated hydroperoxide radicals, HO_n, and the superoxide and ozonide anions, O_2^- and O_3^-. These species are involved in the chemistry of the atmosphere and are responsible for maintaining the troposphere clean, but they also play an important role in environmental processes, where are used in pollutant abatement, and also in biological systems originating oxidative stress and consequently cell damage. This review examines the common chemistry connection. Of ROS in these different areas and provide thermodynamic and other physico-chemical properties in gas phase and water solution for the main species are discussed. (Acc. Chem. Res., **2015**, ***48***, 575-583.)

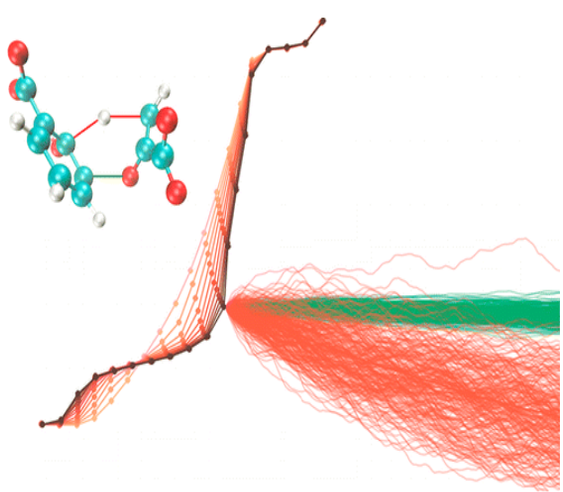
Fitting simulated structures of Intrinsically Disordered Proteins to experimental data

Intrinsically Disordered Proteins (IDPs) do not fold into stable structures, and they have to be represented by a large ensemble of conformations. Modelling these conformations is tough, because subtle changes in the environment, as well as small errors in the force fields, result in relevant population shifts. Because NMR provides tools to characterize IDPs in solution, we have developed a method available as an open-source software that fits simulated ensembles to NMR data. The software is written in Python and the algorithm is based on the Maximum Entropy Principle. Application of this method to a virus protein revealed the importance of an initial good modelling, as the NMR data is not able to fully determine the structural properties of the IDPs conformations in the ensemble . (*Phys. Chem. Chem. Phys.*, **2014**, *47*, 26030-26039)



Enzymatic Minimum Free Energy Paths

The calculation of reaction paths remains the best computational tool to determine enzymatic reaction mechanisms. Steps that go through low free energy barriers are to be preferred, but free energies are determined by both enthalpy and entropy. These calculations are difficult to perform when the reaction coordinate that defines the mechanism is complex, a common situation in enzymes. We have implemented a method based on Roux's Swarms of Trajectories that works for any reaction path, simply defined by the initial and final structures. We implemented this method in the pDynamo library so that it can now be applied with hybrid QM/MM calculations. (*J. Phys. Chem. B*, **2015**, *119*, 1103-1113)



BIOORGANIC CHEMISTRY GROUP

We employ the modern medicinal chemistry techniques (combinatorial chemistry, in silico design and construction of chemical libraries, solid phase synthesis, drug delivery methods) for the identification of hit compounds against targets of pharmacological interest. Complementarily, the chemical modulation of these hits for their conversion into lead compounds for further development in collaboration with pharma and biotech companies has been intensively pursued.

STAFF

ANGEL MESSEGUER PEYPOCH, GROUP LEADER

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TECHNICIANS

CRISTIAN LASTRE
CECILIA DOMINGO

PH. D. STUDENTS

LAURA VAZQUEZ
MIQUEL VIDAL MOSQUERA

ARTICLES

Apaf-1 inhibitors protect from unwanted cell death in In vivo models of kidney ischemia and chemotherapy induced ototoxicity

Orzáez, M.; Sancho, M.; Marchán, S.; Mondragón, L.; Montava, R.; Valero, J.G.; Landeta, O.; Basañez, G.; Carbajo, R.J.; Pineda-Lucena, A.; Bujons, J.; Moure, A.; Messeguer, A.; Lagunas, C.; Herrero, C.; Pérez-Payá, E.

PLoS ONE, 9, e110979**, 2014**.

Effect of triazine derivatives on neuronal nicotinic receptors

Vázquez-Romero, A.; Criado, M.; Messeguer, A.; Vidal-Mosquera, M.; Mulet, J.; Sala, F.; Sala, S.

ACS Chem. Neuroscience, 5, 683-689, **2014**.

Synthesis, biological evaluation and structure-activity relationships of new quinoxaline derivatives as anti-Plasmodium falciparum agents

Gil, A.; Pabón, A.; Galiano, S.; Burguete, A.; Pérez-Silanes, S.; Deharo, E.; Monge, A.; Aldana, I.

Molecules, 19, 2166-2180, **2014**.

Positional Scanning Synthesis of a Peptoid Library Yields New Inducers of Apoptosis that Target Karyopherins and Tubulin

Vendrell-Navarro, G.; Rúa, F.; Bujons, J.; Brockmeyer, A.; Janning, P.; Ziegler, S.; Messeguer, A.; Waldmann, H.

Chembiochem, 16, 1580-1587, **2015**.

Inhibitory effect of positively charged triazine antagonists of prokineticin receptors on the transient receptor vanilloid type-1 (TRPV1) channel

De Petrocellis, L.; Schiano Moriello, A.; Byun, J.S.; Sohn, J.M.; Lee, J.Y.; Vázquez-Romero, A.; Garrido, M.; Messeguer, A.; Zhang, F.-X.; Zamponi, G.W.; Deplano, A.; Congiu, C.; Onnis, V.; Balboni, G.; Di Marzo, V.

Pharmacol. Res., 99, 362-369, **2015**.

Efficient synthesis of conformationally restricted apoptosis inhibitors bearing a triazole moiety.
Corredor, M., Garrido, M. Bujons, J., Orzáez, M., Sancho, M., Pérez-Payá, E., Alfonso, I., Messeguer, A. .
Chem. Eur J., **2015**, *21*, 14122-14128.

Apaf-1 inhibition protect cells recovery from apoptosis

Gortat, A., Sancho, M., Mondragón, L., Messeguer, A., Pérez-Payá, E., Orzaez, M.

Protein & Cell, 6(11), 833-843 **2015**

En el vintè aniversari de la Conferència Fèlix Serratosa.

Messeguer, A.

Revista de la Societat Catalana de Química, **2015**, no. 14, 55-65.

PROJECTS AND CONTRACTS

Prolonged inhibition of semaphorin3a pathway via a bio-degradable implant towards a better therapy for visual sensory impairments

CCEE, 304884

2012-2015

Modulación química de rutas de señalización celular relevantes en enfermedades degenerativas: generación de cabezas de serie

Nacional, SAF2011-30542-C02-01

2012-2014

Consolider ingenio 2010: equipo de investigacion "the spanish ion channel initative (sici) para investigación.

2008-2014

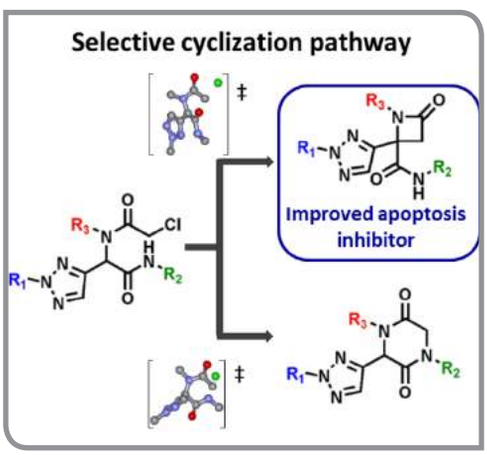
Diseño y síntesis de análogos químicos de proteínas Ras descubiertos por Allinky

Contrato con la empresa "Allinky Biopharma"

2011-2016

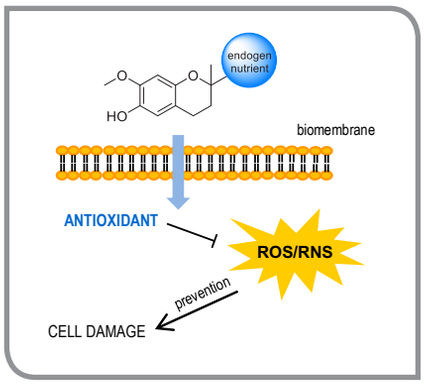
RESEARCH HIGHLIGHTS

1. Apoptosis modulators. We have developed the third and fourth generation of potential apoptosis inhibitors trying to restrict the conformational freedom of previous families and then improve their activity and selectivity. The syntheses of these restricted analogues have been carried out through an Ugi multicomponent reaction followed by an intramolecular cyclization. The unexpected formation of a beta-lactam scaffold led us to study the course of the intramolecular cyclization of the Ugi adducts.



Among these beta-lactam derivatives we identified compounds exhibiting higher apoptosis inhibitory activity in comparison with our previous hits (collaboration with the group of Dr. Mar Orzáez, Centro Prìncipe Felipe, Valencia). A collaboration with Dr. Mario Adrián Ramos (Fundación Jiménez Diaz, Madrid), to study the activity of selected members of this collection (in some cases coupled to models of therapeutic polymers) in models of renal diseases, is also in due course. More recently, the design and development of apoptosis inducers, also in collaboration with the group of Dr. Mar Orzáez, has led to the identification of initial hit compounds bearing a novel chemical structure.

2. Antioxidants and neuroprotection agents. A library of CR-6 (an antioxidant discovered in our laboratory) derivatives directed to identify compounds capable of crossing the blood brain barrier (BBB) more effectively than the parent compound, has been designed and synthesized. The ability of the components of this library to preserve the antioxidant activity of CR-6 has been confirmed by in vitro and ex-vivo assays. In addition, compounds have not exhibited toxicity. In vivo assays addressed to identify components of this library that cross the BBB are in due course.



On the other hand, in close collaboration with the group of Prof. Diego Muñoz-Torrero of the Faculty of Pharmacy of the University of Barcelona, we have synthesized a collection of hybrid compounds containing selectd CR-6 derivatives attached to highly active acetylcholinesterase inhibitors. These compounds are addressed to tackle pharmacological targets related to Alzheimer disease. A wide variety of in vitro and ex-vivo assays are also in due course.

3. Collaboration with pharma companies. We highlight the collaboration with Allinky Biopharma, a small biotech company located in Madrid, focused in the development of compounds for the treatment of cancer and of inflammatory diseases. Our group has supervised the medicinal chemistry approaches addressed to the identification of lead compounds. Likewise, we have completed the chemical design and preparation, in close collaboration with the group of Prof. Balbino Alarcón (Centro de Biología Molecular Severo Ochoaa, CSIC) of a lead compound addressed to the treatment of immunodiseases. This compound has been licensed to a pharma company and its pharmaceutical development is in due course. Finally, we have continued our collaboration with Bionure, S.L. for the development of a compound discovered in our group and licensed to this company for the treatment of autoimmune diseases.

DEPARTMENT OF BIOMEDICINAL CHEMISTRY

DEPARTMENT OF BIOMEDICINAL CHEMISTRY

Head: Amadeu Llebaria Soldevila

The Department of Biomedicinal Chemistry is focused in multidsciplinar research involving chemical methods and bioactive molecules. The projects focus on peptides, lipids and glycoconjugates as well as chemical approaches for small molecule therapeutics. The investigations encompass the rational design of active molecules in metabolic pathways, glycolipids and sphingolipids, and therapies for transthyretin amyloidosis , pain or articular diseases. Some new chemical techniques for molecule design and synthesis are combined with computational, biological and analytical expertise and instrumental techniques to define a collective of researchers working in the interface of chemistry and biology with a wide perspective and singular cooperativity with external groups.

RESEARCH GROUPS

- Research Unit on BioActive Molecules
- Synthesis and Biomedical Applications of Peptides
- Unit of Glycoconjugate Chemistry
- Chemical Biology
- Medicinal Chemistry

RESEARCH UNIT ON BIOACTIVE MOLECULES

The Research Unit on BioActive Molecules works on the discovery of small molecules with activity on biologically relevant processes, with special interest on sphingolipid metabolism and functions. Sphingolipids play essential roles in the outcome and progression of diseases, including both rare diseases (sphingolipidosis) and diseases of high socio-economic impact (cancer, infectious diseases, diabetes 2, neurodegenerative diseases, etc.) thereby providing attractive targets to develop tools of use in diagnosis and prognosis, and leads in drug discovery. The research conducted encompasses from the design and synthesis of molecules and libraries to their biological study in cell lines, including sphingolipidomics.

STAFF

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INGRID NIEVES CALATRAVA
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MIREIA CASASAMPERE
POL SANLLEHÍ FIGUEROLA
ANA PAU CABELLO
RAQUEL CALDERON ALMENDRO

PUBLICATIONS (ARTICLES)

Acid sphingomyelinase determines melanoma progression and metastatic behaviour via the microphtalmia-associated transcription factor signalling pathway

Bizzozero, L.; Cazzato, D.; Cervia, D.; Assi, E.; Simbari, F.; Pagni, F.; De Palma, C.; Monno, A.; Verdelli, C.; Querini, P.R.; Russo, V.; Clementi, E.; Perrotta, C.

Cell Death Differentiation 21, 507-523, **2014.**

Anti-inflammatory action of lipid nanocarrier-delivered myriocin: Therapeutic potential in cystic fibrosis

Caretti, A.; Bragonzi, A.; Facchini, M.; De Fino, I.; Riva, C.; Gasco, P.; Musicanti, C.; Casas, J.; Fabriàs, G.; Ghidoni, R.; Signorelli, P.

Biochim. Biophys. Acta (General subjects), 1840, 586-594, **2014.**

Characterization of complex lipid mixtures in contaminant exposed JEG-3 cells using liquid chromatography and high-resolution mass spectrometry

Gorrochategui, E.; Casas, J.; Perez-Albaladejo, E.; Jauregui, O.; Porte, C.; Lacorte, S.

Environ. Sci. Pollution Res., 21, 11907-11916, **2014.**

Inhibition of dihydroceramide desaturase activity by the sphingosine kinase inhibitor SKI II

Cingolani, F.; Casasampere, M.; Sanllehí, P.; Casas, J.; Bujons, J.; Fabrias, G.

J. Lipid Res., 55, 1711-1720, **2014.**

Molecular cloning and knockdown of galactocerebrosidase in zebrafish: New insights into the pathogenesis of Krabbe's disease

Zizioli, D.; Guarienti, M.; Tobia, C.; Gariano, G.; Borsani, G.; Bresciani, R.; Ronca, R.; Giacopuzzi, E.; Preti, A.; Gaudenzi, G.; Belleri, M.; Di Salle, E.; Fabrias, G.; Casas, J.; Ribatti, D.; Monti, E.; Presta, M.

Biochim. Biophys. Acta - Molecular Basis of Disease, 1842, 665-675, **2014.**

On-tissue localization of ceramides and other sphingolipids by MALDI mass spectrometry imaging

Jones, E.E.; Dworski, S.; Canals, D.; Casas, J.; Fabrias, G.; Schoenling, D.; Levade, T.; Denlinger, C.; Hannun, Y.A.; Medin, J.A.; Drake, R.R.

Anal. Chem., 86, 8303-8311, **2014.**

Glucocerebrosidase enhancers for selected gaucher disease genotypes by modification of alpha;-1-C-substituted Imino- D -xylitols (DIXs) by click chemistry

Serra-Vinardell, J.; Díaz, L.; Casas, J.; Grinberg, D.; Vilageliu, L.; Michelakakis, H.; Mavridou, I.; Aerts, J.M.F.G.; Decroocq, C.; Compain, P.; Delgado, A.

ChemMedChem, 9, 1744-1754, **2014.**

Long-term increased carnitine palmitoyltransferase 1A expression in ventromedial hypotalamus causes hyperphagia and alters the hypothalamic lipidomic profile

Mera, P.; Mir, J.F.; Fabriàs, G.; Casas, J.; Costa, A.S.H.; Malandrino, M.I.; Fernández-López, J.-A.; Remesar, X.; Gao, S.; Chohnan, S.; Rodríguez-Peña, M.S.; Petry, H.; Asins, G.; Hegardt, F.G.; Herrero, L.; Serra, D.

PLoS ONE, 9, **2014.**

Perfluorinated chemicals: Differential toxicity, inhibition of aromatase activity and alteration of cellular lipids in human placental cells

Gorrochategui, E.; Pérez-Albaladejo, E.; Casas, J.; Lacorte, S.; Porte, C.

Toxicol. Applied Pharmacol., 277, 124-130, **2014.**

Selective chaperone effect of aminocyclitol derivatives on G202R and other mutant glucocerebrosidases causing Gaucher disease

Serra-Vinardell, J.; Díaz, L.; Guitiérrez-De Terán, H.; Sánchez-Ollé, G.; Bujons, J.; Michelakakis, H.; Mavridou, I.; Aerts, J.M.F.G.; Delgado, A.; Grinberg, D.; Vilageliu, L.; Casas, J.

Int. J. Biochem. Cell Biol., 54, 245-254, **2014.**

The composition of West Nile virus lipid envelope unveils a role of sphingolipid metabolism in flavivirus biogenesis

Martín-Acebes, M.A.; Merino-Ramos, T.; Blázquez, A.-B.; Casas, J.; Escribano-Romero, E.; Sobrino, F.; Saiz, J.-C.

J. Virol., 88, 12041-12054, **2014.**

Evaluation of the phototransformation of the antiviral zanamivir in surface waters through identification of transformation products

Zonja, B.; Gonçalves, C.; Pérez, S.; Delgado, A.; Petrovic, M.; Alpendurada, M.F.; Barceló, D.

J. Hazardous Mat., 265, 296-304, **2014.**

Mechanistic studies on the intramolecular cyclization of O-tosyl phytosphingosines to jaspines

Crehuet, R.; Mormeneo, D.; Anglada, J.M.; Delgado, A.

Nat. Product Comm., 9, 1087-1090, **2014.**

Simultaneous determination of diclofenac, its human metabolites and microbial nitration/nitrosation transformation products in wastewaters by liquid chromatography/quadrupole-linear ion trap mass spectrometry

Osorio, V.; Imbert-Bouchard, M.; Zonja, B.; Abad, J.-L.; Pérez, S.; Barceló, D.

J. Chrom.. A, 1347, 63-71, **2014.**

Structure elucidation of phototransformation products of unapproved analogs of the erectile dysfunction drug sildenafil in artificial freshwater with UPLC-Q Exactive-MS

Aceña, J.; Pérez, S.; Gardinali, P.; Abad, J.-L.; Eichhorn, P.; Heuett, N.; Barceló, D.

J. Mass Spectrometry, 49, 1279-1289, **2014.**

A straightforward synthesis of the CERT inhibitor (1' R,3' S)-HPA-12

Abad, J.-L.; Armero, I.; Delgado, A.

Tetrahedron Lett., 56, 1706-1708, **2015.**

Azide-tagged sphingolipids: New tools for metabolic flux analysis

Garrido, M.; Abad, J.-L.; Fabriàs, G.; Casas, J.; Delgado, A.

Chembiochem, 16, 641-650**, 2015.**

Chemometric strategy for untargeted lipidomics: Biomarker detection and identification in stressed human placental cells

Gorrochategui, E.; Casas, J.; Porte, C.; Lacorte, S.; Tauler, R.

Anal. Chim. Acta, 854, 20-33, **2015.**

Coordinated regulation of the orosomucoid-like gene family expression controls de novo ceramide synthesis in mammalian cells

Kiefer, K.; Carreras-Sureda, A.; García-López, R.; Rubio--Moscardó, F.; Casas, J.; Fabriàs, G.; Vicente, R.

J. Biol. Chem., 290, 2822-2830, **2015.**

Obesogens beyond vertebrates: Lipid perturbation by tributyltin in the crustacean Daphnia magna

Jordão, R.; Casas, J.; Fabrias, G.; Campos, B.; Piña, B.; Lemos, M.F.L.; Soares, A.M.V.M.; Tauler, R.; Barata, C.

Environ. Health Perspect., 123, 813-819, **2015.**

Efficacy of AdiDetox in reducing the toxicity of fumonisin B1 in rats

Denli, M.; Blandon, J.C.; Salado, S.; Guynot, M.E.; Casas, J.; Pérez, J.F.

Food Chem. Toxicol., 78, 60-63, **2015.**

New oleyl glycoside as anti-cancer agent that targets on neutral sphingomyelinase

Romero-Ramírez, L.; García-Álvarez, I.; Casas, J.; Barreda-Manso, M.A.; Yanguas-Casás, N.; Nieto-Sampedro, M.; Fernández-Mayoralas, A.

Biochem. Pharmacol., 97, 158-172, **2015.**

Fluorescent polyene ceramide analogues as membrane probes

Nieves, I.; Artetxe, I.; Abad, J.-L.; Alonso, A.; Busto, J.V.; Fajarí, L.; Montes, L.R.; Sot, J.; Delgado, A.; Goñi, F.M.

Langmuir, 31, 2484-2492, **2015.**

LC-HRMS suspect screening for detection-based prioritization of iodinated contrast media photodegradates in surface waters

Zonja, B.; Delgado, A.; Pérez, S.; Barceló, D.

Environ. Sci. Technol., 49, 3464-3472, **2015.**

Myristic acid potentiates palmitic acid-induced lipotoxicity and steatohepatitis associated with lipodystrophy by sustaining de novo ceramide synthesis

Martínez, L.; Torres, S.; Baulies, A.; Alarcón-Vila, C.; Elena, M.; Fabriàs, G.; Casas, J; Caballeria, J; Fernandez--Checa, J.C.; García-Ruiz, C.

Oncotarget 6, 41479-96, **2015.**

Activity of neutral and alkaline ceramidases on fluorogenic N-acylated coumarin-containing aminodiols.

Casasampere, M.; Camacho, L.; Cingolani, F.; Casas, J.; Egido-Gabás, M.; Abad, J.-L.; Bedia, C.; Xu, R.; Wang, K.; Canals, D.; Hannun, Y.-A.; Mao, C.; Fabrias, G.

J Lipid Res. 56, 2019-28, **2015.**

Natural grape extracts regulate colon cancer cells malignancy.

Signorelli, P.; Fabiani, C.; Brizzolari, A.; Paroni, R.; Casas, J.; Fabriàs, G.; Rossi, D.; Ghidoni, R.; Caretti, A.

Nutr Cancer 67, 494-503, **2015.**

Modification of the Host Cell Lipid Metabolism Induced by Hypolipidemic Drugs Targeting the Acetyl Coenzyme A Carboxylase Impairs West Nile Virus Replication.

Merino-Ramos, T.; Vázquez-Calvo, Á.; Casas, J.; Sobrino, F.; Saiz, J.C.; Martín-Acebes, M.A.

Antimicrob Agents Chemother. 60, 307-15, **2015.**

BOOK CHAPTERS

Nieves, I.; Sanllehí, P.; Abad, J.-L; Fabriàs, G.; Casas, J.; Delgado. A.

Chemical Probes of Sphingolipid Metabolizing Enzymes. In *Bioactive Sphingolipids in Cancer Biology and Therapy.* Yusuf A. Hannun, Chiara Luberto, Cungui Mao, Lina Marie Obeid (Eds.) pp 437-470 Springer International Publishing Switzerland 2015.

REASEARCH PROJECTS

Dihidroesfingolipidos y autofagia en cáncer. Vías metabólicas y mecanismos moleculares implicados en la respuesta de las células tumorales a fármacos inductores de autofagia.

Nacional, SAF2011-22444

2012-2014

Ayudas para apoyar las actividades de los grupos de investigación para el año 2009. Nombre del grupo: Research unit on bioactive molecules (RUBAM)

Generalitat de Catalunya, 2009SGR1072

2009-2014

Esfingolípids com a diana per a la recuperació de les lesions de la medul.la espinal: el paper de la esfingosina-1-fosfat

Fundació La Marato de TV3, 112130

2012-2015

Esfingolípids com a diana per a la recuperació de les lesions de la medul.la espinal: el paper de la esfingosina-1-fosfat

Fundació La Marato de TV3, 112132

2012-2015.

Chemometric and High-Throughput Omics Analytical Methods for Assessment of Global Change Effects on Environmental and Biological Systems

European Research Council (ERC), 32073

2014-2019

Transautophagy: European Network of Multidisciplinary Research and Translation of Autophagy Knowledge

European Union (COST Action), CA15138

2015-2017

Knowing the enemy: a mechanistic approach to fight against OPIDN

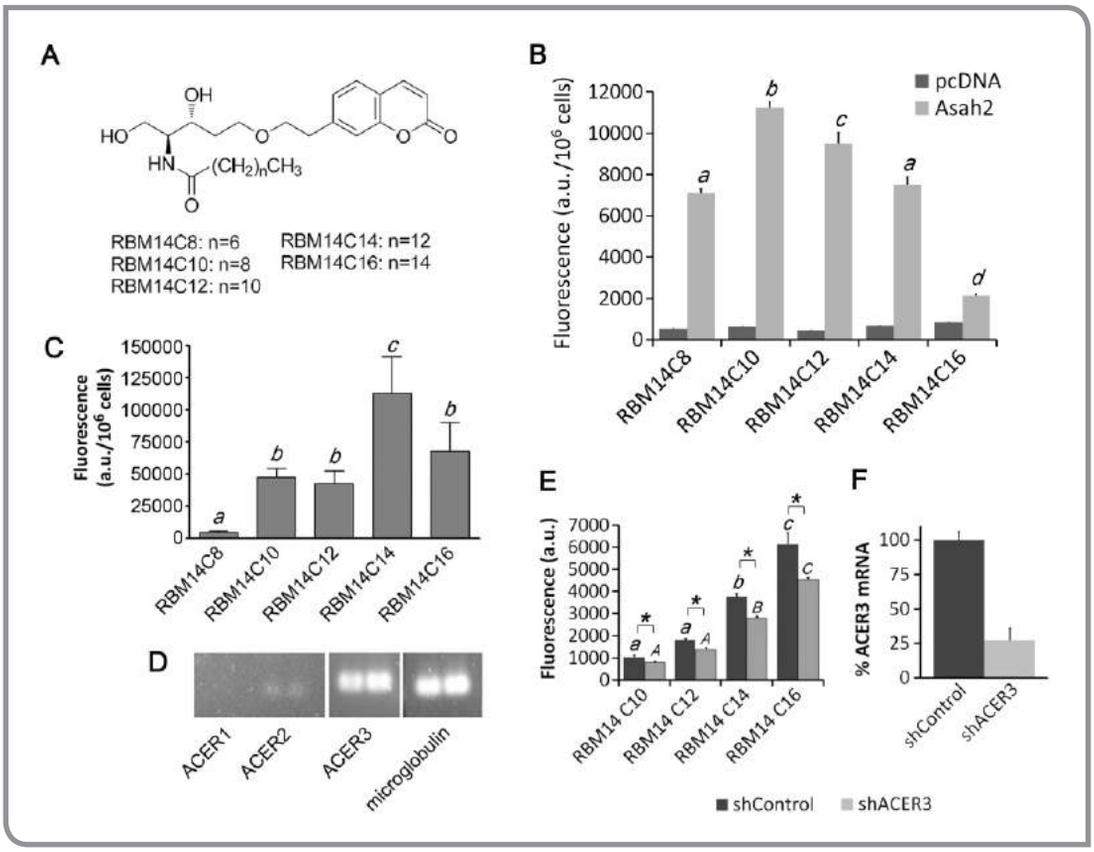
North Atlantic Treaty Organization (NATO), 984777

2015-2018

RESEARCH HIGHLIGHTS

Activity of neutral and alkaline ceramidases on fluorogenic N-acylated coumarine containing aminodiols

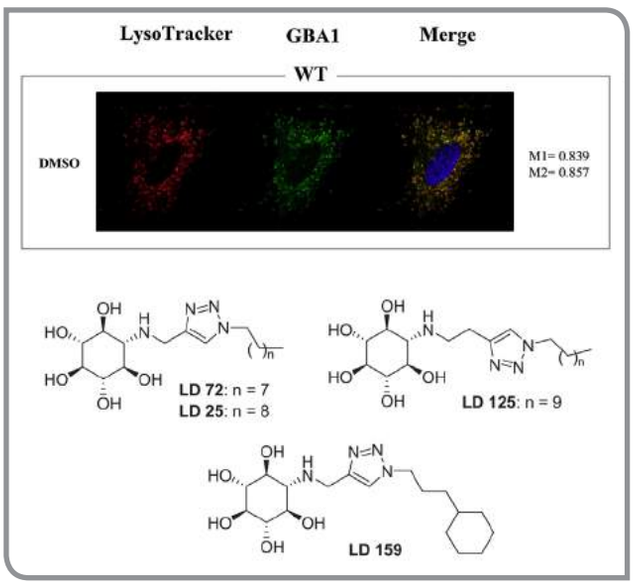
Ceramidases catalyze the cleavage of ceramides into sphingosine and fatty acids. Previously, we reported on the use of the fluorogenic ceramide analogues RBM14 to determine acid ceramidase (AC) activity. In this work we investigated the activity of other amidohydrolases on compounds RBM14. Both bacterial and human purified neutral ceramidases (NC), as well as ectopically expressed mouse neutral ceramidase hydrolyzed RBM14 with different selectivity depending on the N-acyl chain length. On the other hand, microsomes from ACER3 knockdown cells were less competent at hydrolyzing RBM14C12, RBM12C14 and RBM14C16 than controls, while microsomes from ACER2 and ACER3 overexpressing cells showed no activity towards the RBM14 substrates. Conversely, N-acylethanolamine-hydrolyzing acid amidase (NAAA) overexpressing cells hydrolyzed RBM14C14 and RBM14C16 at acidic pH. Overall, NC, ACER3 and, to a lesser extent, NAAA, hydrolyze fluorogenic RBM14 compounds. Although the selectivity of the substrates towards ceramidases can be modulated by the length of the *N*-acyl chain, none of them was specific for a particular enzyme. Despite the lack of specificity, these substrates should prove useful in library screening programmes aimed at identifying potent and selective inhibitors for NC and ACER3.

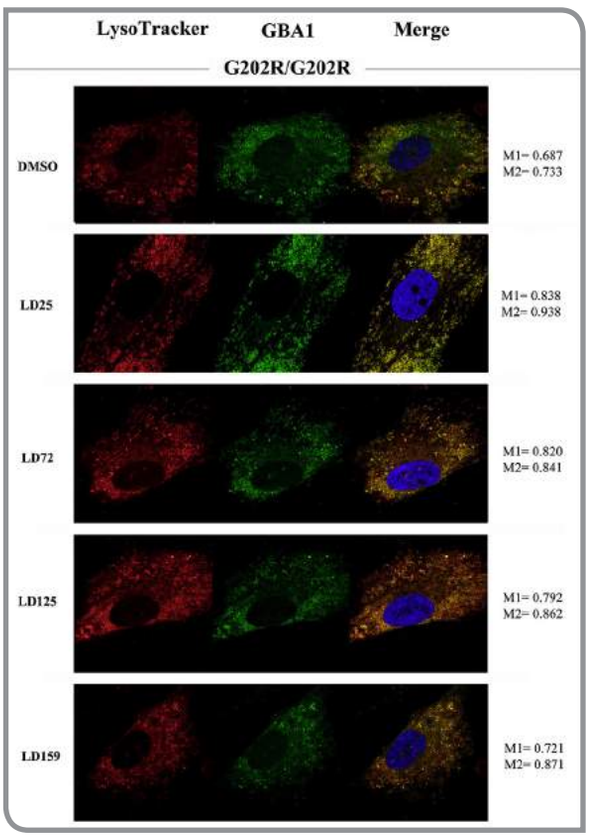


A. Structure of fluorogenic ceramidase substrates. B. Hydrolysis of RBM14 by neutral ceramidase in live Farber cells transfected with the neutral ceramidase gene (Asah2) or the empty (pcDNA5) plasmid. C. Hydrolysis of RBM14 alkaline ceramidase 3 (ACER3) in intact neutral ceramidase knockout cells. D, Content of alkaline ceramidase transcripts as analyzed by agarose gel electrophoresis. E. activity of microsomes isolated from ACER3 knockdown and mock HCT116 cells over RBM14. Incubations were carried out with 6 µg of protein in 50 mM HEPES buffer with 1 mM CaCl2 at pH 9.0. B, ACER3 mRNA levels in ACER3 knockdown and mock HCT116 cells as determined by qPCR. The substrates were tested at 40 µM. Data are the mean ± SD of three to five independent experiments with triplicates. Data were analyzed by one-way ANOVA test followed by Bonferroni's multiple comparison test. Different letters denote statistically significant difference between groups ($p<0.05$).

Selective chaperone effect of aminocyclitol derivatives on G202R and other mutant glucocerebrosidases causing Gaucher disease

Gaucher disease is an autosomal recessive lysosomal disorder characterized by the accumulation of glucosylceramide as a result of a deficiency of the enzyme glucocerebrosidase. Several competitive glucocerebrosidase inhibitors are able to act as pharmacological chaperones for an efficient rescue of the mutated, misfolded forms of the enzyme. In this work we report on the ability of several aminocyclitols to increase the residual glucocerebrosidase activity in patient fibroblasts with different genotypes. Some of the compounds were slightly active on fibroblasts bearing some mutations, including the highly prevalent N370S mutation. All compounds were highly active as enzyme activity enhancers on fibroblasts from Gaucher disease patients containing the G202R mutation. Moreover, using the novel tagged sphingolipid ω-azidosphingosine, a reduction in the tagged glucosylceramide accumulation was also observed for selected aminocyclitols. Attempts to explain the activity impairment observed in glucocerebrosidase bearing the G202R mutation by comparative molecular dynamic studies on wild type and the G202R mutated proteins suggest that since the G202R residue is located on the protein surface, altered protein-membrane or protein-protein interactions could account for the observed differences. In conclusion, we have tested novel compounds that have shown some chaperone effect on particular glucocerebrosidase mutant enzymes, supporting the enhancement therapy as an alternative approach for Gaucher disease.





Confocal laser microscope images of immunofluorescence staining for lysosomes (red) and GBA1 (green) in cultured fibroblasts derived from a healthy individual (WT) and a GD patient with the G202R/G202R genotype untreated (DMSO) and after treatment with LD25, LD72, LD125 and LD159 at the indicated concentrations. Nuclei were stained with DAPI (blue). Immunofluorescent labeling of GBA1 was performed with the 8E4 monoclonal antibody, and LysoTracker was used to detect lysosomes. The concentrations of the compounds are: 1 μM of LD25, 5 μM of LD72, 1 μM of LD125, 5 μM of LD159. M1 and M2 = Manders' coefficient.

SYNTHESIS AND BIOMEDICAL APPLICATIONS OF PEPTIDES

The Unit of Synthesis and Biomedical Applications of Peptides (USiBAP) interests focus on peptide chemistry from three different points of view: design, synthesis and therapeutic value of peptide molecules. The overall objectives of the USiBAP research summed up in the use of synthetic peptides in the field of Biomedicine both in improving diagnosis systems and in the design of new therapeutic targets. More specifically, work is being carried out on the design of immunopeptides, on the use of peptides for the development of new biosensors for the diagnosis of human illnesses and on the selection of therapeutic agents of peptide origin through biophysical testing.

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ARTICLES

A cyclic GB virus C derived peptide with anti-HIV-1 activity targets the fusion peptide of HIV-1

Galatola, R.; Vasconcelos, A.; Pérez, Y.; Cruz, A.; Pujol, M.; Alsina, M.A.; Gómara, M.J.; Haro, I.

Eur. J. Med. Chem., 86, 589-604, **2014.**

HIV-1 inhibiting capacity of novel forms of presentation of GB virus C peptide domains is enhanced by coordination to gold compounds.

Gómara, M.J.; Galatola, R.; Gutiérrez, A.; Gimeno, M.C.; Gatell, J.M.; Sánchez-Merino, V.; Yuste, E.; Haro, I.

Curr. Med. Chem., 21, 238-250, **2014.**

Modification of FP-HIV activity by peptide sequences of GB virus C: A biophysical approach

Domènech, O.; Ortiz, A.; Pujol, M.; Haro, I.; Muñoz, M.; Alsina, M.A.; Prat, J.; Busquets, M.A.; Girona, V.

Biochim. Biophys. Acta – Biomembranes, 1838, 1274-1280, **2014.**

The use of citrullinated peptides for the diagnosis and prognosis of rheumatoid arthritis

Haro, Isabel; Gomara, Maria J.

Curr. Topics Med. Chem., 14, 2729-2733, **2014.**

Updating the use of synthetic peptides as inhibitors of HIV-1 entry
Gómara, M.J.; Haro, I.
Curr. Med. Chem., 21, 1188-1200, **2014.**

A study of HIV-1 FP inhibition by GBV-C peptides using lipid nano-assemblies

Ortiz, A.; Domènech, O.; Muñoz-Juncosa, M.; Prat, J.; Haro, I.; Girona, V.; Alsina, M.A.; Pujol, M.

Coll. Surf. A: Physicochem. Eng. Aspects, 480, 184-190, **2015.**

Conjugation of cell-penetrating peptides with poly(Lactic-co-glycolic acid)-polyethylene glycol nanoparticles improves ocular drug delivery

Vasconcelos, A.; Vega, E.; Pérez, Y.; Gómara, M.J.; García, M.L.; Haro, I.

Int. J. Nanomed., 10, 609-631, **2015.**

Miscibility and langmuir studies of the interaction of E2 (279-298) peptide sequence of hepatitis G virus/GB virus-C with dipalmitoylphosphatidyl choline and dimiristoylphosphatidyl choline phospholipids

Miñones, J.; Muñoz, M.; Miñones Trillo, J.; Haro, I.; Busquets, M.A.; Alsina, M.A.

Langmuir, 31, 10161-10172, **2015.**

Surface behavior of peptides from E1 GBV-C protein: Interaction with anionic model membranes and importance in HIV-1 FP inhibition

Galatola, R.; Cruz, A.; Gómara, M.J.; Prat, J.; Alsina, M.A.; Haro, I.; Pujol, M.

Biochim. Biophys. Acta – Biomembranes, 1848, 392-407, **2015.**

RESEARCH PROJECTS

Péptidos sintéticos y nanosistemas derivatizados con construcciones peptídicas del GBV-C como potenciales agentes anti-HIV-1 y reactivos de diagnóstico de infección por GBV-C

Nacional, CTQ2012-37589-C02-01

2013-2015

Diseño de nanosistemas peptídicos de liberación controlada para la administración ocular de fármacos

Internacional, 2011CU0003

2011-2015

Analysis of the structure-activity relationships of anti-myotonic dystrophy hexapeptides

Nacional, Telemaratón RTVE

2015-2107

RESEARCH HIGHLIGHTS

HIV-1 INHIBITING CAPACITY OF NOVEL FORMS OF PRESENTATION OF GB VIRUS C PEPTIDE DOMAINS IS ENHANCED BY COORDINATION TO GOLD COMPOUNDS

At present, interest in viral fusion and entry inhibitors is growing significantly, since they can be applied in combined therapies or when resistance to other antiretroviral drugs is encountered. Furthermore, these inhibitors act before the virus enters the cell, which could have the same potential as the inducing of immunity by a vaccine.

Following the report of beneficial effects for HIV-infected patients of co-infection by GB virus C (GBV-C), our research group decided to study synthetic GBV-C peptides and their relationship with HIV-1. This paper reports the design and synthesis of new forms of presentation of two peptide inhibitors corresponding to the envelope proteins E1 and E2 of GBV-C, together with a study of their anti-HIV-1 activity. Homogeneous and heterogeneous multiple antigenic peptides (MAPs), lipophilic derivatizations, cyclization and peptide–gold conjugations are the chemical design strategies adopted (Figure 1). Our aim was to enhance the anti-viral potency of the GBV-C peptide domains. Of all the GBV-C peptide derivatives studied, peptide–gold complexes derived from the (22-39) sequence of the GBV-C E1 protein were the most active entry inhibitors. These results support the putative modulation of HIV-1 infection by the GBV-C E1 protein and open new perspectives for the development of novel peptide-derived HIV-1 entry inhibitors.

CONJUGATION OF CELL-PENETRATING PEPTIDES WITH POLY(LACTIC-CO-GLYCOLIC ACID)-POLYETHYLENE GLYCOL NANOPARTICLES IMPROVES OCULAR DRUG DELIVERY

The bioavailability of ophthalmic drugs in aqueous solutions is usually low due to their rapid elimination after mucosal instillation; a consequence of reflex blinking and tear drainage, as well as of the presence of the corneal barrier. In fact, only 5% of the applied dose reaches intraocular tissues after corneal penetration. Research into biomaterials has therefore included the use of biodegradable polymeric nanoparticles (NPs) in

ocular drug delivery; one of the most promising applications of NPs, as they offer a controlled release profile of a drug which is entrapped in the polymeric matrix. In this work, a peptide for ocular delivery (POD) and human immunodeficiency virus transactivator (HIV-Tat) were conjugated with biodegradable poly(D,L-lactide-co-glycolide)–polyethylene glycol (PLGA-PEG) nanoparticles (NPs) in an attempt to improve ocular drug bioavailability. The NPs were prepared by the solvent displacement method following two different pathways. One involved preparation of PLGA NPs followed by PEG and peptide conjugation (PLGA-NPs-PEG-peptide); the other involved self-assembly of PLGA-PEG and the PLGA-PEG-peptide copolymer followed by NP formulation (Figure 2). *In vivo* anti-inflammatory efficacy was assessed in rabbit eye after topical instillation of sodium arachidonate (Figure 3). Of the formulations developed, the PLGA-PEG-POD-NPs were the smaller particles, and exhibited greater entrapment efficiency and more sustained release. The positive charge on the surface of these NPs, due to the conjugation with the positively charged peptide, facilitated penetration into the corneal epithelium resulting in more effective prevention of ocular inflammation. The *in vitro* toxicity of the NPs developed was very low; no ocular irritation *in vitro (*HET-CAM*)* or *in vivo* (Draize test) was detected. Taken together, these data demonstrate that PLGA-PEG-POD-NPs are promising vehicles for ocular drug delivery.

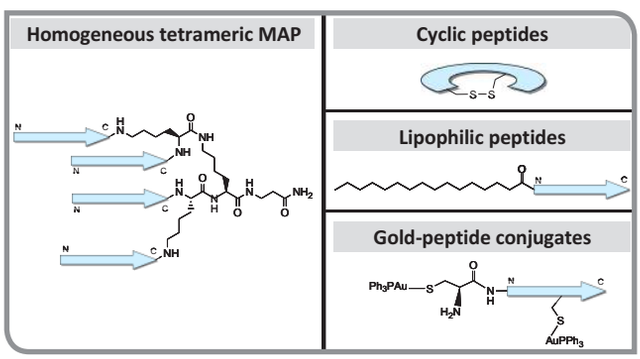

Figure 1. Chemical modifications to design new forms of presentation of GBV-C peptide domains

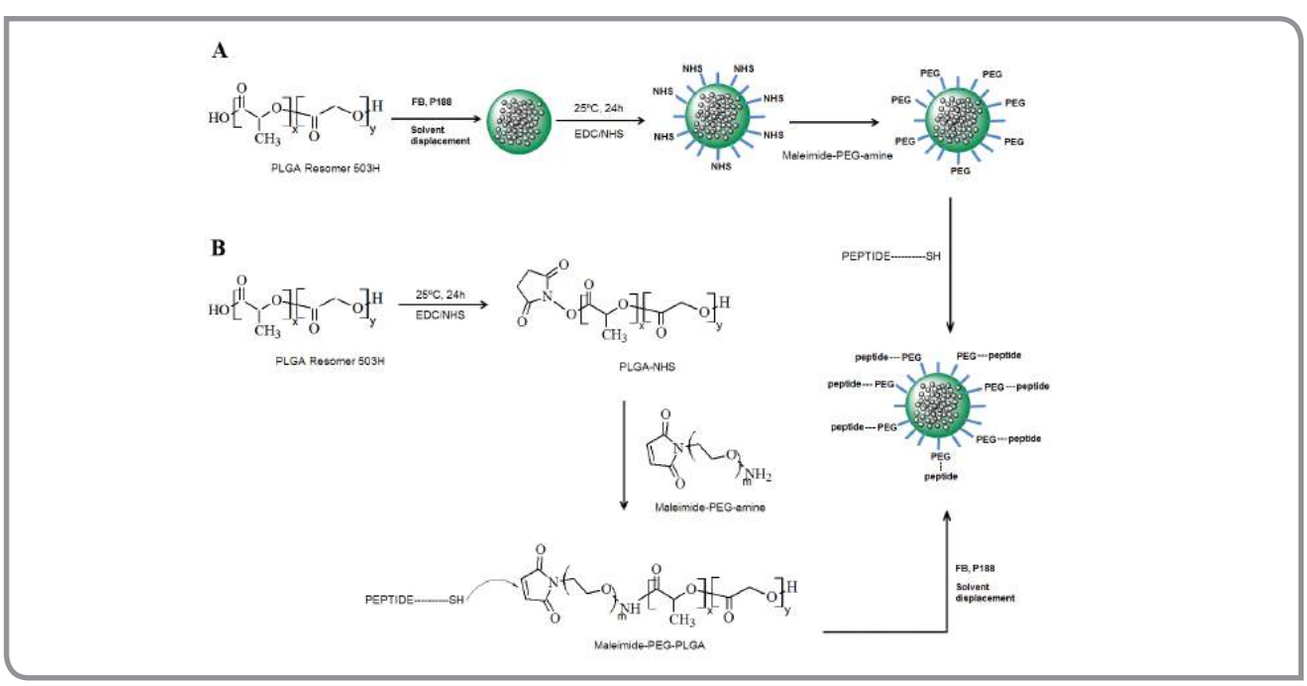

Figure 2. Synthesis of (A) PLGA-NPs-PEG-Peptide and (B) PLGA-PEG-Peptide polymer followed NPs preparation

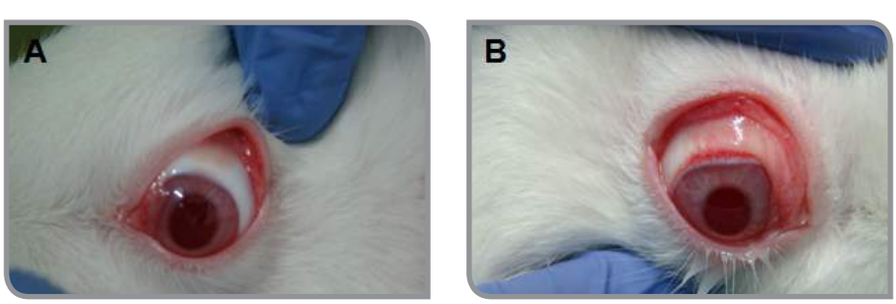

Figure 3. Draize test after instillation of PLGA-PEG-POD-NPs (A) and inflammation induced by Sodium arachidonate (B)

UNIT OF GLYCOCONJUGATE CHEMISTRY

The aim of the Unit is to study biochemical or medicinal chemistry issues by using chemical methodologies. Most frequently used tools are peptide and carbohydrate chemistry, halogenation reactions, aqueous organometallic catalysis and proteomic techniques. Traditional fields of interest are enzyme catalysis, pain and immunity related mechanisms and more recently, transthyretin amyloidosis inhibitors and Alzheimer disease (AD) interfering compounds. Current research activities involve: 1) Study of pain and immunity related compounds. 2) Effects of halogenation on biological properties of active compounds. 3) Drug discovery for transthyretin related amyloid rare diseases. 4) Protein-protein interaction modulation by small molecules to identify AD interfering compounds. 5) Proteomic characterization of G-protein coupled opioid receptors. All these activities are carried out in multidisciplinary projects involving computer scientists, biochemical, biological, pharmacological, conformational (NMR), crystallographic and nuclear chemistry groups at national and international level.

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ARTICLES

Transthyretin stabilization by iododiflunisal promotes amyloid-beta peptide clearance, decreases its deposition, and ameliorates cognitive deficits in an Alzheimer's disease mouse model

Ribeiro, C.A.; Oliveira, S.M.; Guido, L.F.; Magalhães, A.; Valencia, G.; Arsequell, G.; Saraiva, M.J.; Cardoso, I.

J. Alzheimers Dis., 39, 357-370, **2014**.

Modulation of the interaction between a peptide ligand and a G protein-coupled receptor by halogen atoms

Rosa, M.; Caltabiano, G.; Barreto-Valer, K.; Gonzalez-Nunez, V.; Gómez-Tamayo, J.C.; Ardá, A.; Jiménez-Barbero, J.; Pardo, L.; Rodríguez, R.E.; Arsequell, G.; Valencia, G.

ACS Med. Chem. Lett., 6, 872-876, **2015**.

Optimized Proteomic Mass Spectrometry Characterization of Recombinant Human m-Opioid Receptor Functionally Expressed in Pichia pastoris Cell Lines

Rosa, M.; Bech-Serra, J.J.; Canals, F.; Zajac, J.M.; Talmont, F.; Arsequell, G.; Valencia, G.

J. Proteome Res., 14, 3162-3173, **2015**.

Tuning transthyretin amyloidosis inhibition properties of iododiflunisal by combinatorial engineering of the nonsalicylic ring substitutions.

Vilaró M, Nieto J, La Parra JR, Almeida MR, Ballesteros A, Planas A, Arsequell G, Valencia G.

ACS Comb. Sci., 17, 32-38, **2015**.

Influence of polar side chains modifications on the dual enkephalinase inhibitory activity and conformation of human opiorphin, a pain perception related peptide.

Rosa M, Marcelo F, Calle LP, Rougeot C, Jiménez-Barbero J, Arsequell G, Valencia G.

Bioorg. Med. Chem. Lett., 25, 5190-5193, **2015**.

PROJECTS AND CONTRACTS

Proteomic analysis of post-translational modifications of transthyretin as an activity marker in patients with hereditary amyloidosis by TTR mutation: a case-control study.

Fundación La Marató de TV3 (2007: Enfermedades minoritarias). Proyecto coordinado de cuatro grupos. Coordinador de Proyecto: Dr. Josep Maria Campistol (Hospital Clínico de Barcelona)

2011-2014

Síntesis asimétrica y sistemas insaturados: Retos y oportunidades para la catálisis en síntesis orgánica selectiva.

Plan Estatal de Investigación Científica y Técnica y de Innovación 2013-2016 (CTQ 2013-41511-P). Área temática gestión: Ciencias y Tecnologías Químicas. Subárea temática gestión: Química Básica. Coordinador de Proyecto: Dr. José Manuel González Díaz (Universidad de Oviedo).

2014-2016

Rational screening programme for stabilising compounds of the transthyretin-Aß binding as potential modulating drugs of Alzheimer disease.

Fundación La Marató de TV3 (2013: Enfermedades neurodegenerativas). Proyecto coordinado de cinco grupos. Coordinador de Proyecto: Dr. Gemma Arsequell Ruiz. (IQAC-CSIC).

2015-2017

RESEARCH HIGHLIGHTS

Protein-protein interaction modulation by small molecules to identify AD interfering compounds. These studies are an extension of the drug discovery effort initiated in year 2000 to find drug candidates for a group of rare diseases associated to transthyretin (TTR) which is a thyroid hormone transporter protein. These systemic amyloid diseases are always triggered by single point hereditary or spontaneous mutations on the protein. The pharmacological intervention we have been pursuing relies in small molecule compounds that resemble thyroid hormones and attach to the binding pocked of TTR and thus stabilize its tetrameric structure by preventing its dissociation and further misfolding and aggregation of its monomers into amyloid fibrils and deposits. In the course of this research we have found that a particular set of TTR stabilizing compounds favour the formation of TTR-Aβ interactions when studied *in vitro*. This has prompted us to study the activity of one of such compounds, namely iododiflunisal, when administered in an AD animal model. By using an AβPPswe/PS1A246E model and orally administering the drug we have found that the drug is able to stabilize TTR in the plasma of these animals. Also, it was evidenced that the drug penetrated into the brain. The drug decreased Aβ levels and Aβ deposition in the brain. Cognitive functions associated with AD-like neuropathology were also ameliorated in these animals [*J. Alzheimers Dis*. **2014**, *39*, 357-370]. This work conducted in association with our long standing partners at the IBMC of University of Porto is continued throughout a project of Fundació La Marató de TV3 starting in year 2015. The project is aimed at the characterization of the molecular events involved in these physiological events and to identify drugs with similar activity profiles by applying drug repurposing methodologies.

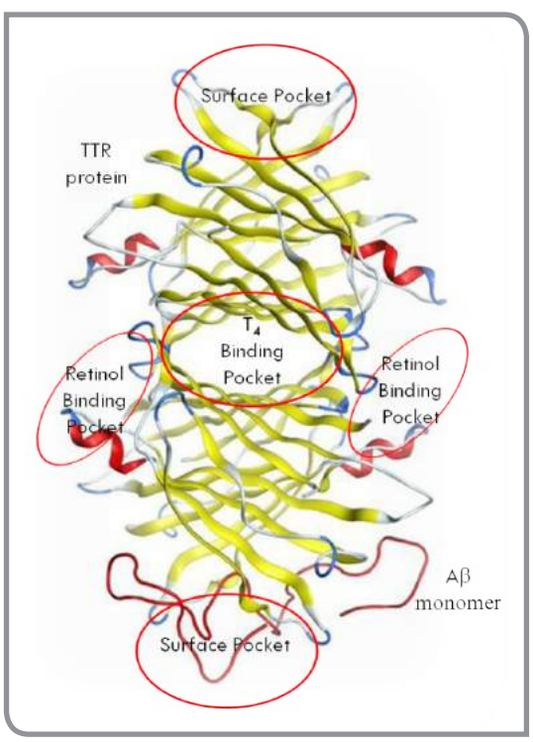

Figure 1. TTR-Aβ-iododiflunisal model.

Proteomic characterization of G-protein coupled opioid receptors. In the context of our long standing interest on the characterization and study of pain related molecules we have embarked on the characterization of opioid receptors. This was one of the aims of a former project of Fundació La Marató de TV3 on call of year 2006 that has been a chapter of the PhD thesis of Dr. Mònica Rosa (2013). Although chimeric forms of the opioid receptors have been recently crystallized (2012)

their structural knowledge is still far from perfect. To contribute to this structural knowledge other complementary approaches such as proteomic analyses are being developed. In our paper, *J. Proteome Res*. 2015, 14, 3162-3173, 2015] we report the preparation and purification of a cloned human μ-opioid receptor conducted in association with the group of Dr. Zajac and Dr. Talmont from the CNRS of Toulouse. This material was further concentrated and digested either in-gel and in-solution with different proteases (trypsin, chymotrypsin, proteinase K). The resulting digests were analyzed by different techniques like MALDI-TOF and nano- liquid chromatography coupled with tandem MS. These analyses afforded and overall sequence coverage of up to >80%, a level of description first attained by a GPCR opioid receptor and one of the six such high-coverage MS-based analyses of any GPCR protein.

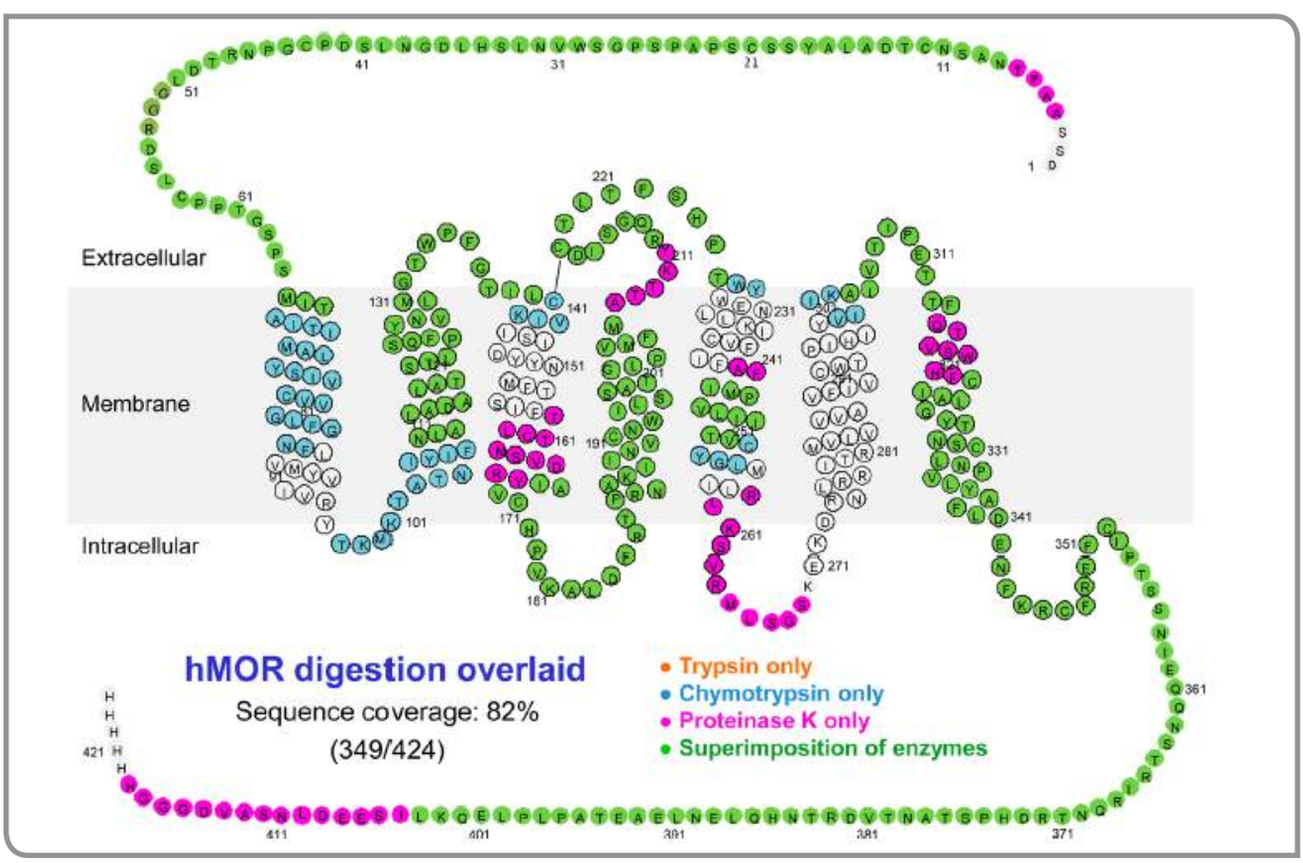

Figure 2. Two dimensional serpentine representation of hMOR-c-myc-6-his sequence coverage of peptides identified by MALDI-TOF-MS and nanoLC-MS/MS after enzymatic digestions.

MEDICINAL CHEMISTRY

The group is devoted to the discovery of small molecules with activity on biologically relevant processes, including medicinal chemistry and chemical biology. The projects in in basic research are in the borderline between chemistry and Biology with the goal to find molecules useful to study the basic processes and mechanisms and to develop new therapeutics for diseases. Some of the projects are related to optopharmacology of GPCRs, glycolipids in immunology, pharmacological chaperones for lysosomal diseases, and chemical methods for native protein labelling.

Besides its basic research activities, the group is actively involved in R+D+i industrial projects concerted with companies working mainly in chemicals, pharmaceutics, diagnostics, biotechnology products and biosciences. The lab is providing research support and chemical expertise and advice to academic groups or companies in medicinal chemistry, synthesis, analytical development and molecular probes.

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ARTICLES

A double effect molecular switch leads to a novel potent negative allosteric modulator of metabotropic glutamate receptor 5

Gómez-Santacana, X.; Rovira, X.; Dalton, J.A.; Goudet, C.; Pin, J.P.; Gorostiza, P.; Giraldo, J.; Llebaria, A.

MedChemComm, 5, 1548-1554, **2014.**

An allosteric modulator to control endogenous G protein-coupled receptors with light

Pittolo, S., Gómez-Santacana, X., Eckelt, K., Rovira, X., Dalton, J., Goudet, C., Pin, J.P., Llobet, A., Giraldo, J., Llebaria, A., Gorostiza, P.

Nature Chem. Biol., 10, 813-815, **2014.**

Aziridine ring opening for the synthesis of sphingolipid analogues: Inhibitors of sphingolipid-metabolizing enzymes

Alcaide, A.; Llebaria, A.

J. Org. Chem., 79, 2993-3029, **2014.**

Computational analysis of negative and positive allosteric modulator binding and function in metabotropic glutamate receptor 5 (in)activation

Dalton, J.A.R.; Gómez-Santacana, X.; Llebaria, A.; Giraldo, J.

J. Chem. Inf. Model. 54, 1476-1487, **2014.**

Exploring the active conformation of cyclohexane carboxylate positive allosteric modulators of the type 4 metabotropic glutamate receptor

Rovira, X.; Harrak, Y.; Trapero, A.; González-Bulnes, P.; Malhaire, F.; Pin, J.-P.; Goudet, C.; Giraldo, J.; Llebaria, A.

ChemMedChem, 9, 2685-2698, **2014.**

Glucocerebrosidase inhibitors: Future drugs for the treatment of Gaucher disease?

Trapero, A.; Llebaria, A.

Future Medicinal Chemistry, 6, 975-977, **2014.**

Galacto configured N-aminoaziridines: A new type of irreversible inhibitor of beta;-galactosidases

Alcaide, A.; Trapero, A.; Pérez, Y.; Llebaria, A.

Org. Biomol. Chem., 13, 5690-5697, **2015.**

Overlapping binding sites drive allosteric agonism and positive cooperativity in type 4 metabotropic glutamate receptors

Rovira, X.; Malhaire, F.; Scholler, P.; Rodrigo, J.; Gonzalez-Bulnes, P.; Llebaria, A.; Pin, J.-P.; Giraldo, J.; Goudet, C.

FASEB J., 29, 116-130, **2015.**

Shining Light On An mGlu5 Photoswitchable NAM: A Theoretical Perspective.

Dalton JA, Lans I, Rovira X, Malhaire F, Santacana XG, Pittolo S, Gorostiza P, Llebaria A, Goudet C, Pin JP, Giraldo J.

Curr Neuropharmacol. **2015,** DOI: 10.2174/1570159X13666150407231417

Synthesis and evaluation of hydroxymethylamino-cyclitols as glycosidase inhibitors

Trapero, A.; Egido-Gabás, M.; Bujons, J.; Llebaria, A.

J. Org. Chem., 80, 3512-3529, **2015**

PROJECTS AND CONTRACTS

Ciclitoles como miméticos de carbohidratos y sus efectos en glicoenzimas y activación de células NKT por glicolípidos

Nacional, CTQ2011-29549-C02-01

2012-2014

pH controlled pharmacological chaperones

Nacional, CTQ2011-14868-E

2012-2014

Fundacio La Marato de TV3 para validacio de mglu4 com a diana terapéutica pel tractament multipotencial de les lesions medul.lars

Nacional 2012-2015

Deciphering the role of peripheral and central nervous system metabotropic glutamate receptors in neurophatic pain with photoactivable ligands

LIGHTPAIN

ERA-NET Neuron; Proyecto Europeo , 2013-2015

Moléculas para el Fotocontrol de la Actividad de Proteínas.

Nacional, CTQ2014-57020-R , 2015-2017

RESEARCH HIGHLIGHTS

The group is devoted to the discovery of small molecules with activity on biologically relevant processes, including medicinal chemistry and chemical biology. The projects in in basic research are in the borderline between chemistry and Biology with the goal to find molecules useful to study the basic processes and mechanisms and to develop new therapeutics for diseases. Some of the projects are related to :

1. Optopharmacology. We serach for a precise and effective control of drug action in their target proteins or receptors using light and photochemical techniques. The group has pionerred the effort in a new design approach for drug-like photochromic ligands in animala model diseases that allow the control of motility and other physiologycal functions with light operated molecules. In collaboration with IBEC(barcelona, Spain), The Institut de Neurociències, UAB (Bellaterra, Spain), The

Faculty of Medicine UB (Barcelona, Spain) , IGF-CNRS (Montpellier, France), Universita la Sapienza (Rome, Italy). We have started a project in anew Technology to increase the efficiency of drugs for pain treatment and othe CNS pathologies.

2. New adjuvants for NKT cells. The group is working in molecules with stimulatory activity of the immune response. There's a glycolipid compound alpha-Galactosylceramide (αGC) that is a strong stimulator of iNKT cells, a unique subpopulation of T cells with immunomodulatory properties. The very high potency of αGC on iNKT cell stimulation is associated to different side effects and new molecules are necessary to improve its biological properties and modulate the strong induced response. In this context, we have discovered the high activity of aminocyclitol phytoceramides as iNKT cell activators and we work on the design and stereocontrolled synthesis of new structural analogues. NKT cells are attractive targets for the development of immunotherapies against infections, as vaccine adjuvant and in treatment of cancer and autoimmune diseases. In collaboration with Monash University and University of Melbourne (Australia); Brigham Women Hospital, Harvard Medical School, (Boston, USA); , IBB-UAB (Bellaterra, Spain) and Hospital Germans Trias i Pujol (Badalona, Spain), LIAI, La Jolla (USA), Keck Center USC-Los Angeles (USA) I la Universitat de Ghent University (Belgium).

3. Chemical compounds for pharmacological chaperones. The rescue of mutated proteins that have folding defects is in the origin of several rare diseases including lysosomal diseases. Our approach consists in the study of cell permeable, potent protein ligands to stabilize the misfolded protein and funcional rescue of mutated proteins in rare diseases. In collaboration with the Glycobiology Institute and Oxford University. (UK).

Besides its basic research activities, the group is actively involved in R+D+i industrial projects concerted with companyies working mainly in chemicals, pharmaceutics, diagnostics, biotechnology products and biosciences. The lab is providing research suport and chemical expertise and advice to academic groups or companies in medicinal chemistry, synthesis, analytical development and molecular probes.

In a recent communication of our group (Pittolo et al *Nat Chem Biol* **2014**,*10*, 813-5) we describe a breakthrough development for designing photochromic protein ligands ligands integrating an azobenzene in the scaffold of the reported ligand pharmacophore of known ligands for a target protein of interest. To do this, we searched for mGlu allosteric ligands having high chemical and structural homology with the Ar-N=N-Ar scaffold present in the azobenzene. In this way, the chemical modifications needed to generate the new PCL would have a minimum impact over the parent compound in terms of molecule weight, chemical properties, and steric occupancy. This research co- leaded by the PI of this application and Pau Gorostiza at IBEC with other collaborating groups has been successful to give highly potent drug-like molecules active in cultured cells and in an animal model. We have identified a light-regulated allosteric modulator of the mGlu5 metabotropic glutamate receptor (Figure 1).

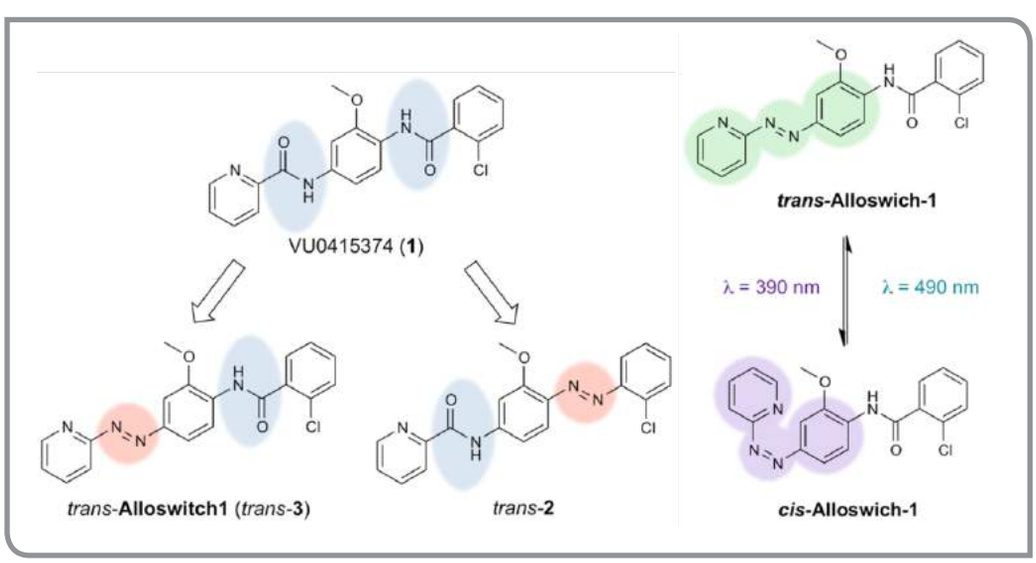

Figure 1. Chemical structure of Alloswitch-1, a photochromic allosteric modulator of metabotropic glutamate receptor mGluR5 based on azobenzene cis-trans photoisomerization

The compound, termed Alloswitch-1, contains a photochromic azobenzene group and acts as a negative allosteric modulator (NAM) of mGlu5 in its *trans* configuration in the dark or under green (500nm) illumination. This compound can switch on/off the receptor in cells expressing the receptor and in brain astrocytes, allowing a full control of the activity of the receptor in vitro (figure 2). When transparent animals such as *Xenopus tropicalis* tadpoles or zebra fish are incubated in the presence of Alloswitch-1 we can control their natatory activity in a reversible manner with violet or green light and without any sign of toxicity. We filed a European Patent application (EP13382374) in September 2013 that is now in PCT extension and we are now interested in exploring further this approach in detail including its extension in mammals.

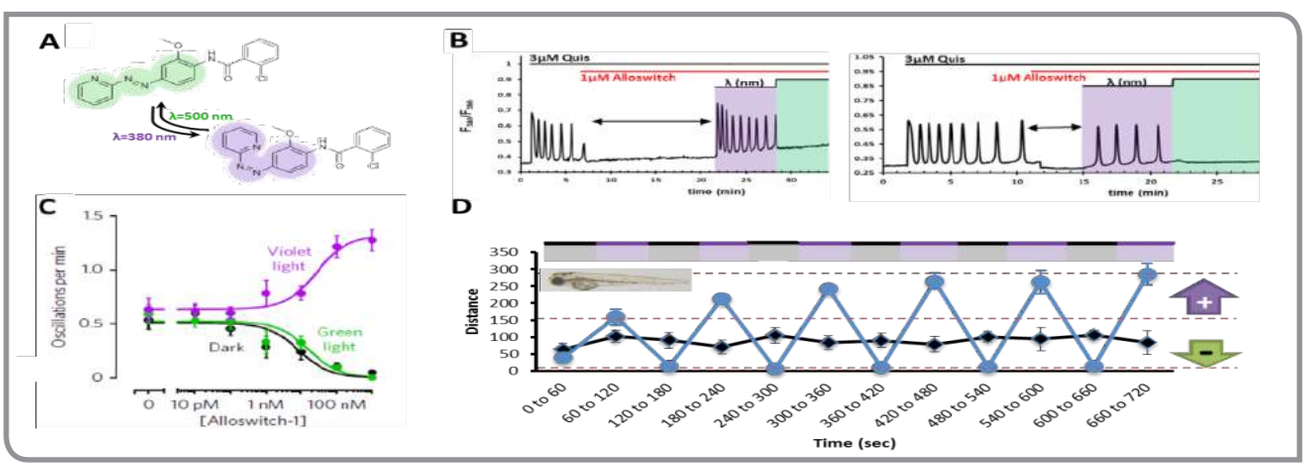

Figure 2 (A) Photoisomerization of Alloswitch-1 from trans to cis configuration, and vice versa, after illumination with violet and green light, respectively. (B) Real-time calcium imaging of mGlu5-expressing cells showing a reversible calcium control with light. (C) Dose dependent effect of the receptor activity under violet light treatment and inhibition under dark or green light conditions. (D) The control of Zebrafish movement with light in animal behavioral assays

CHEMICAL BIOLOGY

Chemical biology is a discipline that applies chemical tools to investigate biological phenomena. Major advances have been seen in biology in the last decade thanks to the application of chemical biology strategies ranging from the synthesis of small molecule modulators of enzymes or protein-protein interactions to the design of new fluorophores, the establishment of new methods for target identification or the development of novel techniques in protein chemistry, among many others.

Our main objective in this field is the development of chemical tools that can contribute to the elucidation of the factors regulating diseases and to get a better understanding of relevant biological processes, with a special focus on autophagy and lipid-modified proteins. As a consequence, our research interests cover various fields of organic chemistry, biochemistry, biophysics and medicinal chemistry, thereby focusing on screen development, design, synthesis and characterization of small-molecule inhibitors, the establishment of novel strategies for peptide and protein chemistry, including protein synthesis, modification and immobilization, and the characterization of lipid-protein interactions.

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ARTICLES

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Doi: 10.1002/9783527687503.ch5

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Triola G.

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Doi: 10.1002/9783527687503.ch7

RESEARCH PROJECTS

Chemical biology of autophagy

CCEE, 333835

2014-2017

Max-Planck partner group

Internacional

2014—2017

Desarrollo de Inhibidores de Atg4B como inhibidores selectivos de Autofagia (CTQ2013-44334-P)

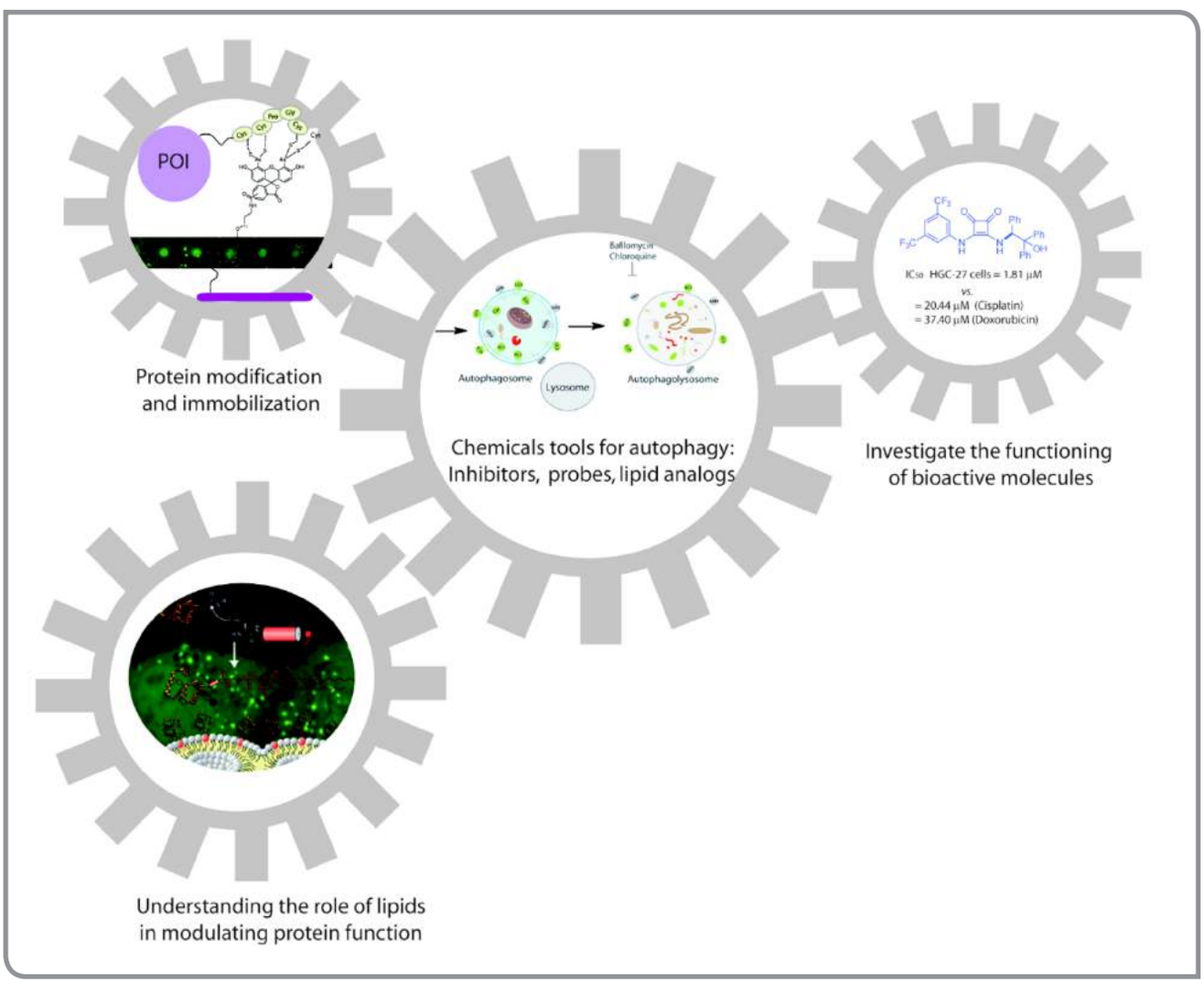
Ministerio de Economía y Competitividad

2014-2016

Proyecto Intramural Especial

Ministerio de Economía y Competitividad

2015-2016



RESEARCH HIGHLIGHTS

Protein Modification and Immobilization

A novel technique for protein immobilization onto CrAsH-modified surfaces has been developed. This approach enables a novel one-step method for protein immobilization based on the stable complex formation between peptides or proteins bearing Tetracysteine (TC)-tags and CrAsH-modified surfaces. This immobilization technique is mild, rapid, it requires only one-hour incubation, and it is compatible with the sensitive nature of proteins. Moreover, our approach overcomes important limitations. Briefly, slide reuse and more importantly, direct detection of immobilized proteins have always been challenging issues in the fabrication of protein microarrays. The His–NTA complex enables slide regeneration but the low affinity of this interaction may result in undesired protein detachment. Alternatively, direct detection usually requires label-free methods that are mostly found only in specialized laboratories. Hence, the developed approach presents additional important features compared to the previously described methods, i.e. a high affinity but reversible binding that can be employed for slide reuse upon DTT incubation and a fluorescence enhancement upon immobilization that enables the direct detection of the immobilized proteins. Moreover, expressed proteins can also be directly immobilized from cellular lysates without prior purification. The immobilized proteins are suitable for protein–protein interaction studies and the fluorescence enhancement upon immobilization can be employed for the direct detection of the immobilized protein without the need for secondary detection methods.

Understanding the role of lipids in modulating protein fuction

We have initiated a project aimed to characterize the role of lipids in modulating the function of lipidated proteins with special focus on autophagy-related processes.

Chemical tools for autophagy

We have started a project for the development of chemical tools to regulate and characterize autophagy. These probe range from small molecules to peptides and lipid derivatives.

Investigate the functioning of bioactive molecules

We have set up a collaboration project with the group of Dr. R.P. Herrera, from the ISQCH (CSIC-University of Zaragoza) directed to investigate the biological activity of squaric acids and squaramides.

4

DEPARTMENT OF CHEMICAL AND BIOMOLECULAR NANOTECHNOLOGY

DEPARTMENT OF CHEMICAL AND BIOMOLECULAR NANOTECHNOLOGY

Head: Jordi Esquena Moret

Chemical and biomolecular Nanotechnology is a wide multidisciplinary field, which can be defined as the study of chemical and biological entities with dimensions in the nanometer range. In this broad field, research at the Department of Chemical and Biomolecular Nanotechnology is focused on understanding of bioactive organic molecules and biomolecules (oligonucleotides, macrobiomolecules, antibodies, organic molecules and drugs), self-organized supramolecular colloidal systems, nanostructured materials and devices at the nanoscale. Thus, the department holds expertise on the design of biosensors based on antibodies, natural molecules with inherent ability to specifically interact with their counter antigen directing their features according to the needs, allowing the smart design of analytical tools for a wide range of applications in diagnostic, foods safety and environment fields. A research field with deep expertise in the Department is the study of oligonucleotides, which allow to design new nucleic acid derivatives with interesting structural properties as well as to control gene expression by antisense and RNA interference mechanisms. The deep expertise on the chemistry of surfactants, namely on their self- aggregation properties, forming complex supramolecular nanostructures (micelles, liquid crystals, vesicles, microemulsions, nano-emulsions, highly concentrated emulsions, etc.) has led to investigate self-assembly, supramolecular chemistry and phase behavior in multicomponent systems. Another important objective is the formation of new nanostructured materials, by templating in self-assemblies and colloidal dispersions, for the formation of (bio) materials with controlled size and morphology, which can be used as novel delivery systems for active components. Moreover, the development of new cell therapy treatments is also of great importance, in the fields of regenerative medicine and tumor therapy. In this research line, the objectives are to develop antitumor therapies using stem cells as vehicles for the local delivery of therapeutic agents, and the study of therapeutic-cell tumor interactions. For these studies, mesenchymal stromal cells, from adipose tissue, are used.

The Department of Chemical and Biomolecular Nanotechnology is formed by consolidated multidisclipinary research teams, with a strong capacity to secure funds from Spanish public institutions, foundations, European programs and contracts of technology transfer to the private sector. All the research groups of the Department belong to the *Centro de Investigaciones Biomédicas en Red en Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN),* and two groups also belong to TECNIO, a network of centers of technological innovation for transfer to the industrial sector.

RESEARCH GROUPS

- Nanobiotechnology for Diagnostics (Nb4D)
- Nucleic Acids Chemistry
- Colloidal an Interfacial Chemistry
- Cell Therapy
- Surface Chemistry

NUCLEIC ACIDS CHEMISTRY

Synthetic oligonucleotides are convenient tools for a large number of studies. The aim of our group is the study of the methodology used for the synthesis of DNA and RNA derivatives in order to obtain new compounds with new and / or improved properties. The projects undertaken along 2014-2015 deal with 1) conjugation of small molecules to DNA and RNA for a potential use in DNA/ RNA therapeutics, 2) the effect of modified bases in the structural and biological properties of oligonucleotides, and 3) the use of modified oligonucleotides in the assembly of nanomaterials and biosensors

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NOEMI BALA
MARC ERES
DIEGO SANJULIAN

ARTICLES

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Puras, G., Martínez-Navarrete, G., Mashal, M., Zarate, J., Agirre, M., Ojeda, E., Grijalvo, S., Eritja, R., Díaz-Tahoces, A., Avilés-Trigueros, M., Fernandez, E., Pedraz, J.L.

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New insights into gene delivery to human neuronal precursor NT2 cells: a comparative study between lipoplexes, nioplexes and polyplexes.

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in *RNA technologies. Chemical Biology of Nucleic Acids: Fundamentals and Clinical Applications*, (Erdmann, V.A., Markiewicz, W.T., Barciszewski, J Eds.) chapter 13, Springer series, pp 227-242, 2014.doi 10.1007/978-3-642-54452-1_13

ACTIVE PROJECTS

Multifuncional nanotechnology for selective detection and treatment of cancer (MULTIFUN)

EC, 262943

Coordinator: Cesar Mediavilla. IQAC participants Groups Leaders: R. Eritja and C. Solans

2011-2015

Nuevos tratamientos para enfermedades degenerativas de la retina (TERET)."

MINECO, RTC-2014-2038-1

2014-2017

Ácidos Nucleicos sintéticos para aplicaciones biomédicas

MINECO, CTQ2014-52588-R

2015-2018

Nanoestructuras de ADN para transfección celular

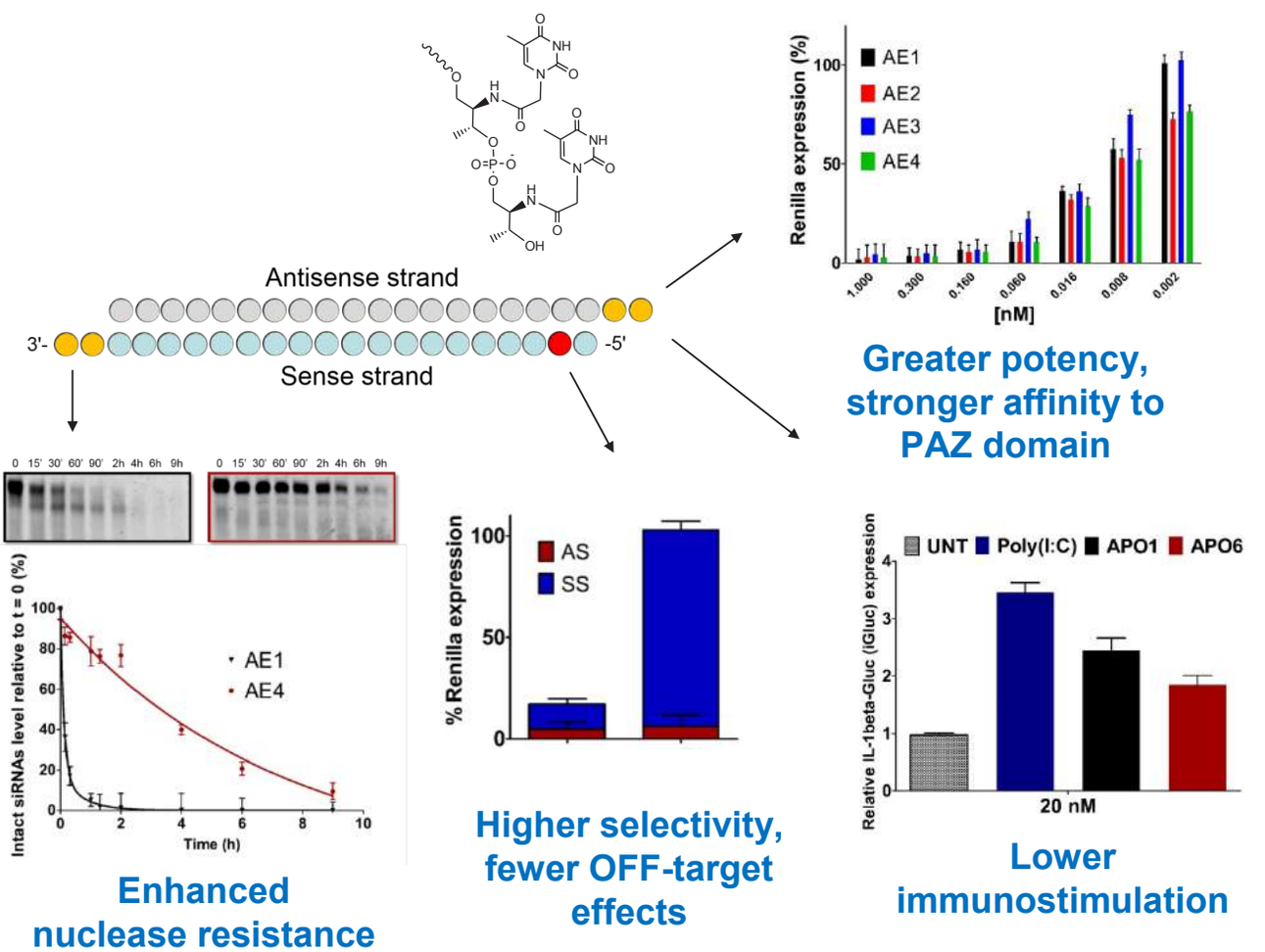
MINECO, CTQ2014-61758-EXP

2015-2017

RESEARCH HIGHLIGHTS

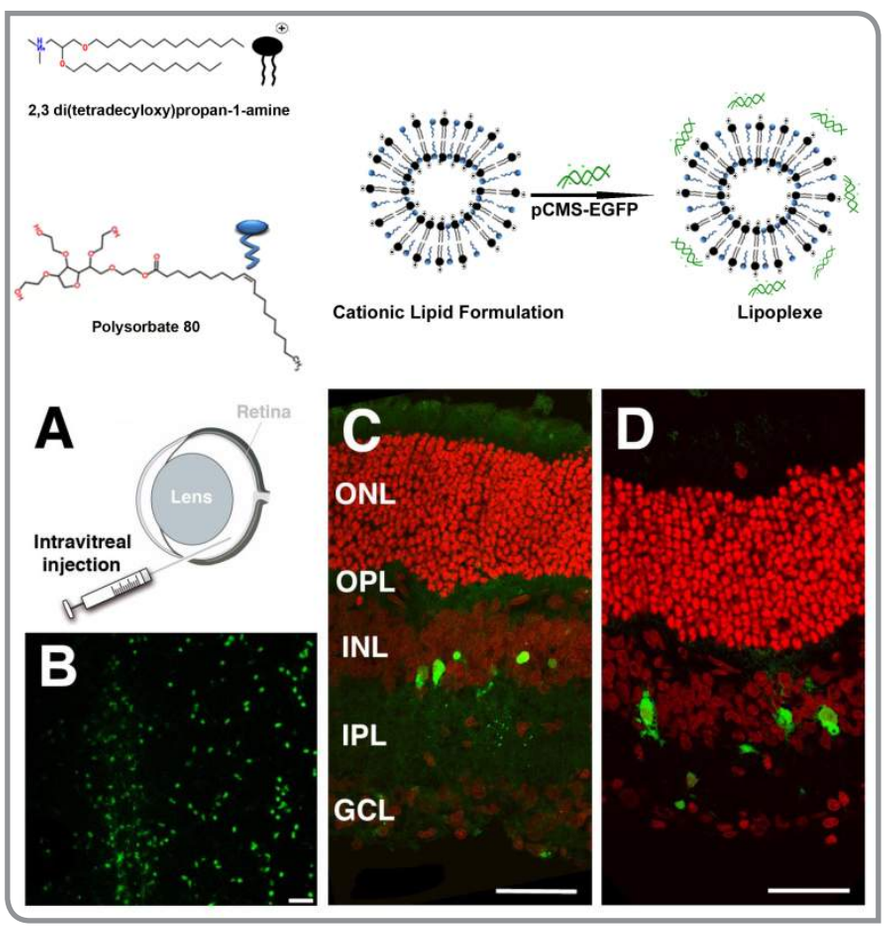
Development of novel siRNA for gene silencing.

The discovery of the RNA interference mechanism has triggered the development of nucleic acids derivatives to generate novel medical treatments. Although the use of synthetic small interfering RNA (siRNA) has been demonstrated, still several issues remain to be solved in order to ensure the potential of this novel medicinal avenue. One of the problems that have been addressed during the last years is the vulnerability of oligonucleotides to nucleases, which limits their practical use. Specifically, we explored the effects of the acyclic L-threoninol backbones in place of natural ribose rings on the biological properties of siRNAs. The introduction of these novel derivatives at the 3'-protuding ends of siRNAs confers a strong nuclease resistance, greater potency by a better affinity to PAZ domain and a lower degree of innate immunostimulation. Finally, the introduction of these derivatives at the 2on position near the 5'-end of the sense strand (see Figure below) avoids the loading of the sense strand into RISC lowering off-target effects. These results will be valuable in the design of therapeutic siRNA.



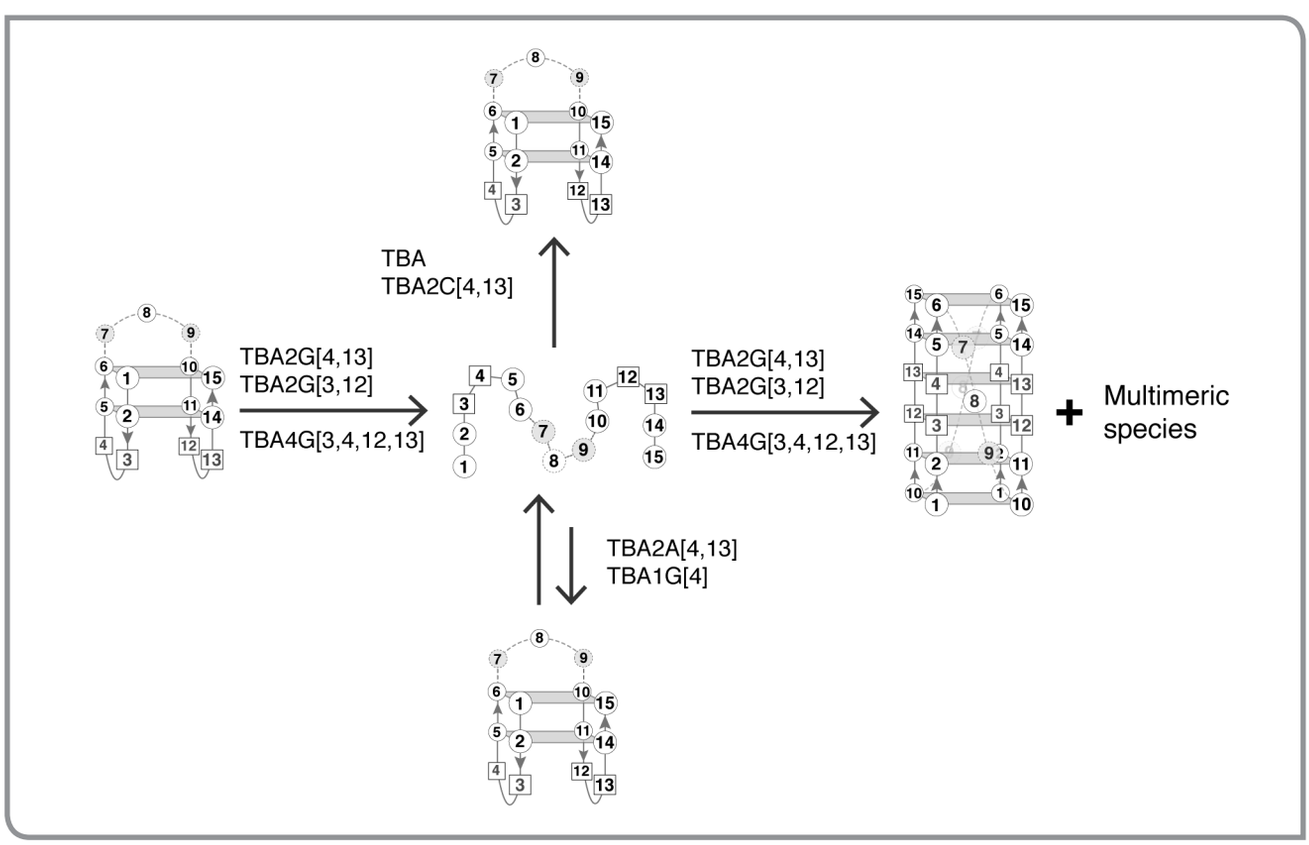
Improvement in gene therapy for the treatment of eye diseases.

So far one of the effective ways to carry genetic material into cells to try to correct genetic problems is to use a virus that is specifically designed for this task. However, this approach presents some security issues and a limitation on the size of the genetic material to be transported. In this collaborative work between the IQAC-CSIC, the Universities of the Basque Country (UPV) and Miguel Hernandez de Alicante (UMH) the development of new non-viral vectors described to transport genetic material into the cells of the retina using nanoparticles based on cationic lipids they have been specially formulated to facilitate their incorporation into the cells of the retina.



Structural polymorphism on guanine-rich oligonucleotides.

Guanine-rich sequences display a large structural variability with folds ranging from duplex to triplex and quadruplex helices. Quadruplexes are polymorphic and can display multiple stoichiometries, parallel and antiparallel strand alignments, with different topological arrangements. We have described the equilibrium between intramolecular antiparallel and intermolecular parallel G-quadruplexes in the thrombin binding aptamer (TBA). The theoretical and experimental studies demonstrate that an apparently simple modification at the loops of TBA induces a large change in the monomeric antiparallel structure of TBA to yield a parallel G-quadruplex exhibiting a novel T-tetrad. Present results illustrate the extreme polymorphism of G-quadruplexes and the ease to manipulate their conformation in solution by nucleotide modification.



NANOBIOTECHNOLOGY FOR DIAGNOSTICS

The Nanobiotechnology for Diagnostics Groupe, formerly **Applied Molecular Receptors Group (AMRg)** has focussed on the development of novel molecular diagnostic tools to provide alternatives to the actual limitations existing in several fields, but particularly in the clinical and food safety areas. The combination of nanotechnological and biotechnological advances has given raise to novel molecular diagnostic approaches to improve efficiency and/or to refine and extend the limits of detection. Nanostructured surfaces and nanoparticles may be the base for the construction of functional hybrid materials consisting of both organic (biomolecules) and inorganic components. Biosensors are between the potential applications of these new immunosensors using antibodies as biorecognition elements displaying fascinating features such as the possibility to respond selectively to biological or bioactive substances and the capability to respond in a physiological manner. The unique properties of certain nanomaterials combined with the excellent features of the antibodies allow envisaging novel exquisitely sensitive chemical and biological sensors.

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ARTICLES

A general perspective of the characterization and quantification of nanoparticles: Imaging, spectroscopic, and separation techniques

Lapresta-Fernández, A., Salinas-Castillo, A., Anderson De La Llana, S., Costa-Fernández, J.M., Domínguez-Meister, S., Cecchini, R., Capitán-Vallvey, L.F., Moreno-Bondi, M.C., Marco, M.-P., Sánchez-López, J.C., Anderson, I.S.

Critical Rev. Solid State Mat. Sc., 39, 423-458, **2014**.

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Valera, E., García-Febrero, R., Pividori, I., Sánchez-Baeza, F., Marco, M.-P.

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Development and impedimetric evaluation of a magnetic interdigitated microelectrode

Sanchez, B., Vega, D., Rodriguez, A., Bragos, R., Marco, M.-P., Valera, E.

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Electrochemical detection of fluoroquinolone antibiotics in milk using a magneto immunosensor

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Sensors, 14, 15965-15980, **2014**.

Extraction-less, rapid assay for the direct detection of 2,4,6-trichloroanisole (TCA) in cork samples

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Food Chem., 157, 221-228, **2014**.

Lipoprotein(a) determination in human serum using a nitrilotriacetic acid derivative immunosensing scaffold on disposable electrodes

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Rapid method based on immunoassay for determination of paraquat residues in wheat, barley and potato

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Mallén, M., Díaz-González, M., Bonilla, D., Salvador, J.P., Marco, M.P., Baldi, A., Fernández-Sánchez, C.

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Ahadian, S., Yamada, S., Ramón-Azcón, J., Ino, K., Shiku, H., Khademhosseini, A., Matsue, T.

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Díaz-González, M.; Pablo Salvador, J.; Bonilla, D.; Pilar Marco, M.; Fernández-Sánchez, C.; Baldi, A.

Biosensors Bioelectr., 74, 698-704, **2015**.

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Pastells, C., Acosta, G., Pascual, N., Albericio, F., Royo, M., Marco, M.-P.

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Immunochemical detection of penicillins by using biohybrid magnetic particles

Broto, M., Matas, S., Babington, R., Marco, M.-P., Galve, R.

Food Control, 51, 381-389, **2015.**

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Muriano, A., Chabottaux, V., Diserens, J.-M., Granier, B., Sanchez-Baeza, F., Marco, M.-P.

Food Chem., 178, 156-163, **2015.**

Microtubule guiding in a multi-walled carbon nanotube circuit

Sikora, A., Ramón-Azcón, J., Sen, M., Kim, K., Nakazawa, H., Umetsu, M., Kumagai, I., Shiku, H., Matsue, T., Teizer, W.

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Development and validation of an enzyme linked immunosorbent assay for fluoroquinolones in animal feeds

Tufa, R.A., Pinacho, D.G., Pascual, N., Granados, M., Companyo, R., Marco, M.P.

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RESEARCH PROJECTS

Plataformas de diagnóstico universal basadas en nanopartículas codificadas con oligonucleótidos y dispositivos de microarrays de DNA

Nacional, MAT2012-38573-C02-01

2013-2015

Electrochemical immunosensor system for the detection of neuroactive trytophan metabolites. Development of immunoreagents and nanostructured biohybrid sensing surfaces

Nacional, CTQ2011-29163-C03-01

2012-2014

Nanotecnología para cardiología y neumococo (NanoCardioCoco)

Nacional IPT2011-1337-010000

2011-2014

Sistemas de detección y cuantificación de biomarcadores de la enfermedad de Alzheimer (KIT-Alzheimer)

Nacional IPT2011-1055-900000

2011-2014

Design and evaluation of a novel impedimetric immunosensor for the diagnosis of sepsis of respiratory origin due to Pseudomonas aeruginosa

Convenio CIBER-BBN/CIBERES/SEPAR

2013-2014

Real-time monitoring of SEA contaminants by an autonomous Lab-on-a-CHIP biosensor (SEA-on-a-CHIP)

European, OCEAN-614168

2014-2017

Molecular links between diabetes and neurodegenerative disorders

MINECO, ISCiii. Integrated Projects of Excellence in CIBER, PIE1400061

2015-2017

RESEARCH HIGHLIGHTS

Throughout 2014 and 2015 the Nb4D group continued to develop antibodies against molecules of interest in the food safety, environmental monitoring and clinical diagnosis fields. Examples of recent developments include the production of antibodies against cardiac biomarkers, cytostatic agents, neurological disease biomarkers and antibiotics.

In the area of infectious diseases the group has made great strides. Two new patents have been presented to the Spanish Office for Patents and Brands for the detection of Pseudomonas aeruginosa and Staphylococcus aureus respectively. The characteristic pentaglycyl cross-bridge of the Staphylococcus aureus peptidoglycan cell wall was chosen as the epitope to develop specific antibodies against these bacteria. An ELISA was subsequently developed and was evaluated using real clinical samples1. The group collaborated with TIR group and the Group on Clinical Microbiology and Experimental Infectious Pathology in the CIBER-BBN financed project NanBioSepRes. The main objective of which was the development and validation of an Impedimetric immunosensor platform to be used for point of care (PoC) clinical diagnosis of Pseudomonas aeruginosa infections. The group will continue to work with these groups on further projects with similar aims.

With the culmination of the European project Conffidence (KBBE2007-211326) the group published various peer-reviewed articles of the research performed for this project, the aim of which was to develop fast effective methods for the detection of contaminants in food and feed samples. An ELISA method for the detection of the banned pesticide paraquat in wheat, barley and potato samples was developed2. The specific antibodies against paraquat were later labelled with CdS nanoparticles (CdSNP) and combined with antigen biofunctional magnetic μ-particles to create electrochemi-

cal nanoprobes which can be measured using graphite composite electrodes (GECs)3. After the immunochemical reaction the CdSNP are dissolved and the metals released are reduced at the electrode and read in the form of current or charge signal by an anodic stripping technique. Due to the amplification effect produced by the CdSNP on the amperometric/ coloumbimetric signal a very high detectability was reached.

Electrochemical detection was also employed to detect fluoroquinolone antibiotics4. The amperometric magento-immunosensor (AMIS) combines magnetic beads biomodified with an antibody against the fluroquinolone family modity, a haptenised enzyme and a magnetic graphite-epoxy composite (mGEC) electrode. Also, the fluoroquinolone enrofloxacin has been successfully determined in hair samples by an ELISA method which is an attractive non-invasive alternative to control misuse of such antibiotic and to ensure food safety by preventing such food derived products arrive to the consumer5. The detection of sulfonamide antibiotics in honey by ELISA was also developed6. Currently there is no legislation regarding the maximum residue levels (MRLs) of antibiotics in honey in Europe as this practice is prohibited but various countries within the EU (e.g. United Kingdom, Belgium) have set up tolerance levels.

Since the beginning of 2014, the group is participating in the 7th Framework Programme European project "SEA-on-a-CHIP". The aim of the project is to develop a miniaturized autonomous, remote and flexible immunosensor platform based on a fully integrated array of micro/nano-electrodes and a microfluidic system in a lab-on-a-chip configuration combined with electrochemical detection for real-time analysis of marine water in multi-stressor conditions. There are 17 partners from various European countries such as Italy, France, Spain, Portugal, UK, Romania, Sweden, Austria, Greece and Norway. The objectives of this project was broadcast on the national television La 2 in their informative programme "La Fabrica de Ideas" on November 2014. Nb4D is using immunoreagents already available to the group but is also producing antibodies against the insecticides deltamethrin and cypermethrin which are toxic to animals such as fish.

The group extended its contract with Pharmasans Labs. Inc. (Wisconsin, USA) for the development of new immunoreagents for diagnostic purposes and has also begun a new project for the detection of substances linked to inflammatory disorders. The group also began a new research agreement with FOSS Analytical A/S from Denmark.

The Custom Antibody Service of the Nb4D group belongs to the NANBIOSIS platform which has been incorporated into the map of Singular Scientific and Technological Infrastructures (ICTS) of the Spanish Ministry of Economy and Competitivity in collaboration with other services provided by CIBER-BBN and with the Jesus Uson Centre for Minimally Invasive Surgery (CCMIJU). NANBIOSIS is orientated towards medical applications and hopes to give a complete service and easy access through its framework that includes the design and production of nanomaterials and biomaterials, their characterization or the characterization of tissues, medical devices or systems from a physical, chemical, functional, toxicological or biological view including pre-clinical validation. The different services are located in Barcelona, Madrid, Zaragoza, Badajoz, Caceres, Valencia and Alava.

As already mentioned the group deposited two new patents in the Spanish Office for Patents. These include P201330312 "Haptens and conjugates derived from pyocycanin, antibodies thereof and immunochemical method for detecting infections caused by Pseudomonas aeruginosa", which has been published as a PCT (WO 2014/135730 A1), and P201530780 "Compuestos y sus usos como haptenos para la detección de S. aureus". In 2014, the patent P200701253 was conceded in Japan (JP 5568466 B2). In 2015, the patent P200931164 was conceded in the United States (US 9,170,227 B2).

Finally, the Nanobiotechnology and Molecular Diagnostics group continues to work on new strategies for the screening of small organic molecules, including electrochemical sensors, optical biosensors, quantum-dot based arrays, microarrays and the standard ELISA.

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2. Garcia-Febrero, R.; Salvador, J. P.; Sanchez-Baeza, F.; Marco, M. P., Rapid method based on immunoassay for determination of paraquat residues in wheat, barley and potato. Food Control 2014, 41 (0), 193-201.
3. Valera, E.; García-Febrero, R.; Pividori, I.; Sánchez-Baeza, F.; Marco, M. P., Coulombimetric immunosensor for paraquat based on electrochemical nanoprobes. Sensors and Actuators B: Chemical 2014, 194 (0), 353-360.
4. Pinacho, D.; Sánchez-Baeza, F.; Pividori, M.-I.; Marco, M.-P., Electrochemical Detection of Fluoroquinolone Antibiotics in Milk Using a Magneto Immunosensor. Sensors 2014, 14 (9), 15965-15980.
5. Fernández, F.; Pinacho, D. G.; Gratacós-Cubarsí, M.; García-Regueiro, J.-A.; Castellari, M.; Sánchez-Baeza, F.; Marco, M. P., Immunochemical Determination of Fluoroquinolone Antibiotics in Cattle Hair: a Strategy to Ensure Food Safety. Food Chemistry 2014, 157, 221-228.
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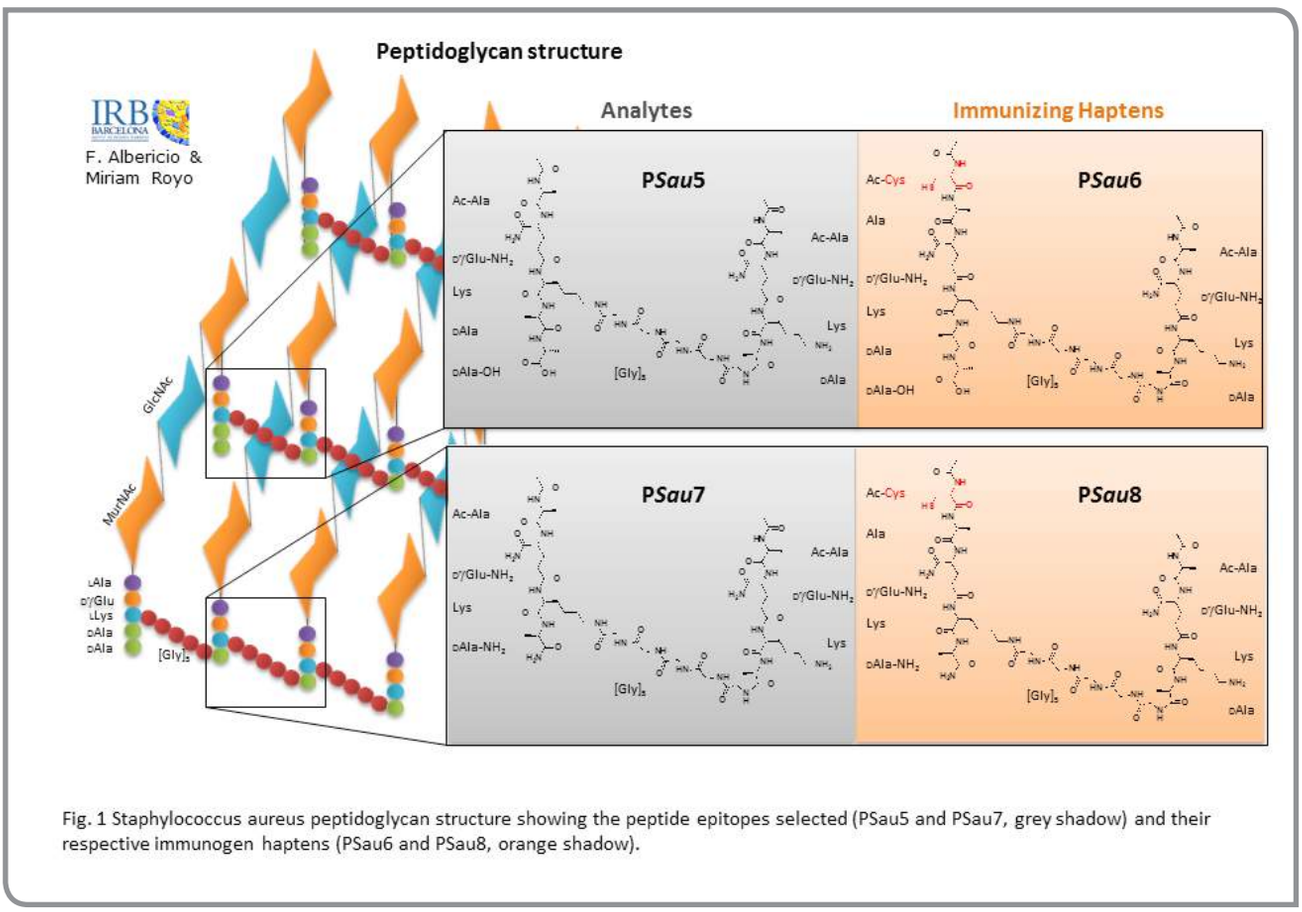

Fig. 1 Staphylococcus aureus peptidoglycan structure showing the peptide epitopes selected (PSau5 and PSau7, grey shadow) and their respective immunogen haptens (PSau6 and PSau8, orange shadow).

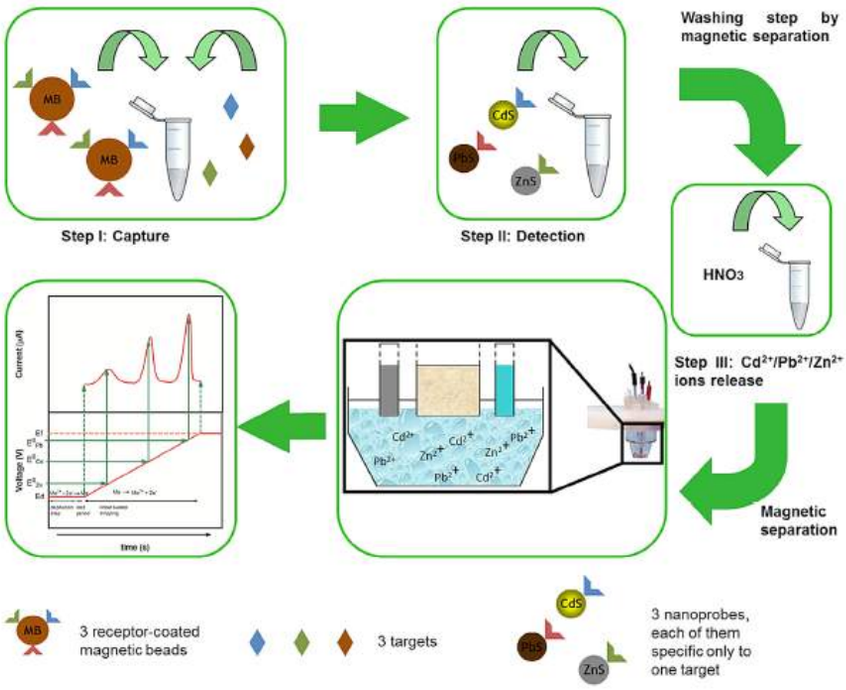

Fig. 2 Schematic explanation of the Electrochemical Coding Technology

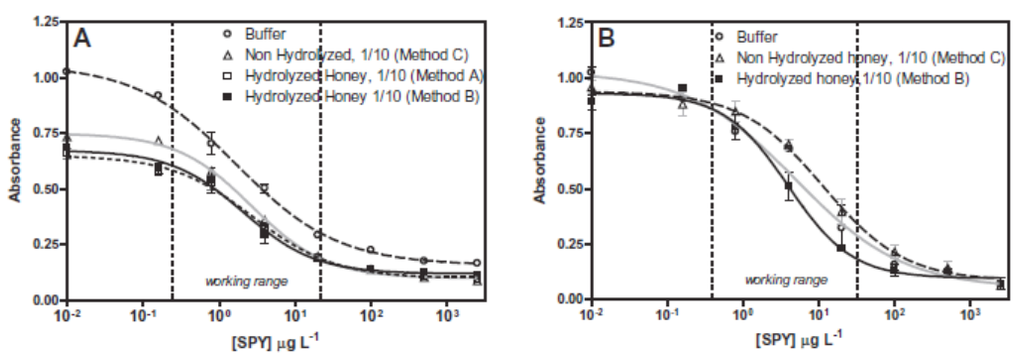

Fig. 3 Calibration curves obtained by the microplate-based iELISA (graph A) and the magneto-iELISA (graph B) in buffer, hydrolysed and non-hydrolysed samples for the detection of sulfonamide antibiotics in honey. Hydrolytic method A (2N HCl, 1 h 45°C): Hydrolytic method B (2N HCl, 5 min 100°C). Each concentration point was measured in triplicates. The concentration in the x-axes refer to the concentration in the honey solution, in order to know the concentration in honey the value has to be multiplied by 10 and expressed in µg kg^{-1}.

COLLOID AND INTERFACIAL CHEMISTRY GROUP

The main objectives of the group are the study of surfactant self-aggregation processes to contribute in the development of nanotechnological applications. The knowledge on basic aspects of surfactant aggregates (micelles, liquid crystals, vesicles) and colloidal dispersions (microemulsions, nano-emulsions, etc.) allows their use as nanoreactors for the preparation of novel nanostructured materials and as controlled drug delivery systems.

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ARTICLES

Conditions that bicontinuous microemulsions must fulfill to be used as template for electrodeposition of nanostructures

Serrà, A.; Gómez, E.; Calderó, G.; Esquena, J.; Solans, C.; Vallés, E.

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Influence of hydrophobically modified inulin (INUTEC NRA) on the stability of vulcanized natural rubber latex

Singh, M.; Esquena, J.; Solans, C.; Booten, K.; Tadros, T.F.

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Influence of nonionic branched-chain alkyl glycosides on a model nano-emulsion for drug delivery systems

Ahmad, N.; Ramsch, R.; Llinàs, M.; Solans, C.; Hashim, R.; Tajuddin, H.A.

Coll. Surf. B: Biointerfaces, 115, 267-274, **2014**.

In situ chitosan gelation initiated by atmospheric plasma treatment

Molina, R.; Jovancic, P.; Vilchez, S.; Tzanov, T.; Solans, C.

Carbohydrate Polymers, 103, 472-479, **2014**.

Effects of surfactant hydrophilicity on the oil solubilization and rheological behavior of a nonionic hexagonal phase

Alam, M.M.; Matsumoto, Y.; Aramaki, K.

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Heavily impregnated ceria nanoparticles with europium oxide: Spectroscopic evidences for homogenous solid solutions and intrinsic structure of Eu 3+-oxygen environments

Avram, D.; Rotaru, C.; Cojocaru, B.; Sanchez-Dominiguez, M.; Florea, M.; Tiseanu, C.

J. Mat. Sci., 49, 2117-2126, **2014.**

Molecular dynamics of spherical nanoparticles in dense polymer melts

Patti, A.

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Phototherapeutic functionality of biocompatible graphene oxide/dendrimer hybrids

Siriviriyanun, A.; Imae, T.; Calderó, G.; Solans, C.

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Polyurethane and polyurea nanoparticles based on polyoxyethylene castor oil derivative surfactant suitable for endovascular applications

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Int. J. Phar., 461, 1-13, **2014**.

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Anal. Bioanal. Chem., 406, 3895-3907, **2014**.

Quantifying the bioadhesive properties of surface-modified polyurethane-urea nanoparticles in the vascular network

Melgar-Lesmes, P.; Morral-Ruíz, G.; Solans, C.; García-Celma, M.J.

Coll. Surf. B: Biointerfaces, 118, 280-288, **2014**.

Synthesis of Mn-Zn ferrite nanoparticles by the oil-in-water microemulsion reaction method

Pemartin, K.; Solans, C.; Alvarez-Quintana, J.; Sanchez-Dominguez, M.

Coll. Surf. A: Physicochem. Engineering Aspects, 451, 161-171, **2014**.

In-situ formation of silver nanoparticles using non-ionic surfactant reverse micelles as nanoreactors

Shrestha, L.K.; Shrestha, R.G.; Vilanova, N.; Rodriguez-Abreu, C.; Ariga, K.

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Rangel-Rodríguez, A.M., Solans, C.; Vilchez, S. Flores-Gallardo, S.G.; Contreras-Esquivel, J.C.; Licea-Jiménez, L.

Appl. Biochem. Biotech. 174, 2941-2950, **2014**.

UV protective textiles by the deposition of functional ethylcellulose nanoparticles.

S. Vílchez-Maldonado, G. Calderó, J. Esquena, R. Molina.

Cellulose, 21 (3), 2133–2145, **2014.**

Local structure and nanoscale homogeneity of CeO2-ZrO 2: Differences and similarities to parent oxides revealed by luminescence with temporal and spectral resolution

Tiseanu, C.; Parvulescu, V.; Avram, D.; Cojocaru, B.; Boutonnet, M.; Sanchez-Dominguez, M.

PhysChemChemPhys, 16, 703-710, **2014**.

Biotinylated polyurethane-urea nanoparticles for targeted theranostics in human hepatocellular carcinoma

Morral-Ruíz, G.; Melgar-Lesmes, P.; López-Vicente, A.; Solans, C.; García-Celma, M.J.

Nano Research, 8, 1729-1745, **2015**.

Design and in vitro evaluation of biocompatible dexamethasone-loaded nanoparticle dispersions, obtained from nano-emulsions, for inhalatory therapy

Fornaguera, C.; Llinàs, M.; Solans, C.; Calderó, G.

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Di Carlo, G.; Lualdi, M.; Venezia, A.M.; Boutonnet, M.; Sanchez-Dominguez, M.

Catalysts, 5, 442-459, **2015**.

Novel non-viral gene delivery systems composed of carbosilane dendron functionalized nanoparticles prepared from nano-emulsions as non-viral carriers for antisense oligonucleotides

Fornaguera, C.; Grijalvo, S.; Galán, M.; Fuentes-Paniagua, E.; De La Mata, F.J.; Gómez, R.; Eritja, R.; Calderó, G.; Solans, C.

Int. J. Pharm., 478, 113-123, **2015**.

Feasibility of the development of reference materials for the detection of Ag nanoparticles in food: neat dispersions and spiked chicken meat

Grombe, R., Allmaier, G., Charoud-Got, J., Dudkiewicz, A., Emteborg, H., Hofmann, T., Larsen, E.H., Lehner, A., Llinàs, M., Loeschner, K., Mølhave, K., Peters, R.J., Seghers, J., Solans, C., von der Kammer, F., Wagner, S., Weigel, S., Linsinger, T.P.J.

Accred. Quality Ass., 20, 3-16, **2015**.

Galantamine-loaded PLGA nanoparticles, from nano-emulsion templating, as novel advanced drug delivery systems to treat neurodegenerative diseases

Fornaguera, C.; Feiner-Gracia, N.; Calderó, G.; García-Celma, M.J.; Solans, C.

Nanoscale, 7, 12076-12084, **2015**.

Interactions of PLGA nanoparticles with blood components: protein adsorption, coagulation, activation of the complement system and hemolysis studies

Fornaguera, C, Calderó, G., Mitjans, M., Vinardell, M.P., Solans, C., Vauthier, C.

Nanoscale, 7, 6045-6058, **2015**.

Multiple emulsions as soft templates for the synthesis of multifunctional silicone porous particles

Vilanova, N.; Kolen'ko, Y.V.; Solans, C.; Rodríguez-Abreu, C.

J. Colloid Interface Sci., 437, 235-243, **2015**.

PLGA nanoparticles prepared by nano-emulsion templating using low-energy methods as efficient nanocarriers for drug delivery across the blood-brain barrier.

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Sikora, E.; Llinas, M.; Garcia-Celma, M.J.; Escribano, E.; Solans, C.

Coll. Surf. B: Biointerfaces, 126, 541-545, **2015**.

Vitamin A Palmitate-beta;-cyclodextrin inclusion complexes: Characterization, protection and emulsification properties

Vilanova, N.; Solans, C.

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Nanoscale electric polarizability of ultrathin biolayers on insulating substrates by electrostatic force microscopy

Dols-Perez, A., Gramse, G., Calò, A., Gomila, G., Fumagalli, L.

Nanoscale, 7, 18327-18336, **2015**

G. J. T. Tiddy, A. Durand, C. Solans, W. Kunz, C. Rodríguez-Abreu. EDITORIAL. *Colloids and Surfaces A: Physicochemical and Engineering Aspects,* 458, 1–2, **2014**

RESEARCH PROJECTS

Estudios experimentales y teóricos de procesos de autoagregación de compuestos anfifílicos biocompatibles para el diseño de nanomateriales avanzados

Nacional, CTQ2011-29336-C03-01

2012-2015

Multifuncional nanotechnology for selective detection and treatment of cancer

CCEE, 262943

2011-2015

Theranostic Magnetic Nanoparticles For Cancer Diagnosis and Treatment: Magnetic Properties and Controlled Release of Anticancer Drugs (TheraMagNano)

Programa TecnioSpring, TECSPR14-2-0033

2015-2017

"Ayudas para apoyar las actividades de los grupos de investigación. Nombre del grupo: Tensioactius"

Generalitat de Catalunya, 2009SGR961

2009-2014

Generalitat de Catalunya, 2014SGR1655

2014-2016

"Asignación del CIBER-BBN 2014 para el desarrollo de los proyectos intramurales y los programas horizontales, y Programa Plataformas CIBER-BBN"

CIBER-BBN

2014, 2015

"Conveni d'ACC1Ó amb la UAB, el PRUAB, el CSIC i el CVC per al foment de la transferència tecnològica"

Pla d'actuació 2014. ACC1Ó (Generalitat de Catalunya). 2014

Pla d'actuació 2015. ACC1Ó (Generalitat de Catalunya). 2015

RESEARCH HIGHLIGHTS

Amphiphile Self-assembly

Self-assembly studies of amphiphilic molecules are conducted in the group as a bottom up approach for the development of well-defined nanostructures in view of their use as nanocarriers (e.g. controlled drug delivery systems), nanoreactors (e.g. synthesis of advanced materials), tailor-made formulations, etc. During this period, the effect of incorporating new nonionic glycolipid surfactants on the properties of a model water/nonionic surfactant/oil system was investigated using branched-chain alkyl glycosides whose structures are closely related to glycero-glycolipids. The surfactants, with identical hydrophobic chain, differed in the polar head group and consequently their effects on the properties of the system were different due to the differences in hydrophilic-lipophilic balance (HLB) properties (**Influence of nonionic branched-chain alkyl glycosides on a model nano-emulsion for drug delivery systems** *Coll. Surf. B: Biointerfaces*, 115, 267-274, **2014**.) . Another topic investigated was the formation of supramolecular structures (so-called inclusion complexes) with β-cyclodextrins and vitamin A palmitate in aqueous media without the need of organic solvents (**Vitamin A Palmitate-beta;-cyclodextrin inclusion complexes: Characterization, protection and emulsification properties** *Food Chem*., 175, 529-535, **2015)**. From the phase solubility diagram it was inferred that the solubility of Vitamin A Palmitate in water increased when encapsulated and that inclusion process takes place in two-stages. Moreover, the vitamin showed a higher stability towards different variables when encapsulated. It was expected that the resulting inclusion complex was amphiphilic (Figure 1 a): with a hydrophilic moiety corresponding to the hydrophilic corona of the β - cyclodextrins and a hydrophobic moiety coming from the non- entrapped carbon chain of the vitamin. Indeed, the inclusion complex presented surface activity as the surface tension was reduced down to 50 mN/m while that of the empty β – cyclodextrins was of the same order as that of water (Figure 1 b).

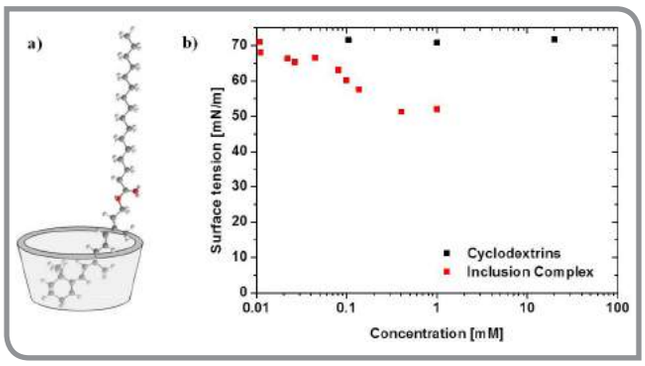


Figure 1. (a) Scheme of the Vitamin A Palmitate–β-cyclodextrin inclusion complex. (b) Surface tension measurements at 25 ºC of empty β -CDs and the inclusion complex (*Food Chem*., 175, 529-535, **2015).**

The results showed that β – cyclodextrins can be a promising vehicle to increase the water solubility, stability and thereby the bioavailability of Vitamin A Palmitate in food fortification to treat Vitamin A deficiency.

Emulsions as soft-templates for the obtention of nano/microparticles

The group has been very active in the study of emulsification processes by low-energy methods in the last ten years. The knowledge and experience gained on this subject has allowed the design of novel, simple and scalable strategies for nanoparticle/microparticle synthesis based on these methods using different types of emulsions. Recently, the attention has been focused to the production of polymeric nanoparticles for pharmaceutical applications. The strategy consists on the preparation of nano-emulsions by low-energy methods using a preformed biocompatible polymer dissolved in a solvent as dispersed phase, followed by solvent evaporation. Using this strategy, multifunctionalized polymeric nanoparticles with controlled size have been designed. Figure 2 shows a schematic representation of the preparation of loperamide (LOP)-loaded and antibody 83D-functionalized Poly-(D,L-lactide-co-glycolide)acid (PLGA)nanoparticles which produced pharmacological effect at the central nervous system proving their capacity to cross the blood-brain barrier (BBB) (**PLGA nanoparticles prepared by nano-emulsion templating using low-energy methods as efficient nanocarriers for drug delivery across the blood-brain barrier**. Control. Rel., 211, 134-143, 2015.)

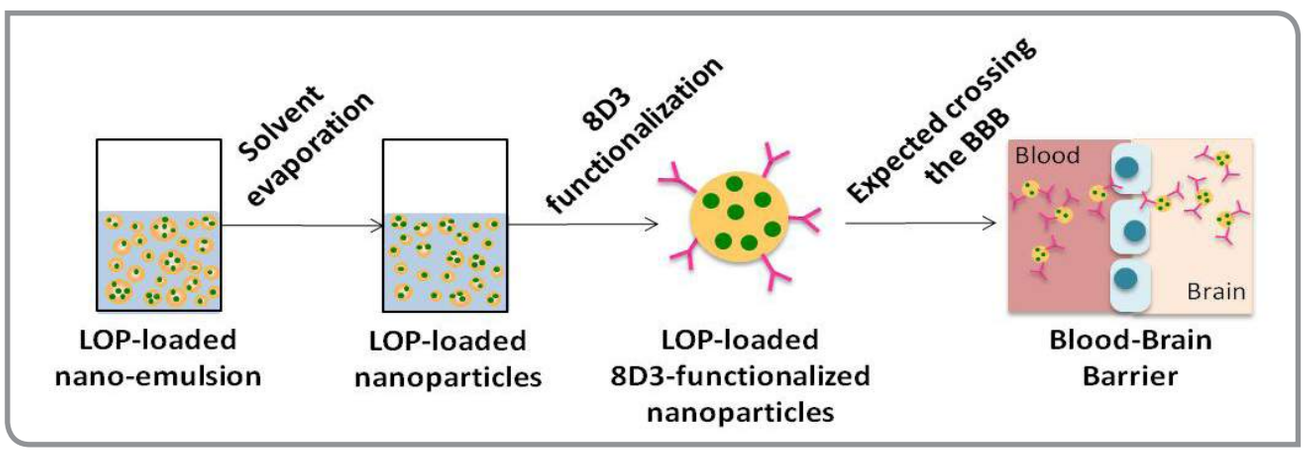


Figure 2. Schematic representation of the process of LOP-loaded nanoparticles preparation from nano-emulsion templating, their functionalization and their use as nanosystems crossing the BBB (*J. Control. Rel*., 211, 134-143, **2015**.)

Moreover, PLGA nanoparticles functionalized with carbosilane cationic dendrons and electrostatically attached to antisense oligonucleotide showed potential as non-viral carriers in antisense therapy (**Novel non-viral gene delivery systems composed of carbosilane dendron functionalized nanoparticles prepared from nano-emulsions as non-viral carriers for antisense oligonucleotides.** *Int. J. Pharm*., 478, 113-123, **2015**). These complexes were non-haemolytic and non-cytotoxic at the concentrations required and their ability to impart cellular uptake was also promising.

Apart from nano-emulsions, we have used multiple water-in-oil-in-water (W1/O/W2) emulsions as soft templates for the synthesis of multifunctional porous particles. We have developed a multiple emulsion templating process to prepare silicone porous particles with tuned mechanical properties using an oil phase constituted by a crosslinkable poly(dimethylsiloxane) (PDMS) oil **Multiple emulsions as soft templates for the synthesis of multifunctional silicone porous particles.** *J. Colloid Interface Sci*., 437, 235-243, **2015**). The silicone particles showed ability to encapsulate functional nanomaterials, such as magnetic nanoparticles. Figure 3 shows that effective removal of organic solvents from aqueous media can be achieved with the hybrid magnetic- silicone nanocomposite. Therefore, these hybrid nanocomposite materials are promising for environmental applications.

These results showed the versatility of multiple emulsion templating as a facile method to integrate inorganic-organic components into particulate, porous materials. The possibility of incorporating nanomaterials with other properties (e.g., optical, fluorescent) using different polymer matrices is a motivation for future work.

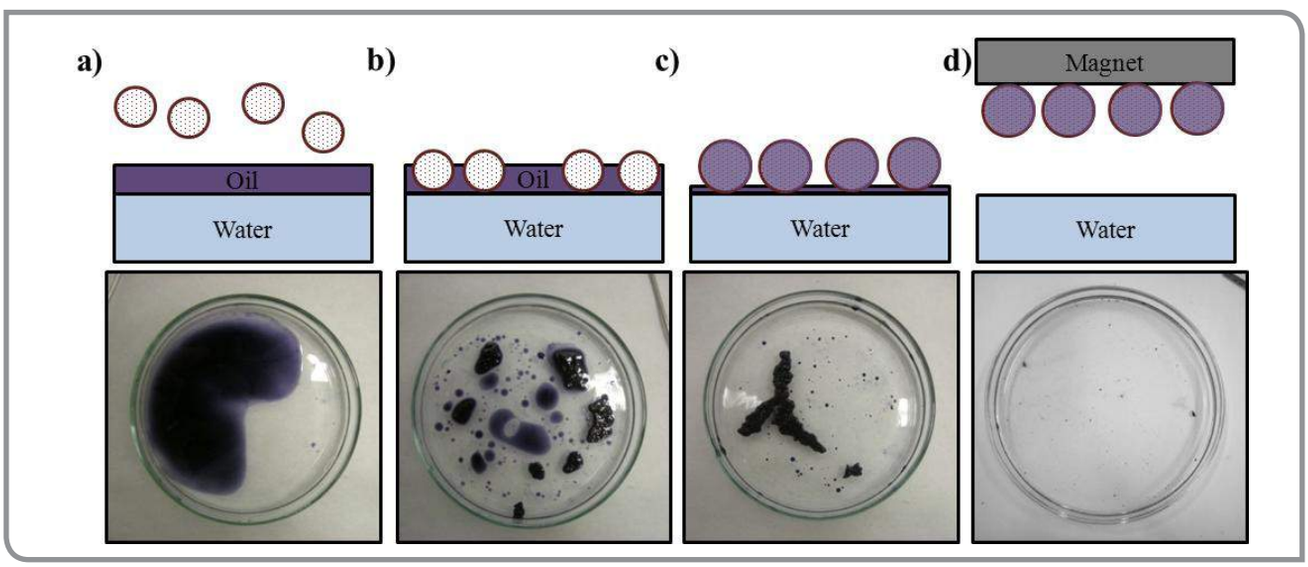
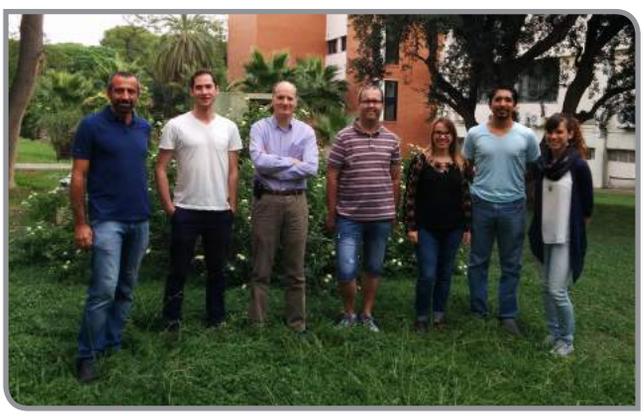


Figure 3. Removal of an oil spill with hybrid silicone particles: 0.5 mL of dyed heptane was poured onto a water surface (a), then 50 mg of hybrid particles were added (b). The organic solvent was absorbed by the particles (c), and finally, swollen particles were removed with the help of a permanent magnet, leaving almost solvent-free clean water (d). *J. Colloid Interface Sci*., 437, 235-243, **2015**

SURFACE CHEMISTRY

The main objective is to study the formation and characterization of structured materials in colloidal systems, and their applications in novel technological processes. The main research lines include: A) Preparation and characterization of organic and inorganic porous materials; B) Formation, characterization and properties of hydrogels and microgels; C) Design and study of novel water-in-water (W/W) emulsions; and D) Development of stimuli-responsive textiles by incorporation of advanced nanostructured materials.



STAFF

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TECHNICIANS

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JONATHAN MIRAS HERNÁNDEZ
FERRAN ROIG ROIG
SILVIA VILCHEZ MALDONADO
YORAN BELDENGRÜN

POST-GRADUATE STUDENTS

LAURA SOBREVIAS BONELLS
MARÍA ELENA BAUTISTA PÉREZ BALTAZAR SILVAN

ARTICLES

Antagonistic effects between magnetite nanoparticles and a hydrophobic surfactant in highly concentrated pickering emulsions

Vílchez, A.; Rodríguez-Abreu, C.; Menner, A.; Bismarck, A.; Esquena, J.

Langmuir, 30, 5064-5074, **2014**.

Conditions that bicontinuous microemulsions must fulfill to be used as template for electrodeposition of nanostructures

Serrà, A.; Gómez, E.; Calderó, G.; Esquena, J.; Solans, C.; Vallés, E.

J. Electroanal. Chem., 720, 101-106, **2014**.

Hafnia-Silica Cryogels: Solvent-Assisted Textural and Catalytic Control in the Citronellal Cyclization

Jimeno, C., Miras, J., Esquena, J.

ChemCatChem, 6, 2626-2633, **2014**.

Influence of hydrophobically modified inulin (INUTEC NRA) on the stability of vulcanized natural rubber latex

Singh, M.; Esquena, J.; Solans, C.; Booten, K.; Tadros, T.F.

Coll. Surf. A: Physicochem. Engin. Aspects, 451, 90-100, **2014**.

PH-dependent loading of Pt nanoparticles protected by dendrimer in calcium phosphate matrices

Fam, Y.; Imae, T.; Miras, J.; Martinez, M.; Esquena, J.

Microporous Mesoporous Mat., 198, 161-169, **2014**.

Synthesis and azo dye photodegradation activity of ZrS2-ZnO nano-composites

Krishnakumar, B.; Imae, T.; Miras, J.; Esquena, J.

Separation Purification Technol., 132, 281-288, **2014**,

UV protective textiles by the deposition of functional ethylcellulose nanoparticles

Vílchez-Maldonado, S.; Calderó, G.; Esquena, J.; Molina, R.

Cellulose, 21, 2133-2145, **2014**.

Sol-gel hybrid membranes loaded with meso/ macroporous SiO2, TiO2-P2O5 and SiO2-TiO2-P2O5 materials for PEMFC applications

Castro, Y., Mosa, J., Aparicio, M., Pérez-Carrillo, L.A., Susana Vílchez, S., Esquena, J., Durán, A.

Materials Chem. Phys., 149, 686-694, **2015**.

RESEARCH PROJECTS AND CONTRACTS

Nuevos apósitos activos biocompatibles basados en factor tisular recombinante con propiedades hemostáticas/sellantes

Proyecto Innpacto, IPT-2012-0348-010000

2013-2014

Formación de emulsiones de Pickering mediante métodos de baja energía para la preparación de nuevos materiales porosos nanocompuestos

Proyecto del plan Nacional de I+D+i, CTQ2011-23842

2012-2014

Biopolymer Based FOOd Delivery Systems

BIBAFOODS, FP7-PEOPLE-2013-ITN, 606713

2014-2018

Diseño y aplicaciones de nuevos micro/nanogeles biocompatibles obtenidos mediante métodos de condensación avanzados (MICRONANOGELES)"

PLAN NACIONAL, CTQ2014-52687-C3-1-P

2015-2017

Novel antimicrobial hydrogels for contact lenses (HYDROLENSES)

Programa TecnioSpring, TECSPR14-2-0044

2015-2017

Ayudas para apoyar las actividades de los grupos de investigación. Nombre del grupo: Tensioactius"

Generalitat de Catalunya, 2009SGR961

2009-2014

Generalitat de Catalunya, 2014SGR1655

2014-2016

Asignación del CIBER-BBN 2014 para el desarrollo de los proyectos intramurales y los programas horizontales, y Programa Plataformas CIBER-BBN"

2014 2015

Conveni d'ACC1Ó amb la UAB, el PRUAB, el CSIC i el CVC per al foment de la transferència tecnològica"

Pla d'actuació 2014. ACC1Ó (Generalitat de Catalunya).

Pla d'actuació 2015. ACC1Ó (Generalitat de Catalunya).

RESEARCH HIGHLIGHTS

FORMATION AND PROPERTIES OF BIOCOMPATIBLE HYDROGELS

Hydrogels are usually defined as three-dimensional networks of highly hydrated polymer materials, with a predominantly elastic rheological behavior. Chemical hydrogels, cross-linked with covalent bonds, can greatly swell and deswell reversibly, without dissolving or losing their structural integrity. Hydrogels are promising scaffold materials for cartilage tissue engineering, because of the high water retention. In special, gelatin hydrogels seem to be a suitable option to recreate the soft organic matter of interbone tissue. Gelatin is a protein obtained by partial hydrolysis of native collagen from animal origin, readily available with low cost. Due to its biocompatibility and biodegradability, this polymer has been used in medical applications. Nevertheless, the main limitation of gelatin for applications in tissue engineering is its high solubility in water. This limitation can be solved by cross-linking. There are different methods for crosslinking, physical, chemical or physico-chemical. Regarding to chemical crosslinking, various compounds can be used to react with the free amino groups of the peptides constituting gelatin as glutaraldehyde, formaldehyde or ethylene glycol diglycidylether. However, these compounds have physiological toxicity. Therefore, in the Surface Chemistry Group naturally occurring cross-linking agents are used such as genipin and transglutaminase. The mechanical properties of these hydrogels can be modulated by controlling crosslinker concentration.

NOVEL WATER-IN-WATER (W/W) EMULSIONS FOR THE PREPARATION OF MICROGELS

This research line focuses on the preparation and characterization of microgel particles, obtained by cross-linking in the disperse phase of water-in-water (W/W) emulsions, with the final aim of studying the microgels as carriers for the delivery of enzymes. The use of microgels as drug delivery vehicles is of interest as they combine the useful aspects of colloidal dispersions with the ones of conventional macrogels. This means they are free-flowing liquids with a high surface to volume ratio, which facilitates mass transport to and from the microgels, but also display controlled swelling, which makes them responsive delivery vehicles. Furthermore microgels are generally hydrophilic and contain a large amount of water, which allows proteins to be incorporated into the microgels with only moderate conformational changes. Biocompatible microgels, in mild conditions, can be prepared in absence of both surfactant and oil, by cross-linking in the internal phase of water-in-water (W/W) emulsions, in order not to harm enzyme activity. W/W emulsions form due to the thermodynamic incompatibility of two hydrophilic high molecular weight polymers in aqueous solutions. In these systems, segregative separation of two aqueous solutions is produced because of negative entropy of mixing, induced by conformational restrictions of the polymers. Our research in water-in-water emulsions focuses on systems with mixtures of proteins and polysaccharides. Some examples include Gelatin-in-Maltodextrin (G/M) emulsions and Carboxymethyl cellulose-in-bovine serum albumin (CMC/BSA) emulsions. These systems allow the formation of Gelatin and Carboxymethyl cellulose microgels, respectively.

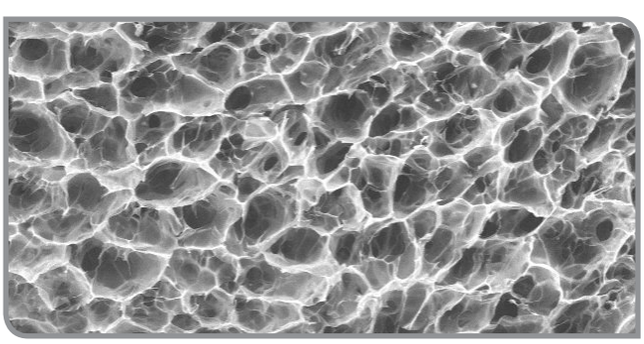

Fig. 1. Scanning electron micrograph of a transglutaminase crosslinked gelatin hydrogel, observed after freeze-drying.

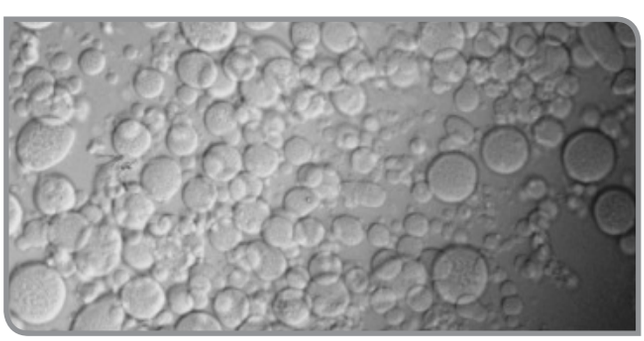

Fig. 2. Optical microscopy of a gelatin microgel.

DESIGN AND FORMULATION OF PICKERING EMULSIONS

It is known that emulsions can be prepared in absence of surfactant, by using particles as stabilizers. These emulsions, denoted as Pickering emulsions, play an important role in numerous industrial applications. Pickering emulsions were prepared with partially hydrophobized nanoparticles, to achieve the optimal wetting properties that enhance emulsion stability. It is well known, that emulsion stability depends on the hydrophilic/hydrophobic character of nanoparticles. Oleic acid was used as a functionalization agent, in order to partially hydrophobize the surface of nanoparticles. Pickering emulsions acquired by this method were of micrometric range and polydisperse, presenting creaming and flocculation as the main destabilization processes. These emulsions were either oil-in-water (O/W) or water-in-oil (W/O). Microscopy observations demonstrated adsorption of nanoparticles at the oil-water interface. In addition, the emulsion stability could be tuned in the presence of electrolytes. Pickering emulsions can also be obtained by a low-energy method based on the Ouzo effect. These emulsions showed smaller droplet size compared to those obtained by a high energy method but were more unstable. Polymerization in the external phase of W/O highly concentrated emulsions allowed to obtain low-density macroporous foams, with nanoparticles anchored on the pore surface.

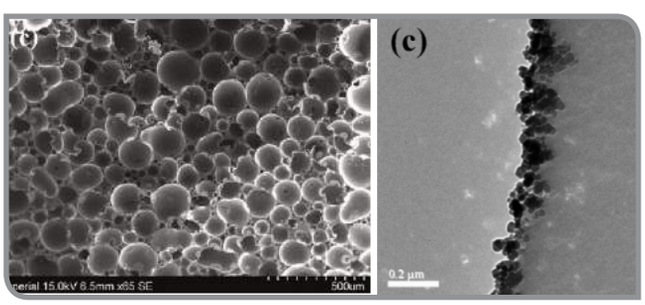

Fig. 3. Examples of a porous solid foams (left, SEM image), and detail of nanoparticles adsorbed at the interface (right, TEM image).

CELL THERAPY

The Cell Therapy group is interested in two related applied-research fields: regenerative medicine and tumor therapy. In the first case, the objective is the analysis of cell behavior in biomaterials used as scaffolds for tissue repair. In the second case, the objective is to develop antitumor therapies using stem cells as vehicles for the local delivery of therapeutic agents and the study of therapeutic-cell tumor interactions. However, both, the procedures and models developed also allow more general analysis of tumor response to chemical and biological agents.

For these studies the group uses mesenchymal stromal cells from adipose tissue. This special stem cell type capable of producing multiple chemokines and growth factors is a very promising therapy agent, not only due to its elevated capacity for multi-lineage differentiation (tissue repair applications) and tumor homing (therapy), but also for its abundance and easy generation from human adipose tissue.

The need to observe the behavior of cells in live animals has led to the development and use of bioluminescence imaging procedures based in the modification of cells with luciferase-gene reporters. Bioluminescence reporters allow the detection and monitoring of cells implanted in live animals, using high sensibility video cameras capable of lineal response ranging six orders of magnitude. In this manner, in spite of the diffusion and absorption of photons by animal tissues, these instruments allow imaging the distribution and proliferation of small populations of bioluminescent cells implanted in live animals. The use of inducible tissue-specific promoters to regulate the expression of luciferase reporters also allows the evaluation of their level of activity and therefore the analysis of changes in gene expression in vivo. Moreover, due to the existence of luciferases that use non cross-reacting substrates, it is possible to monitor two cell populations en the same animal or the expression level of two different reporters in the same cell.

STAFF

JERONIMO BLANCO FERNANDEZ, GROUP LEADER
NURIA RUBIO VIDAL, SENIOR SCIENTIST

PH. D.

MARTA GUERRA REBOLLO
CRISTINA GARRIDO LOPEZ
OSCAR MECA CORTES
LOURDES SANCHEZ CID

ARTICLES

Bioluminescent and micro-computed tomography imaging of bone repair induced by fibrin-binding growth factors

Vila, O.F.; Martino, M.M.; Nebuloni, L.; Kuhn, G.; Pérez-Amodio, S.; Müller, R.; Hubbell, J.A.; Rubio, N.; Blanco, J.

Acta Biomaterialia, 10, 4377-4389, **2014**.

Cyr61 silencing reduces vascularization and dissemination of osteosarcoma tumors

Habel, N.; Vilalta, M.; Bawa, O.; Opolon, P.; Blanco, J.; Fromigue, O.

Oncogene, 14, 3207-3213, **2014**.

Fast-Proliferating adipose tissue mesenchymal-stromal-like cells for therapy

Aguilar, E.; Bagó, J.R.; Soler-Botija, C.; Alieva, M.; Rigola, M.A.; Fuster, C.; Vila, O.F.; Rubio, N.; Blanco, J.

Stem Cells Development, 23, 2908-2920, **2014**.

Evaluation of posterolateral lumbar fusion in sheep using mineral scaffolds seeded with cultured bone marrow cells

Cuenca-López, M.D.; Andrades, J.A.; Gómez, S.; Zamora-Navas, P.; Guerado, E.; Rubio, N.; Blanco, J.; Becerra, J.

Int. J. Mol. Sci., 15, 23359-23376, **2014**.

Postinfarction functional recovery driven by a three-dimensional engineered fibrin patch composed of human umbilical cord blood-derived mesenchymal stem cells

Roura, S.; Soler-Botija, C.; Bagó, J.R.; Llucià-Valldeperas,

A.; Férnandez, M.A.; Gálvez-Montón, C.; Prat-Vidal, C.; Perea-Gil, I.; Blanco, J.; Bayes-Genis, A.

Stem Cells Translational Med., 4, 956-966, **2015**.

In Vitro and in Vivo Demonstration of Photodynamic Activity and Cytoplasm Imaging through TPE Nanoparticles.

Jayaram, DT.; Ramos-Romero, S.; Shankar, BH.; Garrido, C.; Rubio, N.; Sanchez-Cid, L.; Gómez SB.; Blanco, J.; Ramaiah, D.

ACS Chem Biol. Epub Nov 4. **2015.**

RESEARCH PROJECTS

Red de terapia celular – Tercel

Nacional, RD12/0019/0004

01/01/2013-31/12/2016

Terapia combinada basada dos tipos celulares y dos sistemas de activación de fármacos dirigida al nicho vascular de las células madre de glioblastoma

Nacional, SAF2012-33404

01/01/2013-31/12/2015

Terapia fotodinámica contra el sistema vascular tumoral

Nacional, PRI-PIBIN-2011-1011

01/12/2011-01/12/2014

Desarrollo racional de estrategias de terapia celular antitumoral

Nacional, SAF2009-07102

01/01/2010-30/06/2014

Nuevo tratamiento para el glioblastoma multiforme basado en terapia génica no invasiva (Gliogene Delivery)

Nacional, Retos-Colaboración RTC-2014-2077-1

14/09/2014-31/12/2017

Multifunctional Nanoparticles for Cell Therapy (TRANSMAG)

Nacional, Convocatoria Proyectos de Transferencia del CIBER-BBN

17/11/2015-16/11-2017

RESEARCH HIGHLIGHTS

The Cell Therapy Group is involved in two general aspects of cell therapy: regenerative medicine and cell based tumor therapy, as well as, in the advancement of our understanding of the interactions between stem cells and tumor cells. The main advances of the team during 2014 were the completion of the work characterizing a new cell type, "Fast Proliferating Mesenchymal Stem Cells" (FP-MSCs) derived from human mesenchymal cells from adipose tissue (hAMSCs), whit a replication capacity 3,5 fold faster than that of the parental type (Fig. 1). Such cells are expected to be useful in therapeutic strategies requiring large numbers of cells. In tumor therapy, it has been shown that FP-MSCs expressing HSV thymidin kinase have a capacity equivalent to that of hAMSCs for bystander killing of tumors. Moreover, the repeated application of FP-MSCs is able to "chronify" or keeps inhibited a glioblastoma tumor implanted in the mouse brain. In support of our hypothesis that hAMSCs nest in the tumor vascular system, more precisely, in the tumor stem cell niche, we have completed a project showing that the selective elimination of CD133+ tumor stem cells is sufficient to inhibit a tumor of human glioma implanted in the brain of an immune depressed mouse.

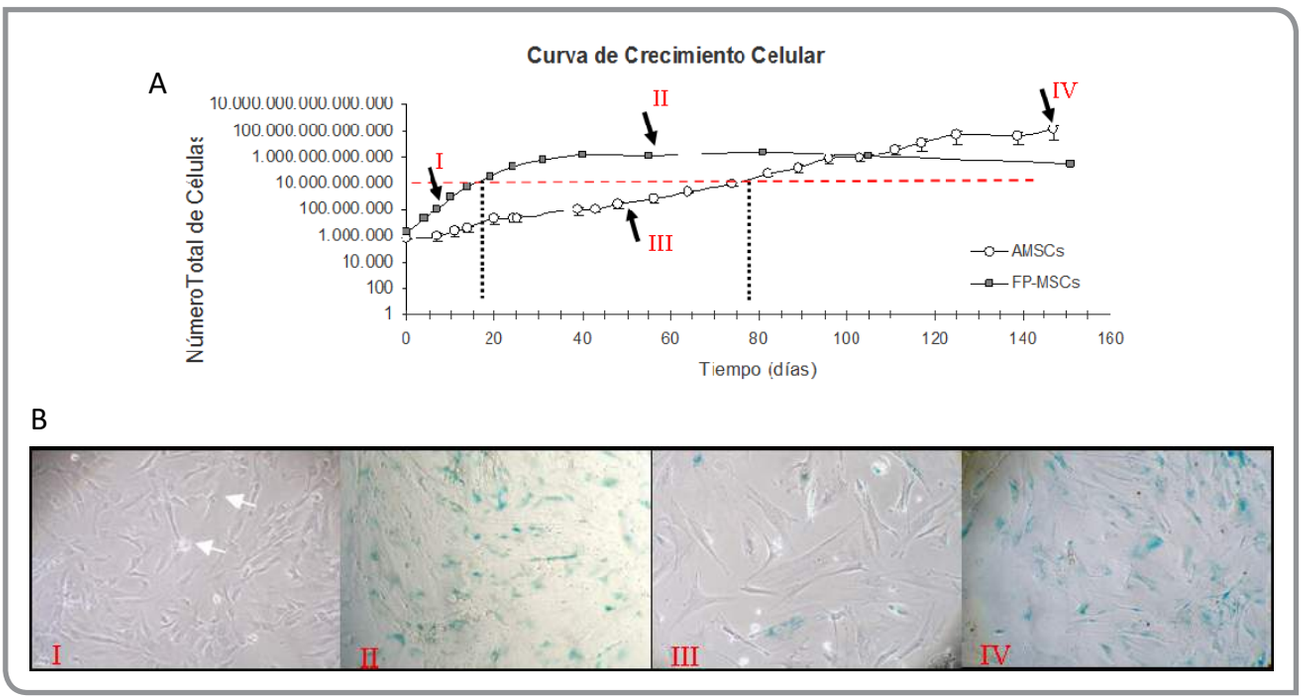

Fig. 1. Proliferation rate of hAMSCs is growth medium dependent. (A) The graph describes the proliferation capacity of hAMSCs in Dulbecco's modified Eagle's medium (DMEM) (open symbols) and in EGM-2 medium (closed symbols) [n = 3 for each condition; error bars, standard deviation (SD)].The red horizontal line marks the 10^{10} cell level. Roman numerals (arrows) indicate the times at which β-galactosidase expression was assayed. (B) β-galactosidase staining (blue), a senescence marker, shows entry of cells in the stationary growth phase. hAMSCs, human adipose-tissue derived MSCs.

In support of our hypothesis that hAMSCs nest in the tumor vascular system, more precisely, in the tumor stem cell niche, we have completed a project showing that the selective elimination of CD133+ or Sox2+ tumor stem cells is sufficient to inhibit a tumor of human glioma implanted in the brain of an immune depressed mouse.

The principal milestone achieved during 2015 has been the discovery that therapeutic mesenchymal stromal cells used for therapy against gliomas do not undergo apoptosis upon administration of the Ganciclovir prodrug, but survive the treatment. Thus, we have to assume that tumor killing effect is mediated by secretion of Ganciclovir phosphate loaded exosomes or a similar mechanism. Moreover, we have also discovered that a consequence of anti-replication therapy against tumors is the appearance of a pool of therapy resistant glioma stem cells that we can detect and quantify by bioluminescence imaging; capable of recapitulating tumors upon release from therapy. We have also fine-tuned the CLARITY procedure that allows visualization of fluorescent tumors in transparent brains. Using this procedure together with confocal microscopy we have identified TR-GSC remnants. We believe that these are the last resource of therapy resistance, thus the main objective in the near future will be its eradication.

The Cell Therapy team has collaborated with CIBER group "Biomaterials for Regenerative Therapies (IBEC), CIBER Laboratory for Bioengineering and Tissue Regeneration (UMA-Bionand), CIBER group of "Nanostructured Surfaces and Nanoparticles (NFP-INA), the Cardiac Insufficiency and Cardiac Regeneration group (Hospital Germans Trias i Pujol), Photosciences and Photonics Institute (National Institute for Interdisciplinary Sciences and Tehcnology, India) and the Physiopathology Orthopedics and Regenerative Medicine Laboratory (Instituto Ortopedico Rzzoli, Italy).

The bioluminescence imaging technology has resulted in 2 research contracts with Instituto de Bioingeniería de Cataluña (IBEC) and 4 contracts with Sagetis Biotech for in vivo testing of biomaterials for tissue regeneration and nanoparticles for drug delivery, respectively.

5

DEPARTMENT OF CHEMICAL AND SURFACTANTS TECHNOLOGY

DEPARTMENT OF CHEMICAL AND SURFACTANTS TECHNOLOGY

Head: Mª Teresa García Ramon

The research in the Department focus on theoretical and applied aspects of product and chemical processes technology with special incidence in the synthesis, the physical chemistry and the biology of surfactants. This research is relevant in the lines of Sustainable Chemistry and Nanotechnology of soft matter and look for environmental and human health improvement. Among the scientific activities, with relation to the Sustainable Chemistry, we can cite: research and development of biocompatible surfactants and ionic liquids, the distribution and effect of surfactants and ionic liquids in the environment, development of non contaminant industrial processes, minimization, recycling and valorization of by-products and wastes of chemical industries. In the Nanotechnology area research is performed concerning adsorption and self-aggregation of surfactant as well as the physical chemistry and biophysics of natural lipids at interfaces and membranes (of natural origin or as physical chemistry models).

RESEARCH GROUPS

- Development of Non-contaminant industrial processes
- Statistical Modelling and Fibre Physics
- Plasma Chemistry
- Biocompatible Surfactants
- Environmental Chemistry of Surfactants and Ionic Liquids
- Physical Chemistry of Surfactant Systems
- Textiles and Cosmetic Innovations
- Biophysics of Lipids and Interphases

DEVELOPMENT OF NON-CONTAMINANT INDUSTRIAL PROCESSES

Despite efforts in recent years to establish a more sustainable tanning industry to the environment, it is still considered responsible of a notorious pollution. Consequently, the research activities of the group are focused to develop and implement cleaner technologies to attain a more environmentally friendly leather industry both from the point of view of manufacture as in the reduction/recycling of waste that this industry produces. Moreover, the activities of the group have been also focused to the development and implementation of instrumental techniques for the analysis of the main chemicals involved in the leather manufacturing processes.

STAFF

AGUSTÍ MARSAL MONGE, GROUP LEADER

PH. D.

SARA CUADROS DOMÉNECH

TRAINING STUDENTS

NICOLAS CHEVALIER (May 2014-July 2014)

ARTICLES

Determination of hexavalent chromium in leather by ion-exchange chromatography

Font, J.; Pérez, C.; Reyes, M.R.; Cobos, M.; Combalia, F.; Marsal, A.

J. Soc. Leather Technol. Chem., 98, 151-157, **2014**.

Effect of the fatliquoring on leather comfort. Part I. Softness and compressibility of leather

Manich, A.M.; Barenys, J.; Martínez, L.; Lloria, J.; Marsal, A

Journal of AQEIC, 65(4), 119-129, **2014**

Alternative fungicides for the leather industry: DIMPTS and IPBC

Cuadros, S.; Font, J.; Manresa, Mª. A.; Ollé, Ll.; Marsal, A

Journal of AQEIC, 65(3), 79-92, **2014**

Valorization of tannery wastes: Lipoamino acid surfactant mixtures from the protein fraction of process wastewater

Bautista, M.E.; Pérez, L.; García, M.T.; Cuadros, S.; Marsal, A.

Chem. Engineering J., 262, 399-408, **2015.**

New method to determine chromium VI in leather

Font.; Pérez, C.; Marsal, A

International Leather Maker, 11, 49-50, **2015**

RESEARCH PROJECTS

Tecnologías limpias en tenería: Producción de cueros libres de formaldehído

Nacional, CTQ2013-43029-P
2014-2016

Ayudas para apoyar las actividades de los grupos de investigación para el año 2014.

Nombre del grupo: Tensioactius i química sostenible

Generalitat 2014 SGR 836
2014-2018

RESEARCH HIGHLIGHTS

Any industrial activity generates wastes to a greater or lesser extent and the growing demands of environmental respect in the production processes force companies to reuse the most of their wastes. The leather industry generates a considerable amount of wastes. Each tone of raw hide yields 200 kg of finished leather, 50 m3 of contaminated wastewater and the rest are solid wastes. In tannery, the main pollution load is produced in the beamhouse operation (stages before tanning). For every 100 kg of dry sheepskins, 15 kg of solubilized proteins that contain 18 % nitrogen end up in wastewater following beamhouse operations. The separation of the dissolved protein fraction represents not only a way to significantly reduce the contamination of beamhouse wastewaters but also provides a residue, the separated protein fraction, which depending on its purity level may have different applications.

The use of the separated protein fraction from the beamhouse wastewaters for the production of surfactants is one of the research activities developed by this research group in the biennial 2014-2015. The method developed for the production of surfactants consisted of several stages: i) acid precipitation of the effluents of a hair-pulping beamhouse process of hides by adding 2M sulfuric acid solution up to the isoelectric point for the recovery of the protein fraction; ii) degreasing process of the protein fraction with dichloromethane during 5 hours; iii) hydrolysis of the degreased protein fraction with 6 N HCl during 24 hours for the production of amino acids; iv) introduction of a fatty acid residue, as an acid chloride (decanoyl chloride or dodecanoyl chloride), to the amino acids in a strong alkaline aqueous medium. This reaction was carried out for different amino acid/acid chloride molar ratios. Once prepared, the physico-chemical and biological properties of the surfactants were investigated. The obtained surfactant mixtures show very low cmc values indicating that these surfactants form aggregates at very low concentrations. They are very efficient in reducing the surface tension of water and form lamellar liquid crystal structure and very stable O/W emulsions and foams. In addition, these surfactants are readily biodegradable and result to be non-toxic or only slightly toxic to the aquatic environment. The obtained surfactant mixtures could be used as green solubilizers, green emulsifiers or foaming agents in different industrial applications. Our results confirm that it is possible the valorization of a waste of the tanning industry that entails the reduction of the pollution load from this sector.

Formaldehyde has a wide and varied application in the tanning industry being in the retanning process where the application is more important since it participates in two groups of synthetic organic tannin agents i) syntans; based on the condensation of aromatic compounds such as phenols or naphthols with formaldehyde and ii) resins; condensation products between formaldehyde and various amines, amino acids, melamine, cyanamide, urea, etc. Resins are susceptible to partial hydrolysis and release formaldehyde. Therefore, the source of formaldehyde detected in leather may be: free formaldehyde and formaldehyde released from the partial hydrolysis of the retanning resins. However, due to the carcinogenic character to humans attributed to formaldehyde, its presence in leather should be below the permitted limits or, even, avoided.

Therefore, the production of leathers free from formaldehyde is another research activity initiated by this research group in the biennial 2014-2015. To this end, several aspects have been considered: i) revision and possible improvements of two analytical methods currently available ((EN ISO 17226 (Parts 1 and 2)) for the determination of formaldehyde in leather; ii) comparative study between quantification of formaldehyde by HPLC (EN ISO Standard 17226. Part 1) and quantification by colorimetric analysis (EN ISO Standard 17226. Part 2) in the analysis of the same leathers; iii) influence of vegetable extracts on the reduction of formaldehyde content in leathers retanned with formaldehyde–based resins (melamine-formaldehyde and dicyandiamide-formaldehyde); iv) influence of the chemical structure of dyes used in the dyeing process on the reduction of formaldehyde content in leathers retanned with formaldehyde–based resins (melamine-formaldehyde and dicyandiamide-formaldehyde). Nowadays, it is carried out the analysis of results, which will be the subject of future publications.

STATISTICAL MODELLING AND FIBRE PHYSICS

Research work is focussed on the study of structure-property relationships of natural, synthetic and sustainable fibrous materials, particularly with regard to thermal, mechanical, viscoelastic and relaxation behaviour. The influence of novel more sustainable industrial processing on the structure and properties of fibrous materials are also taken into account.

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MIREIA PEÑA

ARTICLES

Effect of processing and wearing on viscoelastic modeling of polylactide/wool and polyester/wool woven fabrics subjected to bursting

Manich, A.M.; Miguel, R.; Silva, M.J.S.; Lucas, J.; Martí, M.; Cayuela, D.

Textile Res. J., 84, 1961-1975, **2014.**

.....

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Cayuela, D.; Cot, M.; Riva, M.; Sanchez, R.J.; Sánchez-Loredo, M.G.; Algaba, I.; Manich, A.M.

J. Macromol. Sci., Part A: Pure Applied Chem., 51, 831-841, **2014.**

.....

Water sorption evaluation of stratum corneum

Barba, C.; Baratto, A.; Martí, M.; Semenzato, A.; Baratto, G.; Manich, A.M.; Parra, J.L.; Coderch, L.

Thermochim. Acta, 583, 43-48, **2014**

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Proteomic and transcriptomic analysis of rice tranglutaminase and chloroplast-related proteins

Campos, N.; Torné, J.M.; Bleda, M.J.; Manich, A.; Urreta, I.; Montalbán, I.A.; Castañón, S.; Moncalean, P.; Santos, M.

Plant Sci., 229, 142-153, **2014.**

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Seam slippage and seam strength behavior of elastic woven fabrics under static loading

Namiranian, R.; Najar, S.S.; Etrati, S.M.; Manich, A.M.

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Effect of texturing on porosity and critical dissolution time of polyamide 6.6 multifilaments

Cayuela, D.; Maillo, J.; Morales, C.; Manich, A.M.

Fibers Polymers, 15, 297-301, **2014.**

Effect of the Fatliquoring on Leather Comfort. Part I: Softness and Compressibility of leather

Manich, A.M.; Barenys, J.; Martínez, L.; Lloria, J.; Marsal, A.

Journal of AQEIC, 65, 4, 119-129, **2014.**

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Effect of water treatment on the fibre-matrix bonding and durability of cellulose fibre cement composites

Aradanuy, M.; Claramunt, J.; Ventura, H.; Manich, A.M.

J Biobased Mater. Bioenergy 9, 486-492, **2015.**

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Effect of lipid modification on stratum corneum permeability

Barba, C.; Martí, M.;Semenzato, A.; Baratto, G.; Manich, A.M.; Coderch, L.

J Therm Anal Calorim, 120, 1, 297-305, **2015.**

.....

Effect of the presence of an ester of montanic acids with multifunctional alcohols in the composites of titanium dioxide nanoparticles with poly (ethylene terephthalate) in their non-isothermal crystallization.

Manich, A.M.; Cot, M.; Algaba, I.; Cayuela, D.

J. Macromol. Sci., Part A: Pure Applied Chem., 52, 770-777, **2015.**

RESEARCH PROJECTS

Cinéticas de sorción/desorción de humedad y distribución de tamaño de poro en fibras vegetales

Nacional, 201280E035
2011-2014

.....

Composites de altas prestaciones de nanoparticulas ceramicas en fibras de poliester: propiedades y aplicaciones

Nacional, MAT2010-20324-C02-02
2011-2014

.....

Lavado en seco de lana eco-eficiente con recuperación total de subproductos

Nacional, IPT-2012-0644-310000
2012-2015

Tecnologías limpias en tenería: producción de cueros libres de formaldehido

Nacional, CTQ2013-43029-P
2014-2016

.....

Mitigation of environmental impact caused by DWOR textile finishing chemicals studying their non-toxic alternatives (MIDWOR)

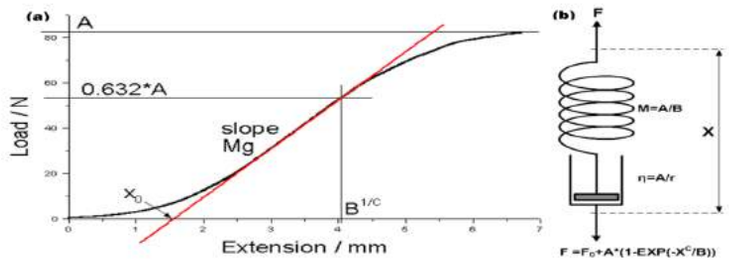
Europeo, 2015-2018

RESEARCH HIGHLIGHTS

Renewable resources

The replacement of polyester by polylactide, an aliphatic polyester derived from renewable resources imply the study of compatibility when mixed with natural fibres like wool and cotton. The evolution of mechanical properties of washed and heat set blended PET/Wool and PLA/Wool fabrics have been studied after subjecting them to a conventional process of dyeing and decatizing. Fabrics were gradually worn by abrasion using a Martindale Wear and Abrasion tester. The viscoelastic behaviour of the fabrics when multidirectional extended was simulated and modelled using a modified non-linear Maxwell model. The three steps of fibre decrimping and orientation, fibre stretching and maximum yield and breaking have been analyzed.

PET/Wool fabrics show a more linear behaviour than PLA/Wool ones and the influence of weave, finishing and wearing on the viscoelastic behaviour of PLA/Wool fabrics were highly relevant when compared with that on PET/Wool ones. It seems that when blended with PET, wool develops its felting effect along finishing and wearing, while when blended with PLA, the felting effect of wool is hardly developed due to the lower resistance of PLA to hydrolysis and its lower thermal stability. PLA fibre properties need to be improved probably through the development of new L-D lactide (PLDLA) copolymers of different ratios between components and molecular weights to reach the optimal desirable properties for the fibre



Fibre characteristics significantly influence model coefficients and their useful life can be predicted from their compositional and processing parameters.

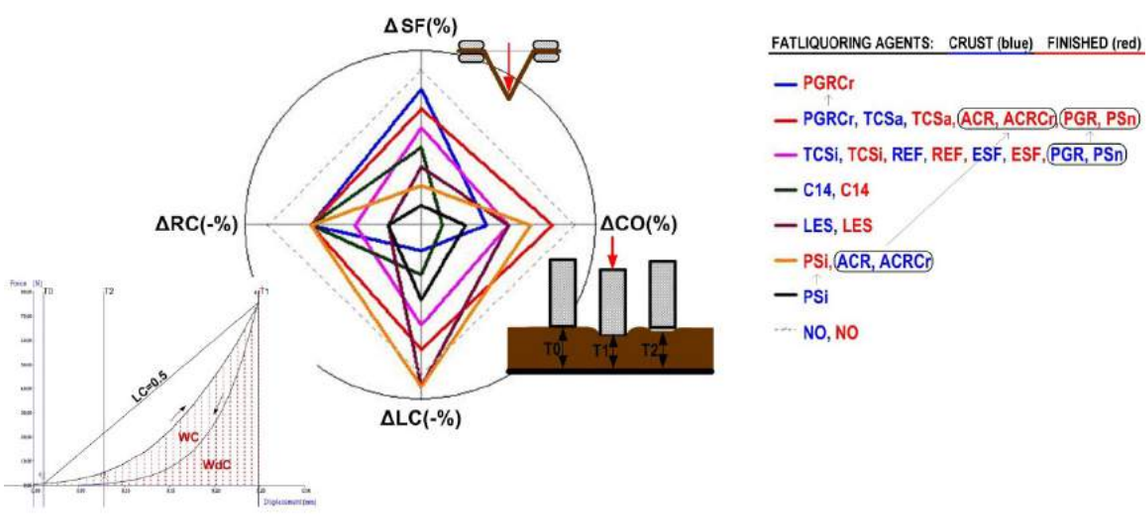
LEATHER PROCESSING

The comfort of leather is a relevant aspect that makes the end user to select this material instead of other alternative materials. This comfort depends largely on the physical, mechanical and organoleptic characteristics of the finished leather from which the final articles will be manufactured. Among the post-tanning operations, fatliquoring and retanning plays a great influence on the properties of leather, especially those related to handle.

The influence of different fatliquors on softness and compressional behavior of leather has been studied. The considered fatliquors have been the following:

- Soy lecithin *LES*
- Sulphited triglycerides of colza oil *TCSi*
- Acrylic polymer (waterproofing agent) *ACR*
- Fatty Polymers (sarcosinates) *PGR*
- Sulphated triglycerides of colza oil *TCSa*
- Phosphoric Ester *ESF*
- C14 Paraffin *C14*
- Sulphonated paraffin *PSn*
- Sulphited fish oil *PSi*

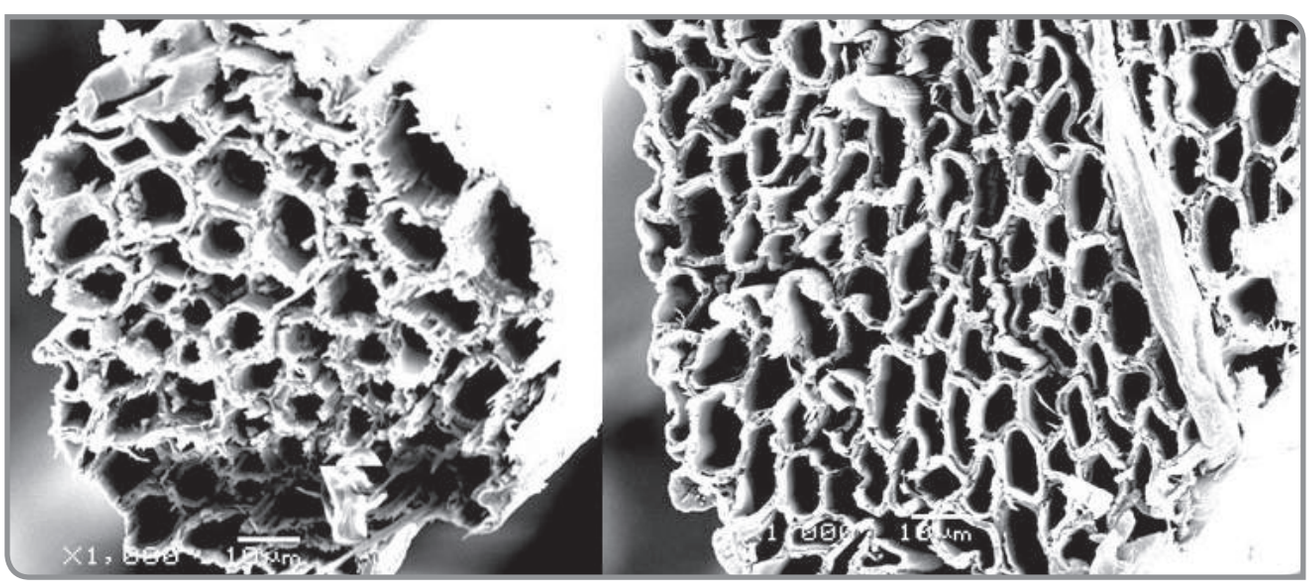
Compressibility and softness of both "crust" and finished leathers have been evaluated and based on the experimental results, treatments with similar effects were grouped, and the characteristic effects of each group on compressibility and softness were identified.



Variations in softness, compressibility, linearity of compression and resilience in compression, enabled us to group the different fatliquors based on the effects on softness and compressibility. This enables manufacturers to fit their products according to final specifications.

Stabilisation of natural fibers for reinforcing composites

Wetting and drying treatments of vegetable fibers influences the fiber-matrix bond strength of cement based composites. Treatments modifies morphology, mechanical properties, drying kinetics and thermal stability were determined with scanning electronic microscopy (SEM) and X-ray diffraction (XRD), tensile tests and thermogravimetric analysis (TGA) respectively. The treatment of the fibers results in an increase of the interfacial shear strength on the cement composites improving also the durability to wet/dry cycling. The modification of the cross section after wetting and drying cycles can be observed in the following plot.



PLASMA CHEMISTRY

The research in Plasma Chemistry Group is focused on the technological applications of non-thermal plasmas (low and atmospheric pressure). Plasma technologies allow modulating surface properties of a material by means of increasing surface hydrophycility (using oxidizing gases), providing hydrophobicity or oleophobicity (using fluorinated gases), incorporation of new functional groups (using gases containing amines) or by means of film deposition or polymerization of functional or multifunctional thin films (using polymerizing and reactive gases). Thus, high performance materials can be obtained without modifying bulk properties.

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ARTICLES

Assessment of a dielectric barrier discharge plasma reactor at atmospheric pressure for the removal of bisphenol A and tributyltin

Hijosa-Valsero, M.; Molina, R.; Bayona, J.M.

Environ. Technol., 35, 1418-1426, **2014**.

Hydrophilic-oleophobic coatings on cellulosic materials by plasma assisted polymerization in liquid phase and fluorosurfactant complexation.

Molina, R.; Gómez, M.; Kan, C.-W.; Bertran, E.

Cellulose, 21, 729-739, **2014**.

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Kwong, C.H.; Ng, S.P.; Kan, C.W.; Molina, R.

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In situ chitosan gelation initiated by atmospheric plasma treatment

Molina, R.; Jovancic, P.; Vilchez, S.; Tzanov, T.; Solans, C.

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UV protective textiles by the deposition of functional ethylcellulose nanoparticles

Vílchez-Maldonado, S., Calderó, G., Esquena, J., Molina, R.

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Synthesis of Thermo-Sensitive Hydrogels from Free Radical Copolymerization of NIPAAm with MBA Initiated by Atmospheric Plasma Treatment

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BOOK CHAPTERS

Novel synthesis pathways for PNIPAAm-based hydrogels and their application in thermosensitive textiles.

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in Handbook of Smart Textiles, (Tao, X. Ed.) Springer Verlag, pp 953-984, 2015.

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RESEARCH PROJECTS

Control ambiental y de procesos con dispositivos responsivos con capas nanoestructuradas fabricadas por tecnologías innovadoras de vacio y plasmas.

MAT2013-40852-R. MINECO

2014-2016

.....

Nuevas nanoestructuras 1d-hibridas multifuncionales para el desarrollo de nanosistemas autoalimentados.

MAT2013-42900-P. MINECO

2014-2016

.....

Development of stimuli sensitive textile coatings using plasma in liquids (PLASMABIOGELS).

TECSPR13-1-0026

ACCIÓ-Generalitat de Catalunya, VII Programa Marco de la UE-People Programme (Marie Curie Actions)

2014-2016

.....

Plasma-enhanced Synthesis of Textile Material Surfaces with Ultra-liquid Repellency under Atmospheric Condition.

2011HK0015. CSIC/RGC (Proyecto Bilateral)

2012-2014

RESEARCH HIGHLIGHTS

The activity and interest of the group deals with different plasma processes:

Surface functionalization: tailoring of adhesion and wetting properties.

Plasma treatment in liquids: elimination of contaminants in wastewater and plasma initiated polymerization for development of stimuli sensitive polymer coatings.

Plasma treatment of biomaterials: sterilization, plasma in medicine (cancer treatment and rare diseases), use of plasma in agriculture and food.

Development of atmospheric plasma configuration for advances technologies

Different configurations of atmospheric plasmas have been developed in the plasma chemistry group for specific treatments (Figure 1). Dielectric barrier discharge (DBD) plasma reactor has been use for surface treatment of polymers, seeds, elimination of chemical compounds in waste water and in situ polymerization of monomer solutions in liquids. This configuration allows the treatment of large area samples but has the disadvantage that treatments have to be done in batch. Jet plasma configuration has been used for surface treatment of polymers and it is a localized treatment affecting the surrounding area of the jet. Additionally surface plasma configuration have also been obtained in order to modify polymers and has the advantage that plasma patterning can be performed attending to the electrode form.

DBD plasma Jet Plasma Surface Plasma

Fig. 1. Plasma configurations for advances technologies.

Plasma initiated polymerization in liquids

Atmospheric plasma can be applied to aqueous solutions with monomers or polymers in order to obtain hydrogels or films with specific properties. Experimental parameters such as monomer concentration and plasma power plays an important role in the properties and morphology of the films obtained (Figure 2). In this context, atmospheric dielectric barrier discharge (DBD)

plasma has been employed in order to obtain stimuli response films by polymerizing monomer aqueous solutions of hydrophilic vinyl monomers N-isopropylacrylamide (NIPAAm) and acrylic acid or to facilitate the gelation of biopolymer chitosan.

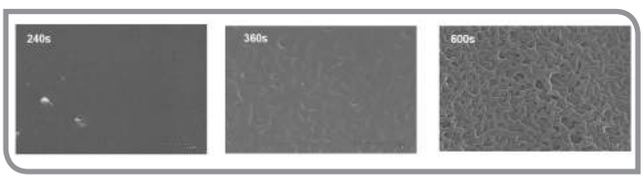

Figure 2. SEM images of N-isopropylacrylamide (NIPAAm) solution (1%) as a function of plasma treatment time.

In order to obtain hydrophobic films, plasma polymerization of a fluorinated monomer in ethanol solution has been successfully performed in order to confer water repellence properties to textile substrates.

In BIOPLASMAGELS project, in situ liquid phase plasma polymerization process has been used to produce and deposit the poly (N-isopropyl acrylamide), pNIPAAm based hydrogels and their mixtures with hydroxypropyl-β-cyclodextrin (HP-β-CD) for functional finishing of textiles and polymeric surfaces (particularly for transdermal drug release applications). Both low and atmospheric pressure plasma discharges have been already employed to graft pNIPAAm to surfaces for functional textile finishing, but state of the art technologies basically rely on plasma induce grafting where plasma is used as separate substrate pretreatment prior to graft polymerization of monomers or their specific mixtures on textiles in conventional way (in the presence of initiators, chemical accelerators and/or cross-linkers or by introduction of monomers in vapour and gas phase directly inside the plasma reactor).

These results clearly demonstrated that scientific approach is feasible and that would be possible to gain cutting-edge knowledge necessary for prospect implementation of plasma liquid technology to industrial environment. Enlarging the application of atmospheric DBD plasma discharges in the field of synthesis and functionalization of stimuli-responsive hydrogels would reveal a whole new class of materials with unprecedented functionalities and performances. The use of liquid plasma technology for functional textile coatings is still an emerging field with a lot of scientific challenges unsolved but with an immense potential for diverse applications.

BIOCOMPATIBLE SURFACTANTS

Surfactants are chemical products consumed in large quantities every day on a worldwide scale. In recent years, environmental concerns and regulatory pressure have provided the driving force to partly replace petrochemical-based surfactants with those based on naturally occurring renewable sources. The hope that such surfactants would be biodegradable and biocompatible has provided strong incentive for the research of less irritant and less toxic consumer-friendly surfactants. Biodegradability, low toxicity, and antimicrobial activity are properties common to surfactants derived from amino acids. The activity of Biocompatible Surfactants group deals with the fundamental and applied chemical research of novel environmentally friendly surfactants from amino acids, as alternatives to conventional surfactants to be applied in cosmetic, pharmaceutical and food industrial formulations. These surfactants can be classified as specialty surfactants with biodegradable, antimicrobial and low toxicity profiles, and characteristic self-aggregation properties

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ARTICLES

A novel synergistic formulation between a cationic surfactant from lysine and hyaluronic acid as an antimicrobial coating for advanced cellulose materials

Bracic, M.; Pérez, L.; Infante, R.; Kogej, K.; Hribernik, S.; Sauperl, O.; Zemljic, L.F.

Cellulose, 21, 2647-2663, **2014.**

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Cationic vesicles based on biocompatible diacyl glycerol-arginine surfactants: Physicochemical properties, antimicrobial activity, encapsulation efficiency and drug release

Tavano, L.; Pinazo, A.; Abo-Riya, M.; Infante, M.R.; Manresa, M.A.; Muzzalupo, R.; Pérez, L.

Coll. Surf. B: Biointerfaces, 120, 160-167, **2014.**

.....

Characterization and stability of catanionic vesicles formed by pseudo-tetraalkyl surfactant mixtures

Pucci, C.; Pérez, L.; La Mesa, C.; Pons, R.

Soft Matter, 10, 9657-9667, **2014.**

.....

Complex rhamnolipid mixture characterization and its influence on DPPC bilayer organization

Haba, E.; Pinazo, A.; Pons, R.; Pérez, L., Manresa, A.

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DNA gel particles: An overview

Morán, M.C.; Vinardell, M.P.; Infante, M.R.; Miguel, M.G.; Lindman, B.

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Gemini surfactants from natural amino acids

Pérez, L.; Pinazo, A.; Pons, R.; Infante, M.

Adv. Colloid Interface Sci., 205, 134-155, **2014.**

Lysine-based surfactants in nanovesicle formulations: the role of cationic charge position and hydrophobicity in in vitro cytotoxicity and intracellular delivery

Nogueira, D.R., Morán, C., Mitjans, M., Pérez, L., Ramos, D., De Lapuente, J., Vinardell, M P.

Nanotoxicol., 8, 404-421, **2014.**

Self-assembly and antimicrobial activity of long-chain amide-functionalized ionic liquids in aqueous solution

García, M.T., Ribosa, I., Pérez, L., Manresa, A., Comelles, F.

Coll. Surf. B: Biointerfaces, 123, 318-325, **2014.**

Interfacial Chiral Selection by Bulk Species

Dong, H., Ignes-Mullol J., Claret, J.,Pinazo A., Pérez L., Sagues F.

Chemistry- A European Journal, 20, 7396-7401, **2014**

Catanionic vesicles and DNA complexes: A strategy towards novel gene delivery systems

Pucci, C., Scipioni, A., Diociaiuti, M., La Mesa, C., Pérez, L., Pons, R.

RSC Adv., 5, 81168- 81175, **2015.**

Nanoparticles incorporating pH-responsive surfactants as a viable approach to improve the intracellular drug delivery

Nogueira, D.R., Scheeren, L.E., Vinardell, M.P., Mitjans, M., Infante, M. R., Rolim, C.M.B.

Mat. Sci. Engin. C-Biomimetic and supramolecular systems, 57, 100-106, **2015.**

Valorization of tannery wastes: Lipoamino acid surfactant mixtures from the protein fraction of process wastewater

Bautista, M.E.; Pérez, L.; García, M.T.; Cuadros, S.; Marsal, A.

Chem. Engineering J., 262, 399-408, **2015.**

Interaction of Sodium Hyaluronate with a Biocompatible Cationic Surfactant from Lysine: A Binding Study

Bracic, M., Hansson P., Pérez L., Zemlijic L.F., Kogej K.

Langmuir, 31, 12043-12053, **2015**

PROJECTS AND CONTRACTS

Tensioactivos poliméricos antimicrobianos preparados a partir de biopolímeros y tensioactivos catiónicos derivados de aminoácidos

Nacional, MAT2012-38047-C02-02

2013-2015

Ayudas para apoyar las actividades de los grupos de investigación para el año 2009. Nombre del grupo: Tensioactius i química sostenible

Generalitat, 2009SGR1331

2009-2014

Food Waste Valorisation (EUBis Action), COST ACTION TD1203

EUBis COST Action.

Enero 2013-Diciembre 2016

Aplicaciones no convencionales de tensioactivos y liquidos ionicos derivados de aminoácidos naturales en nanotecnología y química sostenible

Nacional, CTQ2013-41514-P

2014-2016.

Proline based surfactants

2015 – 2016, Industrias MARCA

Pharmaceutical formulations with arginine.

2015, Laboratorios Torlan

RESEARCH HIGHLIGHTS

In the last two years, our efforts have been directed towards the exploration of possible applications of cationic surfactants derived from amino acids. Two types of surfactants have been studied, lysine based surfactants with one fatty or two fatty chains and glycero arginine based surfactants. The results achieved are highlighted below.

Glycerol arginine based surfactants

Vesicles have been shown to be a promising delivery system for a large number of pharmaceutical compounds. Glycerol arginine surfactants can form stable cationic vesicular systems by themselves as well as in the presence of DPPC as a membrane additive. The physicochemical properties of these vesicles are modulated by the alkyl chain length of the surfactant and by the surfactant/DPPC ratio. These systems have antimicrobial properties against the three bacterial strains tested. The antimicrobial efficacy of the vesicles based only on cationic lipids is strongly affected by the hydrophobicity of lipids. The introduction of DPPC strongly decreases the antibacterial activity of these systems. Formulations based on vesicles prepared with these pH sensitive surfactants represent a great innovation in the pharmaceutical area, because of their dual function, encapsulation and antibacterial properties.

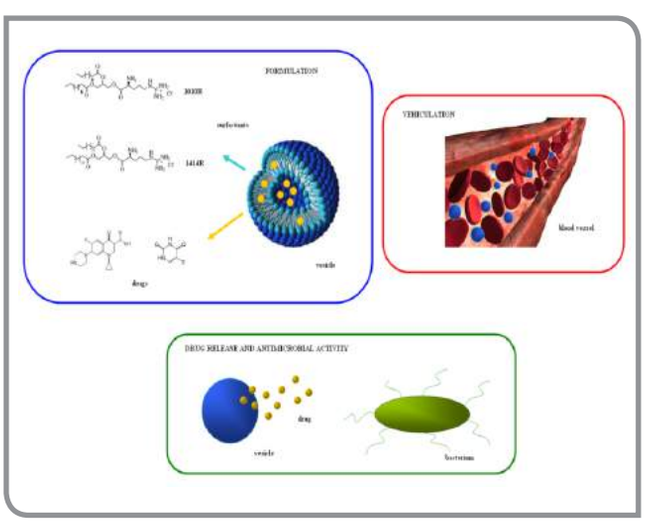

Figure 1. Cationic vesicles based on biocompatible arginine based surfactants.

Lysine based cationic surfactants with one fatty chain

Our group has recently synthesized cationic surfactants of the type Nε -acyl lysine methyl ester hydrochloride salts for which the alkyl chain length has been varied from 12 to 16 carbon atoms.

Medical textiles attracted a lot of interest over the past decade and are among the fastest growing textile fields today. They are predominantly used as implants, for wound healing and disease curing. One of the more desirable properties for these applications is their antimicrobial activity. A novel synergistic formulations between a biopolymer hyaluronic acid and a lysine-derived surfactant has been developed as a functional textile material coating. The textile fabric trated with this coating exhibits excellent antimicrobial activity towards gram-positive (*S. Aureus and S. Agalactiae*) and gram-negative (*E.Coli*) pathogens as well as towards two types of pathogen fungi (*C. Albicans* and *C. Glabrata*). These kinds of functionalised fibres could find applications as would healing and medical textiles.

When preparing aqueous mixtures for applications, special attention has to be paid to the interaction between ionic surfactants and polyelectrolytes of opposite charge because these can alter the unique properties of each of the components in the mixture. Understanding these interactions is therefore crucial for optimizing the performance of the polyion-surfactant ion mixtures. In this context, theoretical study of interactions of lysine surfactant with a completely ionized hyaluronic acid in aqueous solutions have studied. Several isotherms anomalies were observed which were explained by proposing equilibrium between the protonated (charged) and deprotonated (uncharged) forms of lysine surfactant (see figure).

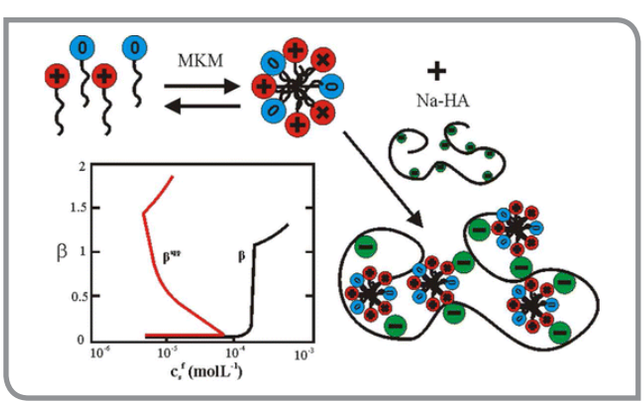

Figure 2. Interaction of Sodium Hyaluronate with a biocompatible cationic surfactant from Lysine

Understanding nanomaterial interactions within cells is of increasing importance for assessing their toxicity and cellular transport. Nanovesicles containing lysine based surfactants were used to assess whether these cationic compounds increase the likelihood of intracellular delivery and modulate toxicity. The cationic charge position and hydrophobicity of surfactants determine the nanovesicles interactions within the cell and, thus, the resulting toxicity and intracellular behavior after cell uptake of the nanomaterial. The insights into some toxicity mechanisms of these new nanomaterials contribute in reducing the uncertainty surrounding their potential health hazars.

Lysine based anionic surfactants with two fatty chains

The pH-responsive delivery systems have brought new advances in the field of functional nanodevices and might allow more accurate and controllable delivery of specific cargoes, which is expected to result in promising applications in different clinical therapies. A family of chitosan-tripolyphosphate nanoparticles for intracellular drug delivery, which were designed using two pH-sensitive lysine based surfactants were studied. The nanostructures incorporating the surfactants cause negligible membrane permeabilization at pH 7.4. However, at acidic pH, prevailing in endosomes, membrane-destabilizing activity in an erythrocyte lysis assay became evident.When pH decreased to 6.6 and 5.4, hemolityc capability of chitosan naboparticles increases along with the raise of concentration. Furthermore, studies with cell culture showed that these pH-responsive nanoparticles displayed low cytotoxic effects against 3T3 fibroblasts. The influence of chitosan molecular weigth, chitosan-tripolyphosphate ratio, nanoparticle size and nature of the surfactant counterion on the membrane-disruptive properties of nanoparticles was estudied in detail. The results showed that by inserting the lysine-based surfactants into chitosan nanoparticles, pH-sensitive membranolytic and potentially endosomolytic nanocarriers were developed, which therefore, demonstrated ideal feasibility for intracellular drug delivery.

Biosurfactants

Rhamnolipids are one of the most important classes of biosurfactants produced by microorganisms using a wide range of carbon sources, from a simple carbon source like glucose to complex wastes such as the used cooking oils. Despite the importance the interactions between rhamnolipids and membranes play in their biological mechanism of action, very little is known, especially regarding rhamnolipid-phospholipid molecular interactions. We learn about the rhamnolipid-dipalmitoyl phosphatidyl choline (DPPC) molecular interactions using small angle X-ray scattering (SAXS), size and z-potencial. The biosurfactant forms ordered bilayers with long repeting distances; these long repeating distances are stabilized by the charging of the bilayer and also by a strong fluidity of the bilayers. The ability of Rhamnolipids to increase the fluidity of DPPC bilayers is parallel to the increase of vesicle permeation and may be related with the strong haemolytic power of these molecules.

Portadas de revistas

Journal cover. Bracic, M., Hansson P., Pérez L., Zemlijic L.F., Kogej K.

Langmuir 2015, 31(48), 13063-13264.

ENVIRONMENTAL CHEMISTRY OF SURFACTANTS AND IONIC LIQUIDS

The main objective is the study of the physicochemical and biological properties related to the behaviour, fate and effects of surfactants and ionic liquids in the environment for the design and selection of environmentally friendly compounds. Our research activities are mainly focused on the bioavailability, biodegradability and toxicity of surfactants and ionic liquids in the aquatic environment.

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CECILE BOGAERT
KARINE HOVAGHIMIAN
FLORANE METIVIER

ARTICLES

Micellization of sodium laurylethoxysulfate (SLES) and short chain imidazolium ionic liquids in aqueous solution

Comelles, F.; Ribosa, I.; González, J.J.; Garcia, M.T.

J. Coll. Interface Sci., 425, 44-51, **2014**.

.....

Self-assembly and antimicrobial activity of long-chain amide-functionalized ionic liquids in aqueous solution

Garcia, M.T.; Ribosa, I.; Perez, L.; Manresa, A.; Comelles, F.

Coll. Surf. B: Biointerfaces, 123, 318-325, **2014**.

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Catanionic surfactant formation from the interaction of the cationic surfactant hexadecyltrimethylammonium bromide (CTAB) and the ionic liquid 1-butyl-3-methylimidazolium octyl sulfate (bmim-octyl SO4) in aqueous solution

Comelles, F.; Ribosa, I.; Gonzalez, J.J.; Garcia, M.T.

Coll. Surf. A: Physicochem. Eng. Aspects, 484, 136-143, **2015**.

.....

Skin delivery of antioxidant surfactants based on gallic acid and hydroxytyrosol

Alonso, C.; Lucas, R.; Barba, C.; Marti, M.; Rubio, L.; Comelles, F.; Morales, J.C.; Coderch, L.; Parra, J.L.

J. Pharm. Pharmacol., 67, 900-908, **2015**.

.....

Nitrogen-containing ionic liquids: Biodegradation studies and utility in base-mediated reactions

Ford, L.; Ylijoki, K.E.O.; Garcia, M.T.; Singer, R.D.; Scammells, P.J.

Austr. J. Chem., 68, 849-857, **2015**.

.....

Valorization of tannery wastes: Lipoamino acid surfactant mixtures from the protein fraction of process wastewater

Bautista, M.E.; Pérez, L.; García, M.T.; Cuadros, S.; Marsal, A.

Chem. Engineering J., 262, 399-408, **2015**.

RESEARCH PROJECTS

Aplicaciones no convencionales de tensioactivos y líquidos iónicos derivados de aminoácidos naturales en nanotecnología y química sostenible.

MINECO
IP1: R. Pons; IP2: M.T. García

.....

Food Waste Valorisation

EUBis COST Action TD 1203
2013-2016

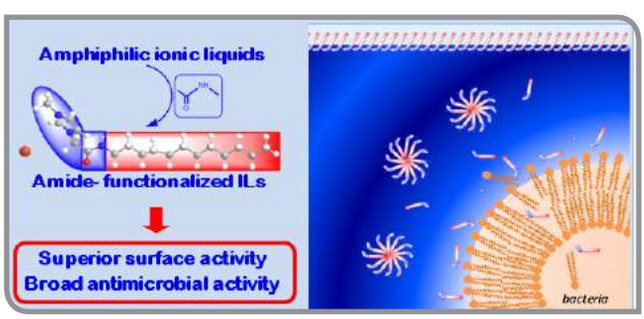
RESEARCH HIGHLIGHTS

Biodegradability of Ionic Liquids

Ionic liquids (ILs) are salts composed by an organic cation and an organic or inorganic anion that melt below 100 ºC of temperature. Ionic liquids are deemed greener solvent alternatives in chemical synthesis mainly because of their negligible vapor pressure, high thermal stability, low flammability and reusability in chemical applications. The non-volatility of ILs under operational conditions minimizes their impact on air quality during their life cycle. However, their impact on soil and water is certainly of considerable concern at the time of their disposal. Research in this area is currently vital as ILs are likely to make a transition from academic laboratories to large scale operations where disposal of any chemical is a major concern. In collaboration with the research group of the Professor Peter Scammells (Monash University), different structural parameters promoting biodegradation of ionic liquids commonly used as reaction media have been identified. Further to our studies probing the biodegradability of some pyridinium ILs, other cyclic and acyclic alkyl ammonium ILs were prepared and their susceptibility to biodegradation was studied. Several of these ILs contain tertiary amines, whose basicity we hoped to exploit for synthetic purposes, by using the IL as both solvent and reagent/catalyst. Basic ILs have been utilized for several diverse reactions including Heck coupling, copper free Sonogashira coupling, Knoevenagel condensation, condensation reactions to generate heterocycles, transesterification and bromination of alkenes.

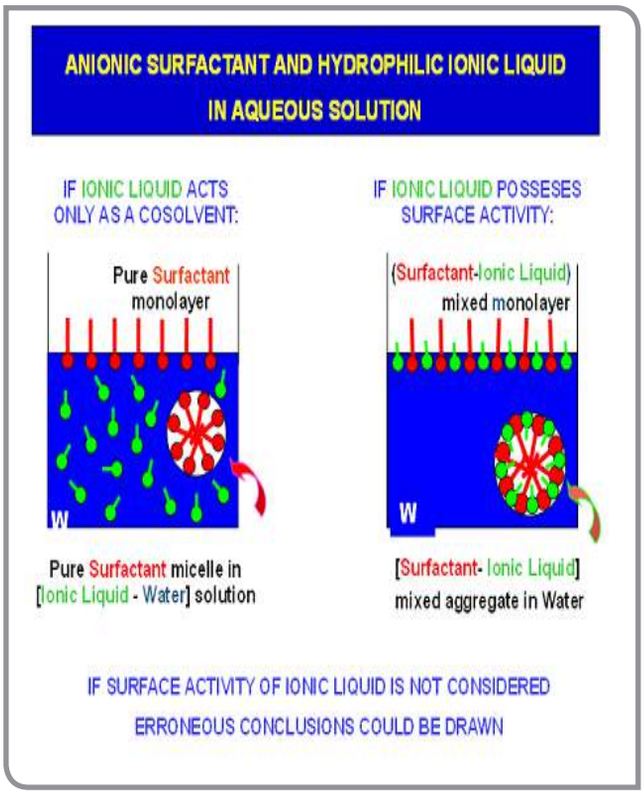
Self-assembly and antimicrobial activity of amide-functionalized ionic liquids

Long chain imidazolium and pyridinium based ILs possess an inherent amphiphilic nature and exhibit interfacial and aggregation behavior analogous to that displayed by conventional surfactants as we previously showed. Besides to interfacial activity, they can exhibit significant biological activity against bacteria and fungi. The ability of some organic functionalities to modify the specific properties of the ionic liquids by their incorporation in the cation and/or anion structure prompted us to synthesize two series of long alkyl chain (C_6-C_{14}) ionic liquids based on imidazolium and pyridinium cations containing an amide functional group in the hydrophobic side chain attached to the polar head i to investigate the effect of this strong hydrogen bonding functionality on their physico-chemical and biological properties. Long-chain ILs with an amide functional group in the alkyl side chain behave as cationic surfactants in aqueous solution and possess a superior surface activity as compared to the corresponding simple alkyl substituted ionic liquids. Its tendency to self-assembly increases with the elongation of the alkyl chain length attached to the polar headgroup. The cmc values obtained for amide-functionalized ILs are lower than for non-functionalized salts indicating that the introduction of an amide group in the alkyl side chain facilitates micellization likely by the hydrogen-bonding between amide groups in the head group region. The incorporation of an amide group significantly improves the thermal stability of the ILs as compared to non-functionalized ionic liquids. Imidazolium- and pyridinium-based ILs containing an amide moiety show a broad-spectrum of antimicrobial activity against common bacteria and fungi and their efficiency as antimicrobial agents is related to the length of the alkyl side chain being the C12 homologous the most effective antimicrobial agent. The better understanding of the factors affecting micellization and biological activity of the long-chain ionic liquids is expected to contribute to the design and development of new functionalized ionic liquids with improved physicochemical and biological properties for separation processes, bio-catalysis and preparation of nanoestructured materials.



Mixed aggregate formation in different binary systems composed by ionic liquids and surfactants

Ionic liquids (ILs) with short alkyl chains are considered as alternative solvents in several industrial applications and basic research. As a consequence, in most of the studies involving ionic liquids and surfactants, neat ILs or aqueous ILs solutions are considered the dilution media of conventional surfactants. However, another possible role of ionic liquids according to its structure is to act itself as a surface active compound when dissolved in water. Whereas this behaviour is well known for long alkyl chain ionic liquids as the C_6-C_{14} ILs based on imidazolium and pyridinium cations prepared in our lab with an ester or amide group or without any functionality, in previous studies we also reported the surface activity of several short alkyl chain ionic liquids. In our recent research we considered the aggregation of several binary systems formed by a conventional anionic surfactant (sodium laurylethoxysulfate) or a cationic surfactant (hexadecyltrimethylammonium bromide) and different short ionic liquids. When sodium laurylethoxysulfate (SLES) was dissolved in aqueous solutions of three ionic liquids with the same cation 1-butyl-3-methylimidazolium but different anions (octyl sulfate, methyl sulphate, tetrafluoro borate) a strong decrease of the surface tension with respect to the individual values of the components was produced because of the formation of mixed micelles and mixed monolayers. The synergism produced was quantified by applying the equations of the Regular Solution Theory for binary surfactant systems. In another study, opposite charged compounds as the cationic surfactant hexadecyltrimethylammonium bromide (CTAB) and the anionic surface active IL 1-butyl-3-methylimidazolium octylsulfate were considered. Samples of different physical appearance were obtained depending on the mole fraction of *α*CTAB suggesting different kind of aggregates: from vesicles of the catanionic surfactant formed (CTA-octylSO4) to mixed micelles. The very low critical aggregation concentration (*cac*) and surface tension value at the *cac* (*γ*cac) reveal the exceptional surface activity of these mixtures, attributable to the formation of the CTA-octylSO4 catanionic surfactant.



PHYSICAL CHEMISTRY OF SURFACTANT SYSTEMS

The general subject of the research is the physical chemistry of systems based on surfactants. This subject lies within the framework of colloids and nanotechnology in its bottom-up approach and is closely related to Soft Matter. We focus on the dynamics of transformation (emulsification and solubilisation) and the phase behaviour of new surfactants, in particular, those derived from biocompatible natural products. The characterisation of stable and unstable structures allows for the exploration of applications of simple water-surfactant systems and their complexes with biological molecules or with inorganic molecules. The main techniques are SAXS-WAXS, light scattering, tensiometry, conductivity and selective electrode.

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ARTICLES

Atomic model and micelle dynamics of QS-21 saponin

Pedebos, C., Pol-Fachin, L., Pons, R., Teixeira, C.V., Teixeira, H.

Molecules, 19, 3744-3760, **2014.**

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Characterization and stability of catanionic vesicles formed by pseudo-tetraalkyl surfactant mixtures

Pucci, C., Pérez, L., La Mesa, C., Pons, R.

Soft Matter, 10, 9657-9667, **2014.**

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Complex rhamnolipid mixture characterization and its influence on DPPC bilayer organization

Haba, E., Pinazo, A., Pons, R., Pérez, L., Manresa, A.

Biochim. Biophys. Acta – Biomembranes, 1838, 776-783, **2014.**

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Gemini surfactants from natural amino acids

Pérez, L., Pinazo, A., Pons, R., Infante, M.

Adv. Colloid Interface Sci., 205, 134-155, **2014.**

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Release of DNA and surfactant from gel particles: The receptor solution effect and the dehydration-hydration aspects

Mezei, A., Pons, R.

Coll. Surf. B: Biointerfaces, 123, 279-285, **2014.**

.....

Topical anti-inflammatory potential of quercetin in lipid-based nanosystems: In vivo and in vitro evaluation

Caddeo, C., Díez-Sales, O., Pons, R., Fernàndez-Busquets, X., Fadda, A.M., Manconi, M.

Pharm. Res., 31, 959-968, **2014.**

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Catanionic vesicles and DNA complexes: A strategy towards novel gene delivery systems

Pucci, C., Scipioni, A., Diociaiuti, M., La Mesa, C., Pérez, L., Pons, R.

RSC Adv., 5, 81168- 81175, **2015.**

Chiral cyclobutane beta-amino acid-based amphiphiles: Influence of cis/trans stereochemistry on solution self-aggregation and recognition

Sorrenti, A., Illa, O., Pons, R., Ortuño, R.M.

Langmuir, 31, 9608-9618, **2015.**

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Effect of fatty acids on self-assembly of soybean lecithin systems

Godoy, C.A., Valiente, M., Pons, R., Montalvo, G.

Coll. Surf. B: Biointerfaces, 131, 21-28, **2015.**

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Faceted phospholipid vesicles tailored for the delivery of Santolina insularis essential oil to the skin

Castangia, I., Manca, M.L., Caddeo, C., Maxia, A., Murgia, S., Pons, R., Demurtas, D., Pando, D., Falconieri, D., Peris, J.E., Fadda, A.M., Manconi, M.

Coll. Surf. B: Biointerfaces, 132, 185-193, **2015.**

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Niosomes based on synthetic cationic lipids for gene delivery: The influence of polar head-groups on the transfection efficiency in HEK-293, ARPE-19 and MSC-D1 cells

Ojeda, E., Puras, G., Agirre, M., Zárate, J., Grijalvo, S., Pons, R., Eritja, R., Martinez-Navarrete, G., Soto-Sanchez, C., Fernández, E., Pedraz, J.L.

Org. Biomol. Chem., 13, 1068-1081, **2015.**

BOOK CHAPTERS

Experimental techniques used for the characterization of soft nanoparticles

Callejas-Fernández, J.; Ramos, J.; Sanz, O.; Forcada, J.; Ortega-Vinuesa, J.L.; Martín-Molina, A., Rodríguez-Valverde, M.A., Tirado-Miranda, M., Schmitt, A., Sierra-Martin, B., Maldonadovaldivia, A., Fernández-Barbero, A., Pons, R., Capitán-Vallvey, L.F., Salinas-Castillo, A., Lapresta-Fernández, A., Vázquez, B., Aguilar, M.R., San Román, J.

RSC Nanosci. Nanotech., 19, 108, **2014.**

RESEARCH PROJECTS

Aplicaciones no convencionales de tensioactivos y líquidos iónicos derivados de aminoácidos naturales en nanotecnología y química sostenible.

MINECO- CTQ2013-41514-P
2014-2016
PI: R. Pons y M.T. García

.....

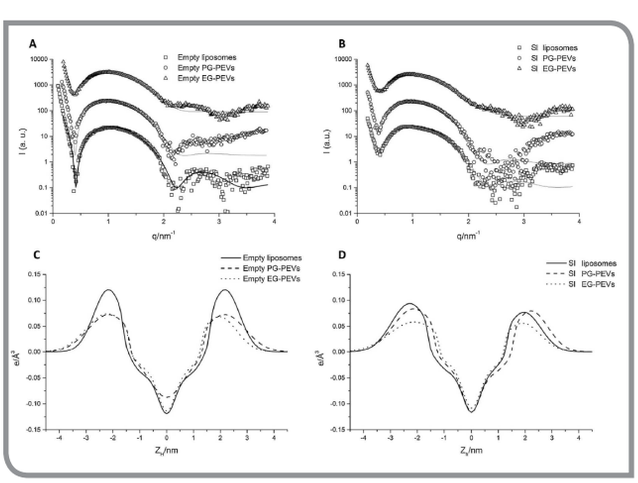
SaCS: Self-assembling Colloidal Systems.
Consorcio CELLS Sincrotrón ALBA, ID 2013110789
2014:
PI: C. Caddeo

.....

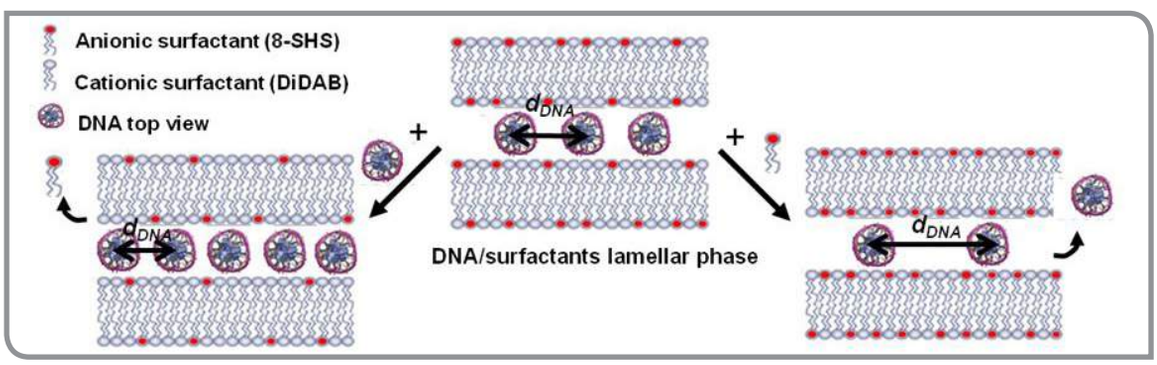
Dynamics of cationic surfactant-DNA complex formation.
Consorcio CELLS Sincrotrón ALBA, ID 2014071017
2015
P.I.: R. Pons

RESEARCH HIGHLIGHTS

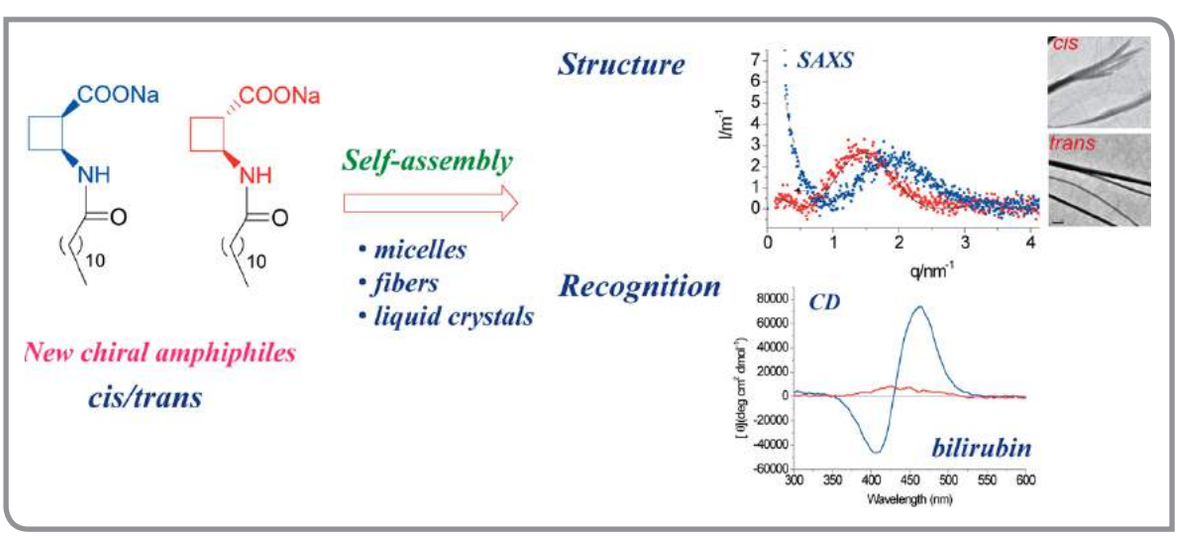
The characterisation of vesicles and bilayers has been pursued in two directions. First, liposomes based on natural phospholipids have been studied to determine the effect of drug additives, whether the additive perturbs the bilayer organization and multilamellarity and/or can be detected as an adsorbed layer. Second, vesicles formed by synthetic molecules have been characterized in order to knowing the molecular parameters at the bilayer. By using a model of the bilayer electronic density combined with a multilayer interaction model, the electronic profiles of the bialyers can be extracted; recently we have implemented also asymmetric bilayer models like the ones that can be observed in the figure. In the upper graphs, the scattered x-ray intensity, as obtained at synchrotron ALBA, is plotted as a function of the scattering q vector together with the best fits. The corresponding bilayer electronic profiles can be observed in the bottom row.



We have also focussed on the formation of complexes of DNA with cationic or catanionic systems. We have studied the stability and release characteristics of such systems. In particular, a form of specific signal release could be obtained in catanionic systems. Those vesicular systems release DNA when further anionic surfactant is incorporated to the medium while they compact further and release anionic surfactant If additional DNA is present in the medium.



We have pursued studies on the phase behaviour of natural lipoaminoacids and other amphiphilic molecules. We have studied the effect of isomery in the self-assembly of non-natural aminoacids derived from cyclobutane. In the monomeric form small differences in pKa were observed which induced differences in pKa shifts upon protonation. The stereochemistry strongly influences the self-assembly promoting either globular or fibrilar aggregates. Among other features, chiral recognition behaviour in front of bilirubin was observed.



TEXTILES AND COSMETIC INNOVATIONS

The main research lines of this group are: lipid assembling (liposomes, microspheres, bilayers, etc.) lipokeratinic tissues (skin, wool and human hair), percutaneous absorption and physicochemical characterization of colloids with potential industrial applications

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LAIA RUBIO TOLEDANO

PH. D. STUDENTS

VICTOR CARRER VIVES

ARTICLES

Water sorption evaluation of stratum corneum

Barba, C., Baratto, A., Martí, M.; Semenzato, A., Baratto, G., Manich, A.M., Parra, J.L., Coderch, L.

Thermochim. Acta, 583, 43-48, **2014**

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Bicellar systems as vehicle for the treatment of impaired skin

Rubio, L., Alonso, C., Rodríguez, G., Cócera, M., Barbosa-Barros, L., Coderch, L., De La Maza, A., Parra, J.L., López, O.

Eur. J. Pharm. Biopharm., 86, 212-218, **2014.**

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Gallic acid vehiculized through liposomes or mixed micelles in biofunctional textiles

Martí, M., Martínez, V., Lis, M.J., Valldeperas, J., de la Maza, A., Parra, J.L., Coderch, L.

J. Textile Inst., 105, 175-186, **2014.**

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In vivo and in vitro evaluation of topical formulations containing physiological lipid mixture for replacement of skin barrier function

Barba, C., Parra, J.L., Coderch, L., Semenzato, A.

Giornale Ital. Derm.Venereol., 149, 347-353, **2014.**

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Textiles with gallic acid microspheres: In vitro release characteristics

Martí, M., Martínez, V., Carreras, N., Alonso, C., Lis, M.J., Parra, J.L., Coderch, L.

J. Microencapsulation, 31, 535-541, **2014.**

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Antioxidative effects and percutaneous absorption of five polyphenols

Alonso, C., Rubio, L., Touriño, S., Marti, M.,Barba, C., Fernández-Campos, F., Coderch, L., Parra, J.L.

*Free Radical Biology and Medicine***,** 75, 149-155**, 2014**

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Advanced hair damage model from ultra-violet radiation in the presence of copper

Marsh, J.M., Davis, M.G., Flagler, M.J., Sun, Y., Chaudhary, T., Mamak, M., McComb, D.W., Williams, R.E.A., Greis, K.D., Rubio, L., Coderch, L.
Int. J. Cosm. Sci., 37, 532-541, **2015.**

Effect of lipid modification on stratum corneum permeability

Barba, C., Martí, M., Semenzato, A., Baratto, G., Manich, A.M., Coderch, L.

J. Thermal Anal. Calorim., 120, 297-305, **2015.**

Skin delivery of antioxidant surfactants based on gallic acid and hydroxytyrosol

Alonso, C., Lucas, R., Barba, C., Marti, M., Rubio, L., Comelles, F., Morales, J.C., Coderch, L., Parra, J.L.

J. Pharm. Pharmacol., 67, 900-908, **2015.**

Mass transport model through the skin by microencapsulation system

Carreras, N., Alonso, C., Martí, M., Lis, M.J.

J. Microencapsulation, 32, 358-363, **2015.**

Percutaneous absorption of topical antinflamatories. A comparative study between predicted models and in vitro permeation results

Carrer, V., Alonso, C., Zanuy, M., Espinosa, S., Córdoba, M., Godessart, N., Vidal, B., Coderch, L.

Basic &Clinical Pharmacology & Toxicology, 117, **2015**

BOOK CHAPTERS

The role of liposomes in textile dyeing

Martí, M., de la Maza, A., Parra, J.L., Coderch, L.

Liposomes, Lipid Bilayers and Model Membranes. From Basic Research to Application. Pabst, G., Kucerka, N., Nieh, M-P., Katsaras, J. eds. CRC Press. (U.K.) ISBN-13: 978-1-4665-0709-8, 401-414, **2014**

NATIONAL ARTICLES

Permeación en Piel de un Ácido Gálico Sede un Cosmetico-Textil: Tejidos de Algodón y Poliamida

M. Martí, C. Alonso, V. Martínez, M. Lis, A. de la Maza, J.L. Parra y L. Coderch,

Revista de Química e Industria Textil, 211, 35-39, **2014**

WDS: Lavado en Seco de la Lana Eco-Eficiente con Recuperación Total de Sub-Productos

J. Iglesias, LL. Alerm, M. Tavares, M. Jorba, S. Balsells, L. Coderch y M. Martí

Revista de Química e Industria Textil, 211, 47-51, **2014**

Tejidos Biofuncionales: Modelización Del Transporte De Masa A Través De La Piel M. Martí, C. Alonso, N. Carreras, M. Lis

Revista de Química e Industria Textil, 215, 7-13, **2015**

RESEARCH PROJECTS

Lavado en seco de lana eco-eficiente con recuperación total de subproductos.

Nacional, IPT-2012-0644-310000
2013-2015

Eco-efficient wool dry scouring with total by products recovery

CCEE, LIFE11 ENV/ES/588
2012-2015

Plataforma Tecnológica INNODERM

Retos Colaboración – Prg Retos de la Soc. RTC-2014-1901-1
2014-2016

Sistemas lipídicos avanzados para la vehiculización de antioxidantes en aplicaciones dermatológicas

CTQ2013-44998-P
2014-2017

Físicoquímica i estructuració vesicular de lipids i biopolimers bacterians

2014 SGR 1325
2014-2017

Mitigation of environmental impact caused by DWOR textile finishing Chemicals studying their non-toxic alternatives

(MIDWOR), LIFE14 ENV/ES/000670
2015-2018

CONTRACTS

Protein Degradation Evaluation of Hair treated with 5 antioxidants. SES/13/24

The Procter and Gamble Comp
4/2014 -4/2015

.....

Eficacia hidratante y efecto barrera de un polímero bacteriano SES/13/22

UB, Bosch i Gimpera
2/2014 -6/2014

.....

Absorción Percutánea "in vitro" de tres formulaciones conteniendo un antiinflamatorio SAS/14/03

UB
2/2014 -5/2014

.....

Eficacia de un serum en piel humana. SES/14/02

MartíDerm
3/2014 -7/2014

.....

Elasticidad, Firmeza y Antiarrugas de una mascarilla de arcilla. SES/14/06

Pharmaclay/CIC BIOGUNE
3/2014 -6/2014

.....

Study of the in Vitro percutaneous absorption of a maximum of 20 compounds using pig skin samples. SAS/14/09

Almirall S.A.
5/2014 -5/2015

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Ceramide content in 3 keratin composite samples SES/14/004

Down Meats Group
9/2014 -12/2014

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Coloración de la piel debido al tratamiento tópico de dos formulaciones placebo SES/14/013

Reig Jofre S.A.
9/2014 -3/2015

.....

Action of Surfactants in the epidermal barrier SES/14/16

UNIFARCO (S. Giustina, Italia)
12/2014-12/2015

Eficacia antioxidante en cabello humano por fluorescencia SES/14/21.

Provital (Barberá del Vallés)
12/2014- 3/2016

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Studio comparativo preliminar de la liberación "in vitro" de dos formulaciones conteniendo dos principios activos. SED/15/04

Almirall S.A.
2/2015 -5/2015

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Addendum of Study of the in Vitro percutaneous absorption of a maximum of 20 compounds using pig skin samples. SED/15/05

Almirall S.A.
3/2015 -3/2016

.....

2nd Addendum of Study of the in Vitro percutaneous absorption of a maximum of 20 compounds using pig skin samples. SED/15/16

Almirall S.A.
3/2016 -12/2016

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Análisis cuantitativo de un principio activo por HPLC SED/15/09

Bicosome
11/2015-1/2017

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Estudio comparativo de la liberación "in vitro" de tres sistemas conteniendo un principio activo SED/15/17

Bicosome
11/2015- 1/2016

.....

Análisis cuantitativo de nucleopure por HPLC SED/15/19

Bicosome

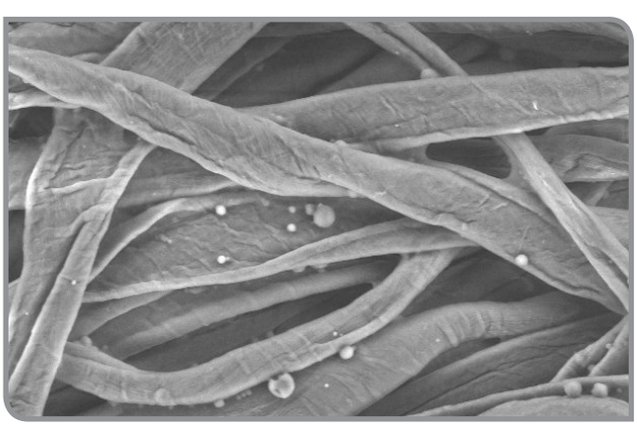
11/2015-1/2017

MAIN ACTIVITIES

The main scientific activity of this group focuses on the study of cosmetic and textile application of vehicles, able to encapsulate active principles. These lipid structures, such as liposomes, microspheres, etc., modulate the penetration of the actives in the different substrates. The effectiveness of the topical application on skin or hair to improve the hydration and skin barrier function, lipid peroxidation, etc. is evaluated. Percutaneous absorption profile of these formulations after being applied directly to the skin or through biofunctional textiles are also being studied. The basic knowledge of hydrophilic-lipophilic balance of lipid-proteinaceous keratin systems, such as wool, human hair and stratum corneum of human skin is also being explored. This knowledge is essential to design formulations for industrial application in the textile, cosmetic and dermopharmaceutic fields. Therefore, the main research highlights are the followings:

Biofunctional textiles and their effectiveness on skin

Biofunctional textiles are able to release therapeutic compounds or cosmetics to the skin. The biofunctional textiles contain microscopic capsules of ingredients that break as the fabric rubs the skin, releasing the actives. Absorption and desorption behaviour of active agents embedded into the different biofunctional textiles should be taken into account when determining the amount of active agents incorporated into these textiles and when following the delivery mechanism as the fabric comes into contact with the skin. Microcapsules, microspheres, mixed micelles and liposomes were used as vehicles to be applied mainly in cotton and polyamide.

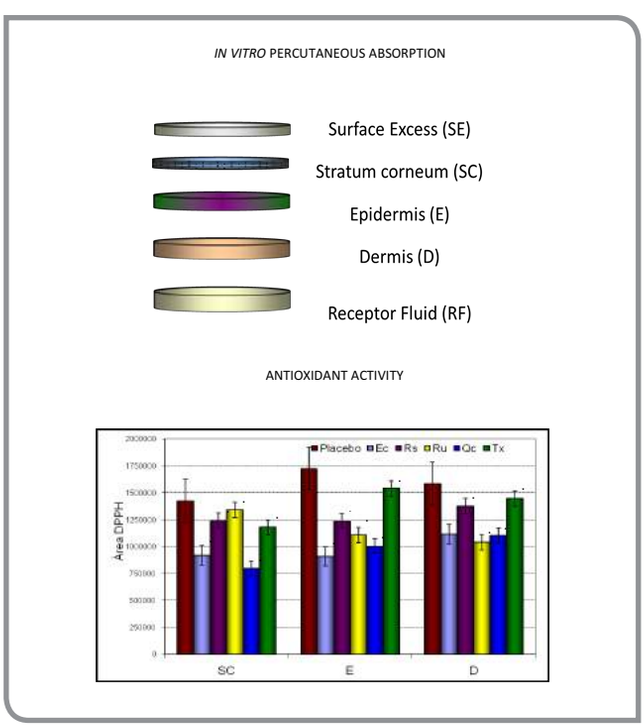


Acid Gallic encapsulated in PCL-Microspheres and applied onto cotton fabric

Antioxidants such as resveratrol and gallic acid were mainly studied. The passage of the active principle through different skin layers were detected "in vitro". Most actives embedded within biofunctional textiles promoted an interesting reservoir effect. A general kinetic model for a microencapsulated structure as a mass transport system trough the skin was applied. Then this model could predict the penetration profile of encapsulated substances. The passage of the active principle through the skin layers have also been detected "in vivo". In this research, textiles were applied onto volunteer forearms to determine their antioxidant efficacy. Lipoperoxide formation was evaluated by a non-invasive ex vivo method and a clear inhibition was found demonstrating the effectiveness of the cosme-to-textiles.

Antioxidants on skin and hair

A new strategy was designed to evaluate the antioxidant effectiveness of five topically applied polyphenols following skin penetration profiles; epicatechin, resveratrol, rutin, quercitin and trolox. The percutaneous absorption was obtained by an in vitro methodology using porcine skin biopsies and the antioxidant activity was determined by the DPPH* method. The antioxidant



Absorbance of DPPH• radical obtained in the assay with antioxidant skin extracts (Stratum Corneum SC, Epidermis E and Dermis D) after percutaneous absorption.

evaluation of each skin compartment suggested that resveratrol and rutin were the most effective topically applied compounds in view of their antioxidant activity and their skin penetration profile. Besides, percutaneous absorption of two antioxidants, gallic acid and hydroxytyrosol and their lipophilic derivatives with surface activity were evaluated. These antioxidants were present in all layers of the skin and the content is higher for the antioxidant surfactants (ester derivatives). This particular behavior could be due to the higher hydrophobicity of this compound and the presence of surface activity in the antioxidant surfactants.

Damage to hair from UV exposure has been well reported, however the mechanism of formation and propagation of reactive oxygen species (ROS) are not fully understood. We studied these mechanisms exploring the role of copper in accelerating the formation of ROS and identifying strategies to reduce the hair damage caused by these reactive species. The role of copper in accelerating UV damage to hair has been demonstrated as well as the ability of chelants such as edds and histidine in shampoo and conditioner products to reduce this damage.

Skin permeability

This group also works into the cosmetic field, studying changes in the water properties of stratum corneum from skin, etc. Reactive cosmetic treatments of skin often impair fiber structure, resulting in an adverse effect on water absorption. The moisture absorption/desorption isotherm curves and the kinetics of these processes are studied in this research. Human and pig skin were evaluated obtaining similar apparent diffusion coefficients, indicating their suitability for permeation studies. They behaved as expected, with a characteristic hysteresis between moisture uptake and desorption. The effect of lipid depletion was also followed by dynamic vapour sorption analyses. The general increase of the diffusion coefficients indicates the key role of the lipids in maintaining the adequate water permeability. TEM visualization confirmed the modification of lipid structure of samples treated with organic solvents and surfactants.

The effects of different chemical cosmetic treatments on skin are also evaluated by water absorption/desorption curves. Diffusion coefficients indicate the permeability of the fibre related to its integrity. Besides biophysical measurements "in vivo" such as TEWL or hydration were carried out to evaluate protecting and repairing effect of different barrier repair cosmetic formulations. Hydration was maintained but TEWL was clearly reduced which implies an improvement of the skin barrier.

BIOPHYSICS OF LIPIDS AND INTERPHASES

The activities of the group are focused on the study of biophysical, biochemical, physico-chemical and technological aspects applied to certain biological substrates, in which lipids play a relevant role. Particularly, we based our research on the study of colloidal systems formed by lipids and other amphiphilic such as liposomes, micelles, bicelles and bicosomes and also on the understanding of complex biological tissues like skin and mucous. Additionally, the group addresses knowledge to the adaptation of high resolution technologies to be properly applied in the study of both colloidal systems as well as biological tissues. Over the past two years the work in the group is focused on the study of free radicals (FR) formation in the skin and on the degradation of proteins from the extracellular matrix of this tissue by effect of solar radiation and, how advanced lipid systems can alleviating these phenomena.

The general aims pursued in our research are addressed to a final technological applicability in industrial field. Because of the novelty of the raised issues, the group always carries out an initial basic research to obtain information that allows an industrial approach.

STAFF

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PH. D. STUDENTS

ESTIBALITZ FERNÁNDEZ PINTO
VERÓNICA MONER

ARTICLES

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BOOK CHAPTERS

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M. Cócera, G. Rodríguez, L. Rubio, E. Fernández, L. Barbosa-Barros, A. Labrador, M. Sabés, A. de la Maza, O. López

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RESEARCH PROJECTS

Sistemas lipidicos avanzados para la vehiculizacion de antioxidantes en aplicaciones dermatologicas (CTQ2013-44998-P)

ENTIDAD FINANCIADORA: Ministerio de Economía y Competitividad
2014-2017

Fisicoquimica i estructruación vesicular de lipids i biopolímers bacterians. (2014 SGR 1325)

ENTIDAD FINANCIADORA: Generalitat de Catalunya
2014-2016

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2014

Ayudas para apoyar las actividades de los grupos de investigación para el año 2009. Nombre del grupo: Físicoquímica i estructuració vesicular de lipids i biopolimers bacterians

Generalitat de catalunya, 2009SGR1212
2009-2014

Desarrollo de una formulación que estabilice la fosfomicina y aumente la biodisponibilidad del antibiótico

2013-2015

Preparación y caracterización de bicosomas que contengan principios activos cosméticos I

2014-2015

Preparación y caracterización de bicosomas que contengan principios activos cosméticos II

2015-2017

Contrato de Royalties con la empresa Labiana SA

Duración: 2012 en adelante

Contrato de Royalties con la empresa Smartnano SL

2012 en adelante

RESEARCH HIGHLIGHTS

Advanced lipid systems for dermopharmaceutical applications: antibiotics, antifungal, anti-inflammatories, antioxidants.

Based on the knowledge of biophysics of lipids and of the peculiarities of skin structure and physiology, the group has developed new lipid systems, and has demonstrated the great applicability potential of these structures in the field of dermatology. These advanced lipid systems are able to penetrate the skin without promoting damages, even repairing their structure and, they can incorporate all kinds of molecules. When applied on the skin, these nanostructures are retained

in the skin layers delivering molecules with dermo-pharmaceutical interest. This fact potentiates localized effect of incorporated molecules. For antifungal and antibiotics compounds, the antimicrobial efficacy increases when encapsulated in bicelles and bicosomes. In the case of anti-inflammatory, using the appropriate lipid composition and the correct application procedure, a better penetration in the skin can be achieved. Regarding antioxidants, some lipid systems seems to have a blocking effect against UV and IR radiation, this coupled with the fact that it can exert a protective effect of antioxidant molecule also opens potential applications in this field. So the challenge is getting effective treatments for diseases and skin disorders. To this end the phase behavior of different lipid systems is studied. In vitro and in vivo efficacy assays with healthy and diseased skin are needed and in some cases biodistribution studies have to be addressed.

Reducing the harmful effects of solar radiation on the skin

UV radiation induces formation of free radicals (FR) in the skin. Our research evaluates and identifies by means of Electron Paramagnetic Resonance (EPR) six different radicals in the skin: two originated from oxygen centered radicals, one from carbon-centered radicals, and others from hydroxyl, hydrogen and aminoxyl radicals. We have studied the FR scavenging activity of the some lipid nanostructures in skin submitted to solar radiation, and also the effect of including the β-carotene antioxidant in these systems. Bicelles and bicosomes demonstrated stronger morphological stability under UVA-VIS-IRA radiation and higher increase in the stability of the antioxidant incorporated under radiation in comparison with liposomes. This fact is likely due to the scattering properties of the lipid assemblies. EPR revealed that bicelles and bicosomes exert FR scavenging activity on the skin after irradiation. This activity was higher for bicosomes containing β-carotene. Differences regarding scavenging activity between bicelles and bicosomes would probably be due to the different interaction of both systems with the skin. Everything indicates that these nanostructures are promising vehicles for the incorporation of antioxidant molecules into the skin, which would be interesting in order to reinforce the antioxidant barrier of this tissue.

Aplication of Synchrotron radiation in the study of biological materials: membrane models, skin and hair.

These activities are focused on the use of the technique of X-ray scattering at small (SAXS) and wide (WAXS) angles using Synchrotron source. These studies allow a deeper understanding of the behavior of different membrane model with strong lipid involvement and also of complex lipokeratinic tissues, particularly skin and hair. Our research is conducted to optimize the experimental conditions that generate information about skin lipids, responsible from the cutaneous barrier function and also about from skin collagen, the main structural protein of the skin. Characterization of skin at different conditions is useful for diagnosis of various skin disorders, taking a particular interest in the diagnosis of skin tissue invaded by melanoma. Another technique based on Synchrotron radiation is IR microspectroscopy. This methodology allows mapping samples and also monitoring different molecules inside the tissues.

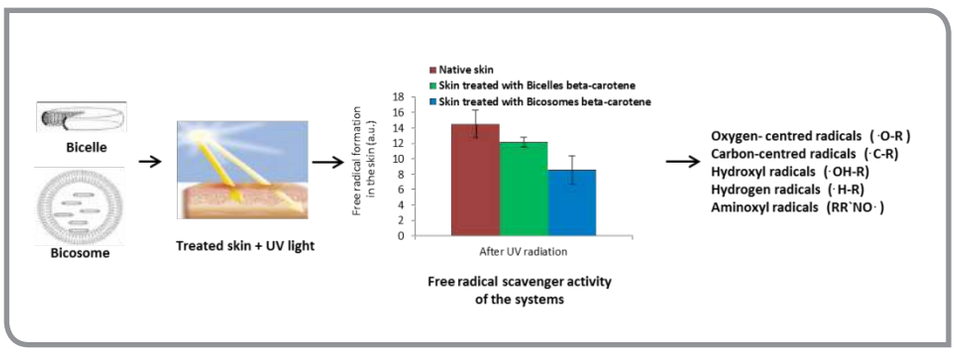

Fig. 1: Scheme showing bicelle and bicosome structure and FR scavenger activity of these lipid systems

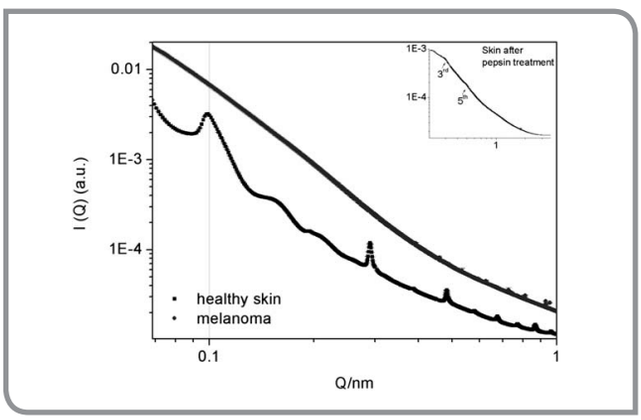

Fig 2. SAXS profile of collagen from healthy skin (down) and skin invaded by melanoma (up) plotted as scattering intensity. The inset shows collagen affected by pepsin treatment (proteolytic enzyme) for comparing the degradation of the collagen molecule.

6

COLLABORATIVE LEAVE AT UNIVERSITY OF REGENSBURG

FUNCTIONAL MATERIALS

Our general research interests are centered in the development of functional materials with applications in areas such as biomedicine, catalysis, molecular sensing, coatings and adhesives, environmental remediation and energy. We believe that the discovery of new versatile and functional materials with solid prospect for practical applications will be intimately associated to inexpensive, simple and scalable processes. Thus, we aim to select the most practical chemical approaches for the synthesis of new materials and fine-tuning specific properties. In this sense, we like to apply in our projects what we call the "KISSu principle" (Keep It Simple and Sustainable). Besides materials synthesis, we maintain a genuine interest for the search of new synthetic methodologies and bioactive molecules (e.g., amidines, metal complexes).

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http://www-oc.chemie.uni-regensburg.de
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PUBLICATIONS (ARTICLES)

A click chemistry organic adhesives experiment

Accurso, A. A.; Finn, M. G.; Fokin, V. V.; Díaz, D. D.

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Gelatin protein-mediated direct Aldol reaction

Kühbeck, D.; Bachl, J.; Schön, E.-M.; Gotor-Fernández, V.; Díaz Díaz, D.

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EDITORIAL

Díaz, D. D. (Editorial)

Welcome to Gels - An Interdisciplinary Open Access Journal for a Growing Scientific Community

Gels **2014**,1, 1-2 (DOI: 10.3390/gels1010001)

BOOK CHAPTER

Díaz, D. D.; Johnson, J. A.

Photo-responsive hydrogels for adaptive membranes

In "Smart Membranes and Sensors. Synthesis, Characterization and Applications", Annarosa Gugliuzza (ed.), Scrivener Publishing LLC - Wiley, Ch 2, pp 21-52, **2014** (ISBN: 9781118423790)

RESEARCH HIGHLIGHTS

MULTISTIMULI RESPONSIVE SUPRAMOLECULAR GELS

The ability of natural systems to alter function in direct response to environmental conditions has inspired many scientists to fabricate 'smart' materials that respond to temperature, light, pH, electro/magnetic field, mechanical stress and/or chemical stimuli. These responses are usually manifested as remarkable changes from the molecular (e.g., conformational state, hierarchical order) to the macroscopic level (e.g., shape, surface properties). Among many

types of stimuli responsive materials, self-assembled viscoelastic gels of both organic solvents (organogels) and water (hydrogels) have been recognized as promising materials for bottom-up nanofabrication tools in various fields such as biomedicine, catalysis, membranes, sensors, cosmetics, foods and environmental remediation. In contrast to chemical gels, which are based on covalent bonds (usually cross-linked polymers unable to redissolve), physical (also called supramolecular) gels are made of either low-molecular-weight compounds or polymers (gelators) through extensive non-covalent interactions. Many gels have been found by serendipity rather than rational design, but we are also convinced that serendipity often provides a major opportunity for scientific discovery. We are interested in the development, modification, and applications of new multiresponsive and/or reactive supramolecular gels, including catalytic and self-healing metal-organic gels, as well as in the study of supramolecular chiral amplification with these materials. Herein, we try to find the most simple and reliable synthetic approaches for creating new and complex functions.

HYBRIDIZATION AND STUDY OF FUNCTIONAL POLYMER GELS

Many real-life applications of advanced materials such as SWCNTs are limited by two major problems: (1) their low dispersibility in aqueous solutions due to entanglement and hydrophobic association of the tubes; and (2) their intrinsic cytotoxicity. In this sense, significant progress has been made in the past few years regarding the surface functionalization of SWCNTs with various organic molecules to enhance both solubility and biocompatibility, and their blend with other systems to form composites with greater properties. Thus, the interest of incorporating CNTs into soft hydrogel matrices has grown considerably over the last decade. We envisioned the possibility of using the strain-promoted azide-alkyne cycloaddition (SPAAC) for covalent incorporation of SWCNTs into bioactive hydrogel networks. SPAAC has been proved to proceed efficiently not only in a wide range of conditions like the Cu(I)-catalyzed AAC, but also in the absence of ligands, bases or toxic metals. Thus, potential cytotoxic effects due to enduring entrapment of toxic metal ions especially in highly chelating gel matrices made by CuAAC could be overcome by SPAAC. We are interested in expanding the use of SPAAC and CuAAC to fabricate nanocomposites with tuneable properties such as conductivity, mechanical strength, and morphology, especially for biomedical and membrane applications such as targeted drug/gene delivery or tissue engineering.

In the broad field of polymer gels, we are also interested in the rational design of polymer gelators, including charged systems (e.g., polyelectrolytes), with enhanced gelation efficiency and new functionalities, for which we are employing molecular dynamic simulations with explicit solvent molecules in collaboration with Prof. C. Alemán (UPC).

FINE-TUNING THE BALANCE BETWEEN GELATION AND CRYSTALLIZATION

The formation of supramolecular gels is a result of a well-balanced combination of numerous non-covalent interactions, including those between gelator-gelator, gelator-solvent, aggregate-solvent and solvent-solvent molecules. Usually, a lack of control over these interactions caused an unpredictable competition between crystallization and gelation phenomena. We are learning about the key factors that govern the equilibrium position and how can we favor one of the two processes selectively in order to access to a wider range of materials with different properties from the same building blocks. In this sense, we couldsynthesize either metal-organic-frameworks (MOFs) or metal-organic-gels (MOGs) by small changes in the solvent composition using the same ligand and metal precursors.

CHEMICAL TRANSFORMATIONS IN CONFINED MEDIA

Inspired by nature, much effort has been devoted over the last decade to the study of meso-, micro- and nano-scale reactors. The main reason for this is the fact that many chemical reactions take place with high efficiency in natural confined environments where the motions of reactant molecules are restricted to that in free solution. In concordance, numerous advantages have been also attributed to the use of synthetic nanoreactors including, among others, the possibility of tailoring additional functionalities, organization and orientation of solvent, catalyst and reactant molecules, controllable molecular diffusion, large surface area to volume ratios and reduction of overheating/concentration effects. In our group we wish to understand the changes on kinetics and chemical pathways/selectivities of different types of reactions, including photochemical transformations, that are carried out within nanostructured and stimuli-responsive softgel materials, which can be tuned for working as reaction vessels, biocompatible nanoreactors and/or reusable catalysts. Beyond kinetics and selectivity aspects in comparison to solution phase, this project aims to contribute in building a challenge bridge between solution and biocompatible supramolecular responsive gel-based formulations for the selective activation and control release of bioactive compounds for the treatment of different diseases.

INTRINSIC CATALYTIC FUNCTION OF BIOPOLYMERS AND PROTEINS

With growing concern for our environment and stringent environmental regulations by the governments, emphasis of science and technology is shifting more and more from petrochemical-based feedstocks towards the optimal use of environmentally friendly and sustainable resources and processes. In this regard, direct utilization of products derived from naturally occurring materials has become a prevalent means for a number of high-tech applications. We found that many natural polymers and proteins display an intrinsic ability for catalyzing important chemical transformations such as C-C bond forming reactions, which are in the broad sense a prerequisite for all life on earth.

The fact that natural materials can mediate these reactions under physiological conditions might have a significant impact on the evolution of different chemical compounds in vivo. Within our program we try to focus on these natural materials and understand the variables that can impact their inherent function towards different catalytic processes including cascade and multicomponent reactions. We believe that styding the intrinsic role of proteins in mediating bond formation/cleavage will be crucial for understanding mechanism in evolution and designing "greener" catalysts.

ADHESIVE POLYMERIC MATERIALS

Polymer chemistry has been a rich beneficiary of the ability of click reactions to make molecular connections with absolute fidelity. Polymer synthesis depends on a limited number of processes that include many of the best examples of click reactivity. During the last decade we have been working in collaboration with Prof. M.G. Finn (GaTech) in the development of new bulk polymers with adhesive properties for metal surfaces making use of the copper-catalyzed azide-alkyne cycloaddition. Some of our materials have been found to possess superior adhesive strength than standard commercial glues. We continue working on the improvement of these formulations as well as on the application of this technology in areas such as conductive materials, anti-fouling coatings, or superhydrophobic surfaces.

NANOPARTICLES-CONTAINING MATERIALS

In collaboration with the group of Dr. R. Banerjee (NCL), we participate on the preparation of highly stable metal and covalent organic framework-based materials (e.g., MOFs, COFs) with superior properties for applications in gas adsorption, catalysis, energy storage (e.g., water oxidation, hydrogen evolution), and biomedical applications (e.g., targeted anti-cancer drug delivery, diagnostic imaging). Moreover, we are interested in the development of new physical and chemical strategies to stabilize unstable nanoparticles, and on the use of functional nanoparticles to stabilize other structured materials.

SPIN-OFF ACTIVITIES

Bicosome S.L. is a spin off company of the Institute of Advanced Chemistry of Catalonia (IQAC) founded in 2012 by scientists of the Biophysics of Lipids and Interfaces group. The vision was to create a company that could transform the knowledge of the research group into dermatological and cosmetic products that improve people's quality of life.

Bicosome company develops high performance skin care ingredients based on the patented Bicosome® Technology that are commercialized mainly to the dermocosmetic and pharmaceutical industries.

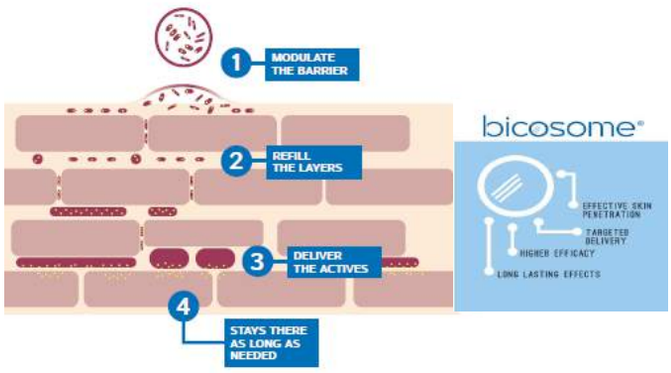
Staff	Advisory Board
Lucyanna Barbosa-Barros, CEO	Santiago Alonso
Rafael Bernad, Business Development	Alfonso de la Maza
Mercedes Cócera, Product Development Scientist	Olga López
Gelen Rodríguez, Product Development Scientist	
Rosana Saldaña, Sales and Marketing Manager	
Montse Baldrich, Administrative Assistant	

How the technology works

Bicosome is in a double-encapsulation system formed by small discoidal structures enclosed in vesicles that interact with the skin through a **biomimetic mechanism** that respects the skin's natural processes.

When applied on the skin, the structures of bicosome respond to the different skin environment, are able to **modulate the skin barrier function** and penetrate the tissue, carrying active ingredients into targeted layers.

Bicosomes can be designed to reach different deepness in the skin. Once in the target layer, they reorganize their structures and grow whilst remaining anchored in between the skin cells, **refilling the natural lipid matrix**. This effect allows for the active ingredients carried by the bicosome structures to be retained in specific skin layers and to be **slowly delivered**. Bicosomes remain anchored in the skin until they are freed following the skin's renewal process. **The driving force is the skin biology itself.**



Proprietary products in the market

bicosome® fs by bicosome®

Bicosome® Filling up system (Bicosome® FS) is a biomimetic filler that delivers bilayer-forming lipid structures in the intercellular spaces of the skin. This allows for lipid matrix replenishment that improves and repairs barrier function and elasticity and firmness parameters. The Bicosome® FS benefits have a prolonged action of at least seven days.

bicotene® by bicosome®

Bicotene® Antiox / UV & IR Protection Complex is a deep sun repair system that stabilises and delivers carotene molecules deep in the epidermis, providing biological sun protection. The supply of carotenes by Bicotene® Antiox reinforces the skin's defence mechanism, reduces the formation of free radicals generated by UV, Vis and IR, protects and repairs cell DNA from UV damage and prevents the degradation of collagen induced by IR radiation.

bicowhite® by bicosome®

Bicowhite® Complex is a brightening/lightening multistep delivery system that works blocking the different processes involved in the hyperpigmentation of the skin. The system incorporates five complementary actives named Azeloglicine, Niacinamide, Alfa-Bisabolol, Vitamin C and Phytic Acid, which are driven by different bicosome structures to the specific skin layer where they have to work.

These products are commercialized to Pharmaceutical and Dermocosmetic through specialized distributors in different markets worldwide.

Co-development projects

Bicosome also partners with Pharmaceutical and Dermocosmetic companies in co-development projects involving the commercialization of tailor made Bicosomes.

IN MEMORIAM

In 2013 and 2014 we were deeply saddened by the loss of two of our colleagues and active staff members Francisco Sanchez Baeza and Nuria Azemar. It was an honor to have known such great people and we truly miss them. In their memory we express our sadness for their loss including dedications to our papers published during 2014 and 2015. Some representative examples are shown below.

Coulombimetric immunosensor for paraquat based on electrochemical nanoprobes. Valera, E., García-Febrero, R., Pividori, I., Sánchez-Baeza, F., Marco, M.-P. *Sensors Actuators, B: Chemical*, *194*, 353-360, **2014**.

Rapid method based on immunoassay for determination of paraquat residues in wheat, barley and potato. Garcia-Febrero, R., Salvador, J.-P., Sánchez-Baeza, F., Marco, M.-P. *Food Control*, *41*, 193-201, **2014.**

Electrochemical detection of fluoroquinolone antibiotics in milk using a magneto immunosensor. Pinacho, D.G., Sánchez-Baeza, F., Pividori, M.-I., Marco, M.-P. *Sensors*, *14*, 15965-15980, **2014.**

Efficient synthesis of conformationally restricted apoptosis inhibitors bearing a triazole moiety. Corredor, M., Garrido, M. Bujons, J., Orzáez, M., Sancho, M., Pérez-Payá, E., Alfonso, I., Messeguer, A. . *Chem. Eur J.*, *21*, 14122-14128, **2015**.

Cationic vesicles based on non-ionic surfactant and synthetic aminolipids mediate delivery of antisense oligonucleotides into mammalian cells Grijalvo, S., Alagia, A., Puras, G., Zarate, J., Pedraz, J.L., Eritja, R. *Coll. Surf. B: Biointerfaces*, *119*, 30-37, **2014**.

DNA nanoarchitectures: steps towards biological applications. Tintoré, M., Eritja, R., Fàbrega, C. *ChemBioChem*, *15*, 1374-1390, **2014**.

Influence of nonionic branched-chain alkyl glycosides on a model nano-emulsion for drug delivery systems. Ahmad, N.; Ramsch, R.; Llinàs, M.; Solans, C.; Hashim, R.; Tajuddin, H.A. *Coll. Surf. B: Biointerfaces*, *115*, 267-274, **2014**.

Oligonucleotide delivery: a patent review (2010-2013). Grijalvo, S., Aviñó, A., Eritja, R. *Expt. Opin. Ther. Patents*, *24*, 801-819, **2014**.

Antagonistic effects between magnetite nanoparticles and a hydrophobic surfactant in highly concentrated pickering emulsions. Vílchez, A.; Rodríguez-Abreu, C.; Menner, A.; Bismarck, A.; Esquena, J. *Langmuir*, *30*, 5064-5074, **2014.**

Design and in vitro evaluation of biocompatible dexamethasone-loaded nanoparticle dispersions, obtained from nano-emulsions, for inhalatory therapy. Fornaguera, C.; Llinàs, M.; Solans, C.; Calderó, G. *Coll. Surf. B: Biointerfaces*, *125*, 58-64, **2015**.

Design of cobalt nanoparticles with tailored structural and morphological properties via o/w and w/o microemulsions and their deposition onto silica. Di Carlo, G., Lualdi, M., Venezia, A.M., Magali Boutonnet, M., Sanchez-Dominguez, M. *Catalysts*, *5*, 442-459, **2015**.

8

FACILITIES AND TECHNOLOGY TRANSFER

IQAC FACILITIES AND TECHNOLOGY TRANSFER

- Custom Antibody Service (CAbS)
- Characterization of Colloidal Dispersions Service
- Microanalysis Service
- Biodegradation and Aquatic Toxicity Service
- Infrared and UV-visible Spectroscopy Service
- Service of Dermocosmetic Assessment
- SAXS-WAXS Service
- Synthesis of High Added Value Molecules Service
- Proteomics Service
- Nuclear Magnetic Resonance Spectroscopy Facility
- Electronic Paramagnetic Resonance (EPR Unit)
- Thermal Analysis and Calorimetry Service
- Lipidomics Core Facility
- Technology Transfer
- Cell Culture Service

CUSTOM ANTIBODY SERVICE

The CAbS is a joint facility established under the umbrella of the IQAC-CSIC and CIBER-BBN. The facility wants to offer a high quality service for customized monoclonal and polyclonal antibody production against many types of antigens including proteins, peptides or small organic molecules. Moreover, CAbS can offer additional services related to the preparation of immunoreagents and development of immunochemical methods and protocols.

STAFF

Mª PILAR MARCO COLÁS (Supervising Scientist)
NURIA PASCUAL DURAN (Technical Director)
ANA GONZÁLEZ GONZÁLEZ (Technician)
JOSEFA CRUZ RODRÍGUEZ (Technician)

Detailed description of the services and features provided by CAbS

A) MONOCLONAL ANTIBODY DEVELOPMENT

The standard service includes:

1. Discussion of the project (screening system, selection criteria, etc.) and planning the work.

2. Immunization, cell fusion, screening and cloning: After their fusion with myeloma cells screening of the best hybridomas will be performed by ELISA using previously supplied antigen. Specific clones will be subcloned by limiting dilution.

3. The customer will receive two cryovials and 10 ml of culture supernatant of each positive clone.

B) POLYCLONAL ANTIBODY DEVELOPMENT

The standard service includes:

1. Discussion of the details of the project including features such as the type of immunogen, the final properties of the antibodies, and the species and number of animals used.

2. Immunization protocol: As accorded by the customer.

3. Isolation of the antiserum

4. ELISA testing: samples obtained on each boosting injection and the final antisera will be tested against the antigen following the criteria agreed upon in the previous discussion with the costumer. The costumer will receive 60-80 mL of the final serum from each rabbit and about 5 mL samples of the pre-immune serum, and the blood extractions made during the immunization protocol after each boosting injection.

C) ADDITIONAL SERVICES:

1. Preparation of bioconjugates: labeled antibodies, haptenized proteins and enzymes, biotynilated and fluorescent probes, gold nanoparticle conjugates, etc.

2. Antibody purification.

3. Development of immunochemical methods: ELISA, immunoaffinity columns, etc.

4. Antibody characterization (Isotyping).

5. Hybridoma cryopreservation.

6. Mycoplasma testing

Unless otherwise stated in a signed agreement, the property of immuno (bio) reagents produced or synthesized and the results obtained regarding establishment of immunochemical methods and procedures will belong to the costumer.

CHARACTERIZATION OF COLLOIDAL DISPERSIONS SERVICE

STAFF

JORDI ESQUENA MORET (Supervising Scientist)
CONXITA SOLANS MARSÀ (Supervising Scientist)
SUSANA VILCHEZ MALDONADO (Technical Assistant)

This service deals with the characterization of nano-structured liquids (e.g. micelles, vesicles, liquid crystals, microemulsions, nano-emulsions etc.) and solid dispersions (e.g. organic inorganic or hybrid nanoparticle suspensions).

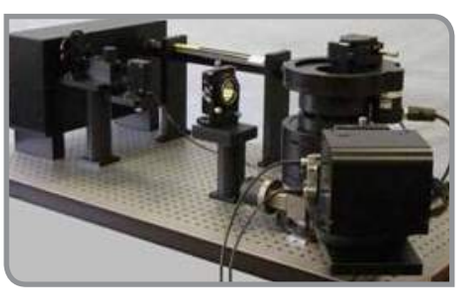
The characterization implies determination of size, morphology, phase transitions, surface, interfacial and rheological properties.

The service responsible group is member of TECNIO (ACC1Ó) and has been awarded with a quality certificate (similar to ISO 9001) by ACC1Ó (Generalitat de Catalunya).

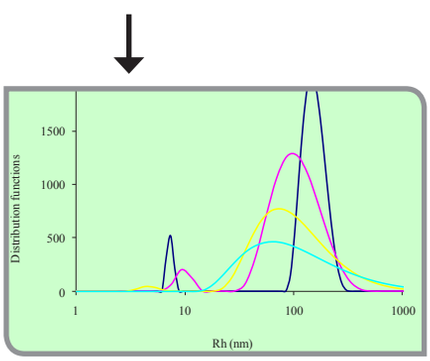
RELEVANT TECHNIQUES:

Static (SLS) and dynamic (DLS) light scattering

Determination of particle size distribution, shape, diffusion coefficient, aggregation number, molecular weight of colloidal dispersions



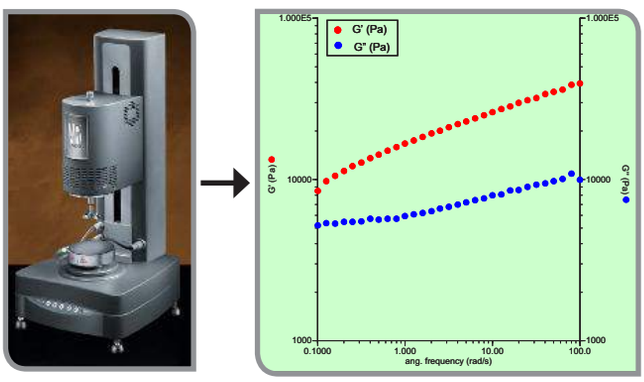
3DDLS Spectrometer



Size distributions of mixed micelle and vesicle dispersions by dynamic light scattering

Rheology

Determination of rheological properties of fluids and soft matter in flow and deformation regimes by steady state (viscosity, shear thinning, shear thickening) and dynamic (elastic and viscous moduli, relaxation time) measurements

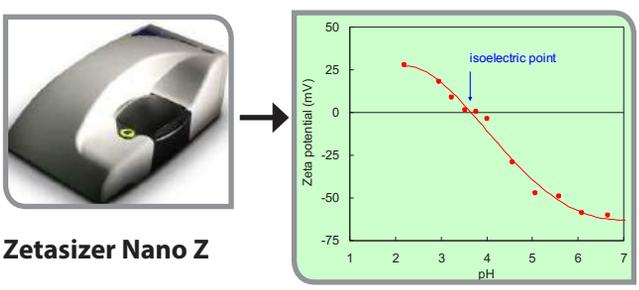


Rheometer AR-G2

Variation of elastic (G') and viscous (G") moduli as a function of frequency

Electrophoretic mobility

Determination of Zeta potential of charged particles



Zetasizer Nano Z

Variation of Zeta potential as a function of pH

High resolution optical microscopy with spectral analysis

This technique allows to visualize nanosize objects (e.g. nanoparticles, nano-emulsions) and to determine the light spectra of the sample analyzed.

Other techniques:

- Laser Light Diffraction
- Light back scattering
- Differential Refractometry
- Tensiometry
- Optical Microscopy

MICROANALYSIS SERVICE

The Microanalysis Service provides micro-determination of total carbon, hydrogen, nitrogen, sulphur (C, H, N, S) and halogens present in a wide range of organic and inorganic compounds.

Since March 1999, Microanalysis Service has been accredited by ENAC, under EN45001 regulation. This was the first accredited elemental microanalysis by the CSIC and the first to be accredited in Spain

As of November 2001, this Service has been accredited under regulation UNE-EN ISO/IEC 17025 for analysis of CHNS until at the end of November 2012.

STAFF

MARIA TERESA VILA TERRADES (Contacting person)
NURIA BARRERA DE PAZ

EQUIPMENT

This facility has the appropriate instruments for accurate sample analysis. Primary Instruments:

1 Elemental Microanalyzer (A5) model Flash 1112, for C,H,N determination.

1 Elemental Microanalyzer (A7) model Flash 2000, for C,H,N,S determination.

2 Mettler Microscale (B3 and B4) models MT5 and MX5.

1 Metrohm Titrando model 808 for Cl,Br,I and F determination.

BIODEGRADATION AND AQUATIC TOXICITY SERVICE

The Biodegradation and Aquatic Toxicity Service of the IQAC offers a full range of standardized test methods (OECD technical guidelines) for the assessment of the biodegradability and toxicity of organic compounds in the aquatic environment.

This service carries out biodegradation and aquatic toxicity tests for internal use and for external clients from industry, public administration, universities, and research organisms. Suitable technology and an expert and qualified staff guarantee the availability of results.

STAFF

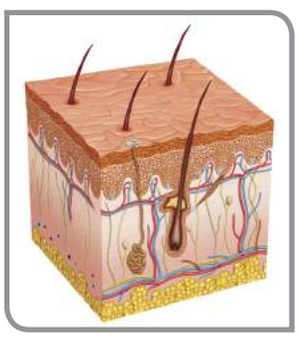
MARÍA TERESA GARCÍA RAMÓN (Supervisig Scientist, contacting person) email: teresa.garcia@iqac.csic.es
ISABEL RIBOSA FORNOVI
FRANCESC COMELLES FOLCH
ISABEL MUÑOZ LIRÓN

SERVICE OF DERMOCOSMETIC ASSESSMENT (SED-IQAC)

SED service undertakes research into the suitability and the technical possibilities of topically applied formulations for consumer use. SED service is divided in three groups: The Skin Absorption **group, the** Skin Efficacy **group and the** Hair Efficacy **group.**

The service developed is focused on the needs of the industry and also on its own research and that of other groups requiring its scientific expertise support.

Service of Dermoscosmetic Assesment (SED) from the IQAC-CSIC, have since May 2012, a Quality System of Management in accordance with the UNE-EN ISO 9001:2008 certified by AENOR with the reference ER-0430/2012.



The Skin Absorption group deals with the knowledge and quantitation of the skin absorption of a given compound topically applied. Using an in vitro methodology officially adopted by the OECD (2004), the distribution of a chemical in the different skin compartments (stratum corneum, epidermis and dermis) can be detected and quantified.

The Skin Efficacy group deals with the experimental design, evaluation and objective diagnostic of the skin efficacy and tolerance of cosmetic and dermatologic formulations topically applied by the use of non-invasive biophysical techniques. Evaluation and diagnosis of other keratinized tissues such as human nails are also evaluated.

The Hair Efficacy group deals with the experimental design and evaluation of the in vitro efficacy of cosmetic formulations applied to the hair.

STAFF

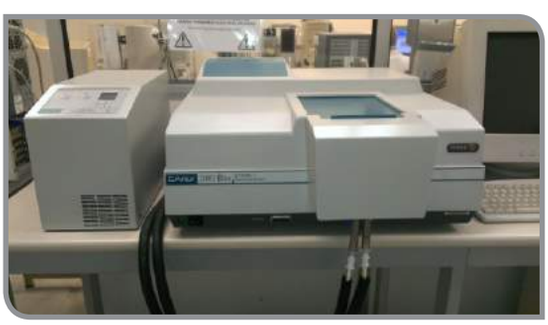
LUISA CODERCH NEGRA
(Supervising Scientist, contacting person)
MERITXELL MARTÍ GELABERT
ISABEL YUSTE HERNÁNDEZ
CRISTINA ALONSO MERINO
CLARA BARBA ALBANELL
LAIA RUBIO TOLEDANO
VÍCTOR CARRER VIVES
VANESSA MARTÍNEZ RODRÍGUEZ

INFRARED AND ULTRAVIOLET VISIBLE SPECTROSCOPY SERVICE

RICARDO MOLINA MANSILLA (Supervising Scientist)
ALBERTO GONZÁLEZ VÍLCHEZ (Technical Assistant)

The Infrared and ultraviolet-visible spectroscopy service is equipped with a middle infrared spectrophotometer (FTIR Avatar 360) with different accessories in order to perform analysis of liquids, films, textile materials and/or powdered substrates. In this way, transmission measurements of chemical and pharmaceutical products can be performed in KBr pellets or over NaCl crystals. The service is also equipped with attenuated total reflectance (ATR) accessories in order to analyze solids, powders or films (diamond ATR, vertical and horizontal ZnSe ATR) and liquids (horizontal ATR tray).

On the other hand the service is equipped with and UV-Visible Cary 400 spectrophotometer (175-900 nm) in order to perform characterization, quantitative analysis and reactions kinetics of chemical compounds.



SAXS-WAXS SERVICE

The SAXS-WAXS service provides measurements with a variety of setups for the determination of structural information of ordered and semi-ordered materials.

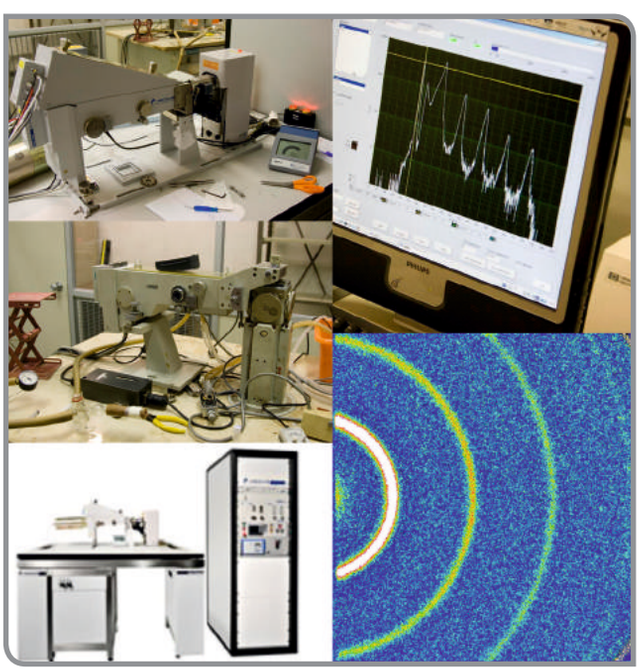
The range of distances of interest falls in the nanoscale domain (0.2-100 nm). It can allow determinations of size, space ordering, morphology, fractal dimension and total interfacial area. The materials comprise surfactant solutions and liquid crystals, mesoporous materials, macromolecules in solution such as proteins or DNA, nanostructured films and any conceivable material with electronic density discontinuities in the above mentioned range. 1D and 2D detectors are available. GISAXS and GIWAXS configurations are also possible.

Services Available

SAXS measurement with lineal collimation
SAXS measurement with point collimation
GISAXS measurements
Use of 2D detector (CCD camera) in SAXS instrument

STAFF

RAMON PONS PONS
(Supervising scientist, contacting person)
JORDI ESQUENA MORET
(Supervising scientist, contacting person)
JAUME CAELLES BALCELLS



SYNTHESIS OF HIGH ADDED VALUE MOLECULES SERVICE (SIMCHEM)

SIMchem is a IQAC-CSIC research facility created in 2009 to give chemical and synthetic support to (R+D+i) activities in industry, university and public organizations. It is projected to fill the gap existing between custom synthesis performed by companies and the synthetic research groups in academy. The service is intended to give a synthetic support to research projects of **chemistry**, **biology**, **biomedicine** and **drug discovery** by providing both skilled personnel, instrumental and laboratory, and taking advantage of the chemical synthetic and analytical expertise of the different groups present in the Institute.

SYNTETIC PROJECTS AND SERVICES:

SIMChem offers chemical services to the chemical and pharmaceutical sectors through personalized and adapted projects to any requirement. You can transfer us your project for development or ask us for an initial bibliographic research and a route design. The project can be defined in a time- or target-basis or through a shared risk approach. The results will be protected by MTA/CDA agreements or patens as your convenience. Our fully equipped laboratories designed for chemical synthesis, skilled staff, and access to spectroscopic and chromatographic techniques required for the purification and characterization steps of the products guarantee a satisfactory result.

ANALYTICAL PROJECTS AND SERVICES:

Accurate chemical analyses are crucial for the successful development of R+D projects and for the correct characterization of products. Our skilled analysts and instruments allow an efficient development of analytical methods as a part of our projects as well as specific and external uses in case a personalized support is not required. The analytical techniques available include: HPLC (analytical and preparative scale); HPLC-MS/MS; GC and GC-MS. We can provide you both with a large assortment of HPLC columns (direct/reverse phase, ionic exchange, preparative, chiral and UPLC columns) and detectors (ELS, UV, fluorescence and PDA, MS/MS detectors).

LINES OF EXPERTISE

- Medicinal Chemistry (parallel synthesis)
- Multistage synthesis, heterocyclic chemistry, lipids synthesis, oligosaccharides synthesis and condensation chemistry
- Development and optimization of reactions and processes
- Analytical support to organic synthesis
- Analytical method development and validation

CONTACTS

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cscsim@cid.csic.es

INSTRUMENTAL AND TECHNIQUES AVAILABLE

SYNTHESIS

- MW
- Radleys
- Manifold

ANALYTICAL AND PURIFICATION TECHNIQUES

- Analytical and preparative HPLC
- Automated flash and MPLC chromatography
- Analytical HPLC-MS/MS

OTHER INSTRUMENTS AND FACILITIES

- SpeedVac and Stuart Sample Concentrator
- Systems for samples evaporation: Thermo Fischer
- Karl Fisher analysis
- Hydrogenation Lab (microscale, low pressure)

PROTEOMICS SERVICE

The Proteomics Service has been recently created to provide support to IQAC and IDAEA researchers as well as other public and private organizations. The service is focused in the analysis of biomolecules (proteins, peptides, oligonucleotides, sugars ...) and large organic molecules (such as polymers, dendrimers, polyphenols and other macromolecules) by MALDI-TOF/TOF mass spectrometry.

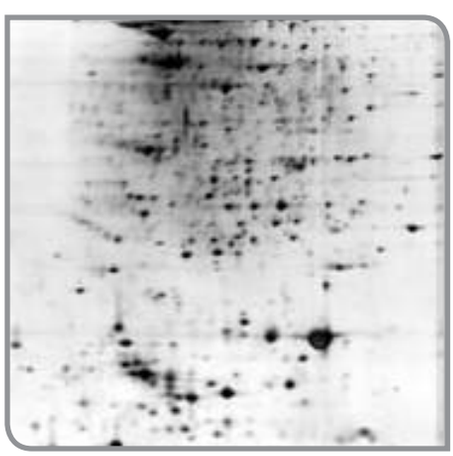
The Service also offers separation, quantification, identification and characterization of peptides and proteins in biological and biomedical systems using two-dimensional electrophoresis and mass spectrometry techniques.

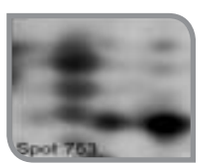
STAFF

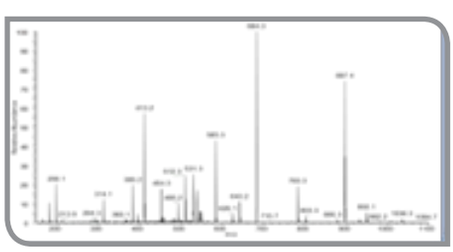
CARME QUERO LÓPEZ (Supervising Scientist)

SERVICES

1. Molecular mass determination by MALDI-TOF mass spectrometry.
2. Identification of proteins by peptide mass fingerprint.
3. Identification of proteins by peptide mass fingerprint and peptide fragmentation by mass spectrometry (MALDI-TOF/TOF).
4. Electrophoresis Separation of proteins by one- and two-dimensional electrophoresis.







NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY FACILITY

The NMR service is a research support facility for the IQAC, other universities and public research organisms, as well as for private companies.

The NMR Facility provides access to the following state-of-the-art methodologies:

- Structure elucidation and quality control in synthetic chemistry by solution 1D/2D-NMR.
- NMR-based drug screening.
- NMR spectra of cells, cell extracts, and metabolomics-by-NMR.
- Diffusion experiments and DOSY.
- Triple resonance experiments for peptides/small proteins.

STAFF

YOLANDA PÉREZ RUIZ (NMR Facility Manager)

The facility has two NMR spectrometers:

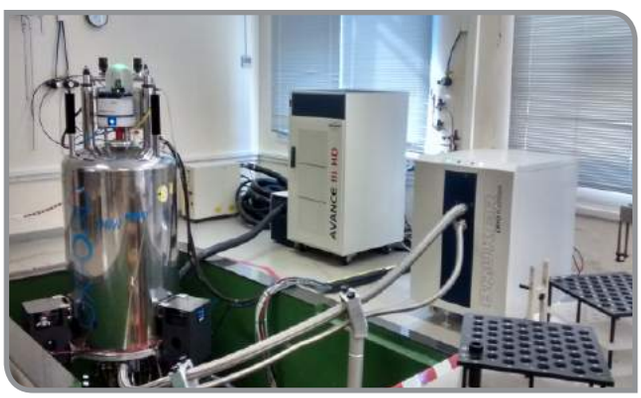
Varian Mercury 400 MHz (9.3950 T) is the walk-up instrument for automated heteronuclear NMR.

The spectrometer has a VNMRS console with Direct Digital receiver with Performa-I Z gradients and OneNMR probe, which can be tuned automatically to any nucleus between ^{15}N and ^{31}P with ProTune System autotuning and is using Agilent's Chempack pulse sequences suitable for most routine measurements. This spectrometer delivers routine, rapid heteronuclear-detected spectra in automation (^{1}H, ^{19}F, ^{31}P, ^{13}C, ^{11}B, ^{15}N, ^{29}Si, ^{2}H, ^{17}O, ^{111}Cd, ^{113}Cd, ^{105}Pd, ^{77}Se, ^{27}Al, ^{119}Sn and ^{195}Pt). An automated 100-sample changer (for standard 8" long/5 mm Ø NMR tubes) and VnmrJ3.2 software allow performing short acquisitions and quick access to spectra during the daytime hours (9 am to 7 pm), while longer experiments such as 2D HSQC or HMBC are submitted to run overnight or week-ends.

Bruker AVANCEIIIHD 500 MHz (11.7440 T field strength) with TCI Cryoprobe and SampleXPressLite 18-charger.

This system is highly suited for metabolomics studies, the study of complex biomolecules like small proteins, peptides and nucleic acids, and routine ^{1}H and ^{13}C NMR experiments on small molecules. The spectrometer is equipped with a three-channel AVANCEIIIHD console, z-gradients (55 G/cm) and an inverse detection TCI (^{1}H, ^{13}C and ^{15}N) cryoprobe, with ^{1}H direct detection, ^{13}C and ^{15}N indirect-detection. Is the instrument of choice for more demanding samples, and is frequently used for the full characterization of samples where tiny amounts of material are available. The spectrometer uses Topspin 3.5 software on a Linux Workstation.

This NMR system was purchased with financial support from MINECO-FEDER CSIC13-4E-2076 grant.



ELECTRONIC PARAMAGNETIC RESONANCE (EPR UNIT)

STAFF

LLUÍS JULIÀ BARGÉS (EPR UNIT SCIENTIFIC MANAGER)
LLUÍS FAJARÍ AGUDO (EPR UNIT TECHNICAL MANAGER)
AVENCIA DIEZ ORTEGO (TECHNICAL ASSISTANT)

Equipped with a Bruker EPR/ESR spectrometer EMX, with a microwave bridge of X-band (~9 GHz) EMX premium X, magnet of 10" ER073 with a power supply of 12 KW ER083.

The following accessories are available: Standard or double cavity; different container samples (quartz tubes, quartz capillaries,cells, flat cells for tissue); liquid nitrogen dewar and variable temperature accessory: cryostat, liquid nitrogen transfer line (120 K – 373 K); intelligent temperature controler ITC 503S from Oxford Instruments; continuous flow cryostat system of liquid helium (4.2 K - 300 K); gas flow controller from Oxford Instruments; high vacuum unit HP40B2 from Vacuubrand; "in situ" radiation source of UV-vis. 500 W Oriel pressure mercury lamp. Power supply Newport 69910; Bruker software acquisition, processing and simulation spectra WINEPR and SimFonia

THERMAL ANALYSIS SERVICE

STAFF

ALBERT M. MANICH BOU (Supervising scientist)
JOSEP CARILLA AUGET (Contacting person)
SONIA PEREZ RENTERO (Technician)

TAS was formally founded in 1999, in order to meet the growing needs in this field of existing research groups, currently in IQAC, and collaborate in the process of innovation and industrial development.

The following techniques are available:

- Differential scanning calorimetry DSC
- Microdifferential scanning calorimetry
- Thermogravimetric analysis TGA
- Dynamic vapor sorption DVS
- Thermomechanical analysis TMA

LIPIDOMICS CORE FACILITY

The Lipidomics Core Facility conducts comprehensive analysis of cellular lipids that encompass fatty acyls, glycerolipids, glycerophospholipids and sphingolipids. Such studies are possible with the advent of sophisticated mass spectrometric techniques. The services include sample preparation, lipid identification by mass spectrometry, LC-MS lipid profiling, LC-MS lipid quantification, and training in sample preparation methods.

STAFF

JOSEFINA CASAS (Supervising Scientist)
EVA DALMAU (Technician)

SERVICES

Determination of the sphingolipid composition.

Addition of internal standards, extraction, purification and analysis by UPLC-TOF. Compounds are identified by its retention time and exact mass. The identification and quantification of sphingosine, sphinganine, sphingosine-1-phosphate and sphinganine-1-phosphate is carried out by HPLC-MS/ MS.

Class of compounds: Sphingosine and dihydrosphingosine, sphingosine-1-phosphate and sphinganine-1-phosphate, ceramide and dihydroceramide, sphingomyelin and dihydrosphingomyelin, hexosylceramide (glucosyl- and galactosyl-ceramide), lactosylceramide and dihydrolactosylceramide. Identification and relative amount of ganglioside molecular species.

Determination of the glycerolipid and glycerophospholipid composition.

Addition of internal standards, extraction, purification and analysis by UPLC-TOF. Compounds are identified by its retention time and exact mass. Available internal standards: triacylglicerol, diacylglycoreol, monoacylglicerol, phosphatidylcholine, plasmalogen, lysophosphatidylcholine, lysoplasmalogen, phosphatidylserine, lysophosphatidylserine,phosphatidylethanolamine, lysophosphatidylethanolamine. The number of carbon atoms and double bonds of the acyl groups will be indicated, but not it localization. It is possible to detect and quantify cholesteryl esters.

KNOWLEDGE TRANSFER UNIT

STAFF

ISABEL MASIP Ph.D

Knowledge Transfer Manager

Deputy Vice-Presidency for Knowledge Transfer

The Knowledge Transfer Unit promotes and manages the relationships between researchers of IQAC and companies and research organizations. The final purpose is to promote innovation and support the transfer of knowledge and results to companies.

Different collaborative approaches are offered:

- Advice to solve technological needs through cooperation and research contracts with IQAC's groups
- License of technologies protected by patents or other intellectual property protection modes.

TECHNOLOGIES AVAILABLE

As a result of an excellent research, IQAC has generated products, technologies and know-how in different technological fields.

The Centre has a number of patented technologies and materials (such as antibodies, etc) that can be commercialized by companies through licensing agreements.

LIFE SCIENCES

Medical diagnosis

- *IQAC_019*. Test for early diagnosis of rheumatoid arthritis based on chimeric fibrin and filaggrin peptides.
- *IQAC_043*. Immunoassay for rapid detection of oral anticoagulants in blood.
- *IQAC_047*. Immunoassay for rapid diagnosis of infectious diseases caused by *Pseudomonas aeruginosa*.
- *IQAC_053*. Immunoassay for detection of infections caused by *Staphylococcus aureus*.

Neurosciences

- *IQAC_049*. Optopharmacological compounds targeting mGlu5 receptors.
- *IQAC_042*. Treatment of diseases and degenerative processes caused by apoptosis.

Inflammatory diseases

- *IQAC_009*. Modified siRNAs for silencing TNF-α gene expression to treat inflammatory diseases.
- *IQAC_012*. Optimization of the therapeutic potential of siRNA by formation of complexes with plasma components.

Pain

- *IQAC_022*. Pain treatment based on TRPV1 channel blockers.

Antivirals

- *IQAC_055*. Antiviral agents for prevention and treatment of AIDS and Hepatitis C.

Metabolic Diseases

- IQAC_052. Treatment of non-alcoholic fatty liver disease.

CHEMICAL TECHNOLOGY

Biosensors

- *IQAC_003*. Three-dimensional biosensor for detection of analytes in a biological sample.
- *IQAC_004*. Biosensor device for simultaneous detection of several biological samples in solution.

Surfactants

- *IQAC_054*. Biocompatible cationic aminoacid surfactants.

Measuring devices

- *IQAC_051*. New gravimetric humidity measuring sensor

Characterisation Devices

- *IQAC_023*. Kratky type X-ray scattering cameras modified to work under controlled atmosphere conditions.

CELL CULTURE SERVICE

SCC
SERVICIO DE CULTIVOS CELULARES

The Cell Culture Service (SCC) is a research support unit that offers either in-house research groups from IQAC and IDAEA or external laboratories the equipment and appropriate facilities to carry out *in vitro* culture and maintenance of human and animal cell lines in order to perform bioassays in several aspects of the biomedical and toxicological sciences.

The Service provide biosafety level 2 (BSL-2) facilities, suitable for work involving agents of moderate potential hazard to personnel and the environment, and all work is performed using approved BSL-2 guidelines.

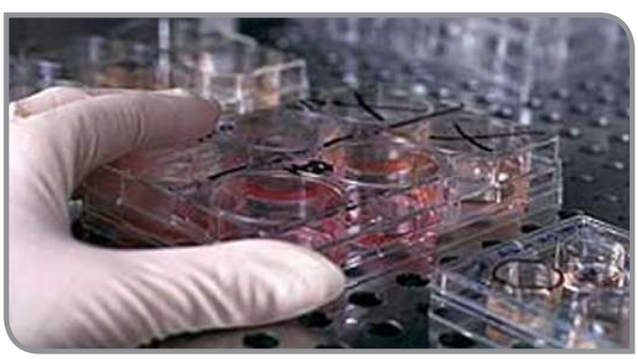
STAFF

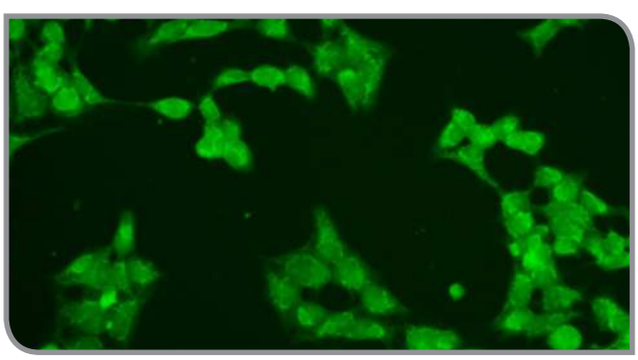
GEMMA FABRIÀS DOMINGO (Supervising Scientist)
IGNACIO PÉREZ POMEDA (Technical Director, Contacting person)

EQUIPMENT

The facilities are equipped with the following instruments and devices:

- 4 Laminar flow cabinets (Class I).
- 1 Biological safety cabinet (Class II).
- 7 CO_2 incubators set up for mammalian cells.
- 2 Incubators set up for non-mammalian cells.
- 2 Liquid nitrogen tanks for cell cryopreservation.
- 4 Refrigerators and freezers.
- 1 Phase contrast inverted microscope.
- 1 Fluorescence microscope equipped with a digital camera.
- 2 Thermostatic water baths.
- 1 Tabletop refrigerated centrifuge.
- 1 Countess automatic cell counter.
- 1 Guava EasyCyte flow cytometer.





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ANNEXES

LIST OF PERSONNEL

SCIENTIFIC STAFF

Abad Saiz, José Luis	Científico Titular
Alfonso Rodríguez, Ignacio	Científico Titular
Anglada Rull, Josep Maria	Investigador Científico
Arsequell Ruiz, Gemma	Investigador Científico
Azemar Sazatornil, Núria	Investigador OPIS (març 2014)
Blanco Fernández, Jerónimo	Investigador Científico
Bosch Verderol, Pilar	Científico Titular
Bujons Vilas, Jordi	Científico Titular
Caminal Saperas, Glòria	Investigador Científico
Casas Brugulat, Josefina	Investigador Científico
Clapés Saborit, Pere	Profesor de Investigación
Coderch Negra, Luisa	Profesor de Investigación
Coll Toledano, Josep	Profesor de Investigación
Comelles Folch, Francesc	Científico Titular
Cot Cosp, Jaume	Profesor de Investigación
Crehuet Simón, Ramon	Científico Titular
Delgado Cirilo, Antonio	Profesor de Universidad
Díaz Díaz, David	Científico Titular
Eritja Casadellà, Ramon	Profesor de Investigación
Esquena Moret, Jordi	Científico Titular
Fabriàs Domingo, Gemma	Profesor de Investigación
Galve Bosch, Roger	Científico Titular
García Ramon, Mª Teresa	Científico Titular
Gomara Elena, Mª José	Científico Titular
Guerrero Pérez, Angel	Profesor de Investigación
Haro Villar, Isabel	Investigador Científico
Infante Martínez-Pardo, Mª Rosa	Profesor de Investigación
Joglar Tamargo, Jesús	Científico Titular
Julià Bargés, Lluís	Investigador Científico
Llebaria Soldevila, Amadeu	Investigador Científico
López Serrano, Olga	Investigador Científico
Manich Bou, Albert Mª	Investigador Científico
Marco Colás, Mª Pilar	Profesor de Investigación
Marsal Monge, Agustí	Investigador Científico
Maza Ribera, Alfonso de la	Profesor de Investigación
Messeguer Peypoch, Àngel	Profesor de Investigación
Molina Mansilla, Ricardo	Científico Titular
Olivella, Santiago	Profesor de Investigación
Pérez Muñoz, Lourdes	Científico Titular
Pinazo Gassol, Aurora	Científico Titular
Pons Pons, Ramon	Investigador Científico
Rosell Pellisé, Gloria	Profesor de Universidad
Solans Marsà, Conxita	Profesor de Investigación
Torres Simó, Josep Lluis	Profesor de Investigación
Triola, Gemma	Científico Titular
Valencia Parera, Gregori	Investigador Científico

TECHNICAL STAFF

Barrera de Paz, Nuria	Ayudante de Investigación
Bleda Hernández, Mª José	Titulado técnico
Carrera Altarriba, Imma	Auxiliar de Investigación
Caelles Balcells, Jaume	Técnico Especializado de OPIS
Carilla Auguet, José	Técnico Especializado de OPIS
Díez Ortego, Avencia	Ayudante de Investigación
Fajarí Agudo, Luis	Técnico Superior Especializado
Ferrero Virgos, Carmen	Ayudante de Investigación
González Chaparro, Juan José	Ayudante de Investigación
Lloria Tolrà, Juan	Técnico Especializado de OPIS
Martí Gelabert, Meritxell	Ayudante de Investigación
Muñoz Lirón, Isabel	Ayudante de Investigación
Pascual Durán, Nuria	Téc. Sup. Especializado de OPIS
Pérez Pomeda, Ignacio	Téc. Sup. Especializado de OPIS
Pérez Ruiz, Yolanda	Téc. Sup. Especializado de OPIS
Sindreu Grañé, Montserrat	Ayudante de Investigación
Vila Terrades, Mª Teresa	Técnico Especializado de OPIS
Yuste Hernández, Isabel	Ayudante de Investigación

ADMINISTRATION STAFF

Beltrán Fabregat, Lídia	Auxiliar de Administración
Moliner Ferrer, Leonor	Auxiliar de Administración

POSTDOCTORAL FELLOWS

ALCAIDE LÓPEZ, ANNA
ALONSO MERINO, CRISTINA
AVIÑÓ ANDRÉS, ANNA MARIA
BARBA ALBANELL, CLARA
BARRERA VILARMAU, SUSANA
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CONTANT, SHEILA
CORREDOR, MIRIAM
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HOVAGHIMIAN, KARINE
JORDAN, ANDREW
KACZEREWSKA, OLGA
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PANARELLO, SILVIA
ROSSI, LORENZO
VILARÓ, GEMMA
WILLAY, EMELINE

LIST OF PUBLICATIONS OF IQAC ORDERED BY IMPACT FACTOR

2014 (average impact factor $IF_{1/2}$= 4.275: ---).

Publication	Nº	IF 2013	Class.
Accounts Chem Res	1	24,348	ISI
Nature Chemical Biology	1	13,217	ISI
J Am Chem Soc	3	11,444	ISI
Adv Funct Mater	1	10,439	ISI
PNAS	1	9,809	ISI
Nucleic Acids Res	1	8,808	ISI
Advances In Colloid And Interface Science	2	8,636	ISI
Oncogene	2	8,559	ISI
Cell Death And Differentiation	1	8,385	ISI
Nanotoxicology	1	7,336	ISI
Journal Of Controlled Release	1	7,261	ISI
Green Chem.	1	6,852	ISI
Chem Commun	5	6,718	ISI
Org Lett	1	6,324	ISI
Applied Catalysis B: Environmental	1	6,007	ISI
Anal. Chem.	2	5,825	ISI
Lab Chip	1	5,748	ISI
Chem-Eur J	7	5,696	ISI
Acta Biomaterialia	1	5,684	ISI
Crit Rev Food Sci	1	5,548	ISI
Adv. Synth. Catal	1	5,542	ISI
J Med Chem	1	5,480	ISI
Chemcatchem	1	5,044	ISI
Bioresource Technol	1	5,039	ISI
Bioconjugate Chem	1	4,821	ISI
J Lipid Res	1	4,730	ISI
Eurosurveillance	1	4,659	ISI
J. Virol.	1	4,648	ISI
J Org Chem	7	4,638	ISI
Journal Of Nutritional Biochemistry	1	4,592	ISI
Anal Chim Acta	1	4,517	ISI
Obesity	1	4,389	ISI
Langmuir	1	4,384	ISI
Journal Of Hazardous Materials	1	4,331	ISI
Colloid Surface B	7	4,287	ISI
J Chromatogr A	1	4,258	ISI
Eur J Pharm Biopharm	1	4,245	ISI
Int. Journal Of Biochemistry & Cell Biology	1	4,240	ISI
Acs Chem. Neurosci.	1	4,210	ISI
Stem Cells And Development	1	4,202	ISI
Phys Chem Chem Phys	3	4,198	ISI
Soft Matter	1	4,151	ISI
Plant Science	1	4,114	ISI
J Chem Inf Model	1	4,068	ISI
Future Med Chem	1	4,000	ISI
FEBS J	1	3,986	ISI
Pharmaceutical Research	2	3,952	ISI
J Proteomics	1	3,929	ISI
Carbohyd Polym	1	3,916	ISI
Sensor Actuat B-Chem	2	3,840	ISI
BBA-Gen Subjects	3	3,829	ISI
Int J Pharmaceut	1	3,785	ISI
Curr Med Chem	2	3,715	ISI
RSC Adv	2	3,708	ISI
Toxicol Appl Pharm	1	3,630	ISI
J Alzheimers Dis	1	3,612	ISI
Anal Bioanal Chem	3	3,578	ISI
J Colloid Interf Sci	1	3,552	ISI
Plos One	3	3,534	ISI
Talanta	1	3,511	ISI
Chemosphere	1	3,499	ISI
Curr Top Med Chem	1	3,453	ISI
Expt. Opin. Ther. Pat.	1	3,441	ISI
Eur J Med Chem	1	3,432	ISI
Bba-Biomembranes	2	3,431	ISI
J. Phys. Chem. B	1	3,377	ISI
Food Chem	1	3,259	ISI
Micropor Mesopor Mat	1	3,209	ISI
Science Of The Total Environment	1	3,163	ISI
J Agr Food Chem	1	3,107	ISI
Separation And Purification Technology	1	3,065	ISI
Chembiochem	1	3,060	ISI
Food Res Int	1	3,050	ISI
Chemmedchem.	2	3,046	ISI
Cellulose	3	3,033	ISI
J Electroanal Chem	1	2,871	ISI
Food Control	1	2,819	ISI
Environ Sci Pollut Res	1	2,757	ISI
Crit. Rev. Sol. State Mat. Sci.	1	2,714	ISI
J. Mass Spectrom	1	2,709	ISI
Biol Chem	1	2,689	ISI
J Pest Sci	1	2,664	ISI
Med. Chem. Commun.	1	2,626	ISI
Colloid Surface A	3	2,354	ISI
Int J Mol Sci	1	2,339	ISI
Medical And Veterinary Entomology	1	2,333	ISI
Lipids In Health And Disease	1	2,310	ISI
J Mater Sci	1	2,305	ISI
J Nanopart Res	1	2,278	ISI
Thermochim Acta	1	2,105	ISI
Molecules	5	2,095	ISI
Sensors	1	2,048	ISI
Journal Of Microencapsulation	1	1,878	ISI
Appl Biochem Biotechnol	1	1,687	ISI
Helv Chim Acta	1	1,394	ISI
J Surfactants Deterg	1	1,352	ISI
J Nanosci Nanotechno	1	1,339	ISI
Text Res J	1	1,332	ISI
Environ Technol	1	1,197	ISI
Fibers And Polymers	2	1,113	ISI
Nat Prod Commun	5	0,924	ISI
Indian Journal Of Fibre & Textile Research	1	0,778	ISI
The Journal Of The Textile Institute	1	0,770	ISI
J Macromol Sci A	1	0,740	ISI
Giornale Italiano Di Dermatologia E Venereologia	1	0,491	ISI
J Soc Leath Tech Ch	1	0,414	ISI
Acs Sustainable Chemistry And Engineering	1	**********	Non-ISI
Aust. J. Educ. Chem.	1	**********	Non-ISI
Cascade Biocatalysis : Integrating Stereoselective And Environmentally Friendly Reactions	1	**********	Book
J Mater Chem. A	1	**********	Non-ISI
Nanosci. Nanotechnol. Asia	1	**********	Non-ISI
Rna Technologies. Chemical Biology Of Nucleic Acids: Fundamentals And Clinical Applications	1	**********	Book
Smart Membranes And Sensors	1	**********	Book

2015 (average impact factor $IF_{½}$= 4,414: ----).

Publication	CLASS.	If 2014	Nº
Nature Chemistry	ISI	25,325	1
Accounts Chem Res	ISI	22,323	1
Angew Chem Int Edit	ISI	11,261	2
PNAS	ISI	9,674	1
Kidney International	ISI	8,563	1
Environ Health Perspect	ISI	7,977	1
Journal Of Controlled Release	ISI	7,705	1
Nanoscale	ISI	7,394	3
Nano Research	ISI	7,010	1
Chem Commun	ISI	6,834	3
Biosens Bioelectron	ISI	6,409	2
Oncotarget	ISI	6,359	1
Anal. Chem.	ISI	5,886	2
Chem-Eur J	ISI	5,731	5
Stem Cells Trans Med	ISI	5,709	1
Adv. Synth. Catal.	ISI	5,663	2
Sci. Rep.	ISI	5,578	1
Journal Of Biomedical Nanotechnology	ISI	5,338	1
Environ. Sci. Technol.	ISI	5,330	2
Faseb J	ISI	5,043	1
Biochemical Pharmacology	ISI	5,009	1
Disease Models & Mechanisms	ISI	4,973	1
J Org Chem	ISI	4,721	1
Mol. Nutr. Food Res.	ISI	4,603	1
The Journal Of Biological Chemistry	ISI	4,573	1
Journal Of Hazardous Materials	ISI	4,529	1
Anal Chim Acta	ISI	4,513	3
Phys Chem Chem Phys	ISI	4,493	2
Langmuir	ISI	4,457	4
J Lipid Res	ISI	4,421	1
Pharmacological Research	ISI	4,408	1
Mol. Pharmaceutics	ISI	4,384	2
International Journal Of Nanomedicine	ISI	4,383	1
Chem Eng J	ISI	4,321	1
Dalton Trans.	ISI	4,197	1
J. Proteome Res.	ISI	4,173	1
J Chromatogr A	ISI	4,169	1
Colloid Surface B	ISI	4,152	5
Crystengcomm	ISI	4,034	2
Soft Matter	ISI	4,029	1
Eur J Pharm Biopharm	ISI	3,975	1
Metabolomics	ISI	3,855	1
RSC Adv	ISI	3,840	5
BBA-Biomembranes	ISI	3,836	1
Int J Pharmaceut	ISI	3,650	1
Org Biomol Chem	ISI	3,562	4
British Journal Of Nutrition	ISI	3,453	1
Current Pharmaceutical Design	ISI	3,452	1
Eur J Med Chem	ISI	3,447	1
Food Chem	ISI	3,391	2
J Colloid Interf Sci	ISI	3,368	1
ACS Comb. Sci.	ISI	3,317	1
J. Phys. Chem. B	ISI	3,302	2
Amino Acids	ISI	3,293	1
Protein & Cell	ISI	3,247	1
ACS Med. Chem. Lett.	ISI	3,120	1
Chembiochem	ISI	3,088	4
Materials Science And Engineering C	ISI	3,088	1
New J Chem	ISI	3,086	1
Catalysts	ISI	2,964	1
Food And Chemical Toxicology	ISI	2,895	1
Biomedical Microdevices	ISI	2,877	1
Int J Mol Sci	ISI	2,862	2
Drug Testing Anal.	ISI	2,859	1
Food Control	ISI	2,806	2
Food Funct.	ISI	2,791	1
Colloid Surface A	ISI	2,752	3
Tetrahedron	ISI	2,641	1
Insect Molecular Biology	ISI	2,589	1
Med. Chem. Commun.	ISI	2,495	1
Bioorg Med Chem Lett	ISI	2,420	2
Molecules	ISI	2,416	2
Tetrahedron Letters	ISI	2,379	1
Basic &Clinical Pharmacology & Toxicology	ISI	2,377	1
Bioinspir. Biomim.	ISI	2,354	1
Journal Of Pharmacy And Pharmacology	ISI	2,264	1
Nutr Cancer	ISI	2,241	1
Environ. Sci.: Processes Impacts	ISI	2,171	1
Current Organic Chemistry	ISI	2,157	1
Insect Science	ISI	2,144	1
Materials Chem. Phys.	ISI	2,101	1
J Therm Anal Calorim	ISI	2,042	1
J Microen Nano	ISI	1,585	1
Aust. J. Chem.	ISI	1,558	1
Int J Cosm Sci	ISI	1,377	1
Int. J. Environ. Res	ISI	1,100	1
Accred. Quality Ass.	ISI	1,010	1
J Macromol Sci A	ISI	0,809	1
J Bio Mat Bioeng	ISI	0,653	1
Int. J. Cancer Stud. Res.	ISI	0,546	1
Antioxidants	Non-ISI	**********	1
Cosmetics And Toiletries	Non-ISI	**********	1
Gels	Non-ISI	**********	1
International Leather Maker	Non-ISI	**********	1
J. Med. Pharm. Innov.	Non-ISI	**********	1
Macromol. Symp.	Non-ISI	**********	1
Molbank	Non-ISI	**********	1
Nachr. Chem.	Non-ISI	**********	1
Personal Care Europe	Non-ISI	**********	1
Proc. Spie 9343, Laser Resonators, Microresonators, And Beam Control Xvii	Non-ISI	**********	1
Revista SCQ	Non-ISI	**********	2
RNA Dis.	Non-ISI	**********	1
Synthesis	Non-ISI	**********	1
Handbook Of Smart Textiles	BOOK	**********	1