iQAC

Biennial Report 2016-2017

CSIC

Consejo Superior de Investigaciones Científicas

Index

DIRECTOR'S FOREWORD

The Institute for Advanced Chemistry of Catalonia (IQAC) is one of the research centers of the Spanish National Research Council (CSIC). The Institute is located in Barcelona and it was created to perform 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 2016-2017, 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 industrial 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, mainly thanks to the heroic efforts of its scientists.

During 2016-2017 the Institute has achieved a high number of publications (more than 130 per year) as well as the highest average impact factor (4.71) with 13 papers published in journals with an impact factor higher than 10. This represents a clear increase 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.

Gemma Fabriàs Domingo
Director of IQAC

STRUCTURE AND GENERAL RESULTS

HISTORY

The Institute for Advanced Chemistry of Catalonia was created in 2007 to better accommodate the interests of scientists of the Chemistry areas working at the "Center for Research and Development" (CID) and to provide a greater external projection of the activities of these scientists within the frame of the Spanish National Research Council (CSIC). The Institute inherits the long and fruitful research tradition in Organic Chemistry and Chemical Technology initiated by mid-1900's. In 1967, after a productive activity in the University of Barcelona, Prof. Pascual Vila and his co-workers moved into the CSIC Institute of Organic Chemistry of Barcelona, placed at CID. At the same time, CSIC scientists working in the field of tanning and textile Technology, such as Prof. A. Barella, Prof. R. Audivert and Prof. E. Gratacós, were also incorporated into CID to later create the Institute for Chemical and Textile Technology. These moves fostered the emergence and further consolidation of the two main research areas at CID: Organic Chemistry and Chemical Technology. During many years the CID has been the referent of the CSIC Chemistry in Catalonia. Not only many graduate students and post-docs trained in this Center have moved to relevant positions in academic institutions and in private sectors, but CID has been the seed of outstanding research centers in Catalonia. In 1996, a joined action of the bioorganic, theoretical and technological groups together with teams working on chemical issues related to the environment led to the creation of the Institute for Chemical and Environmental Research of Barcelona (IIQAB). During the ten-year period of IIQAB, the Institute became a referent in the fields of Environmental Chemistry, Biological Chemistry, Theoretical and Computational Chemistry, Sustainable Chemistry and selected items of Chemical Technology. Some of these fields have remained active and have been reinforced at IQAC since its creation in 2007. Furthermore, during its 10 years of life, research on Nanobiotechnology has emerged as a potent working area at the Institute. The apparent heterogeneity of the active research areas at IQAC is clearly compensated by the wide opportunities of their mutual interaction, making IQAC a solid and modern Institute that looks at the future leaning on three key pillars: the robustness of the Chemistry tradition in our Centre, the enthusiasm and expertise of its personnel and the firm willingness warmly welcome staff scientists not trained in the Institute, providing them with the best possible conditions to carry out their research in a competitive, friendly and collaborative environment.

IQAC is formed by around 200 professionals, including staff researchers, contracted doctors, Ph. D. students, technicians, and personnel devoted to administration and management. IQAC is organized into four departments and around 20 research groups. In addition, our Institute holds a set of scientific and technical facilities run by highly qualified scientists and technical personnel with a solid background and long lasting expertise. These facilities are available not only to IQAC research groups, but also to potential users from both academia and private institutions. In any case, the technical services from IQAC are always wide open to attend any inquiry and to offer their best efforts to find adequate responses to specific needs.

INSTITUTE BOARD MEMBERS

Ramon Eritja Casadellà
Director (until December 2016)

Gemma Fabriàs Domingo
Director (from January 2017)

Ramon Pons Pons
Deputy Director (until December2016)

Maria Pilar Marco Colàs
Deputy Director (from January 2017)

Joan Ricard Ibáñez Villar
Head of Administration (until April 2017)

Lluís Fajarí Agudo
Head of Administration (from Maig 2017)

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

Meritxell Martí Gelabert
Personnel Representative

Ignacio Pérez Pomeda/Maite Vila Terrades
Personnel Representative

ADMINISTRATION

Director
Ramon Eritja Casadellà (until December 2016)
Gemma Fabrià Domingo (from January 2017)

Deputy Director
Ramon Pons Pons (until December 2016)
Maria Pilar Marco Colàs (from January 2017)

Head of Administration
Joan Ricard Ibáñez Villar (until April 2017)
Lluís Fajarí Agudo (from June 2017)

Secretaries
Lídia Beltran Fabregat
Leonor Moliner Ferrer

«AD HONOREM» MEMBERS

Àngel Messeguer Peypoch
Conxita Solans Marsà
Ángel Guerrero Pérez
Alfons de la Maza Ribera
Jerónimo Blanco Fernández

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
- Chemical Biology

Department of Biomedicinal Chemistry

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

Department of Chemical and Biomolecular Nanotechnology

- Nanobiotechnology for Diagnostics (Nb4D)
- Nucleic Acids Chemistry
- Colloid and Interfacial Chemistry
- Cell Therapy
- Surface Chemistry

Department of Chemical and Surfactants Technology

- Biocompatible Surfactants
- Environmental Chemistry of Surfactants and Ionic Liquids
- Physical Chemistry of Surfactant Systems
- Biophysics of Lipids and Interphases
- Plasma Chemistry
- Textiles and Cosmetic Innovations
- Sustainable processes and materials characterization

Collaborative Leave at University of Regensburg

- David Diaz Diaz

SPIN-OFF Activities

- Bicosome, S.L.

IQAC FACILITIES AND TECHNOLOGY TRANSFER

- Characterisation of colloidal dispersions Service
- Custom Antibody Service (CAbS)
- Microanalysis Service
- Biodegradation and Aquatic Toxicity Service
- Nuclear Magnetic Resonance Spectroscopy
- Service of Dermocosmetic Assesment
- SAXS-WAXS Service
- Synthesis of High Added Value Molecules
- Thermal Analysis and Calorimetry Service
- Proteomics Service
- Infrared and UV-visible Spectroscopy Service
- Lipidomics Core Facility
- Electronic Paramagnetic Resonance (EPR UNIT)
- Knowledge Tranfer Unit
- Cell Culture Unit

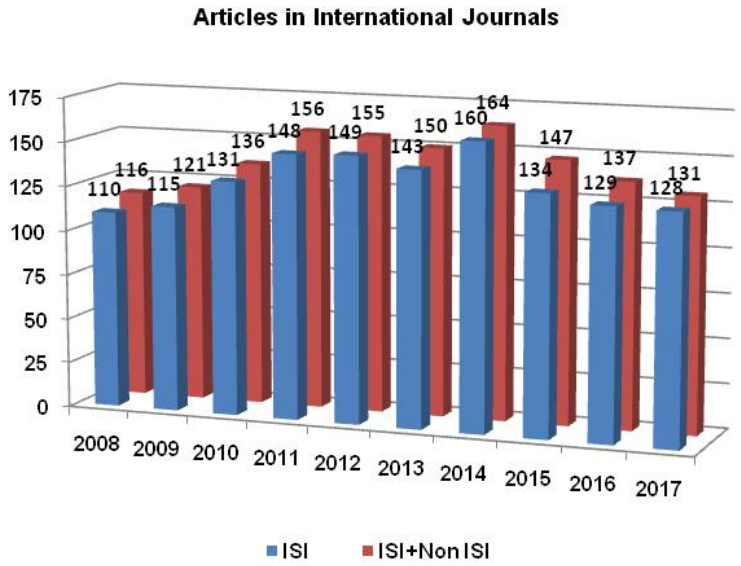
NUMERICAL SUMMARIES

PERSONNEL	Staff		Technicians	Postdocs	Ph. D. Students + undergrads
	Scientists	Technicians			
Biological Chemistry and Molecular Modelling	15	1	2	11	24
Biomedicinal Chemistry	10	2	9	5	24
Chemical and Biomolecular Nanotechnology	8	0	2	25	32
Chemical and Surfactants Technology	11	6	5	8	25
Collaborative leave	1	0	0	0	8
Facilities	13	9	4	10	5
TOTAL	58	18	22	59	118

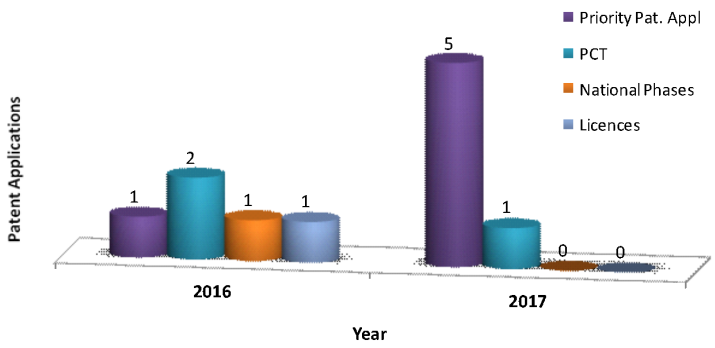
SCIENTIFIC OUTPUT	ISI Journals	Non-ISI	Book chapters
Biological Chemistry and Molecular Modelling	89	0	2
Biomedicinal Chemistry	53	0	0
Chemical and Biomolecular Nanotechnology	63	2	0
Chemical and Surfactants Technology	44	1	0
Collaborative leave	28	3	0
Facilities	4	0	0
TOTAL	**281**	**6**	**2**

ACADEMIC OUTPUT	PhD Thesis	Courses	Conferences
Biological Chemistry and Molecular Modelling	8	10	9
Biomedicinal Chemistry	10	3	2
Chemical and Biomolecular Nanotechnology	7	7	5
Chemical and Surfactants Technology	0	4	0
Collaborative leave	4	0	6
TOTAL	**29**	**24**	**22**

EVOLUTION OF THE NUMBER OF ARTICLES IN THE PAST TEN YEARS



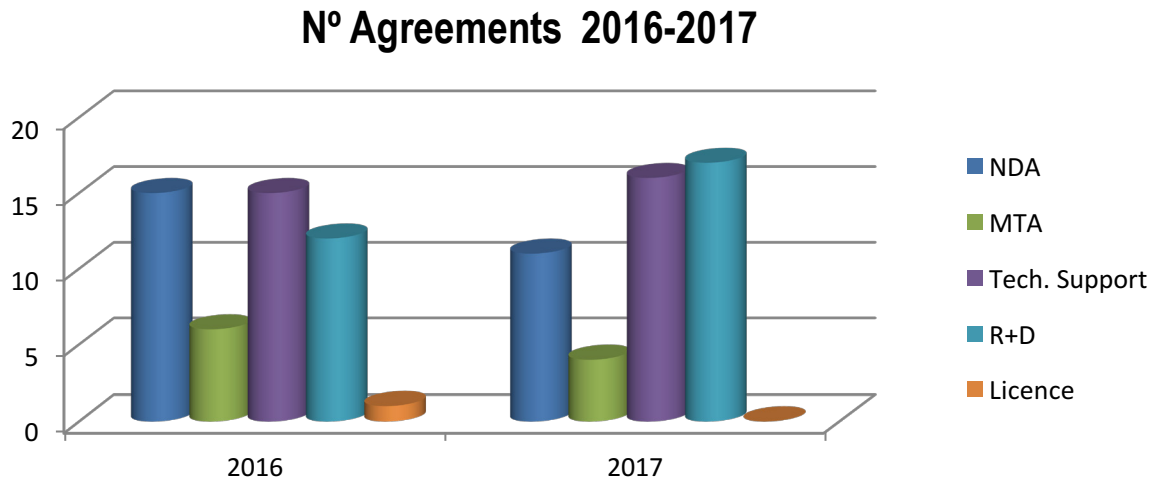
PATENTS



TECHNOLOGICAL OUTPUT	2016	2017	TOTAL
Priority Patent Appl.	1	5	6
PCT	2	1	3
National Phase	1	0	1
Licences	1	0	1

KNOWLEDGE TRANSFER ACTIVITY

Number of contracts with companies signed



PARTNERSHIPS AND INSTITUTIONAL AGREEMENTS

ciber-bbn
Biomedical Research Networking Center
Bioengineering, Biomaterials, Nanomedicine

Four groups of IQAC (Colloid and Interfacial Chemistry, Cell Therapy, Nucleic Acid Chemistry, and Nanobiotechnology for Diagnostics) belong 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. The Center's research aims at developing systems for prevention, diagnosis and monitoring and related technologies for specific treatments such as Regenerative Medicine and Nanotherapies.

TECNIO
Be tech. Be competitive

Four Research Groups of IQAC-CSIC are members of 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. Initially, the Group of Colloidal and Interfacial Chemistry, and the Group of Surface Chemistry joined TECNIO and constituted the colloidal and interfacial chemistry unit (QCI) in TECNIO. Later, two more IQAC research Groups, the Custom Antibody Service (CAbS) and the Synthesis of High Added Value Molecules Service, were also accepted in the TECNIO network.

nanbiosis

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

AWARDS, CERTIFICATIONS, SPIN-OFFS

2016. A. Llebaria awarded The Grünenthal Foundation Award for Pain Research in the Basic Research category for the paper "Dynamic modulation of inflammatory pain-related affective and sensory symptoms by optical control of amygdala metabotropic glutamate receptor 4".

2016. R. Eritja. Recipient of the Sentinels of Science Award by Publons. 10% top reviewers in the field "Biochemistry, Genetics and Molecular Biology. 2016.

2016. D. Díaz. DFG Heisenberg Professorship, Extension Award (Germany)

2016. Solà, J.; Bolte, M.; Alfonso, I. Best flash presentation award: "Conformational promiscuity in clickamers". III Bienal of the Chemical Biology group RSEQ. Madrid 21-22 March, 2016.

2016. Conxita Solans. Premio Micela, otorgado por el Comité Español de la Detergencia

2016. Conxita Solans. Premio FORMULA-Pierre Fillet del Grupo de Formulación de la Sociedad de Química de Francia.

2017. A. Llebaria awarded The Grünenthal Foundation Award for Pain Research in the Preclinical Research category for the paper "Optical control of pain in vivo with a photoactive mGlu5 receptor negative allosteric modulator".

2017. Best Poster Award. R. Eritja, at the 7th Cambridge Symposium on Nucleic Acids Chemistry & Biology. Cambridge (England), September 3-6, 2017

2017. R. Eritja. Recipient of the 1% Top Reviewers Award in the Multidisciplinary field by Publons.

2017. D. Díaz. Acreditation as "Profesor Titular" by the ANECA agency from the Spanish Ministry of Education

2017. D. Díaz. Appointed as Honorary Adjunt Professor of Jiangsu University (China). Initiative of Prof. Songjun Li, President of the Chinese Advanced Materials Society

2017. D. Díaz. Appointed as Honorary Member of the Sociedad Argentina de Investigación en Química Orgánica (Argentina)

2017. Marc A. Oliver. The Best Poster Award at the 20th Int. Hair Science Symposium, Desden, September 6-8, 2017

2017. Solà, J.; Bolte, M.; Alfonso, I. Best poster award: "Metal driven assembly of peptidic foldamers: formation of molecular tapes". II Workshop on Chemistry of Group 11 Elements. Barcelona.

María José Gómara. Diploma tutorització projecte "Pèptids sintètics per l'estudi de la coinfecció GBV-C/HIV-1" de les assignatures Pràcticum I, Pràcticum II i Treball Fi de Grau de l'ensenyament Grau de Ciències Biomèdiques (UB). Curs acadèmic 2016-17.

Isabel Haro. Diploma tutorització projecte "Pèptids sintètics citrulinats en la diagnosis de l'artritis reumatoide" de les assignatures Pràcticum I, Pràcticum II i Treball Fi de Grau de l'ensenyament Grau de Biologia (UB). Curs acadèmic 2016-17.

INVITED ORAL COMMUNICATIONS

D. Díaz. Johannes Kepler University Linz, Austria. 2016.

D. Díaz. University of Paderborn, Germany. 2016.

D. Díaz. IISER, Pune, India. 2016.

D. Díaz. University of Stuttgart, Germany. 2016.

Conxita Solans Marsà. The Key Role of Surfactant Self-Assemblies in Emulsification by Low-Energy Methods. 21st International Symposium on Surfactants in Solution (Jinan, China, 05/06/2016 - 11/06/2016)

Symposium honouring Professor Conxita Solans 30th Conference of the European Colloid and Interface Society (ECIS 2016) Roma (Italia), 04/09/2016 - 09/09/2016)

María José Gómara. "A targeting strategy for a new peptide entry inhibitor with anti-HIV-1 activity" 6th EUCHEMS Chemistry Congress. Sevilla, 11-15 de September de 2016

J.L. Blin, P. Riachy, F. Roig, M. J. García-Celma, M. J. Stébé, J. Esquena and C. Solans. Formulation of a Nano-Emulsions-Based System for Loading and Releasing of Ketoprofen. International Conference of Physical Chemisty. (Galati, Romania, 21/09/2016 – 23/09/2016)

A. Llebaria. Moving azobenzene photoisomerization from the flask to the brain. International Symposium on Photopharmacology, Groningen (The Netherlands), February 2017

A. Llebaria. Using light and photoregulated allosteric ligands for precise control of mGluRs activity in vivo. Gordon Research Conference on Molecular Pharmacology, Lucca (Italy), March 2017

Nanocellulose in Applied Colloids and Interfaces: A Review 7th CIS-MANA International Mini-Workshop. National Institute of Materials Science. Tsukuba, Japan 10/3/2017

C. Rodriguez Abreu. Iron Oxide Nanocolloids And Nanocomposites: New Insights And Routes Towards Applications. The 7th Asian Conference on Colloid&Interface Science (ACCIS2017) Kuala Lumpur, Malaysia 8/8/2017 - 11/8/2017

Josep M. Anglada. Atmospheric oxidation of NH3by NO3and OH radicals. Proton coupled electron transfer versus Hydrogen atom transfer reaction mechanisms.34thInternational Symposium on Free Radicals Hayama, Japón. 27 Agosto-1 Sept 2017

Josep M. Anglada. Oxidation of atmospheric trace gases by radicals. Proton coupled electron transfer versus Hydrogen atom transfer reaction mechanisms. 11th European Conference on Theoretical and Computational Chemistry. Barcelona, 4-7-sept. 2017

C. Rodriguez Abreu. Dye Self-Assemblies for the Bottom-Up Fabrication of Nanostructured Fibrillar Materials 6th Asian Symposium on Advanced Materials (ASAM-6 2017) Hanoi, Vietnam 7/9/2017 - 30/9/2017

A. Llebaria. Precise control of native membrane receptors with light and photoactive molecules. RECI VI meeting (Red Española de Canales Iónicos), Santiago de Compostela (Spain), September 2017

A. Llebaria. Precise dynamic photocontrol of native mGluRs with azobenzene allosteric ligands. 9th International Meeting on Metabotropic Glutamate Receptors, Taormina (Italy), October 2017

A. Llebaria. Photopharmacology: spatiotemporal control of native receptors in vivo with allosteric photoswitchable ligands. 5th GPCR Targeted Screening - European Pharma Summit, Berlin (Germany) November 2017

D. Díaz. Universidad de Buenos Aires, Argentina. 2017.

D. Díaz. Universidad Nacional de San Luis, Argentina. 2017.

D. Díaz. Jiangsu University, Zhenjiang, China. 2017.

D. Díaz. Northwestern Polytechnical University, School of Science, Xi'an, China. 2017.

D. Díaz. Autonomous University of Madrid, Madrid, Spain. 2017.

D. Díaz. Institute for Advanced Chemistry of Catalonia, Barcelona, Spain. 2017

D. Díaz. Georgia Institute of Technology, Atlanta, USA. 2017.

D. Díaz. University of La Laguna, IUBO, Tenerife, Spain. 2017.

D. Díaz. Kyushu University, Fukuoka, Japan. 2017.

C. Rodríguez-Abreu. Nano-Droplet Systems by Surfactant Self-Assembly: Principles and some Applications. International Conference on Functional Nanomaterials and Nanotechnology (ICFNN-2017) Kathmandu, Nepal 10/10/2017 - 13/10/2017

C. Solans. Nano-Emulsions: Overview of Formation by Low Energy Methods and Advanced Applications. Meeting of Japan Research Institute of Materials and Technology. Noda, Japan 1/12/2017 - 2/12/2017

INVITED CONFERENCES OR LECTURES

"Homochiral self-sorting of dynamic macrocyclic pseudopeptides", Workshop on Supramolecular Systems Chemistry, Barcelona, Spain, February 2016.

Solà, J.; Bolte, M.; Alfonso, I. Best flash presentation award: "Conformational promiscuity in clickamers". III Bienal of the Chemical Biology group RSEQ. Madrid 21-22 March, 2016.

D. Díaz. PNG2016, KTH Royal Institute of Technology, Stockholm, Sweden. 2016.

D. Díaz. EuCheMS Chemistry Congress, Sevilla, Spain. 2016.

I. Alfonso. "Química Supramolecular: la química más allá de las molecules", Residencia de Estudiantes del CSIC, Barcelona, Spain, May 2016.

R. Eritja. DNA origami, a source of inspiration in nucleic acids chemistry. "40 Years of Synthetic Oligonucleotides: How a Revolution in Chemistry Empowered a New Biology – A Symposium in Honor of Keiichi Itakura", Duarte, CA, USA 17 May 2016.

S. Grijalvo. Nioplexes and supramolecular hydrogel hybrid materials as nucleic acid delivery platforms. ICREA Conference on functional nanocontainers, Tarragona, Spain, October 17-20, 2016.

Solà, J.; Bolte, M.; Alfonso, I. Best poster award: "Metal driven assembly of peptidic foldamers: formation of molecular tapes". II Workshop on Chemistry of Group 11 Elements. Barcelona, January 2017.

I. Haro. "Diseño, síntesis y aplicaciones biomédicas de péptidos". Ciclo de Conferencias del Instituto de Química Orgánica General (IQOG/CSIC) patrocinadas por la Real Sociedad Española de Química (RSEQ), 8 Febrero 2017.

"Unraveling the multistimuli responses of a dynamic complex system of macrocyclic pseudopeptides using statistical analyses", Systems Chemistry in Paris, Paris, France, February 2017

A. Llebaria. Visiting lecturer at the Université Paris Descartes, Paris, invited by Dr. Francine Archer, Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, May 2017

D. Díaz. Symposium on Photofunctional Chemistry and Molecular Systems, Fukuoka, Japan. 2017.

D. Díaz. XXI SINAQO, San Luis, Argentina. 2017.

D. Díaz. Sino-German Symposium on Space Biomaterials and Systems Chemistry, Xi'an, China. 2017.

D. Díaz. 254th ACS National Meeting & Exposition, Washington, USA. 2017.

R. Eritja DNA-nanostructures as source of inspirations for novel potential applications. XXXVI Reunión Bienal de la Real Sociedad Española de Química. Sitges (Barcelona), June 25-29, 2017.

R. Eritja. Novel and versatile approaches for DNA-based nanosensing based on nucleic acid triplex formation. Keynote speaker at the VIII International Congress on Analytical Nanoscience and nanotechnology. Barcelona, July 3-5, 2017.

I. Alfonso. "On the road from Supramolecular to Biological Chemistry", XXXVI Biennial meeting of RSEQ, Sitges, Spain, July 2017

I. Alfonso. "Dynamic Complex Chemical Systems from Pseudopeptidic Disulfides", SysChem 2017 Conference – Cost Action CM1304, Sopron, Hungary, September 2017

R. Eritja. Development of novel oligonucleotide conjugates forming G-quadruplex as antivirals and as cell-uptake facilitators. 7th Cambridge Symposium on Nucleic Acids Chemistry & Biology. Cambridge (England), September 3-6, 2017.

Jordi Solà. Espai Ciencia. "Màquines i motors moleculars. Què són, i com i per a què es fabriquen". Octubre centre de Cultura Contemporània. Cicle de conferències Premis Nobel, València. 2017.

J. M. Anglada. Oxidation of atmospheric trace gases. A perspective from theoretical chemistry. University of Helsinki, Finlandia, Division of Atmospheric Sciences. KUMPULA COMPUTATIONAL CHEMISTRY AND PHYSICS SEMINAR SERIES. 30 Noviembre 2017.

PARTICIPATION IN GENERAL PUBLIC EVENTS/ FERIAS

SED Service (Luisa Coderch). Participation in Cosmetorium, Fira 1 Montjuïc, Barcelona, 28-29 September, 2016

A. Llebaria. Participation in the brokerage event EIT Health Spain-Scandinavia CLCs Bilateral meeting, Barcelona, October 2016

A. Llebaria. Participation in the brokerage event BioTECNIO Business Meeting day, Bellaterra, June 2017

A. Llebaria. Participation in the brokerage event Open Innovation Forum -Expoquimia, Barcelona, October 2017

PARTICIPATION IN COMMITTEES

Meritxell Martí was a member of the Organising Committee of the 41º Simposium de la AEQCT, La sotenibilidad, Barcelona, Abril 2016.

A. Llebaria was a member of the Organising Committee of the 19th European Carbohydrate Symposium (EUROCARB), Barcelona, July 2017

Meritxell Martí is member of the Subcommission Solideces y Medida del Color. (AENOR/CTN40/SC1) (Since 2010).

Isabel Haro is member of the Commission of the Area of Chemical Science and Technologies of CSIC (since 2012).

Merittxell Martí was a member of the Organising Committee of the 42º Simposium de la AEQCT, La irrupción digital en la industria textil, Salón Graphispag, Barcelona,Marzo 2017.

COURSES

Master's courses at the Universitat Autonoma de Barcelona during the 2013-2014; 2014-2015; 2015-2016; 2016-2017; 2017-2018 years in "Ingenieria biológica y ambiental" and " Biotecnologia Avanzada" teaching the following subject: **Biocatàlisi Aplicada i Biotransformacions.** Gloria Caminal Saperas.

Master's courses at the Universitat Autonoma de Barcelona during the 2013-2014; 2014-2015; 2015-2016; 2016-2017; 2017-2018 years in "Ingenieria biológica y ambiental" and " Biotecnologia Avanzada" teaching the following subject: **Producció Industrial de Bioproductes.** Gloria Caminal Saperas.

Master's courses at the Universitat Autonoma de Barcelona during the 2013-2014; 2014-2015; 2015-2016; 2016-2017; 2017-2018 years in "Ingenieria biológica y ambiental" and " Biotecnologia Avanzada" teaching the following subject: **Disseny i Operació de Bioprocessos en Planta Pilot.** Gloria Caminal Saperas.

Biocatalysis as a Key Enabling Technology. Training course. Italy, 3-6 October 2017. **Aldolases as catalysts in asymmetric carbon-carbon bond formation**

Bases genéticas y Celulares de la Biotecnologia
R. Eritja
University of Barcelona, 2016 and 2017

Biomolecular Nanoscience.
R. Eritja
University Autonomous of Barcelona, 2016 and 2017

Course on Synthetic oligonucleotides.
R. Eritja
Agencia Española de Medicamentos y Productos Sanitarios. Madrid, 2017

Estadística aplicada a la preformulación y formulación de medicamentos
A M Manich y M J Bleda
Especialización en Farmacia Industrial y Galénica (UB), 2016

Introducción al diseño de experimentos
A M Manich y M J Bleda
Cursos de Formación (CSIC), 2016

Planificación y Diseño de Experimentos
A M Manich y M J Bleda
Curso de Especialización (KERN Pharma), 2017

Introducción al diseño de experimentos
A M Manich y M J Bleda
Cursos de Formación (CSIC), 2017

Isabel Haro. Coordinator of the Course: **"Curso Experimental en Química Biológica, Ambiental y Tecnologías relacionadas"** (Postgrado y Especialización del CSIC), 2016-2017.

Isabel Haro y María José Gómara. Curso del Plan de Formación Interna de la Agencia Española de Medicamentos y Productos Sanitarios (AEMPS): **"Síntesis peptídica en Fase Sólida y en Fase Líquida"**, 21-22 Noviembre 2017.

Carlos Rodriguez Abreu. "**Pharmaceutical Nanotechnology**" Course of the Master on Research, Development and Control of Medicines at the Universitat de Barcelona (2017)

Carlos Rodriguez Abreu. "**Development and formulation of pharmaceuticals**" Course of the Master on Nanoscience and Nanotechnology at the Universitat de Barcelona (2017)

Ramon Crehuet Simon. Curso "**Python para científicos**", (1a edición) plan de formación del CSIC. 30 horas. Marzo 2016.

Ramon Crehuet Simon. Curso "**Python para científicos**", (2a edición) plan de formación del CSIC. 30 horas. Junio 2016.

Ramon Crehuet Simon. Curso "**Python for Scientists**", (2a edición), Curso de postgrado, Universitat de Barcelona (30 horas). Junio 2016.

OUTREACH ACTIVITIES ORGANIZED AT IQAC

R. Eritja. Research on DNA, conference at the Science Week (semana de la Ciencia y tecnologia en el CSIC), 14 November 2016.

R. Eritja. Taller "DNA extraction" Research activities for highschool teachers (El CSIC en el aula. 8 March 2017.

PH.D. THESIS

19-01-2016

NOVES APROXIMACIONS PER A LA DETECCIÓ DE MICROORGANISMES PATÒGENS

Carme Pastells Diez

Organic Chemistry Department. University of Barcelona

Supervisor: Mª P. Marco

28-01-2016

A MULTIPLEXED IMMUNOCHEMICAL DIAGNOSTIC APPROACH FOR CARDIOVASCULAR DISEASE BIOMARKERS.

Gloria Colom San Martí

Faculty of Chemistry. University of Barcelona

Supervisor: Mª P. Marco

29-01-2016

DEVELOPMENT OFLIGHT-MODULATED ALLOSTERIC LIGANDS FOR REMOTE, NON-INVASIVE CONTROL OFNEURONAL RECEPTORS

Silvia Pittolo

Faculty of Medicine. University of Barcelona

Supervisors: A. Llebaria, Pau Gorostiza (IBEC)

09-02-2016

HIDROGELS I MATERIALS POROSOS D'ÀCID HIALURÒNIC ENTRECREUAT COM A SISTEMES D'ALLIBERAMENT CONTROLAT DE FÀRMACS

Ferran Roig Roig

Supervisor: J. Esquena

09-02-2016

CHEMICAL MODULATION OF THE NOCICEPTIVE RECEPTOR TRPV1: SYNTHETIC, BIOLOGICAL AND COMPUTATIONAL STUDIES.

Miguel Vidal Mosquera

Faculty of Chemistry. University Ramon Llull

Supervisors: J. Bujons, A. Messeguer

11-04-2016

New Pseudopeptidic Compounds with Potential Biomedical Applications

Ahmed Hajjaj Mohamed Ahmed Lotfallah

Escuela Superior Técnica de Ciencias Experimentales, Universitat Jaume I de Castellón

Supervisor: Ignacio Alfonso

13-05-2016

DESIGN, SYNTHESIS AND CHARACTERISATION OF PHOTOSWITCHABLE ALLOSTERIC MODULATORS OF METABOTROPIC GLUTAMATE RECEPTORS

Xavier Gómez Santacana

Faculty of Chemistry. University of Barcelona

Supervisors: A. Llebaria, Pau Gorostiza

01-07-2016

ESTUDI DE LA FORMACIÓ DE NANO-EMULSIONS PER MÈTODES DE BAIXA ENERGIA

Maria Homs San Millan

Faculty of Pharmacy. University of Barcelona

Supervisors: C. Solans, J. Esquena

16-09-2016

PRIMARY AMINE THIOUREAS IN ASYMMETRIC ORGANOCATALYSIS

Zeynep Inci Günler

Faculty of Chemistry. Universitat Rovira i Virgili

Supervisor: Ciril Jimeno

16-09-2016

CHEMICAL TOOLS TO INVESTIGATE THE ROLE OF SPHINGOLIPIDS IN DISEASE

Yadira Ordóñez Vivanco

Faculty of Chemistry. University of Barcelona

Supervisor: G. Fabriàs

02-11-2016

DESIGN AND SYNTHESIS OF SPHINGOSINE–1– PHOSPHATE LYASE INHIBITORS AND FLUOROGENIC PROBES FOR THE DEVELOPMENT OF HTS ASSAYS

Pol Sanllehí Figuerola
Faculty of Pharmacy. University of Barcelona

Supervisors: A. Delgado, J. Bujons

03-11-2016

Removal of pharmaceuticals from WWTT streams by biological and physical processes.

Guillem Llorens Blanch

Escola d'Enginyeries. Universitat Autònoma de Barcelona

Supervisors: Gloria Caminal/ Montserrat Sarrà

25-11-2016

AMINOCYCLITOL AND IMINOSUGAR DERIVATIVES RELATED TO GAUCHER DISEASE

Ester Monlleó Mas

Faculty of Chemistry. University of Barcelona

Supervisor: A. Llebaria

09-02-2017

MOLECULAR SELF-ASSEMBLY FOR THE PREPARATION OF NOVEL NANOSTRUCTURED MATERIALS

José Rodrigo Magaña Rodríguez

Faculty of Pharmacy. University of Barcelona

Supervisors: C. Solans, C. Rodríguez Abreu

14-03-2017

SYNTHESIS OF 2-VINYL SPHINGOLIPIDS AS S1PL INHIBIDORS

Raquel Calderón Almendro

Faculty of Pharmacy. University of Barcelona

Supervisors: A. Delgado, J.L. Abad

24-03-2017

METABOLISME DELS ESFINGOLÍPIDS: NOVES METODOLOGIES I EFECTE SOBRE L'AUTOFÀGIA

Mireia Casasampere Ferrer

Faculty of Biology. University of Barcelona

Supervisor: J. Casas

02-05-2017

Anaerobic microbial transformation of chlorinated alkanes in cultures derived from Besós river estuary sediments

Siti Hatijah Mortan

Escola d'Enginyeries. Universitat Autònoma de Barcelona

Supervisors: Gloria Caminal/Ernest Marco-Urrea

09-06-2017

DECIPHERING THE ROLE OF PERIPHERAL AND CENTRAL NERVOUS SYSTEM METABOTROPIC GLUTAMATE RECEPTORS IN NEUROPATHIC PAIN WITH PHOTOACTIVABLE LIGANDS

Joan Font Inglès

Faculty of Chemistry. University of Barcelona

Supervisor: A. Llebaria

23-06-2017

Engineered D-Fructose-6-phosphate aldolase (FSA) in organic synthesis: aliphatic carbonyl compounds as nucleophiles in biocatalytic aldol addition reaction

Raquel Roldán García

Faculty of Pharmacy. University of Barcelona

Supervisors: P. Clapés, J. Joglar

28-06-2017

INSIGHT INTO THE STRUCTURE AND FUNCTION OF ENGINEERED BIOCATALYSTS: SERINE HYDROXYMETHYLTRANSFERASE FROM STREPTOCOCCUS THERMOPHILUS AND HALOHYDRINE DEHALOGENASE D2 FROM GAMMAPROTEOBACTERIUM

Giovanna Petrillo

Faculty of Pharmacy. University of Barcelona

Supervisor: P. Clapés, I. Usón

30-06-2017

SYNTHESIS AND OPTIMIZATION OF NEW SPHINGOLIPID SENSORS FOR METABOLISM AND TRAFFICKING STUDIES

Ana Pou Cabello

Faculty of Pharmacy. University of Barcelona

Supervisors: A. Delgado, J.L. Abad

18-09-2017

Universal diagnostic platforms based on oligonucleotide codified nanoparticles and DNA microarray devices

Marta Broto Avilés

Faculty of Chemistry. University of Barcelona

Supervisor: Mª P. Marco

22-09-2017

Desarrollo de técnicas inmunoquímicas para la detección de biomarcadores cardíacos

Alejandro Hernández Albors

Faculty of Chemistry. University of Barcelona

Supervisor: Mª P. Marco

29-09-2017

Sistemas poliméricos nanoestructurados de péptidos inhibidores del HIV-1 derivados del GB virus C (GBV-C)

Martha Rocío Ariza Sáenz

Faculty of Pharmacy. University of Barcelona

Supervisors: I. Haro, M.L. García

10-11-2017

Process development for hospital wastewater treatment by *Trametes versicolor*

Josep Anton Mir Tutusaus

Escola d'Enginyeries. Universitat Autònoma de Barcelona

Supervisors: Gloria Caminal/Montserrat Sarrà

2017

Synthesis, characterization and application of smart materials based on low-molecular-weight compounds and Polymers

Judith Mayr

Supervisor: David Díaz Díaz

08-2017

Gels as Nanoreactors for Photoinduced Processes

Alex Abramov

Supervisor: David Díaz Díaz

2017

Isosteric replacement: A versatile tool for fine-tuning low molecular weight gelators

Markus Tautz

Supervisor: David Díaz Díaz

2017

Superhydrophobic coatings using low molecular weight gelators

Ting Li

Supervisor: David Díaz Díaz

PATENT APPLICATIONS

Análogos no glicosídicos de alfa-galactosilceramida como activadores de células NKT

A. Llebaria, R. Borràs, C. Serra, A. Alcaide

Application number P201731348

Application date 22 November 2017

Applicant: Consejo Superior de Investigaciones Científicas (CSIC)

PATENTES

M.-P. Marco, N. Pascual, C. Pastells, F, Sanchez-Baeza, A-P Villaverde, E. Rodriguez. Haptenos y conjugados derivados de piocianina. Anticuerpos de los mismos, y método inmunoquímico de detección de infecciones causadas por Pseudomonas aeruginosa. Nº solicitud PCT/ES2014/070161. WO2014135730. 10.5 2016. Patente en fases nacionales.

M.-P Marco, N. Pascual, C. Pastells. Compuestos y sus usos como haptenos para la detección S. aureus. 11.1 2015 (España): Depositada el 3 de junio de 2015. Número de solicitud P201530780. 2016 (PCT) Com-

puestos y sus usos como haptenos para la detección S. aureus. Solicitud internacional PCT/ES2016/070390 el 24 de Mayo de 2016.

Giacomo Saviozzi, J.-P. Salvador Vico, Manuel López de Miguel, Francisco Palacio Bonet, Raquel Pruna Morales, M.-Pilar Marco Colás, Cecilia Laschi Devices and Methods for multiplexing liquid in biosensor micro-chambers. Application number: EP17382269.3. 12th of May, 2017

M.-Pilar Marco, Alejandro Hernandez, J.-Pablo Salvador, Fernando Civeira. Haptenos derivados de lipoproteína (a), conjugados y anticuerpos frente a los mismos. Application number: P201731063, 01 September, 2017.

MEDIA COVERAGE

Journal Covers

R. Eritja. Bioorganic Medicinal Chemistry. Issue 1 January 2017

D. Díaz, R. Eritja. International Journal of Molecular Sciences. Issue 6 June 2017

R. Eritja. ChemBioChem. Issue 12, June 2017

News

R. Eritja. Interviewed by Andres Doncel Canal NTN24. Colombia.

Link: https://vimeo.com/203874011

Press Release

April 18, 2017. Press release on the successful outcomes of the TERET project. Press release in CIBER and Sylentis web pages.

January- April 2017. Press release on the article published in Advanced Materials. The information was highlighted in several webs: Biofisica Newsletter (SBE), R+D CSIC, CIBER Newsletter, Willey hot topics, IBEC web page, Catalunya Vanguardista, EFE future, 20 min, GreenArea.

July 2016. Press release on the article published in Nature Communications "Optical control of endogenous receptors and cellular excitability using targeted covalent photoswitches".

January 2017. Press release on the articles published in ACS Central Science "Illuminating Phenylazopyridines To Photoswitch Metabotropic Glutamate Receptors: From the Flask to the Animals" and Molecular Psychiatry "Dynamic modulation of inflammatory pain-related affective and sensory symptoms by optical control of amygdala metabotropic glutamate receptor 4".

April 2017. Press release on the article published in eLife "Optical control of pain in vivo with a photoactive mGlu5 receptor negative allosteric modulator".

November 2017. Press release on the granting of the ERA-NET NEURON 2017 project "Amygdala synaptic neuromodulatory mechanisms and role of mGlu4 in Autism Spectrum Disorders".

BIOLOGICAL CHEMISTRY AND MOLECULAR MODELLING

BIOLOGICAL CHEMISTRY AND MOLECULAR MODELLING

Head: Jordi Bujons Vilàs

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 health promoting agents such as nutraceuticals and functional food components. The nutraceuticals (e.g. antioxidant polyphenols, omega-3 polyunsaturated fatty acids, iminosugars) are natural products obtaine either from agricultural and fishery by-products or by environmentally friendly biosynthetic procedures. The group is mainly centered on the prevention of the modern epidemics of obesity and diabetes. We pay particular attention to oxidative stress, which is a major damaging process mediated by free radicals and occurring in diabetes as well as in other disorders such as cardiovascular disease, cancer, and Alzheimer's disease. The study of free radicals, their reactivity, their use as probes for antioxidant activity and their control or elimination by nutraceuticals is a central goal of our research. The antioxidant activity is measured by Electron Paramagnetic Resonance spectroscopy with the spin trapping and radical scavenging methodology.

We focus on *in vivo* studies with rat models of pre-diabetes in which we test combinations of different nutraceuticals that show complementary activities. The study of the relationship between intestinal microbiota, gut integrity and the health status of the host is also a primary goal in our recent studies. Preventive strategies of the future may include the maintenance of a balanced gut microbiota.

STAFF

JOSEP LLUÍS TORRES
LUIS JULIÁ BARGÉS
LLUÍS FAJARÍ AGUDO

Ph.D.

SARA RAMOS ROMERO

Ph.D. STUDENTS

MERCÈ HEREU PLANELLAS

ARTICLES

Lipidomics to analyze the influence of diets with different EPA:DHA ratios in the progression of Metabolic Syndrome using SHROB rats as a model.

Dasilva, G.; Pazos, M.; García-Egido, E.; Pérez-Jiménez, J.; Torres, J.L.; Giralt, M.; Nogués, M.R.; Medina, I.

Food Chem. 205, 196-203, **2016**. doi: 10.1016/j.foodchem.2016.03.020.

Advances in the analysis of iminocyclitols: methods, sources and bioavailability.

Amézqueta, S.; Torres, J.L.

Talanta, 151, 157-171, **2016**. doi: 10.1016/j.talanta.2016.01.034.

The combined action of omega-3 polyunsaturated fatty acids and grape proanthocyanidins on a rat model of diet-induced metabolic alterations.

Ramos-Romero, S.; Molinar-Toribio, E.; Pérez-Jiménez, J.; Taltavull, N.; Dasilva, G.; Romeu, M.; Medina, I.; Torres, J.L.

Food Funct. 7, 3516-3523, **2016**. doi: 10.1039/C6FO00679E.

Protective effects of fish oil on pre-diabetes: a lipidomic analysis of liver ceramides in rats.

Taltavull, N.; Ras, R.; Mariné, S.; Romeu, M.; Giralt, M.; Méndez, L.; Medina, I.; Ramos-Romero, S.; Torres, J.L.; Nogués, M.R.

Food Funct. 7, 3981-3988, **2016**. doi: 10.1039/c6fo00589

Changes in liver proteins of rats fed standard and high-fat and sucrose diets induced by fish omega-3 PUFAs and their combination with grape polyphenols according to quantitative proteomics.

Méndez, L.; Ciordia, S.; Fernández, M.S.; Juárez, S.; Ramos, A.; Pazos, M.; Gallardo, J.M.; Torres, J.L.; Nogués, M.R.; Medina, I.

J. Nutr. Biochem. 41, 84-97, **2017**. doi: 10.1016/j.jnutbio.2016.12.005

A lipidomic study on the regulation of inflammation and oxidative stress targeted by marine ω-3 PUFA and polyphenols in high- fat high-sucrose diets.

Dasilva, G.; Pazos, M.; García-Egido, E.; Gallardo, J.M.; Ramos-Romero, S.; Torres, J.L.; Romeu, M.; Nogués, M.R.; Medina, I.

J. Nutr. Biochem. 43, 53-67, **2017**. doi:10.1016/j.jnutbio.2017.02.007.

Influence of omega-3 PUFAs on the metabolism of proanthocyanidins in rats.

Molinar-Toribio, E.; Ramos-Romero, S.; Fuguet, E.; Taltavull, N.; Méndez, L.; Romeu, M.; Medina, I.; Torres, J.L.; Pérez-Jiménez, J.

Food Res. Int. 97, 133-140, **2017**. doi: 10.1016/j.foodres.2017.03.046 .

Effects of the combination of ω-3 PUFAs and proanthocyanidins on the gut microbiota of healthy rats.

Ramos-Romero, S.; Hereu, M.; Molinar-Toribio, E.; Almajano, M.P.; Méndez, L.; Medina, I.; Taltavull, N.; Romeu, M.; Nogués, M.R.; Torres, J.L.

Food Res. Int. 97, 364-371 **2017**. doi: 10.1016/j.foodres.2017.04.024

Fate of D-fagomine after oral administration to rats.

Amézqueta, S.; Ramos-Romero, S.; Martínez-Guimet, C.; Moreno, A.; Hereu, M.; Torres, J.L.

J. Agric. Food Chem. 65, 4414-4420, **2017**. doi: 10.1021/acs.jafc.7b01026

Reducing the Harmful Effects of Infrared Radiation on the Skin Using Bicosomes Incorporating ß-Carotene.

Fernández, E.; Fajarí, L.; Rodríguez, G.; Cócera, M.; Moner, V.; Barbosa-Barros, L.; Kamma-Lorger, C.S.; de la Maza, A.; López, O.

Skin Pharmacol Physiol., 29 169-177, **2016.** doi: 10.1159/000447015

DOI: 10.1159/000447015

Stable all-organic radicals with ambipolar charge transport

Reig, M.; Gonzálvez, C.; Jankauskas, V.; Gaidelis, V.; Grazulevicius, J.V.; Fajarí, L.; Juliá, L., Velasco, D

Chem. Eur. J. 22, 18551-18558, **2016.**

Twisted intramolecular charge transfer in a carbazole-based chromophore. The stable [(4-*N*-carbazolyl)-2,3,5,6-tetrachlorophenyl] bis(2,3,5,6-tetrachlorophenyl)methyl radical

Gilabert, A.; Fajarí, L.; Sirés, I.; Reig, M.; Brillas, E.; Velasco, D.; Anglada, J.M.; Juliá, L.

New J. Chem. 41, 8422-8430, **2017.**

BOOK CHAPTERS

Key aspects of polyhenols and health: metabolic fate, mechanisms of action, influence on gut microbiota.

Torres, J.L.; Ramos-Romero, S.; Pérez-Jiménez, J.

In: *Advances in Technologies for Producing Food-relevant Polyphenols*. Chapter 2, pp. 32-66, Cuevas-Valenzuela, J.; Vergara-Salinas, J.R.; Pérez-Correa, J.R. Eds. Contemporary Food Engineering Series, Sun, D-W. Series Ed., ISBN 978-14-987-1497-6, CRC Press. Boca Raton, **2016**.

Analysis and chacterization of polyphenol extracts.

Sáyago-Ayerdi, S.G.; Mercado-Mercado, G.; Ramos-Romero, S.; Torres, J.L.; Pérez-Jiménez, J.

In: *Advances in Technologies for Producing Food-relevant Polyphenols*. Chapter 6, pp. 193-220, Cuevas-Valenzuela, J.; Vergara-Salinas, J.R.; Pérez-Correa, J.R. Eds. Contemporary Food Engineering Series, Sun, D-W. Series Ed., ISBN 978-14-987-1497-6, CRC Press. Boca Raton, **2016**.

RESEARCH PROJECTS

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

National AGL2013-49079-C2-2-R

2014-2017

Grup de Bioquímica Integrativa.

Regional 2014SGR1017

2014-2016

Illegitimate signaling of fruit consumption and obesity pathogenesis

National AGL2013-49500-EXP
2014-2016

New organic materials and their use for the modelation and transformation of energy

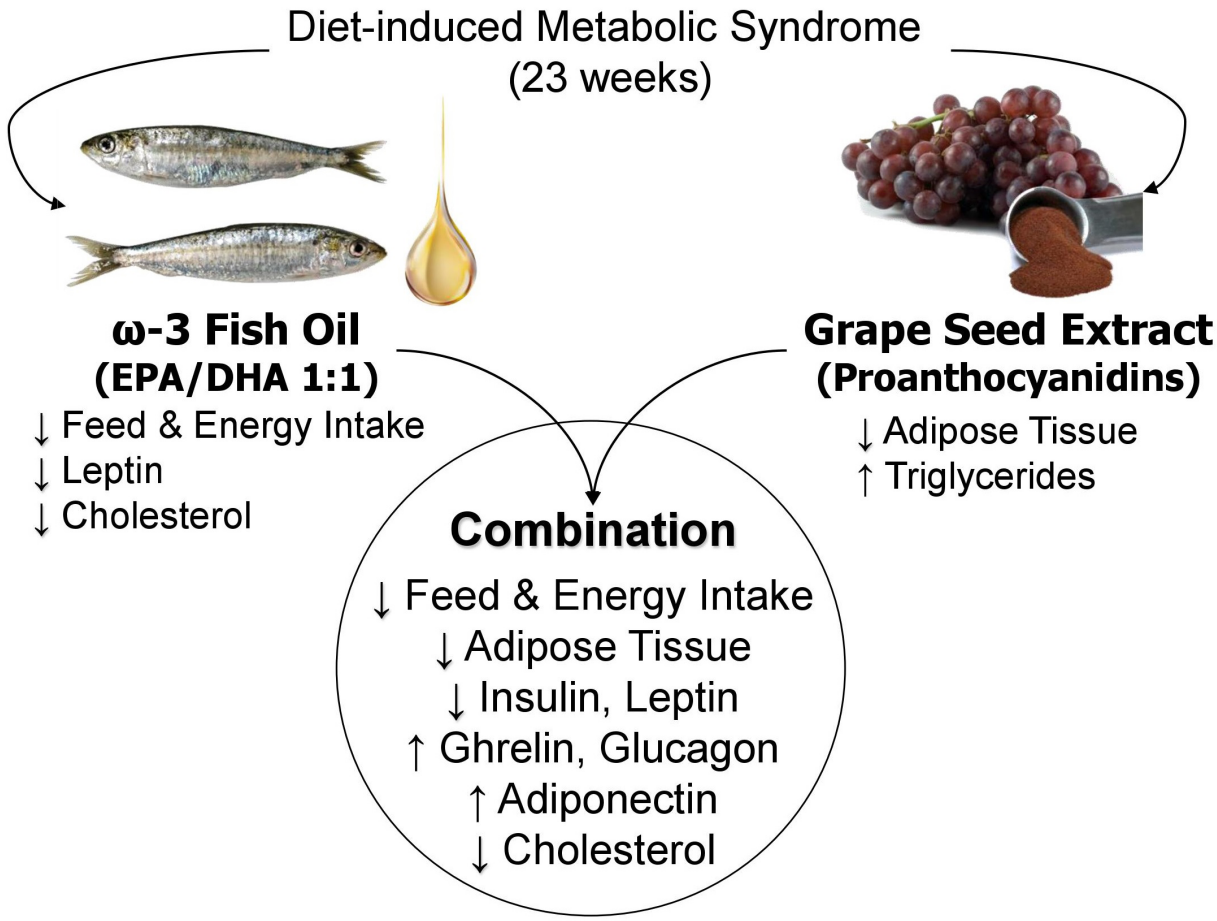
National CTQ2015-65770-P

2016-2018

RESEARCH HIGHLIGHTS

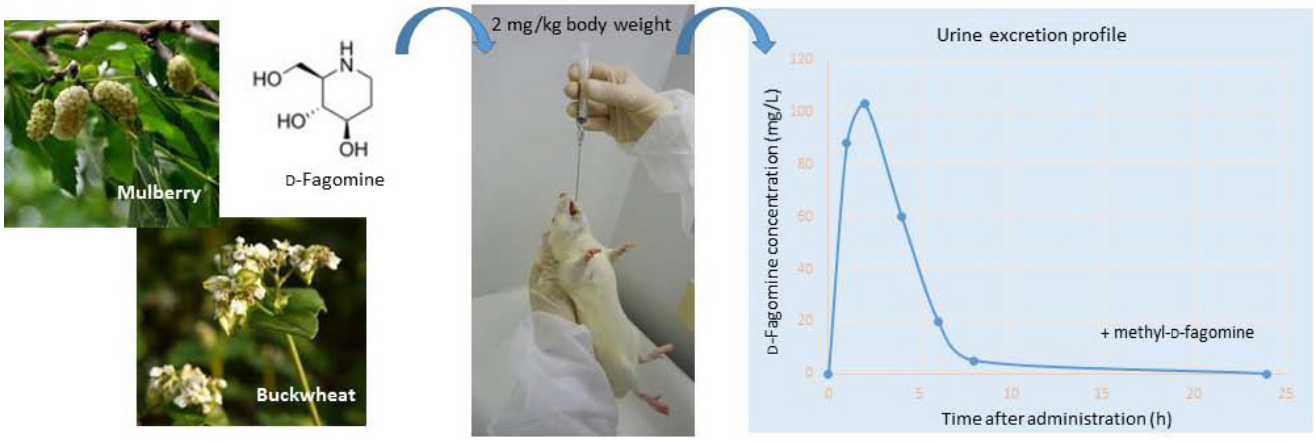
The combined action of omega-3 polyunsaturated fatty acids and grape proanthocyanidins on a rat model of diet-induced metabolic alterations.

Functional food components such as omega-3 polyunsaturated fatty acids (omega-3 PUFAs) and (poly) phenols counteract diet-induced metabolic alterations by complementary mechanisms. To examine the effects of a combination of omega-3 PUFAs and (poly)phenols on such alterations, adult Wistar-Kyoto rats were fed an obesogenic high-fat high-sucrose diet supplemented for 24 weeks with: eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA) 1 :1; proanthocyanidin-rich grape seed extract (GSE), or EPA/DHA 1 :1 + GSE. Body weight, feed intake, and plasma glucose were evaluated every 6 weeks, white adipose tissue weight, insulin, glucagon, ghrelin, adiponectin, cholesterol, and triglycerides were evaluated at the end of the experiment. omega-3 PUFAs reduced plasma leptin and cholesterol levels, but did not modify diet-induced perigonadal fat or plasma insulin levels; while GSE increased plasma triglyceride levels. The combined action of omega-3 PUFAs and the proanthocyanidins reduced plasma insulin and leptin, as well as partially prevented perigonadal fat accumulation. While separate supplementation with omega-3 PUFAs or grape proanthocyanidins may not counteract all the key metabolic changes induced by a high-energy-dense diet, the combination of both supplements reverts altered insulin, leptin and triglyceride levels to normal.



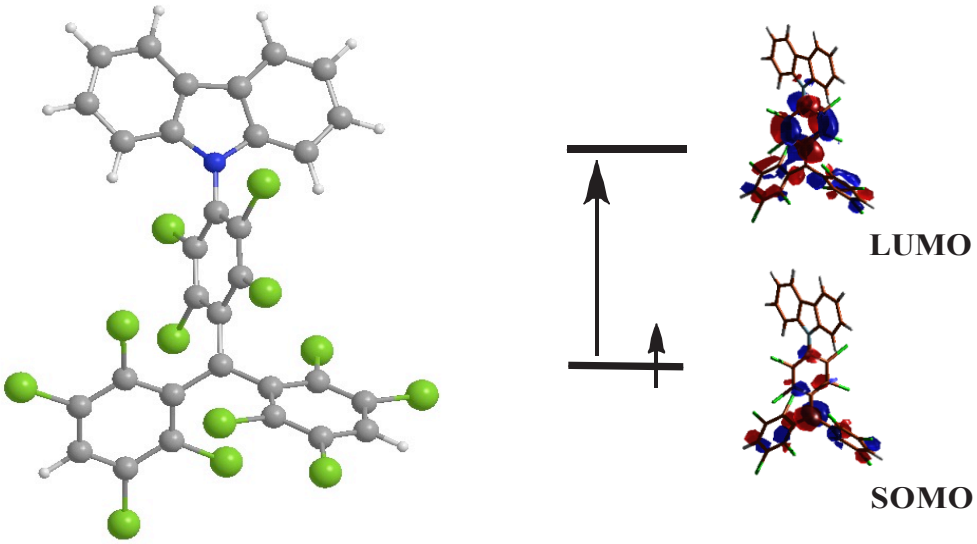
Fate of D-fagomine after oral administration to rats

D-Fagomine is an iminosugar found in buckwheat that is capable of inhibiting the adhesion of potentially pathogenic bacteria to epithelial mucosa. This work evaluated the excretion and metabolism of orally administered D-fagomine. D-Fagomine is partly absorbed (41-84%, dose of 2 mg/kg of body weight) and excreted in urine within 8 h, while the non-absorbed fraction is cleared in feces within 24 h. The concentration of D-fagomine in urine from 1 to 6 h after administration is higher than 10 mg/L, the concentration that inhibits adhesion of *Escherichia coli*. In conclusión, orally administered D-fagomine is partially absorbed and then rapidly excreted in urine, where it reaches a concentration that may be protective against urinary tract infections.



Stable all-organic radicals with ambipolar charge transport

A series of neutral long-lived organic radicals based on the stable [4-(*N*-carbazolyl)-2,6-dichlorophenyl]bis (2,4,6-trichlorophenyl) methyl radical adduct is reported. These compounds exhibit ambipolar charge-transport under ambient conditions owing to their radical character. High electron and hole mobilities up to 10^{-2} and 10^{-3} $cm^2V^{-1}s^{-1}$, respectively, were achieved. The molecular structure of these very stable radical adducts are non-planar to avoid the steric hindrance induced by the chlorine atoms in the molecule.



Molecular structure and transition from the ground to the excited state

BIOTRANSFORMATION AND BIOACTIVE MOLECULES

The research of our group is focused on the development and optimization of new and existing biocatalyst for carbon-carbon bond formation (carboligases). Carboligases have the potential to efficiently access complex molecular scaffolds from simple starting materials, with unparalleled stereoselectivity and without a need for tedious and time-consuming iterative steps for protection and deprotection of sensitive or reactive functional groups. Three goals are pursued: first to develop new cost-efficient and eco-friendly process for the chemical manufacturing industry, second to produce new compounds (i.e. new structure types generating molecular diversity) accessible for investigations in drug discovery and third to engineer the biocatalyst for improving its substrate tolerance, stereoselectivity, and catalytic properties (i.e. towards non-natural reactions) to broaden its window of applicability. The research includes computational models for substrate-protein interaction essential for biocatalyst optimization by structure-guided protein engineering.

STAFF

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ROSER MARÍN VALLS
CARLA TUR MEL·LO
GIOVANNA PETRILLO
CARLOS JOSÉ MORENO FONTALBA

ARTICLES

Breaking the Dogma of Aldolase Specificity: Simple Aliphatic Ketones and Aldehydes are Nucleophiles for Fructose-6-phosphate Aldolase.

Roldán, R.; Sanchez-Moreno, I.; Scheidt, T.; Hélaine, V.; Lemaire, M.; Parella, T.; Clapés, P.; Fessner, W.-D.; Guérard-Hélaine, C.

Chem. Eur. J., 23, 5005-5009, **2017**.

Intramolecular Benzoin Reaction Catalyzed by Benzaldehyde Lyase from Pseudomonas Fluorescens Biovar I.

Hernández, K.; Parella, T.; Petrillo, G.; Usón, I.; Wandtke, C. M.; Joglar, J.; Bujons, J.; Clapés, P.

Angew. Chem. Int. Ed., 56, 5304-5307, **2017**.

2-Keto-3-Deoxy-L-Rhamnonate Aldolase (YfaU) as Catalyst in Aldol Additions of Pyruvate to Amino Aldehyde Derivatives.

Hernández, K.; Gómez, A.; Joglar, J.; Bujons, J.; Parella, T.; Clapés, P.

Adv. Synth. Catal., 359, 2090-2100, **2017**.

Combining Aldolases and Transaminases for the Synthesis of 2-Amino-4-hydroxybutanoic Acid.

Hernandez, K.; Bujons, J.; Joglar, J.; Charnock, S. J.; Domínguez de María, P.; Fessner, W. D.; Clapés, P.

ACS Catal., 7, 1707-1711, **2017**.

Microvesicle release and micellar attack as the alternative mechanisms involved in the red-blood-cell-membrane solubilization induced by arginine-based surfactants.

Fait, M. E.; Hermet, M.; Comelles, F.; Clapes, P.; Alvarez, H. A.; Prieto, E.; Herlax, V.; Morcelle, S. R.; Bakas, L.

RSC Adv., 7, 37549-37558, **2017**.

Ionization and collision induced dissociation of Steroid bis-glucuronides.

Esquivel, A.; Matabosch, X.; Kotronoulas, A.; Balcells, G.; Joglar, J.; Ventura, R.

J. Mass Spectrom., 52, 759–769, **2017**.

LC-MS/MS detection of unaltered glucuronoconjugated metabolites of metandienone.

Esquivel, A.; Pozo, O. J.; Garrostas, L.; Balcells, G; Gómez, C.; Kotronoulas, A.; Joglar, J.; Ventura, R.

Drug Test. Anal., *9*, 534–544, **2017**.

Evaluation of two glucuronides resistant to enzymatic hydrolysis as markers of testosterone oral administration.

Kotronoulas, A.; Gomez, A.; Segura, J.; Ventura, R.; Joglar, J.; Pozo, O. J.

J. Steroid Biochem. Mol. Biol., *165*, 212–218, **2017**.

The first fluorogenic sensor for sphingosine-1-phosphate lyase activity in intact cells.

Sanllehi, P.; Casasampere, M.; Abad, J. L.; Fabrias, G.; Lopez, O.; Bujons, J.; Casas, J.; Delgado, A.

Chem Commun (Camb), 53, 5441-5444, **2017** .

Entropy-driven homochiral self-sorting of a dynamic library.

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

Chem Commun (Camb), 53, 4274-4277, **2017**.

Comparison between several reactors with *Trametes versicolor* immobilized on lignocellulosic support for the continuos treatments of hospital wastewater.

Torán J.; Blánquez P.; Caminal G.

Bioresour Technol, 243, 966-974, **2017.**

Fungal treatment for the removal of endocrine disrupting compounds from reverse osmosis concentrate: Identification and monitoring of transformation products of benzotriazoles.

Llorca M.; Badia-Fabregat M.; Rodríguex-Mozaz S.; Caminal G.; Vicent T.; Barceló D.

Chemosphere, 184,1054-1070, **2017**

Pharmaceuticals removal and microbial community assessment in a continuos fungal treatment on non-sterile real hospital wastewater after a coagulation-flocculation pretreatment.

Mir-Tutusaus J.A.; Parladé E.; Llorca M.; Vilagrasa M.; Barceló D.; Rodriguez-Mozaz S.; Martinez-Alonso M.; Gaju N.; Caminal G.; Sarrà M.

Water Res, 116,65-75, **2017**

Detoxification of 1,1,2-trichloroethane to ethene in a biorreactor co-culture of *Dehalogenimonas and Dehalococcoides mccartyi* strains.

Hatijah Mortan S.; Martín-González L.; Vicent T.; Caminal G.;Nijenhuis I.; Adrian L.; Marco-Urrea E.

J Hazard Mater, 331,218-225, **2017**

Study of the effect of the bacterial and fungal communities present in real wastewater effluents on the performance of fungal treatments.

Badia-Fabregat M.; Lucas D.; Tuomivirta T.; Fritze H.; Pennanen T.; Rodríguez-Mozaz S.;Barceló D.; Caminal G.; Vicent T.

Sci Total Environ, 579, 366-377, **2017**

A *Streptomyces lividans* Sip Y deficient strain as a host for protein production: standardization of operational alternatives for model proteins.

Gabarró M.; Gullón S.; Vicente R.; Caminal G.; Perez-Mellado R.; López-Santín J.

J Chem Technol Biotechnol, 92, 217-223, **2017**

Engineered D-Fructose-6-phosphate aldolase (FSA) in organic synthesis: aliphatic carbonyl compounds as nucleophiles in biocatalytic aldol addition reaction.

Raquel Roldán García

Faculty of Pharmacy and Food Sciences, University of Barcelona

Supervisors: P. Clapés/J. Joglar

23 June 2017

Insight into the structure and function of engineered biocatalysts: Serine hydroxymethyltransferase from *Streptococcus thermophilus* and Halohydrine dehalogenase D2 from *Gammaproteobacterium*

Giovanna Petrillo

Faculty of Pharmacy and Food Sciences, University of Barcelona

Supervisors: P. Clapés/I. Usón

28 June 2017

Process development for hospital wastewater treatment by *Trametes versicolor*

Josep Anton Mir Tutusaus

Escola d'Enginyeries. Universitat Autònoma de Barcelona

Supervisors: Gloria Caminal/Montserrat Sarrà

10 November 2017

Anaerobic microbial transformation of chlorinated alkanes in cultures derived from Besós river estuary sediments

Siti Hatijah Mortan

Escola d'Enginyeries. Universitat Autònoma de Barcelona

Supervisors: Gloria Caminal/Ernest Marco-Urrea

2 May 2017

Bacterial versus human sphingosine-1-phosphate lyase (S1PL) in the design of potential S1PL inhibitors.

Sanllehi, P.; Abad, J. L.; Casas, J.; Bujons, J.; Delgado, A.,

Bioorg Med Chem, 24, 4381-9, **2016**.

Studies on the inhibition of sphingosine-1-phosphate lyase by stabilized reaction intermediates and stereodefined azido phosphates.

Sanllehi, P.; Abad, J. L.; Bujons, J.; Casas, J.; Delgado, A.

Eur. J. Med. Chem., 123, 905-15, **2016**.

Cationic Peptides and Peptidomimetics Bind Glycosaminoglycans as Potential Sema3A Pathway Inhibitors.

Corredor, M.; Bonet, R.; Moure, A.; Domingo, C.; Bujons, J.; Alfonso, I.; Perez, Y.; Messeguer, A.

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Balcells, G.; Pozo, O. J.; Garrostas, L.; Esquivel, A.; Matabosch, X.; Kotronoulas, A.; Joglar, J.; Ventura, R.

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Inhibitor versus chaperone behaviour of D-fagomine, DAB and LAB sp2-iminosugar conjugates against glycosidases: A structure–activity relationship study in Gaucher fibroblasts.

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Minimalist Protein Engineering of an Aldolase Provokes Unprecedented Substrate Promiscuity.

Güclü, D.; Szekrenyi, A.; Garrabou, X.; Kickstein, M.; Junker, S.; Clapés, P.; Fessner, W.-D.

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Inhibitory properties of 1,4-dideoxy-1,4-imino-d-arabinitol (DAB) derivatives acting on glycogen metabolising enzymes.

Diaz-Lobo, M.; Concia, A. L.; Gomez, L.; Clapés, P.; Fita, I.; Guinovart, J. J.; Ferrer, J. C.

Org. Biomol. Chem., 14, 9105-9113, **2016**.

A microbial consortium from a biomixture swiftly degrades high concentrations of carbofuran in fluidized-bed reactors

Castro-Gutiérrez V.; Masís-Mora M.; Caminal G.; Vicent T.; Carazo-Rojas E.; Mora-López M.; Rodríguez-Rodríguez C.E.

Process Biochem, 51,1585-1593, **2016**

Continuous treatment of non-sterile hospital wastewater by T*rametes versicolor:* How to increase fungal viability by means of operational strategies and pretreatments

Mir-Tutusaus J.a.; Sarrà M.; Caminal G.

J hazard Mater, 318, 561-570, **2016**

Continuos fungal treatment of non-sterile veterinary hospital effluent: pharmaceuticals removal and microbial community assessment

Badia-Fabregat M.; Lucas D.; Pereira M.A.; Alves M.; Pennanen T.; Fritze H.; Rodríguez-Mozaz S.;Barceló D.;Vicent T.; Caminal G.

Appl. Microbiol Biotechnol, 100, 2401-2415, **2016**

Fungal treatment for the removal of antibiotics and antibiotic resistance genes in veterinary hospital wastewater

Lucas D.; Badia-Fabregat M.; Vicent T.; Caminal G.; Rodríguez-Mozaz S.;Balcázar J.L.; Barceló D.

Chemosphere, 152, 301-308, **2016**

Using promoter libraries to reduce metabolic burder due to plasmid-encoded proteins in recombinant *Escherichia coli*.

Pasini M.; Fernández-Castañé A.; Jaramillo A.; de Mas C.; Caminal G.; Ferrer P.

New Biotech, 33, 78-90, **2016**

Design and synthesis of sphingosine-1-phosphate lyase inhibitors and fluorogenic probes for the development of HTS assays

Pol Sanllehí Figuerola

Faculty of Pharmacy and Food Sciences, University of Barcelona

Supervisors: A. Delgado, J. Bujons

03/11/2016

Chemical modulation of the nociceptive receptor TRPV1: Synthetic, biological and computational studies.

Miquel Vidal Mosquera

Institut Químic de Sarrià, Universitat Ramon Llull

Supervisors: A. Messeguer, J. Bujons

09/02/2016

Removal of pharmaceuticals from WWTT streams by biological and physical processes.

Guillem Llorens Blanch

Escola d'Enginyeries. Universitat Autònoma de Barcelona

Supervisors: Gloria Caminal/ Montserrat Sarrà

3 November 2016

BOOK CHAPTERS

Recent Advances in Enzyme-Catalyzed Aldol Addition Reactions.

Clapés, P.

In *Green Biocatalysis*, (Patel, R. N., Ed.) John Wiley & Sons, Inc: Hoboken, New Jersey, **2016**; pp 267-306.

Enzymatic CC Bond Formation.

Clapés, P.

In *Organic Synthesis Using Biocatalysis*, (Goswami, A.; Stewart, J. D.), Eds. Academic Press: **2016**; pp 285-337.

RESEARCH PROJECTS

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

European Union Framewok Programme Horizon 2020: Carbazymes-635595

2015 – 2019

Desarrollo de biocatalizadores para la formación de enlaces carbono-carbono orientadas a transformaciones estratégicas de interés industrial (CARBOLINK).

National: CTQ2015-63563-R

2016 - 2018

Desarrollo de procesos de bioremediación para la eliminación de contaminantes de uso agrícola (plaguicidas) e industrial (disolventes halogenados) en aguas y suelo" (BECAS)

National: CTM 2016-75587-C2-1-R

2016-2018

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

Intensificación de procesos multienzimaticos.

National: CTQ2014-53114-R

2015-2017

Hongos, algas y bacterias en la degradación de fármacos. Depuración de efluentes de hospital por hongos

Nacional, CTM 2013-48545-C2-1-R

2014-2016.

RESEARCH HIGHLIGHTS

Minimalist Protein Engineering of an Aldolase Provokes Unprecedented Substrate Promiscuity. *ACS Catal.* **2016**, *6*, 1848-1852. Minimalist engineering can extensively broaden the substrate scope of native D-fructose-6-phosphate aldolase (FSA) from *Escherichia coli*, for which hydroxyacetone is the most proficient substrate, to accept an unprecedented wide variety of alternative nucleophiles (Figure 1).

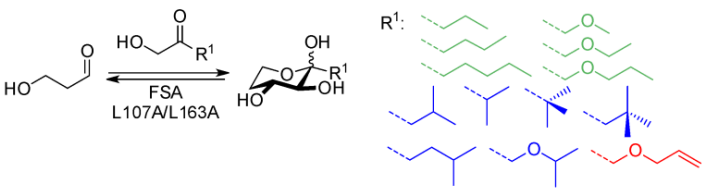

Figure 1

Combining Aldolases and Transaminases for the Synthesis of 2-Amino-4-hydroxybutanoic Acid (Homoserine). *ACS Catal.* **2017,** *7*, 1707-1711**.** In this work, the stereoselective synthesis of (*S*)- and (*R*)-2-amino-4-hydroxybutanoic acid was accomplished using a systems biocatalysis approach comprising a biocatalytic one-pot cyclic cascade by coupling of an aldol reaction with an ensuing stereoselective transamination (Figure 2).

Intramolecular Benzoin Reaction Catalyzed by Benzaldehyde Lyase from Pseudomonas Fluorescens Biovar I. *Angew. Chem. Int. Ed.* **2017**, *56*, 5304-530. Intramolecular benzoin reactions catalyzed by benzaldehyde lyase from Pseudomonas fluorescens biovar I (BAL) are reported (Figure 3).

2-Keto-3-Deoxy-l-Rhamnonate Aldolase (YfaU) as Catalyst in Aldol Additions of Pyruvate to Amino Aldehyde Derivatives. *Adv. Synth. Catal.* **2017**, *359*, 2090-2100. Pyruvate aldolases are privileged catalysts for a straightforward access to keto acid compounds. A Class II pyruvate aldolase from *E. coli* K-12, 2-keto-3-deoxy-L-rhamnonate aldolase (YfaU), was successfully applied to the synthesis of amino acid derivatives of proline, pipecolic acid, and pyrrolizidine-3-carboxylic acid (Figure 4).

Breaking the Dogma of Aldolase Specificity: Simple Aliphatic Ketones and Aldehydes are Nucleophiles for Fructose-6-phosphate Aldolase. *Chem. Eur. J.* **2017,** *23*, 5005-5009. An exceptional widening of the nucleophile substrate scope that offers a rapid entry, in good yields and high stereoselectivity, to less oxygenated alkyl ketones and aldehydes, which was hitherto impossible.

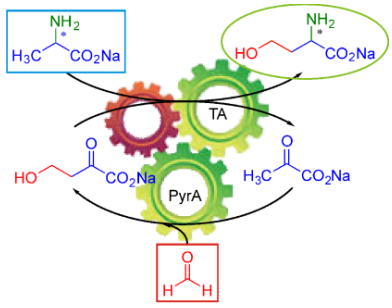

Figure 2

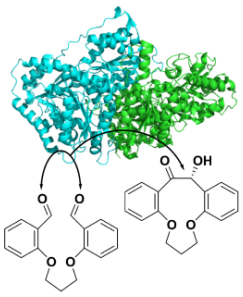

Figure 3

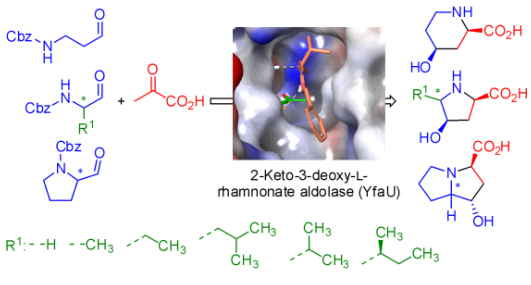

Figure 4

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, self-assembling processes and catalysis, 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, constitutional dynamic chemistry and rate acceleration by non-covalent interactions. Additionally, we collaborate with several groups (both at IQAC and outside) to study biomolecular and biomimetic systems from a supramolecular point of view.

STAFF

IGNACIO ALFONSO RODRÍGUEZ
CIRIL JIMENO MOLLET
JORDI SOLÀ I OLLER

Ph.D.

DANIEL CARBAJO LÓPEZ

Ph.D. STUDENT

MARÍA LAFUENTE FABRA
ANNA SERRA PONT
LUCÍA TAPIA PÉREZ

ARTICLES

From Simplicity to Complex Systems with Bioinspired Pseudopeptides

Alfonso, I.

Chem. Commun., 52, 239-250, **2016**

Cationic Peptides and Peptidomimetics Bind Glycosaminoglycans as Potential Sema3A Pathway Inhibitors

Corredor, M.; Bonet, R.; Moure, A.; Domingo, C.; Bujons, J.; Alfonso, I.; Pérez, Y.; Messeguer, A.

Biophys. Journal, 110, 1291-1303, **2016**

Anion Recognition and Induced Self-Assembly of an a,g-Cyclic Peptide To Form Spherical Clusters

Rodríguez-Vázquez, N.; Amorín, M.; Alfonso. I.; Granja, J. R.

Angew. Chem. Int. Ed, 55, 4504-4508, **2016**

Trichloromethanesulfonyl chloride: a convenient chlorinating reagent for aldehydes

C. Jimeno, L. Cao, P. Renaud.

J. Org. Chem., 81, 1251-1255, **2016**

Deciphering the Roles of Multiple Additives in Organocatalyzed Michael Additions

Günler, Z. I.; Companyó, X.; Alfonso, I.; Burés, J.; Jimeno, C.; Pericàs, M. A.

Chem. Commun., 52, 6821-6824, **2016**

Water in asymmetric organocatalytic systems: a global perspective

C. Jimeno

Org. Biomol. Chem., 14, 6147-6164, **2016**

Metal driven assembly of peptidic foldamers: formation of molecular tapes

Solà, J.; Bolte, M.; Alfonso, I.

CrystEngComm, 18, 3793- 3798, **2016**

Pseudopeptidic fluorescent on-off pH sensor based on pyrene excimer emission: Imaging of acidic cellular organelles

Faggi, E.; Serra-Vinardell, J.; Pandey, M.D.; Casas, J.; Fabriàs, G.; Luis, S. V.; Alfonso, I.

Sensor Actuat. B-Chem., 234, 633-640, **2016**

A regioselective synthesis of a new family of β-lactams bearing a triazole moiety as potential apoptosis inhibitors

Garrido, M.; Corredor, M.; Orzáez, M.; Alfonso, I.; Messeguer, A.

ChemistryOpen, 5, 485-494, **2016**

Synthesis and in vitro, ex-vivo and in vivo activity of hybrid compounds linking a potent ROS and RNS scavenger activity with diverse substrates addressed to pass across the blood-brain barrier

L. Vázquez-Jiménez, M. Garrido, M. Miceli, E. Prats, A. Ferrer-Montiel, M. Teixidó, C. Jimeno, A. Messeguer

Eur. J. Med. Chem., 123, 788-802, **2016**

1H NMR metabolomic study of auxotrophic starvation in yeast using Multivariate Curve Resolution-Alternating Least Squares for Pathway Analysis

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

Sci. Rep.-UK, 6, 30982, **2016**

Supramolecular Protection from the Enzymatic Tyrosine Phosphorylation in a Polypeptide

Faggi, E.; Pérez, Y.; Luis, S. V.; Alfonso, I.

Chem. Commun., 52, 8142-8145, **2016**

AuNP–Polymeric Ionic Liquid Composite Multicatalytic Nanoreactors for One-Pot Cascade Reactions

Montolio, S.; Vicent, C.; Aseyev, V.; Alfonso, I.; Burguete, M. I.; Tenhu, H.; García-Verdugo, E.; Luis, S. V.

ACS Catal., 6, 7230-7237, **2016**

Concentration Effect in the Asymmetric Michael Addition of Acetone to Nitrostyrenes Catalyzed by Primary Amine Thioureas

Günler, Z. I.; Alfonso, I.; Jimeno, C.; Pericàs, M. A.

Synthesis, 49, 319-325, **2017**

Pseudopeptidic Compounds for the Generation of Dynamic Combinatorial Libraries of Chemically Diverse Macrocycles in Aqueous Media

Atcher, J.; Solà, J.; Alfonso, I.

Org. Biomol. Chem., 15, 213-219, **2017**

Non-targeted Assignment and Automatic Integration of 1H NMR Metabolomic Dataset Using a Multivariate Curve Resolution Approach

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

Anal. Chim. Acta, 964, 55-66, **2017**

Entropy-driven homochiral self-sorting of a dynamic library

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

Chem. Commun., 53, 4274-4277, **2017**

A copper-templated, bifunctional organocatalyst: a strongly cooperative dynamic system for the aldol reaction

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

Org. Biomol. Chem., 15, 6584-6591, **2017**

Unraveling the multistimuli responses of a complex dynamic system of pseudopeptidic macrocycles

Valdivielso, A. M.; Puig-Castellví, F.; Atcher, J.; Solà, J.; Tauler, R.; Alfonso, I.

Chem. Eur. J., 23, 10789-10799, **2017**

BOOK CHAPTERS

Non-covalent interactions for the preparation of pseudopepidic synthetic compounds and materials

Solà, J., Alfonso, I.

Non-Covalent Interactions in the Synthesis and Design of New Compounds, (Eds: Maharramov, A. M.; Mahmudov, K. T.; Kopylovich, M. N.; Pombeiro, A. J. L.)

John Wiley & Sons, Inc., pp. 391-412, **2016**

PUBLICATIONS

Anion Recognition and Induced Self-Assembly of an a,g-Cyclic Peptide To Form Spherical Clusters

Rodríguez-Vázquez, N.; Amorín, M.; Alfonso. I.; Granja, J. R.

Angew. Chem. Int. Ed, 55, 4504-4508, **2016**

Was selected as **HOT PAPER**

Unraveling the multistimuli responses of a complex dynamic system of pseudopeptidic macrocycles

Valdivielso, A. M.; Puig-Castellví, F.; Atcher, J.; Solà, J.; Tauler, R.; Alfonso, I.

Chem. Eur. J., 23, 10789-10799, **2017**

Was selected as **HOT PAPER** and **FRONT COVER** of the Journal.

FRONT COVER: *Chem. Eur. J* **2017**, *23*, 10700; **Cover Profile**: *Chem. Eur. J* **2017**, *23*, 10702, **Highlighted in:** *Angew .Chem. Int. Ed.* **2017**, *56*,10634–10637.2013-2017

RESEARCH HIGHLIGHTS

The scientific activity of the Supramolecular Chemistry group is inspired by the structural and interactional complexity of living organisms. Trying to understand and apply both forms of complexity in chemical systems, our research encompasses the molecular recognition of biologically relevant molecules, the self-assembly of organic compounds, and the study of dynamic combinatorial chemistry. Our ultimate goals are: (1) Development of new tools in chemical biology for a better understanding of human health related issues. (2) Development of new asymmetric catalysts for an improved efficiency in the use of resources.

Therefore, we conduct research on the development of receptors for the recognition of small biological molecules (anions, amino acids…) and sequences or domains in macrobiomolecules (peptide or DNA sequences). Typically, we make use of pseudopeptides (*Chem. Commun.*, 52, 239-250, **2016**) for the building of molecular recognition systems (either isolated species or networks). We also make use of dynamic combinatorial chemistry for the development of such receptors (including more complex targets, i. e. peptide or DNA sequences) as well as for understanding the behavior of complex chemical systems. It must be highlighted that aqueous media are used throughout our research to ensure the compatibility of our systems with biological media.

Based on our understanding of molecular recognition events and self-assembly, we also develop highly efficient asymmetric organocatalysts for organic synthesis. We intend to make water compatible catalysts operational under sustainable conditions (*Org. Biomol. Chem.*, 14, 6147-6164, **2016**).

Some selected examples of the results published during 2016-2017 are depicted in Figure 1. For instance, we have used pseudopeptidic cages for the modulation of the tyrosine kinases activity, through the encapsulation of the substrate (Figure 1A, *Chem. Commun.*, 52, 8142-8145, **2016**). Thus, the synthetic macrobicycles designed in our lab are able to efficiently bind the EYE peptide sequence alone and within a polypeptide macromolecule, as shown by different techniques (fluorescence and NMR titrations). Moreover, the supramolecular interaction protects the tyrosine residues from the action of the kinases, as also demonstrated by in vitro kinase assays. This study represents a supramolecular approach to kinase modulation, with important biological implications. Also in the chemical biology field, we have designed, prepared and characterized a fluorescent molecule able to detect pH variations with biological relevance, in a sensitive and selective fashion (Figure 1B, *Sensor Actuat. B-Chem.*, 234, 633-640, **2016**). The developed fluorescent probe was used for the fluorescence imaging of acidic organelles in live cells. Regarding the catalysis field, during these years we have improved our metal-templated dynamic organocatalysts by a careful selection of the metal center (Cu) and reaction conditions (Figure 1C, *Org. Biomol. Chem.*, 15, 6584-6591, **2017**). Our results demonstrate the power of the dynamic combinatorial approach for the development of efficient catalysts. Moreover, we have also advanced in the understanding of the behavior of dynamic networks of pseudopeptidic disulfides in aqueous media (Figure 1D). Inspired by biology, we applied different stimuli over a complex dynamic library of macrocyclic pseudopeptides. The use of chemometric analysis has allowed bisecting the effect of different stimuli that were included simultaneously (i.e. pH and ionic strength) or even permitted unraveling stimuli that are experimentally impossible to separate (such as binding to a charge substrate and increase of the ionic strength). These results were selected as hot paper and front cover in a top-rated multidisciplinary chemistry journal (*Chem. Eur. J.*, 23, 10789-10799, **2017**).

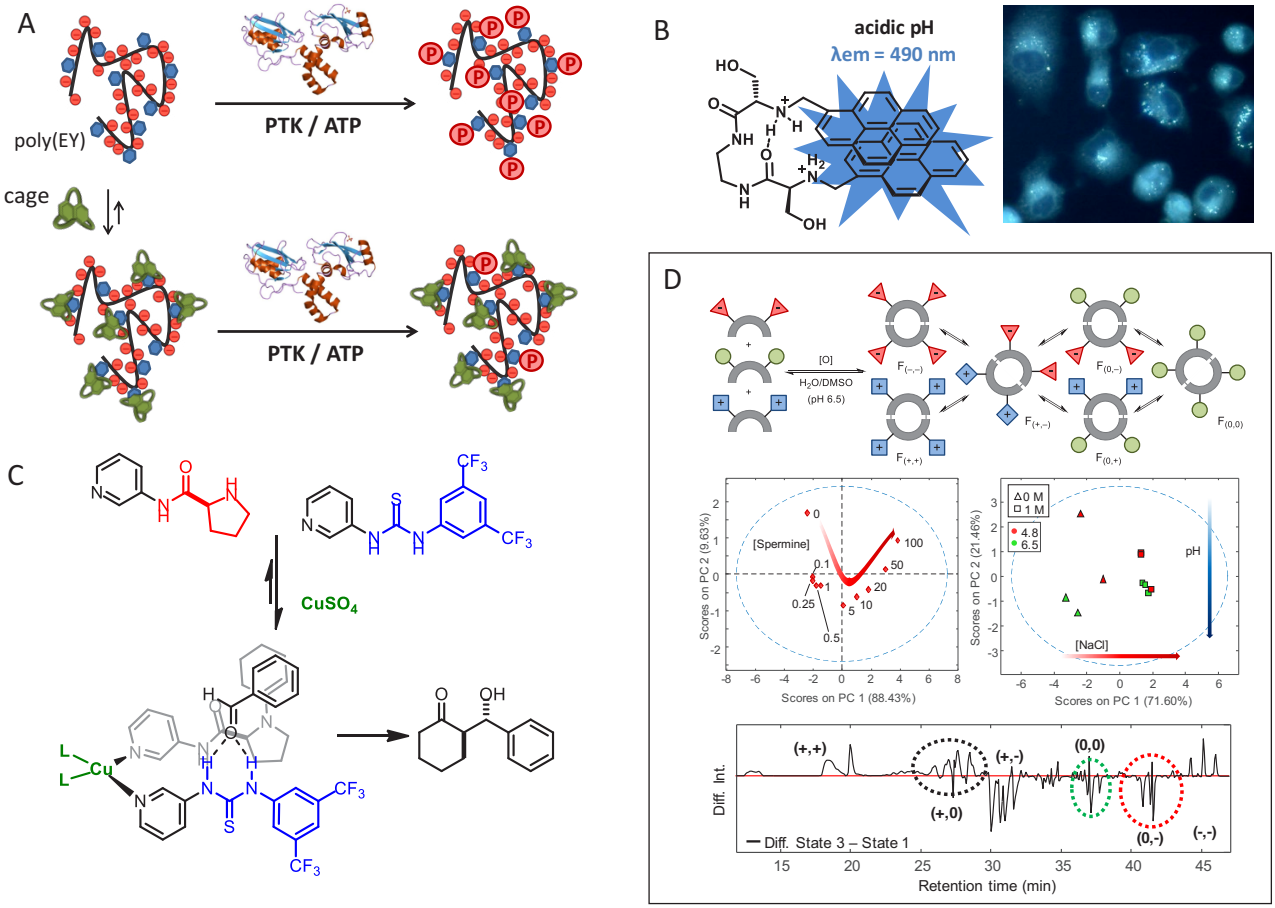

Figure 1. Selected examples for the research in the Supramolecular Chemistry group.

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.

STAFF

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Ph.D.

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MARC PUIGMARTÍ BORRELL
SERGIO LÓPEZ ROMERO

Ph.D. STUDENTS

AROA DOMÍNGUEZ CUADRADO

UNDERGRADUATE STUDENTS

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ANNA GÓMEZ BALLESTER

TECHNICIAN

JUANA MARÍA ROZALEN MECA

ARTICLES

Sexual communication in day-flying Lepidoptera with special reference to castniids or 'butter-fly-moths'

Sarto i Monteys, V.; Quero, C.; Santa-Cruz, M.C.; Rosell, G.; Guerrero, A.

Bull. Entomol. Res., 106 (4), 421-431, **2016.** DOI: 10.1017/S0007485316000158

Synthesis, functional assays, electrophysiological activity and field tests of pheromone antagonists of the tomato leafminer *Tuta absoluta*

Dominguez, A.; Puigmartí, M.; Bosch, M.P.; Rosell, G.; Crehuet, R.; Ortiz, A.; Quero, C.; Guerrero, A.

J. Agric. Food Chem., 64 (18), 3523-3532, **2016.** DOI: 10.1021/acs.jafc.6b00674

Plant volatiles challenge inhibition by structural analogues of the sex pheromone in *Lobesia botrana* (Lepidoptera: Tortricidae)

Sans, A.; Morán, M.; Riba, M.; Guerrero, A.; Roig, J.; Gemeno, C.

Eur. J. Entomol., 113, 579-586, **2016**. DOI: 10.14411/eje.2016.078

MALDI-TOF MS Imaging evidences spatial differences in the degradation of solid polycaprolactone diol in water under aerobic and denitrifying conditions

Rivas, D.; Ginebreda, A.; Pérez, S.; Quero, C.; Barceló, D.

Sci. Total Environ., 566-567, 27-33, **2016**. DOI:10.1016/j.scitotenv.2016.05.090

Using a polymer probe characterized by MALDI-TOF/MS to assess river ecosystem functioning: From polymer selection to field tests

Ginebreda, A.; Rivas, D.; Elosegi, A.; Pozo, J.; Pérez, S.; Quero, C.; Barceló, D.

Sci. Total Environ., 573, 532-540, **2016**. DOI: 10.1016/j.scitotenv.2016.08.135

New and convenient chemoenzymatic syntheses of (*S*)-2-hydroxy-3-octanone, major pheromone component of *Xylotrechus* spp., and its *R* enantiomer

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

Synthesis, 49 (7), 1561-1568, **2017**. DOI: 10.1055/s-0036-1588666

Factors influencing aversive learning in the Oriental fruit fly, *Bactrocera dorsalis*

Liu, J.L.; Chen, H.L.; Chen, X.Y.; Cui, R.K.; Guerrero, A.; Zeng, X.N.

J. Comp. Physiol. A, 203, 57-65, **2017**. DOI 10.1007/s00359-016-1135-7

Sexual communication in castniid moths: Males mark their territories and appear to bear all chemical burden

Quero, C.; Sarto i Monteys, V.; Rosell, G.; Puigmartí, M.; Guerrero, A.

PLoS ONE, 12(2): e0171166, **2017.** DOI 10.1371/journal.pone.0171166

Short-term peripheral sensitization by brief exposure to pheromone components in *Spodoptera littoralis*

López, S.; Guerrero, A.; Bleda, M.J.; Quero, C.

J. Comp. Physiol. A, 203, 973-982, **2017.** DOI:10.1007/s00359-017-1205-5

A temporal comparison of sex-aggregation pheromone gland content and dynamics of release in three members of the *Lutzomyia longipalpis* (Diptera: Psychodidae) species complex

González, M.A.; Bandi, K.K.; Bell, M.J.; Brazil, R.P.; Dilger, E.; Guerrero, A.; Orin, C.; Hamilton, J.G.C.

PLoS Negl. Trop. Dis., 11 (12), e0006071, **2017**. https://doi.org/10.1371/journal.pntd.0006071

BOOK CHAPTERS

The Moroccan Locust *Dociostaurus maroccanus* (Thunberg). Biology, Economic Impact and Control

Guerrero, A.; Coca-Abia, M.M.; Quero, C.

Advances in Animal Sciences and Zoology, O.P. Jenkins ed., vol. 10, 13-57, **2017**, Nova Sci. Pub. Inc. Hauppauge, N.Y. ISBN: 978-1-53612-024-0

RESEARCH PROJECTS

Ayudas para apoyar las actividades dels Grups de Recerca.

Grup de Recerca Consolidat: Unitat d'Ecologia Quimica (UCE)

Generalitat de Catalunya, 2014 SGR 707

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.

2013-2018

Trabajo técnico para la detección de extractos feromonales de *Coroebus undatus*

Departament d'Agricultura, Ramaderia, Pesca i Alimentació (Generalitat de Catalunya) (Exped. AG-2016-183).

2016

Estudios dirigidos al conocimiento de la comunicación química en acrídidos-plaga de la Península Ibérica. Posible incidencia en sistemas de control integrado

MINECO (AGL2015-66469-R)

2016-2018

Treball tècnic per a la caracterització d'extractes feromonals de *Coroebus undatus*, per a la síntesi de feromones de *Matsucoccus feytaudi*, per a l'assessorament sobre control integrat d'altres plagues forestals i per a la divulgació del resultat del treballs realitzats

Generalitat de Catalunya (Exped. AG-2017-222)
2017-2018

RESEARCH HIGHLIGHTS

Development of new pheromone antagonists of the tomato leafminer *Tuta absoluta*

The tomato leafminer, *Tuta absoluta* (Meyrick) (Lepidoptera: Gelechiidae), is a very harmful pest of tomato and other Solanaceae (potato, eggplant, sweet pepper and tobacco), and has been recently considered the major serious threat to tomato plants in Europe (http://www.tutaabsoluta.com/tuta-absoluta). In a previous paper (Puigmartí et al., Synthesis 47, 961, 2015) we developed an improved new synthesis of the two components of the sex pheromone **1** and **2** of the insect in high overall yields (Figure 1). In the search for new strategies to control this pest, we have designed, prepared and tested new chemicals as possible antagonists of the sex pheromone of the leafminer.

The chemicals are the trifluoromethyl ketones **3,5** and the methyl ketones **4,6** structurally analogues to the triene **1** and diene **2**. Most of the chemicals intrinsically exerted some electrophysiological activity on the insect antennae, and inhibited the electroantennographic response to the pheromone when vapors of the antagonist were passed over the antennae. In addition, trifluoromethyl ketone **3** elicited a moderate antiesterase activity on the pheromone degrading enzymes of the antennae, and in the field all chemicals, particularly methyl ketone **5**, notably decreased the number of catches when mixed with the pheromone in 1:1 and 10:1 ratio, regardless the infestation level of the plot (as an example, see Figure 2). Our results suggest that methyl ketone **5** is a good behavioral antagonist of the pheromone to be considered as putative agent to control the pest in new future integrated pest management strategies.

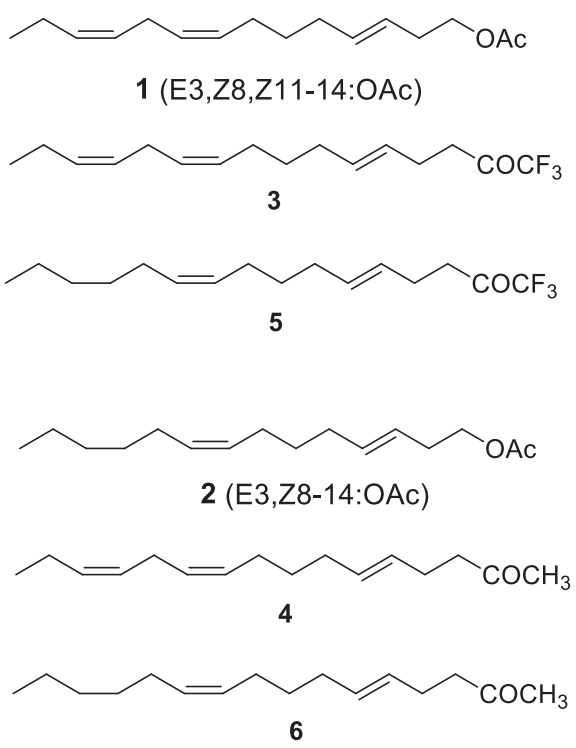
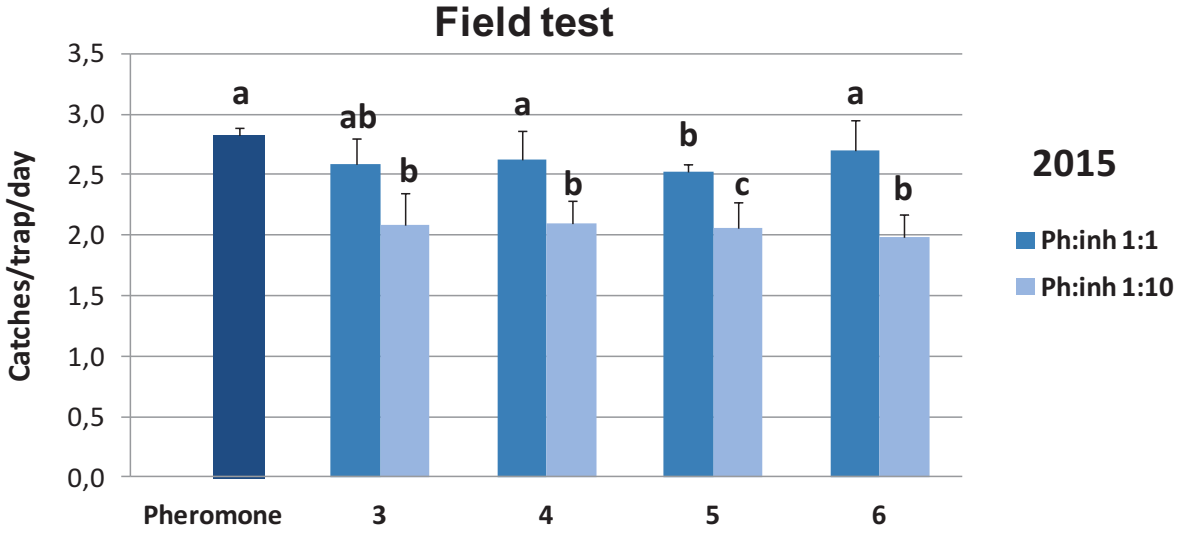


Figure 1

Figure 2. Number of catches (±SD) of *T. absoluta* males by pheromone and mixtures of pheromone and compounds **3, 4, 5, 6** in 1:1 and 1:10 ratios in 2015. For each compound bars with different letters are significantly different from catches with the pheromone (Kruskal-Wallis non-parametric test followed by Wilcoxon rank-sum test, P≤0.05).



Advances in the sexual communication of castniid moths

In the course of our project directed to the study of the chemical communication of the palm borer *Paysandisia archon* (Lepidoptera: Castniidae), we have suggested that castniid moths display a butterfly-like reproductive behavior, i.e., they use visual stimuli for mate location and females have apparently lost their pheromone glands in an evolutionary context, an unparalleled attribute in the world of moths. To support this assumption, we have reviewed the sexual communication strategy of day-flying Lepidoptera, either butterflies or moths with diurnal habits, paying particular attention to castniids and to their suggested butterfly-like partner-finding strategy (Sarto i Monteys et al., Bull. Ent. Res. 106, 421, 2016). We have now identified for the first time three new compounds, namely *n*-octadecyl acetate, (Z)-9-octadecenyl acetate and (E,Z)-2,13-octadecadienyl acetate, in males of *P. archon*, which could be involved in their short-range courtship behavior. These compounds are produced in a ring-shaped gland of the male terminalia and have occasionally been detected in very minor amounts (ng) in ovipositor extracts of females, but only *while mating or just after mating* suggesting that they are absorbed by female terminal scales while in copula (Figure 3). Males also produce (E,Z)-2,13-octadecadienol in large amounts in their midleg basitarsi to mark their territory by rubbing their midlegs against the upper side of nearby leaves, especially palm leaves. In addition, we have confirmed the presence of Z,E and E,E-farnesal in male hindwings extracts (Sarto et al., PLoS ONE 7, e29282, 2012) although the biological significance of farnesals in this species is still unknown. Our results point out that the chemical communication of *P. archon* relies mostly on males, which appear to bear all chemical burden in this respect.

Sensitization induced by exposure to pheromone components in *Spodoptera littoralis*

The ability of males to find females is mediated by pheromone blends emitted by conspecific females, which activate pheromone-sensitive male olfactory sensory neurons with a high degree of sensitivity. In this process, a series of behavioral responses are induced in both sexes to facilitate a successful mating. These responses can be affected by pre-exposure to female-produced sex pheromone or synthetic attractants. Pre-exposure of males to the sex pheromone may produce a reduction in the behavioral response (habituation) or a gradual increase in the response without any learned association (sensitization). We have investigated the sensitization effect induced in *Spodoptera littoralis* by pre-exposure of males to the major sex pheromone component (*Z*,*E*)-9,11-tetradecadienyl acetate and to the minor components (*Z*,*E*)-9,12-tetradecadienyl acetate and (*Z*)-9-tetradecenyl acetate. The electroantennographic responses of male antennae to the conjugated diene acetate at 1 and 10 µg and to the unconjugated acetate at 10 µg at three different times

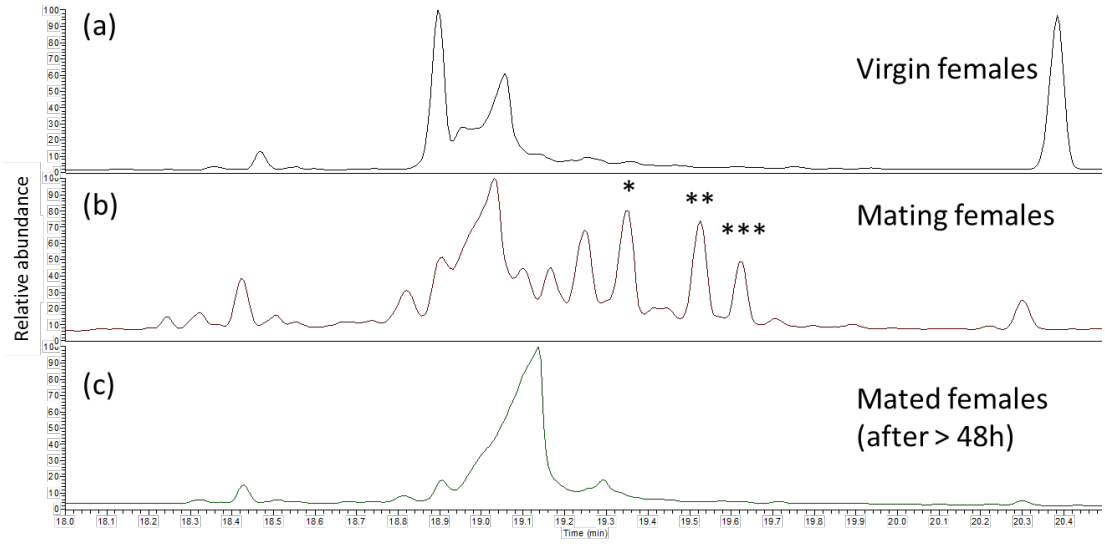


Figure 3. Chromatograms of GC-MS analysis of extracts of the ovipositor of *P. archon* virgin females (a), during mating (b), and after mating (c). (*) = Z9-18:Ac, (**) = E2,Z13-18:Ac, (***) = 18:Ac. The other compounds shown in the figure are fatty acids (stearic, oleic and linoleic acids), long chain hydrocarbons and column phase artifacts.

(11, 22 and 33 min) after pre-exposure (T=0 min) were significantly higher than those at T=0 (Figure 4). No increase of sensitivity to the pheromone was elicited by the minor monoene acetate. In addition, pre-exposed antennae to sub-threshold amounts (0.1, 1 and 10 ng) of the major pheromone component also induced an increased response to the chemical at different times (5 and 15 min) after exposure.

Our results reveal that pre-exposed isolated antennae display a short-term higher sensitivity at the peripheral level when compared to naive antennae. In addition, we provide evidence of a peripheral sensitization mediated not only by the major pheromone component, but also by the minor unconjugated diene acetate, and the induction of this sensitivity appears to be dependent on the pre-exposure dose and the time span between pre-exposure and subsequent recordings. The sensitization effect displayed by sex pheromone components may represent an additional tool that males rely on for a more effective discrimination of the olfactory bouquets present in the environment, particularly of those pertaining to closely related species, with the aim of finding conspecific mates more efficiently.

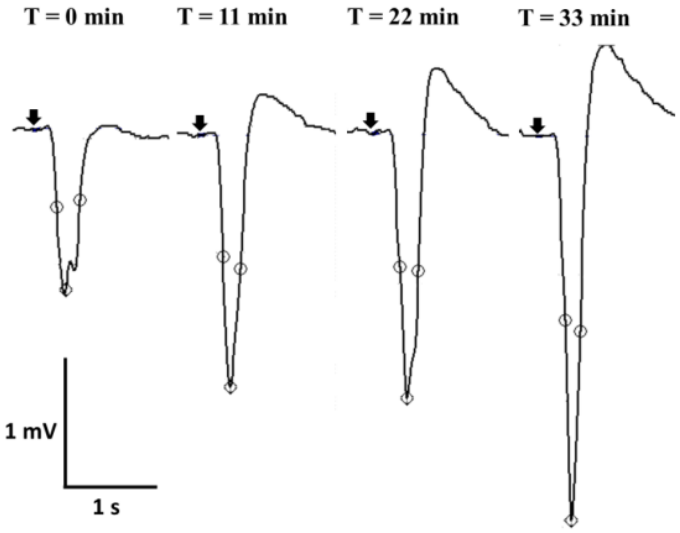


Figure 4. Illustrative electroantennographic responses of an excised antenna to 10 µg of *Z*9,*E*12-14:OAc at T = 0 min (pre-exposure) and three different times (11, 22 and 33 min) after pre-exposure. Black arrows denote when puffing was done.

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 Intrinsically Disordered Proteins and enzyme catalysis.

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ARTICLES

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. Struct. Chem. ***2016,*** *27*, 231-242

DOI: 10.1007/s11224-015-0717-2

Impact of the water dimer on the atmospheric reactivity of carbonyl oxides.

J. M. Anglada, and A.Solé.

PhysChemChemPhys. ***2016,*** *18*, 17698-17712

DOI: 10.1039/c6cp02531e

Spectroscopic characterization of the ethyl radical-water complex.

Chen Lin, Brian A. Finney, Allan H. Laufer, Josep M. Anglada, and Joseph S. Francisco.

J. Chem. Phys. ***2016,*** *145*, 144301

DOI: 10.1063/1.4963869

Synthesis, Functional Assays, Electrophysiological Activity, and Field Tests of Pheromone Antagonists of the Tomato Leafminer, Tuta absoluta.

Aroa Dominguez, Marc Puigmartí, M. Pilar Bosch, Gloria Rossell, Ramon Crehuet, Antonio Ortiz, Carmen Quero, Angel Guerrero.

J. Agric. Food Chem., ***2016***, 64, 3523–3532
DOI: 10.1021/acs.jafc.6b00674

The stability of a- Hydroperoxyalkyl Radicals.

Josep M. Anglada, Ramon Crehuet, and Joseph S. Francisco.

Chemistry a European Journal. ***2016,*** *22, 18092-18100*

DOI: 10.1002/chem.201604499

Role of Proton Tunneling and Metal Free Organocatalysis in Decomposition of Methanediol: A Theoretical Study.

Manoj Kumar, Josep M. Anglada, and Joseph S. Francisco.

J. Phys. Chem. A, ***2017***, *121* , 4318–4325.

DOI: 10.1021/acs.jpca.7b01864

Computational insights into the CH3Cl + OH chemical reaction dynamics at the air-water interface.

Marilia Martins-Costa, Josep M. Anglada, and Manuel Ruiz-López.

ChemPhysChem., ***2017***, *18*, 1-10

DOI: 10.1002/cphc.201700437

Twisted intramolecular charge transfer in a carbazole-based chromophore: the stable [(4-N-carbazolyl)-2,3,5,6-tetrachlorophenyl]bis(2,3,5,6-tetrachlorophenyl)methyl radical.

Alejandra Gilabert, Lluios Fajarí, Ignasi Sirés, Marta Reig, Enric Brillas, Dolores Velasco, Josep M. Anglada, Lluis Juliá.

New Journal of Chemistry, 2017, ***41***, 8422-8430

DOI: 10.1039/c7nj00733g

Design of Hückel–Möbius Topological Switches with High Nonlinear Optical Properties.

M Torrent-Sucarrat, S Navarro, E Marcos, JM Anglada, JM Luis.

J. Phys. Chem. C., ***2017***,*121*,18348-19357

DOI: 10.1021/acs.jpcc.7b05900

Relevance of the DFT method to study expanded porphyrins with different topologies.

M. Torrent-Sucarrat, S. Navarro, F.P. Cossio, J. M. Anglada, J. M. Luis. J. Comput. Chem., ***2017***, *38*, 2819-2828

DOI: 10.1002/jcc.25074.

Impact of cloud water droplets on OH production rate from peroxide photolysis.

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

Phys Chem. Chem. Phys. ***2017***, *19*, 31621-31627

DOI: 10.1039/C7CP06813A

The Atmospheric Oxidation of HONO by OH, Cl, and ClO Radicals.

Josep M. Anglada and Albert Solé.

J. Phys. Chem. A, ***2017***, 121, 9698-9707.

DOI: 10.1021/acs.jpca.7b10715

Structural basis of human PCNA sliding on DNA

Matteo De March, Nekane Merino, Susana Barrera-Vilarmau, Ramon Crehuet, Silvia Onesti, Francisco J Blanco, Alfredo De Biasio.

Nature Comm., ***2017***, 8, 13935, **DOI**:10.1038/ncomms13935

Dsentangling polydispersity ini the PCNA– p15PAF complex, a disordered, transient and multivalent macromolecular assembly

Tiago N Cordeiro, Po-chia Chen, Alfredo De Biasio, Nathalie Sibille, Francisco J Blanco, Jochen S Hub, Ramon Crehuet, Pau Bernadó.

Nucleic Acids Res., ***2017***, 5, pp.1501-1515.
DOI: 10.1093/nar/gkw1183

RESEARCH PROJECTS

Especies Reactivas de Oxígeno: De la fase gas a la interfase aire-agua y la disolución acuosa. Secretaria de Estado de Universidades e Investigación. CTQ2014-59768-P desde:01/01/2015 hasta: 31/12/2017

Cloud droplets as atmospheric catalysts: insights from computer simulations. Proyecto internacional de Cooperación científica CNRS – CSIC (Proyecto PIC2015FR1). desde:01/01/2016 hasta: 31/12/2018

Proteinas intrinsecamente desordenadas: cerrando la brecha entre simulaciones y experimentos (CTQ2016-78636-P) Ministerio de Economía y Competitividad. Desde 30/12/2016 hasta 29/12/2020

RESEARCH HIGHLIGHTS

Impact of water dimer on the atmospheric reactivity of carbonyl oxides. (Phys. Chem. Chem. Phys., 2016, 18, 17698-17712**)**

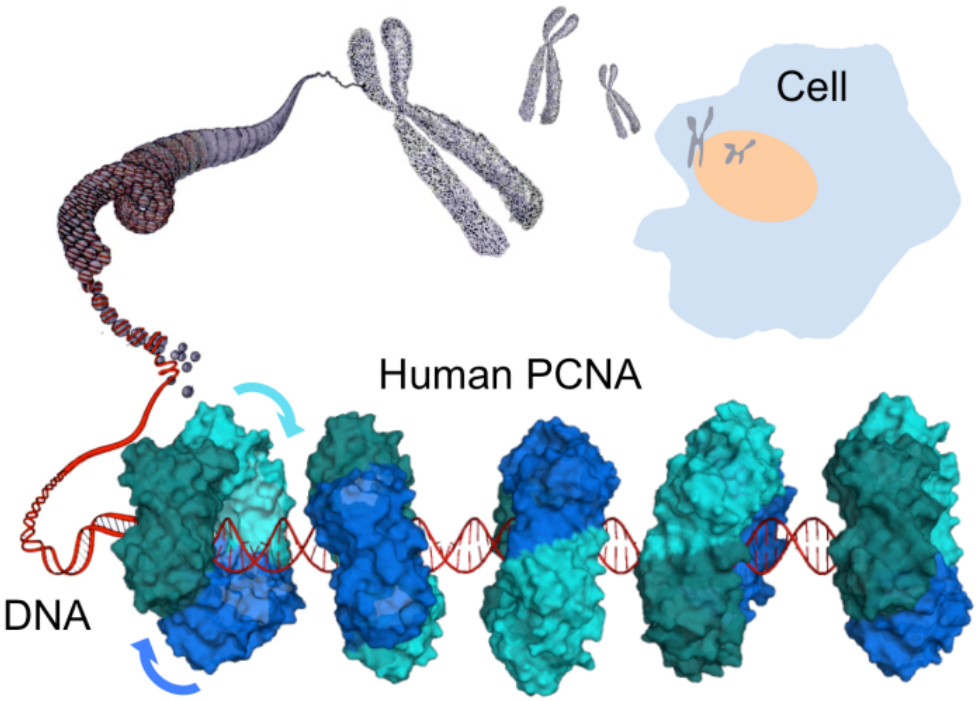
Carbonyl oxides are intermediates in the atmospheric ozonolysis of alkenes and have been identified as important oxidants in the troposphere and as precursors of secondary organic aerosols. Moreover, water vapor is one of the most abundant trace gases in the troposphere and water dimer trigger the atmospheric decomposition of Carbonyl oxides. In this work we have investigated the reactivity of all Carbonyl oxides formed in the ozonolysis of isoprene with water and water dimer. Our calculations show that the nature and position of the substituents in carbonyl oxides play a very important role in the reactivity of these species with both water monomer and water dimer. This fact results in differences on rate constants of up to six orders of magnitude depending on the carbonyl oxide. We have defined an effective rate constant (keff) for the atmospheric reaction of carbonyl oxides with water vapor, which depends on the temperature and on the relative humidity as well. With this keff we show that water dimer, despite its low tropospheric concentration, enhances the atmospheric reactivity of Criegee intermediates, but its effect changes with the nature of carbonyl oxide, ranging between 59 and 295 times in the most favorable case (*syn*-methyl carbonyl oxide), and between 1.4 and 3 times only in the most unfavorable case.

How does the protein PCNA slide along the DNA? (Nucleic Acids Res., ***2017***, 5, pp.1501-1515, Nature Comm., ***2017***, 8, 13935)

DNA replication is a fundamental cellular process that requires a complex machinery. This machinery is composed of several proteins that assemble forming huge complexes. A key player in the initial steps of this complex formation is the PCNA protein. A ring protein that encircles DNA and can move along its strands. But How do they slide on DNA? Is their motion controlled by chemical interactions with DNA? Or do they rather "levitate" on DNA? Our work allows for the first time to visualize, at an atomic level, the interactions between the human sliding clamp PCNA and DNA, and to follow how they evolve in time. This provides the molecular basis for explaining how PCNA slides on DNA – a helical motion based on short-lived polar interactions – and sheds new light onto previous biological observations on PCNA function in DNA replication.

In this work, done in collaboration with F. Blanco's group in BioGune and A. de Biasio in Sincrotrone Trieste, we used X-ray crystallography, Molecular Dynamics and NMR to propose a new cog-wheel-like sliding mechanism. This "cogwheel" mechanism would allow DNA backbone tracking in both directions while retaining DNA-protein contacts that keep the clamp in a defined orientation relative to DNA.

Atmospheric fate of Methyl hydroperoxide. (Phys. Chem. Chem. Phys., 2017, 19, 12331-12342**;** Phys.



Human PCNA slides along the DNA. It helps the formation of the replication complex and, with the help of other proteins, it seems to be able to detect DNA lesions

Chem. Chem. Phys., 2017, 19, 31521-31627; Chemistry A European Journal, 2016, 22, 18092-18100**)**

Methyl hydroperoxide (MHP, CH_3OOH) is among the most important trace gases in the Earth's atmosphere. MHP is mainly formed by reaction between HO_2 and CH_3O_2, the latter being produced in the oxidation of methane, in the ozonolysis of alkenes and from biomass burning. The total emission of MHP to the troposphere is estimated to be 21.7 $Tg \cdot yr^{-1}$, and its atmospheric lifetime of MHP is estimated to be 1-4 days, so that it can be transported through the troposphere constituting a reservoir of peroxy radicals, being an effective way of transferring HO_x radicals through the troposphere and contributing to the atmospheric oxidizing capacity.

The main sinks of MHP are deposition, photolysis (reaction 1), and oxidation by hydroxyl radical (reactions 2-3).

$CH_3OOH + hu \rightarrow CH_3O + OH$ (1)

$CH_3OOH + OH \rightarrow CH_3O_2 + H_2O$ (2a)

$CH_3OOH + OH \rightarrow CH_2OOH + H_2O$ (2b)

$CH_2OOH \rightarrow H_2CO + OH$ (3)

We have investigated these processes, namely the photochemistry in gas phase and in the air-water (air-clouds) interfase (Figure 1) and the atmospheric oxidation by hydroxyl radical at different conditions the relative humidity and temperature (Figure 2). Regarding the photochemistry, we have combined the calculated quantum yields with the measured actinic flux and we estimate that the process occurring at the air-water (air-clouds) intrerfsace accelerate the formation of hydroxyl radical up to 3-4 orders of magnitude. With respect to the oxidation by hydroxyl radical, we have found that water vapor enhances the rate constant of reaction 2a between 2 and 19%, depending on the temperature and relative humidity, whereas reaction 2b is enhanced between 0.3 – 5% under the same conditions.

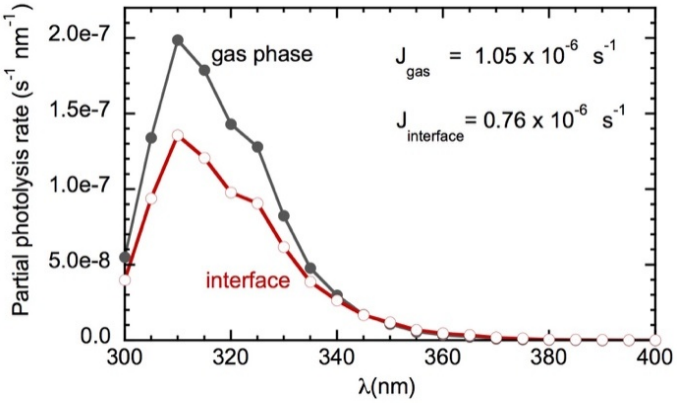


Figure 1. Calculatred photolysis rate of <MHP at gas phase and at the air-water interface.

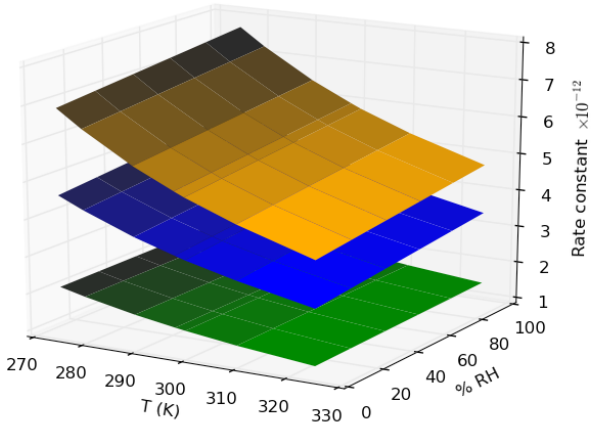


Figure 2. Calculated rate constsants for reaction 2a (blue), reactions 2b (green) and the overall reaction (orange) of MHP by OH as function of themerature and relative hymidity.

CHEMICAL BIOLOGY

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ARTICLES

Squaramides with cytotoxic activity against human gastric carcinoma cells HGC-27: synthesis and mechanism of action

Quintana, M.; Alegre-Requena, J. V.; Marques-Lopez, E.; Herrera, R. P.; Triola, G.

MedChemComm **2016,** *7* (3), 550-61.

High Affinity Immobilization of Proteins Using the CrAsH/TC Tag.

Schulte-Zweckel J; Rosi F; Sreenu D; Schröder H; Niemeyer CM; Triola G.

Molecules **2016,** *21* (6).

BOOK CHAPTERS

Triola, G. (2017), **Protein Lipidation, Elucidation by Chemical Proteomics, and Its Functional Roles.** In: Geiger O. (eds) Biogenesis of Fatty Acids, Lipids and Membranes. Handbook of Hydrocarbon and Lipid Microbiology. Springer, Cham https://doi.org/10.1007/978-3-319-43676-0_50-1

RESEARCH PROJECTS

Max-Planck Partner Group
International
2014—2019

Desarrollo de Inhibidores de Atg4B como inhibidores selectivos de Autofagia (CTQ2013-44334-P)
Ministerio de Economía y Competitividad
2014-2017

Transautophagy
Unión Europea, Cost Action CA15138
2016-2019

RESEARCH HIGHLIGHTS

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 proteins and lipidated proteins. A proteomic approach has been employed to identify novel ceramide-binding proteins, a sphingolipid with a crucial role in controlling essential cellular processes such as apoptosis. Moreover, a lipidomics strategy has been developed with the aim of characterizing the lipid diversity present in lipid-modified proteins.

Chemical tools for autophagy

We have worked towards 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 collaboration projects with the group of Dr. R.P. Herrera and the group of Dr. P. Sanz, both from the ISQCH (CSIC-University of Zaragoza) directed to investigate the biological activity of squaramides and N-heterocyclic carbenes (NHC) Gold and Silver complexes.

BIOMEDICINAL CHEMISTRY

BIOMEDICINAL CHEMISTRY

Head: Amadeu Llebaria Soldevila

The Department of Biomedicinal Chemistry is focused in multidisciplinar 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
- 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.

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MIREIA CASASAMPERE FERRER (finished March 2017)
ANA POU CABELLO (finished June 2017)
RAQUEL CALDERÓN ALMENDRO (finished March 2017)

ARTICLES

Studies on the inhibition of sphingosine-1-phosphate lyase by stabilized reaction intermediates and stereodefined azido phosphates

Sanllehí, P.; Abad, J.-L.; Bujons, J.; Casas, J.; Delgado, A.

Eur. J. Med. Chem., *123*, 905–915, **2016.**

Investigation of original multivalent iminosugars as pharmacological chaperones for the treatment of Gaucher disease

Laigre, E.; Hazelard, D.; Casas, J.; Serra-Vinardell, J.; Michelakakis, H.; Mavridou, I.; Aerts, J. M. F. G.; Delgado, A.; Compain, P.

Carbohydr. Res., *429*, 98–104, **2016.**

3-Ketosphinganine provokes the accumulation of dihydroshingolipids and induces autophagy in cancer cells

Ordóñez, Y. F.; González, J.; Bedia, C.; Casas, J.; Abad, J. L.; Delgado, A.; Fabrias, G.

Mol. Biosyst., *12*, 1166–1173, **2016.**

Dihydroceramide accumulation mediates cytotoxic autophagy of cancer cells via autolysosome destabilization.

Hernández-Tiedra, S.; Fabriàs, G.; Dávila, D.; Salanueva, Í. J.; Casas, J.; Montes, L. R.; Antón, Z.; García-Taboada, E.; Salazar-Roa, M.; Lorente, M.; Nylandsted, J.; Armstrong, J.; López-Valero, I.; McKee, C. S.; Serrano-Puebla, A.; García-López, R.; González-Martínez, J.; Abad, J. L.; Hanada, K.; Boya, P.; Goñi, F.; Guzmán, M.; Lovat, P.; Jäättelä, M.; Alonso, A.; Velasco, G.

Autophagy, *12*, 2213–2229, **2016.**

Inhibition of ceramide de novo synthesis as a postischemic strategy to reduce myocardial reperfusion injury.

Reforgiato, M. R.; Milano, G.; Fabriàs, G.; Casas, J.; Gasco, P.; Paroni, R.; Samaja, M.; Ghidoni, R.; Caretti, A.; Signorelli, P.

Basic Res. Cardiol., *111*, 12, **2016.**

Effect of prenatal steroidal inhibition of sPLA2 in a rat model of preterm lung.

Remesal, A.; De Luca, D.; San Feliciano, L.; Isidoro-Garcia, M.; Minucci, A.; Pocino, K.; Casas, J.; Fabrias, G.; Capoluongo, E. D.; de la Cruz, D. L.

Pulm. Pharmacol. Ther., *36*, 31–36, **2016.**

Inhibitors of sphingosine-1-phosphate metabolism (sphingosine kinases and sphingosine-1-phosphate lyase).

Sanllehí, P.; Abad, J.-L.; Casas, J.; Delgado, A.

Chem. Phys. Lipids, *197*, 69–81, **2016.**

Inhibitors of dihydroceramide desaturase 1: Therapeutic agents and pharmacological tools to decipher the role of dihydroceramides in cell biology.

Casasampere, M.; Ordoñez, Y. F.; Pou, A.; Casas, J.

Chem. Phys. Lipids, *197*, 33–44, **2016.**

Bacterial versus human sphingosine-1-phosphate lyase (S1PL) in the design of potential S1PL inhibitors.

Sanllehí, P.; Abad, J.-L.; Casas, J.; Bujons, J.; Delgado, A.

Bioorg. Med. Chem., *24*, 4381–4389, **2016.**

Ceramide synthases in biomedical research.

Cingolani, F.; Futerman, A. H.; Casas, J.

Chem. Phys. Lipids, *197*, 25–32, **2016.**

De novo ceramide synthesis is involved in acute inflammation during labor

Signorelli, P.; Avagliano, L.; Reforgiato, M. R.; Toppi, N.; Casas, J.; Fabriàs, G.; Marconi, A. M.; Ghidoni, R.; Caretti, A.

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Plasmalogen enrichment in exosomes secreted by a nematode parasite versus those derived from its mouse host: implications for exosome stability and biology

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Myriocin treatment of CF lung infection and inflammation: complex analyses for enigmatic lipids.

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Stereodivergent synthesis of right- and left-handed iminoxylitol heterodimers and monomers. Study of their impact on β-glucocerebrosidase activity

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From the configurational preference of dihydroceramide desaturase-1 towards Δ6-unsaturated substrates to the discovery of a new inhibitor.

Pou, A.; Abad, J.-L.; Ordóñez, Y. F.; Garrido, M.; Casas, J.; Fabriàs, G.; Delgado, A.

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Dihydroceramide desaturase inhibitors induce autophagy via dihydroceramide-dependent and independent mechanisms

Casasampere, M.; Ordóñez, Y. F.; Casas, J.; Fabrias, G.

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The first fluorogenic sensor for sphingosine-1-phosphate lyase activity in intact cells

Sanllehí, P.; Casasampere, M.; Abad, J.-L.; Fabriàs, G.; López, O.; Bujons, J.; Casas, J.; Delgado, A.

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Stereoselective preparation of quaternary 2-vinyl sphingosines and ceramides and their effect on basal sphingolipid metabolism

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New murine Niemann-Pick type C models bearing a pseudoexon-generating mutation recapitulate the main neurobehavioural and molecular features of the disease.

Gómez-Grau, M.; Albaigès, J.; Casas, J.; Auladell, C.; Dierssen, M.; Vilageliu, L.; Grinberg, D.

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The first fluorogenic sensor for sphingosine-1-phosphate lyase activity in intact cells.

Sanllehí, P.; Casasampere, M.; Abad, J.-L.; Fabriàs, G.; López, O.; Bujons, J.; Casas, J.; Delgado, A.

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2-Acetyl-5-tetrahydroxybutyl imidazole (THI) protects 661W cells against oxidative stress.

Fabiani, C.; Zulueta, A.; Bonezzi, F.; Casas, J.; Ghidoni, R.; Signorelli, P.; Caretti, A.

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Jaspine B induces nonapoptotic cell death in gastric cancer cells independently of its inhibition of ceramide synthase

Cingolani, F.; Simbari, F.; Abad, J. L.; Casasampere, M.; Fabrias, G.; Futerman, A. H.; Casas, J.

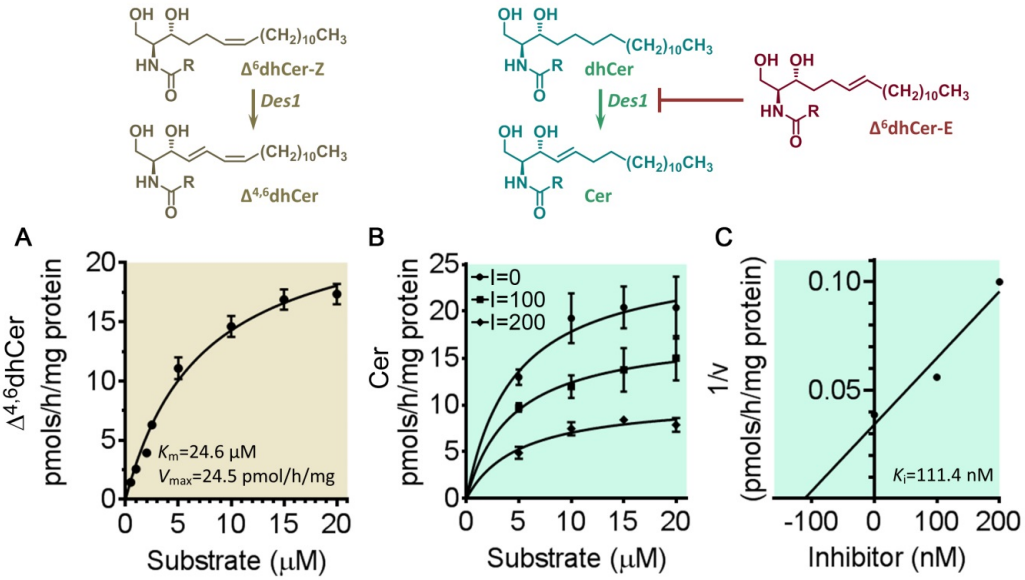
J. Lipid Res., *58*, 1500–1513, **2017.**

RESEARCH HIGHLIGHTS

1. Changing the double bond geometry converts a dihydroceramide desaturase substrate into an inhibitor

Dihydroceramide desaturase 1 (Des1) catalyses the last step of de novo ceramide synthesis, thus regulating the balance between dihydrosphingolipids and sphingolipids. This regulation is of great physiological importance, since ceramides and dihydroceramides exhibit different biological functions. Several reports suggest that the inhibition of Des1 may arise as a therapeutic strategy against different diseases. Hitherto, inhibitors of Des1 directed to the active site include the compounds GT11 and XM462. In addition, some natural products and drugs have also been shown to inhibit Des1. The identification of more potent Des1 inhibitors would greatly benefit from the availability of a high

throughput screening assay (HTS), not yet available, to measure this enzymatic activity. Examples showing that monounsaturated fatty acids are accepted by acyl-CoA desaturases to produce conjugated dienes have been reported. Therefore, an assay for Des1 was designed based on the use as a substrate of a dihydroceramide unsaturated at C6 (Δ6dhCer), whose enzymatic reaction product, the dienic derivative Δ4,6, would be susceptible to undergo a Diels-Alder reaction with a fluorescent dienophile. To evaluate the ability of Des1 to desaturate Δ6dhCer, the two isomers *Z* and *E* were synthesized and tested, showing that compound *Z*, but not *E*, provided the diene product with values of K_m (app) and V_{max} (app) of 7.2 μM and 24.6 pmol/h/mg, respectively. In contrast, the *E*, but not the *Z*, isomer of Δ6dhCer, behaved as a reversible non-competitively Des1 inhibitor, with a K_i value of 111.4 nM. In conclusion, the introduction of a double bond at C6 of dihydroceramides has a different outcome on Des1 activity depending on the double bond geometry. Thus, while the Z isomer is desaturated by Des1 to afford the conjugated Δ4,6 diene, the E isomer is a very potent Des1 inhibitor. The former finding paves the way to the development of HTS methods for Des1 based on Diels–Alder click reaction of the conjugated Des1 diene product with labeled or labelable dienophiles.

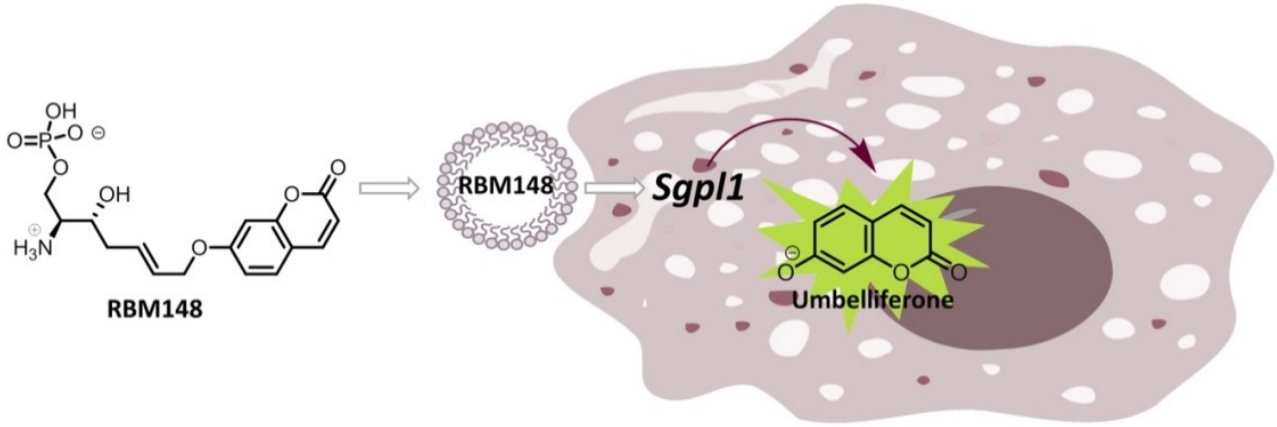


(A) Effect of Δ⁶dhCer-Z concentration on Des1 activity. Michaelis–Menten plot affords the indicated kinetic values. (B) Inhibition of Des1 by Δ⁶dhCer at different substrate (dhCer) and inhibitor concentrations. (C) Linear regression of the plot of reciprocal of $V_{max(app)}$ to inhibitor concentration afforded the indicated K_i value.

2. The first fluorogenic sensor for sphingosine-1-phosphate lyase activity in intact cells

Fluorescent sphingolipid probes represent an interesting contribution to the chemical toolbox. These molecules should prove useful in diagnostics, as well as to investigate sphingolipid metabolizing enzymes in situ or to identify new hits in drug discovery programs. Sphingosine-1-phosphate lyase (Sgpl1) is a pyridoxal phosphate dependent enzyme that catalyzes the cleavage of sphingosine-1- phosphate (S1P) or sphinganine-1-phosphate into (*E*)-2-hexadecenal or 2-hexadecanal, respectively, and ethanolamine phosphate in the catabolism of sphingolipids. Together with S1P kinases and S1P phosphatases, Sgpl1 contributes to cell fate through the so-called "sphingolipid rheostat". Moreover, Sgpl1 is a promising target for the treatment of inflammatory, autoimmune and neurodegenerative diseases. Recently, it has been reported that mutations in the Sgpl1 gene cause different diseases. The development of tools to monitor Sgpl1 activity has attracted the attention of several groups. However, the amphipathic characteristics of the amino phosphate natural substrate or its reported analogues prevent their use in intact cells. In a previous work, we reported on a high throughput screening (HTS) method to monitor Sgpl1 activity in cell lysates, based on the elimination of a fluorescent umbelliferone reporter from the aldehyde resulting from Sgpl1 cleavage of a S1P analogue. The relatively poor kinetic parameters of this compound towards Sgpl1 and its lack of cell permeability prevented its use in live cell studies, hampering the ap-

plicability of the probe. In this work, we report on the development of the new "second generation" probe by applying the principle of vinylogy to the first substrate. Specifically, compound RBM148 exhibited K_m, K_{cat} and K_{cat}/K_m values of 530±52 μM, 426±7 10-3·s-1 and 804 s-1·M-1, respectively. These values are remarkably improved over those of the parent substrate (K_m 1994±121 μM; K_{cat} 101±10 10-3·s-1 and K_{cat}/K_m 51 s-1·M-1). Furthermore, encapsulation of RBM148 into cationic liposomes allows monitoring Sgpl1 activity in living cells.



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

Definition of an 18-mer Synthetic Peptide Derived from the GB virus C E1 Protein as a New HIV-1 Entry Inhibitor

María J Gómara, Víctor Sánchez-Merino, Anna Paús, Alberto Merino-Mansilla, José M Gatell, Eloísa Yuste, Isabel Haro

Biochim. Biophys. Acta., 1860, 1139–1148**, 2016.**

Lipid raft-like liposomes used for targeted delivery of a chimeric entry-inhibitor peptide with anti-HIV-1 activity

María José Gómara, Ignacio Pérez-Pomeda, José María Gatell, Victor Sánchez-Merino, Eloisa Yuste, Isabel Haro

Nanomedicine: Nanotechnology, Biology and Medicine, 13(2), 601-609, **2017.**

Differing specificities and isotypes of anti-citrullinated peptide/protein antibodies in palindromic rheumatism and rheumatoid arthritis

Sonia Cabrera-Villalba, María José Gomara, Juan Cañete, Julio Ramírez, Georgina Salvador, Virginia Ruiz-Esquide, Maria Victoria Hernandez, Jose Inciarte-Mundo, Isabel Haro, Raimon Sanmarti

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Penetration of polymeric nanoparticles loaded with an HIV-1 inhibitor peptide derived from GB virus C using a vaginal mucosa model

Martha Ariza, Marta Espina, Ana C. Calpena, Nuria Bolaños, Maria J. Gómara, Isabel Haro, María L. García

European Journal Pharmaceutics and Biopharmaceutics, 120, 98-106, **2017.**

Anti-Carbamylated Protein Antibodies (CARP) in Palindromic Rheumatism: Prevalence and Clinical Significance

Castellanos-Moreira, R; Ruiz-Esquide, V.; Gomara, MJ; Cabrera-Villalba, S; Rodriguez-Garcia, SC; Salvador, G; Cuervol, A; Ramirez J; Hernandez, MV; Canete, J; Haro, I; Sanmarti, R.

Arthritis & Rheumatology, 69: 480, **2017.**

Structural study of a new HIV-1 entry inhibitor and interaction with the HIV-1 fusion peptide in dodecylphosphocholine micelles

Yolanda Pérez, María J. Gómara, Eloísa Yuste, Patricia Gómez-Gutiérrez, Juan J. Pérez, Isabel Haro

Chemistry: A European Journal, 23, 11703-11713**, 2017.**

Study of the interaction of GB virus C/Hepatitis G virus fusion peptides belonging to the E2 protein with phospholipid Langmuir monolayers

Perez-Lopez, S; Espina, M; Gomara, MJ; Fidalgo, JL; Alsina, MA; Mestres, C; Conde, JM.

Colloids and Surfaces B-Biointerfaces, 158, 278-286, **2017.**

RESEARCH PROJECTS

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

Nacional, Telemaratón RTVE

2015-2017

Participants: Institute of Health Research of Valencia (INCLIVA), Universidad Autónoma de Barcelona, Institut Químic de Sarrià, IQAC/CSIC

Diseño, síntesis y aplicaciones biomédicas de péptidos: inhibidores de entrada del HIV-1 y diagnóstico de la artritis reumatoide

Nacional MINECO/FEDER, CTQ2015-63919-R

2016-2018

Participants: IQAC/CSIC

Anticuerpos frente a péptidos carbamilados en la artritis reumatoide: valor diagnóstico y asociación con respuesta terapéutica

Autonómico, Hospital Clínic

2017-2018

Participants: Hospital Clínic, IQAC/CSIC

Red de Investigación en Inflamación y Enfermedades Reumáticas RIER (Programa Redes Temáticas de Investigación Cooperativa en Salud)

Nacional MINECO (RETICS)

2017-2020

RESEARCH HIGHLIGHTS

DEFINITION OF AN 18-MER SYNTHETIC PEPTIDE AS A NEW HIV-1 ENTRY INHIBITOR AND ITS STRUCTURAL STUDY

A slower progression of AIDS and increased survival in GB Virus C (GBV-C) positive individuals, compared with GBV-C negative individuals has been demonstrated, while the loss of GBV-C viremia was closely associated with a rise in mortality and increased progression of AIDS.

In a first work (*Biochim. Biophys. Acta.,* 1860, 1139–1148, 2016) we try to determine the role of the GBV-C E1 protein in HIV-1 inhibition and it involves the construction of several overlapping peptide libraries scanning the GBV-C E1 protein and the evaluation of their anti-HIV activity in collaboration with the AIDS Research Unit of the Hospital Clinic in Barcelona. Our results indicated that specifically, an 18-mer synthetic peptide from the GBV-C E1 protein, E1(139-156), demonstrated similar antiviral activity against HIVs from viruses from clades A, B, C, D and AE. Competitive ELISA using specific gp41-targeting mAbs, fluorescence resonance energy transfer as well as haemolysis assays indicated that this E1 peptide sequence probably interacts with the highly conserved N-terminal region of the HIV-1 gp41 (the fusion peptide) which is essential for viral entry. As a result of this work we defined a novel peptide lead compound and described the inhibitory role of a highly conserved fragment of the E1 protein. The results together, allow us to consider the non-pathogenic E1 GBV-C protein as an attractive source of peptides for the development of novel anti-HIV therapies. Later we focus on the characterization of the structural features of the above described peptide E1 peptide which are determinant for its anti-HIV-1 activity and secondly, on the study of its interaction of with the proposed viral target (the HIV-1 fusion peptide). Subsequently, in a second article (*Chemistry: A European Journal,* 23, 11703-11713, 2017) we report the peptide structure determined by NMR spectroscopy in DPC micelles solved using restrained molecular dynamics calculations. The acquisition of different NMR experiments in DPC micelles (peptide-peptide titration, diffusion NMR and addition of paramagnetic relaxation agents) allows the

proposal of an inhibition mechanism. We conclude that the selected peptide from non-pathogenic E1 GBV-C protein, with a helix-turn-helix structure, inhibits HIV-1 by binding to the HIV-1 fusion peptide at membrane level interfering with those domains in HIV-1 that are critical for stabilizing the six-helix bundle formation in a membranous environment.

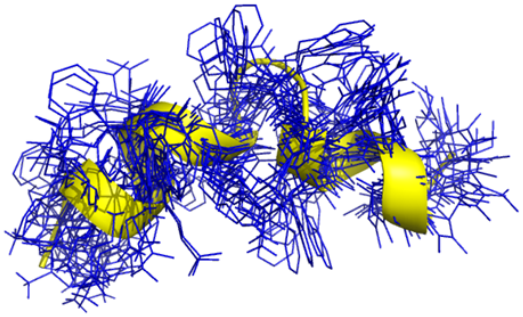

Figure 1. Superposition of the eleven conformations adopted by E1P47 in DPC micelles identified from MD simulations using diverse distance restrains derived from the NMR studies, showing two alternative conformations.

DIFFERING SPECIFICITIES AND ISOTYPES OF ANTI-CITRULLINATED PEPTIDE/PROTEIN ANTIBODIES IN PALINDROMIC RHEUMATISM AND RHEUMATOID ARTHRITIS

Palindromic rheumatism (PR), an intermittent form of arthritis, may, in some cases, evolve to rheumatoid arthritis (RA). A considerable proportion of PR patients have the characteristic autoantibodies found in RA: rheumatoid factor (RF) and/or anti-citrullinated peptide/protein antibodies (ACPA). In a work published in the specialized journal Arthritis Research & Therapy (*Arth. Res. Ther.*, 19,141, 2017) we analyzed differences in the recognition of ACPA and isotypes in patients with PR and RA. ACPA fine specificities (citrullinated peptides of enolase, fibrin, and vimentin) and isotypes (IgG, IgM, IgA) were analyzed in 54 patients with longstanding PR and 54 patients with established RA. We observed a more restricted pattern of ACPA recognition in patients with longstanding PR, with fewer fine specificities (especially in the case of the peptide of citrullinated vimentin) and lower isotype usage than in RA patients, an ACPA repertoire most frequently reported in the preclinical phase of RA or unaffected relatives of RA patients. It may be speculated that some patients with PR who do not evolve to RA may have impaired maturation of the B cell response against citrullinated peptides that may stop the development of chronic arthritis.

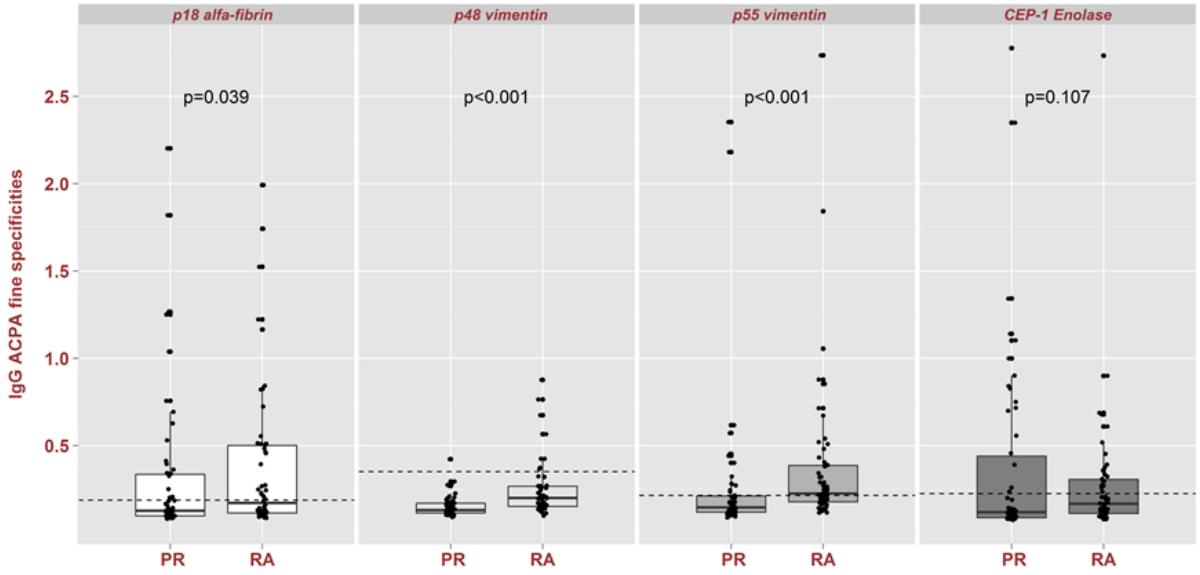

Figure 2. Box plots show levels of anti-citrullinated peptides of enolase, fibrin, and vimentin (ACPAs) for the IgG isotype. ACPA levels were compared in 54 patients with PR and 54 patients with RA. Mann Whitney p-values for the group differences were calculated. Box plots show the median, percentile 25, percentile 75, minimum and maximum. Dots represent the value of one patient's observation. Broken lines indicate the cut-off values.

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, transthyretin amyloidosis inhibitors and more recently, Alzheimer's 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. Proteomic characterization of G-protein coupled opioid receptors.
5. Drug discovery of small molecule chaperones of the interaction of transthyretin and Aβ peptides as drug candidates for Alzheimer's disease.

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.

STAFF

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ELLEN YADIRA COTRINA CELIS

ARTICLES

Role of the sugar moiety on the opioid receptor binding and conformation of a series of enkephalin neoglycopeptides.

Rosa M, Gonzalez-Nunez V, Barreto-Valer K, Marcelo F, Sánchez-Sánchez J, Calle LP, Arévalo JC, Rodríguez RE, Jiménez-Barbero J, Arsequell G, Valencia G.

Bioorg. Med. Chem. **2017**, *25*, 2260-2265.

Insights on the Interaction between Transthyretin and Aβ in Solution. A Saturation Transfer Difference (STD) NMR Analysis of the Role of Iododiflunisal.

Gimeno A, Santos LM, Alemi M, Rivas J, Blasi D, Cotrina EY, Llop J, Valencia G, Cardoso I, Quintana J, Arsequell G, Jiménez-Barbero J.

J. Med. Chem. **2017**, 60, 5749-5758.

RESEARCH PROJECTS

Spanish Ministry for Science and Technology (MINECO) project entitled:

Ministerio de Economia, Industria y Competitividad

Project reference: **PLAN NACIONAL** CTQ2016-76840-R

Principal Investigator: José Manuel González Díaz. University of Oviedo

From 30/12/2016 to 29/12/2019

"*ADDITION AND SUBSTRACTION TRANSFORMATIONS FOR THE CATALYTIC VALORIZATION OF UNSATURATED SYSTEMS*"

Research area: CHEMISTRY

Program reference: PROGRAMA ESTATAL DE INVESTIGACIÓN, DESARROLLO E INNOVACIÓN ORIENTADA

A LOS RETOS DE LA SOCIEDAD. PLAN ESTATAL DE INVESTIGACIÓN CIENTÍFICA Y TÉCNICA Y DE INNOVACIÓN 2013-2016. CALL: CONVOCATORIA DE 2016.

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

Fundación Marató de TV3 (2013): Neurodegenerative diseases call

FUNDACIÓ MARATÓ TV3

2015-2017

Coordinator: Dr. Gemma Arsequell Ruiz. IQAC-CSIC. Barcelona.

Five research teams.

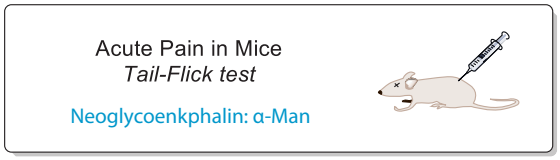
http://www.ccma.cat/tv3/marato/en/projectes-finan-cats/2013/212/

RESEARCH HIGHLIGHTS

The aim of the Unit is to study biochemical or medicinal chemistry issues by using chemical methodologies.

Studies on antinociceptive compounds.

One main aim of the Unit has been the search for new drug candidates for either severe or moderate pain and related mechanisms. Thanks to a project funded by Fundació La Marató 2006, we aimed first to intervene in the metabolic pathway of enkepahalin degradation and started the study of a pain-related molecule called opiorphin, a dual inhibitor of the ectopeptidases neprilysin (NEP) and aminopeptidase N (APN) that metabolizes a number of neuropeptides among them the enkephalins. Opiorphin produces analgesia in humans by inhibiting the enkephalin degradation. On the other hand, we looked at one of the natural metabolites of morphine, the glycoconjugate known as M6G, which was under clinical development for the treatment of pain. During this project we synthesized and tested new analogues of both opiorphin, M6G and other opioid peptides to gain new insights for the discovery of new candidates for analgesic drugs. Research on this field is the result of a long-standing interdisciplinary collaboration with two important research groups in Spain. One of them with expertise in pain research, is lead by Prof. Raquel E. Rodriguez, Director of Instituto de Neurociencias de Castilla y León (INCyL) in Salamanca and the other one with expertise in Structural Biology (NMR studies) lead by Prof. Jesús Jiménez-Barbero at CIC BioGUNE in Derio (Vizcaya).



H-Tyr-DMet-Gly-Phe-**Hyp(** O-α-Man **)**-NH_2

Figure: In vivo study. Antinociceptive tail-flick assay with α-Man neoglycoenkephalin.

Following this line of research, we applied our glycoconjugation methodologies to study important neuropeptides such as enkephalins *(Bioorg. Med. Chem.* **2017**, *25*, 2260-2265). The main aim of the research was to elucidate the role of the sugar moiety of these newly synthesized neoglycopeptides on the opioid receptor binding. The group reported long ago two important glycosides beta-Glucose (Glc) and beta-Galactose (Gal) of (D-Met2, Pro5)-enkephalinamide showing one of the highest antinociceptive activities known. In this work these neoglyconjugates were prepared again together with new ones (derivatives with Mannose, Lactose and Cellobiose). The pharmacological properties of these new neoglycoenkephalins were assessed by radioligand binding assays on isolated μ and δ opioid receptors from zebrafish. A pilot study of the antinociceptive properties of the Man neoglycoenkephalin was conducted on the tail-flick test, after ip administration in mice, to assess the potential permeability of this compound across the Blood Brain Barrier (BBB).The results obtained suggest that the nature of the carbohydrate moiety plays a minor role in determining the binding mode. NMR conformational studies, combined with molecular mechanics calculations, indicated that all glycopeptides present the same major conformation. The evidences provided in this work highlight the relevance for *in vivo* activity of the conjugating bond between the peptide and sugar moieties in opioid glycopeptides.

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 pocket 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 found

that a particular set of TTR stabilizing compounds enhance the TTR-Aβ interaction when studied *in vitro*. This prompted us to study the activity of one of such compounds, namely Iododiflunisal (IDIF), when administered in an AD animal model. By using an AβPPswe/PS1A246E model and orally administering the drug we 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 neuropathologies were also ameliorated in these animals.

Small molecule enhancer of the TTR/Aβ interaction

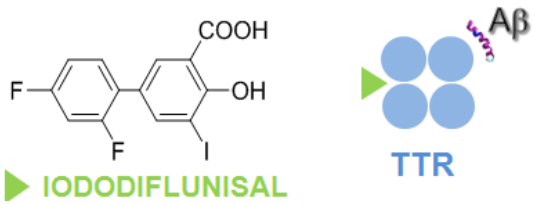


Figure: Iododiflunisal (IDIF) in the TTR/Aβ interaction.

This work was conducted in association with our long standing partners at the IBMC of Porto (Portugal). These *in vivo* studies prompted us to settle a drug discovery program focused in the discovery of small-molecule compounds enhancers of the transthyretin-Aβ interaction that may lead to potential AD modulating drugs. The project received a grant from Fundació La Marató de TV3 (Neurodegenerative diseases, 2013): "Setting a rational screening program for transthyretin-Aβ binding stabilizing compounds that may lead to potential Alzheimer´s disease modulating drugs". The consortia is integrated by five multidisciplinary research teams with tracked expertise in different disciplines and with a translational vision. The project gathers experts in computational chemistry, medicinal chemistry/radiochemistry, structural and cell biology, molecular neurobiology of AD and molecular imaging.

By structural and computational studies we have found that Aβ(12–28) is the main recognition element of the Aβ peptide in the interaction with TTR. The NMR results, assisted by molecular modeling protocols, have provided the first structural model for the TTR-Aβ interaction, as well as for the ternary complex formed in the presence of IDIF. These results have been published in *J. Med. Chem.* **2017**, *60*, 5749-5758.

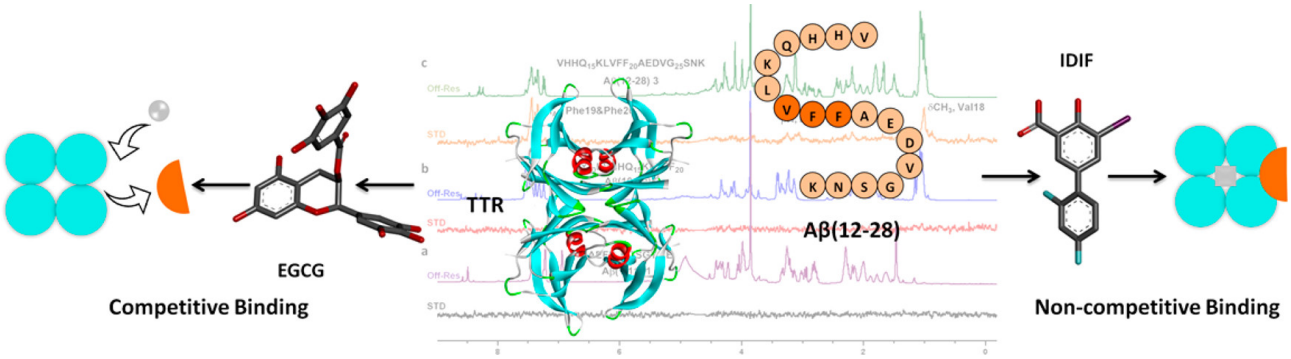


Figure: NMR studies of the interaction of TTR and Aβ peptides.

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 research projects are in the borderline between chemistry and biology with the goal to find molecules useful to study basic processes and mechanisms and to develop new therapeutics for diseases. Main research topics include photopharmacology, immunotherapy 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, pharmaceuticals, diagnostics, biotechnology and biosciences. The lab is providing research support and chemical expertise and advice to academic groups or companies in custom synthesis, process development, medicinal chemistry and analytical methods development.

STAFF

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TERESA SARRIAS SOLA
CAROLINA CERA RIBAS

ARTICLES

Allosteric control of an asymmetric transduction in a G protein-coupled receptor heterodimer

Liu J, Zhang Z, Moreno-Delgado D, Dalton JA, Rovira X, Trapero A, Goudet C, Llebaria A, Giraldo J, Yuan Q, Rondard P, Huang S, Liu J, Pin JP

eLife, 6, e26985, **2017**

Optical control of pain in vivo with a photoactive mGlu5 receptor negative allosteric modulator

Font J, López-Cano M, Notartomaso S, Scarselli P, Di Pietro P, Bresolí-Obach R, Battaglia G, Malhaire F, Rovira X, Catena J, Giraldo J, Pin JP, Fernández-Dueñas V, Goudet C, Nonell S, Nicoletti F, Llebaria A, Ciruela F

eLife, 6, e23545, **2017**

Positional isomers of bispyridine benzene derivatives induce efficacy changes on mGlu5 negative allosteric modulation

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

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Illuminating Phenylazopyridines to Photoswitch Metabotropic Glutamate Receptors: From the Flask to the Animals

Gómez-Santacana X, Pittolo S, Rovira X, Lopez M, Zussy C, Dalton JAR, Faucherre A, Jopling C, Pin JP, Ciruela F, Goudet C, Giraldo J, Gorostiza P, Llebaria A

ACS Central Sci., 3(1), 81-91, **2017**

Dynamic modulation of inflammatory pain-related affective and sensory symptoms by optical control of amygdala metabotropic glutamate receptor 4

Zussy C, Gómez-Santacana X, Rovira X, de Bundel D, Ferrazzo S, Bosch D, Asede D, Malhaire F, Acher F, Giraldo J, Valjent E, Ehrlich I, Ferraguti F, Pin JP, Llebaria A, Goudet C

Mol. Psychiatr., ePub, **2016**

OptoGluNAM4.1, a Photoswitchable Allosteric Antagonist for Real-Time Control of mGlu4 Receptor Activity

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Optical control of endogenous receptors and cellular excitability using targeted covalent photoswitches

Izquierdo-Serra M, Bautista-Barrufet A, Trapero A, Garrido-Charles A, Diaz-Tahoces A, Camarero N, Pittolo S, Valbuena S, Perez-Jimenez A, Gay M, Garcia-Moll A, Rodriguez-Escrich C, Lerma J, De La Villa P, Fernandez E, Pericas MA, Llebaria A, Gorostiza P

Nat. Commun., 7, 12221, **2016**

Shining light on an mGlu5 photoswitchable NAM: A theoretical perspective

Dalton JAR, Lans I, Rovira X, Malhaire F, Gómez-Santacana X, Pittolo S, Gorostiza P, Llebaria A, Goudet C, Pin JP, Giraldo J

Curr. Neuropharmacol., 14(5), 441-454, **2016**

RESEARCH PROJECTS

Moléculas para el fotocontrol de la actividad de proteínas.

National, CTQ2014-57020-R

2015-2017

ExPLORER - Exploring Pain using Light-controlled ligands for Optical Regulation of Endogenous Receptors.

International, ANR-16-CE16-0010, Agence Nationale de la Recherche (ANR), France

2016-2019

RESEARCH HIGHLIGHTS

Research activities of the group are focused on drug discovery and chemical biology, aimed at obtaining novel biologically active compounds and their application in new therapies, as well as the development of new pharmacological research tools. Current main lines of research include:

Photopharmacology - Reversible photoswitches

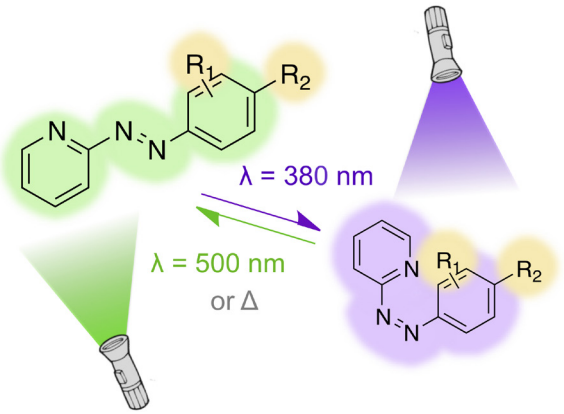
The administration of a photocontrolled ligand in combination with illumination that is patterned in space and time can provide a novel degree of control and regulation of receptor activity. This method would allow focusing the action of the ligand, controlling the location and the temporal extension of its effects. When applied in vivo, the use of photoregulation can reduce side effects by targeting receptors located in specific tissues, establishing personalized drug schedules to patient needs.

In particular, azobenzene photoisomerization can control biological functions. We have obtained phenylazopyridines with light-dependent activity as negative allosteric modulators (NAM) of metabotropic glutamate receptor subtype 5 (mGlu5), that result in atypical pharmacological profiles, both in vitro and in vivo, in studies of zebrafish larva motility and the regulation of the antinociceptive effects in mice. Thus, local administration of a photoswitchable compound combined with irradiation with light in the peripheral tissues of rodents or in the brain results in a precise illumination-dependent analgesic effect.

Also, azobenzene photoswitchable allosteric modulators of mGlu4 allow the

control of endogenous mGlu4 activity with light and reversible inhibition of persistent pain symptoms by receptor photocontrol in the brain of freely behaving animals.

These compounds can be used to define novel and more precise therapeutic treatments for chronic pain and to study in vivo the physiological roles of the receptors.



Photopharmacology - Photolabile caged compounds

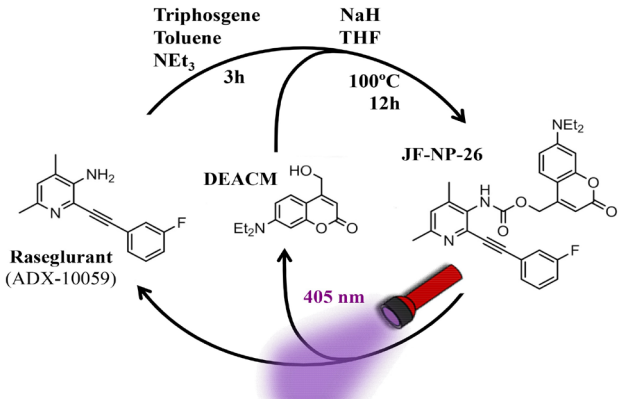
Another approach to control the activity of therapeutic compounds by means of light is through the use of

photolabile compounds. These are caged drugs, inactive while caged, that result in the controlled release of the active compound when irradiatedg with light)

JF-NP-26 is a coumarin-caged derivative of raseglurant, a mGlu5 receptor negative allosteric modulator. Light illumination of JF-NP-26 induces a photochemical reaction releasing the active drug, which effectively controls mGlu5 receptor activity both in ectopic expressing systems and in striatal primary neurons.

After systemic administration of JF-NP-26 in mice, local light-emitting diode (LED)-based illumination, either of the thalamus or the peripheral tissues, induces light-dependent analgesia both in neuropathic and in acute/tonic inflammatory pain models.

This is the first example of photocontrol of analgesia in vivo using a caged mGlu5 receptor negative allosteric modulator



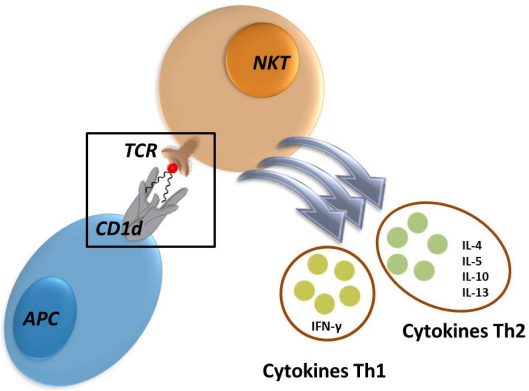
Immunotherapy - Non-glycosidic analogues of α-GalCer as NKT cell activators

Invariant natural killer T cells (iNKT), a unique subpopulation of T cells with immunomodulatory properties involved in a broad range of immune responses, are stimulated by glycolipid antigens, particularly by alpha-galactosylceramide (α-GalCer).

α-GalCer shows an exceptional potency on iNKT cell stimulation which is associated to different side effects. In addition, it simultaneously induces the expression of both Th1 and Th2 cytokines, which have opposite biological functions. Thus, new compounds are needed to achieve selective modulation of cytokine release.

A new family of non-glycosidic analogues of α-GalCer has been developed. They show strong activity in vitro to stimulate iNKT cell proliferation and highly efficient and potent selective cytokine release

These compounds can have application in cancer immunotherapy, for cooperative stimulation of the patient immune system, and as vaccine adjuvants in autoimmune diseases or infections. A patent application has been filed in November 2017.

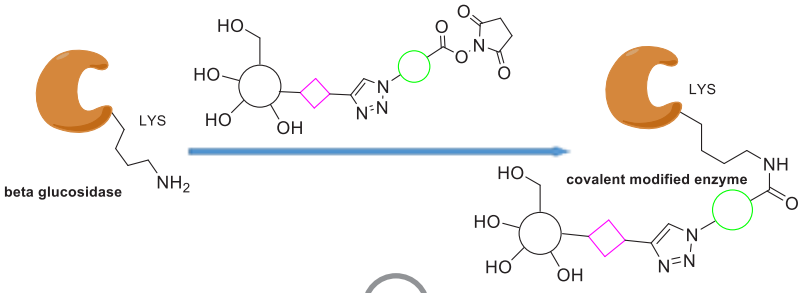


Selective protein labelling

We have developed a protein labelling method that consists in the selective and kinetically controlled conjugation on lysine residues exposed on the surface of the protein near the binding site of the ligand.

This results in a practical chemical method for the selective covalent labelling of wild type proteins with high affinity without requiring previous genetic or chemical modification of the protein. Its modularity allows the application to multiple proteins and ligands

This approach is based on bioortogonal Cu-catalyzed click-chemical reactions, in which a fast triazole synthesis from chemically stable azide and alkyne components results in an N- or S- diversely substituted imino or thiosugar ligand library. The protein affinity of the sugar-like ligand with a short lived NHS-ester group directs the chemical reaction on a terminal amino group of a specific lysine in the native protein.



CHEMICAL AND BIOMOLECULAR NANOTECHNOLOGY

CHEMICAL AND BIOMOLECULAR NANOTECHNOLOGY

Head: Jordi Esquena Moret

Chemical and biomolecular Nanotechnology is a multidisciplinary field, which can be defined as the study of chemical and biological entities on molecular and supramolecular scales, focusing on noncovalent interactions between molecules, which lead to molecular recognition, specific binding, self-assembly and formation of supramolecular nanostructures.

The research at the Department of Chemical and Biomolecular Nanotechnology is focused on bioactive organic molecules and biomolecules (oligonucleotides, macrobiomolecules, antibodies, organic molecules and drugs), self-organized supramolecular colloidal systems, nanostructured materials and devices at the nanoscale. The department has developed expertise on the following fields:

- Design of biosensors based on antibodies as analytical tools for a wide range of applications in diagnostic, food safety and environment.

- Study of oligonucleotides, and, specifically, design of new nucleic acid derivatives with interesting structural properties aimed at controlling gene expression by antisense and RNA interference mechanisms.

- Surfactant formulation based upon their phase behavior in multicomponent systems and their self- aggregation into complex supramolecular nanostructures (micelles, liquid crystals, vesicles, microemulsions, nano-emulsions, highly concentrated emulsions, etc.)

- Formation of new nanostructured materials and delivery systems with controlled size and morphology, using self-assemblies and colloidal templates.

- Development of new cell therapy treatments, especially antitumor therapies using stem cells as vehicles for the local delivery of therapeutic agents.

The Department of Chemical and Biomolecular Nanotechnology integrates consolidated and multidisclipinary research teams, with a proven capacity to secure funds from a wide range of public organizations and companies. All the research groups of the Department belong to the Biomedical Research Networking Center in Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), and three of those groups belong to TECNIO, a network of centers for innovation and technological transfer to the industrial sector.

RESEARCH GROUPS

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

NANOBIOTECHNOLOGY FOR DIAGNOSTICS

The Nanobiotechnology for Diagnostics Group has focused 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.

Objective: Perform research of excellence addressed at solving specific problems and developing know-how and expertise in basic chemical science and perform research at the chemistry-biology interface.

Our mission is to improve the diagnostic efficiency using technologies based on new micro and nano(bio) technologic approximations that will improve the standard of living of the society.

Our vision is to be an important group, internationally reknowned, that contributes with innovative technological alternatives to overtake the actual limitations in the diagnostic field in clinics, food safety and in the environment.

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RAHEEL AHMAD
KLAUDIA LILLA KOPPER
JOSÉ ENRIQUE MONTAGUT CAÑETE
ANA SANCHÍS VILLARIZ

ARTICLES

Novel strategy for sulfapyridine detection using a fully integrated electrochemical Bio-MEMS: Application to honey analysis.

Hassani N.E.A.E., Baraket A., Neto E.T.T., Lee M., Salvador J.-P., Marco M.-P., Bausells J., Bari N.E., Bouchikhi B., Elaissari A., Errachid A., Zine N.. Biosensors and Bioelectronics, 93, 282-288, 2017.

Multimodal plasmonic biosensing nanostructures prepared by DNA-directed immobilization of multifunctional DNA-gold nanoparticles.

Tort N., Salvador J.-P., Marco M.-P.

Biosensors and Bioelectronics, 90, 13-22, 2017

Assessment of analytical methods to determine pyrethroids content of bednets.

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Tropical Medicine and International Health volume 22, 1, 41-51, 2017

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Quantification of interacting cognate odorants with olfactory receptors in nanovesicles.

Marta Sanmartí-Espinal, Patrizia Iavicoli, Annalisa Calò, Marta Taulés, Roger Galve, M. Pilar Marco & Josep Samitier.

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Sanmarti-Espinal M., Galve R., Iavicoli P., Persuy M.-A., Pajot-Augy E., Marco M.-P., Samitier J.

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C. Pastells, M.-P. Marco, P. Loza-Alvarez, L. Pasquardini, L. Lunelli, C. Pederzolli, N. Daldosso, D. Farnesi, S. Berneschi, G.C. Righini,F. Quercioli, G. Nunzi Conti, S. Soria

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Immunochemical Strategy for Quantification of G-Coupled Olfactory Receptor Proteins on Natural Nanovesicles.

Marta Sanmartí-Espinal, Roger Galve, Patrizia Iavicolia, Marie-Annick Persuy, Edith Pajot-Augy, M.-Pilar Marco and Josep Samitier

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Immunochemical Determination of Pyocyanin and 1-Hydroxyphenazine as Potential Biomarkers of Pseudomonas aeruginosa Infections.

Carme Pastells, Nuria Pascual, Francisco Sánchez-Baeza, Francisco and M.-Pilar Marco

Anal. Chem., 88, 1631-1638, 2016, DOI: 10.1021/acs.analchem.5b03490

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J.-Pablo Salvador and M.-Pilar Marco

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Hybrid hydrogel-aligned carbon nanotube scaffolds to enhance cardiac differentiation of embryoid bodies.

Samad Ahadian, Shukuyo Yamada,JavierRamón-Azcón, Mehdi Estili Xiaobin Liang, Ken Nakajima, Hitoshi Shiku, Ali Khademhosseini, Tomokazu Matsue

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The European antibody network's practical guide to finding and validating suitable antibodies for research.

Giovanna Roncador, Pablo Engel, Lorena Maestre, Amanda P. Anderson, Jacqueline L. Cordell, Mark S. Cragg, Vladka, Č. Šerbec, Margaret Jones, Vanda, J. Lisnic, Leonor Kremer, Demin Li, Friedrich Koch-Nolte, Núria Pascual, Jose-Ignacio Rodríguez-Barbosa, Ruurd Torensma, Helen Turley, Karen Pulford and Alison H. Banham.

article: http://dx.doi.org/10.1080/19420862.2015.1100787, mAbs, 8:1, 27-36, 2016.

Bioactivity of dexamethasone-releasing coatings on polymer/magnesium composites.

Fátima Bensiamar1,2,7, Beatriz Olalde3,7, Sandra C Cifuentes4,5, Nerea Argarate3, Garbiñe Atorrasagasti3, José L González-Carrasco2,4, Eduardo García-Rey6, Nuria Vilaboa1,2 and Laura Saldaña1,2,8

2016, Biomedical Materials, Volume 11, Number 5

RESEARCH PROJECTS

Real time monitoring of SEA contaminants by an autonomous Lab-on-a-Chip biosensor (SEA-on-a-CHIP).
Agencia financiadora: European Commission. Desde 01/12/2013 hasta 31/05/2017

Molecular links between diabetes and neurodegenerative diseases
Agencia financiadora: ISCIII. Desde 01/01/2015 hasta 31/12/2017

Grup de Recerca Consolidat.
Agencia financiadora: Agencia de Gestió d'Ajuts Universitaris I de Recerca de la Generalitat de Catalunya, Duración: 2014-2016
Investigador principal: M.-Pilar Marco

Ajuda acreditació Tecnio del grup Nb4D
Agencia financiadora: Generalitat de Catalunya Desde 30/10/2015 hasta 01/05/2017.

New Diagnostics for Infectious Diseases
Agencia financiadora: European Commission Desde 01/03/2016 hasta 29/02/2020

Estrategias Inmunoquímicas de Diagnóstico y Terapia en base al Quorum Sensing (InmunoQS)
Agencia financiadora: Ministerio de Economía y Competitividad Desde 01/01/2016 hasta 31/12/2018. Ajuda acreditación tecnio del grup Nb4D, ACCIO, Ajuts per incentivar els plans d'actuació en transferencia tecnològica dels desenvolupadors catalans, TECDTP15-1-0011 Duración: 30.10.2015-30.102016, Investigador principal: M.-Pilar Marco

FoodSmartphone: Smartphone analyzers for on-site testing of food quality and safety.
Agencia financiadora: European Commission, Desde 01/01/2017 hasta 31/12/2020.
A new approach for the diagnosis of Pseudomonas aeruginosa infections. Agencia financiadora: CAIXAIMPULSE (CI16/00031). Duración: 1.09.2017-31.09.2018. Investigador principal: Miriam Corredor

Ajuda acreditació TECNIO del grup Nb4D.
Agencia financiadora: Generalitat de Catalunya, TECDTP16-1-0009. Desde 02/05/2017 hasta 01/05/2018 .
Grup de Recerca Consolidat. Agencia de Gestió d'Ajuts Universitaris i de Recerca. Generalitat de Catalunya Expedient 2017 SGR 1441, Duración: Diciembre 2017-Diciembre 2019, Investigador Principal: M.-Pilar Marco

RESEARCH HIGHLIGHTS

Financiación en contratos y convenios vigentes con empresas e intituciones (anualidad)

1. Supply of Immunoreagents and Antibodies. Empresa/Administración financiadora: Unisensor SA (Liege, Belgium). Duración: 15.10.2016-14.10.2018.
   Investigador Principal: Dra. M.-Pilar Marco (CSIC)

2. α-Galactosyls diacylglycerolipids (α-GalDAG). Empresa / Administración financiadora: Pharmasan Labs Inc. Duración: 24.04.2017- 23.04.2018.
   Investigador Principal: Dra. M.-Pilar Marco (CSIC)

3. Acuerdo de Explotación de la Patente de Inmunoreactivos para Fluoroquinolonas. Empresa/Administración financiadora: UNISENSOR (Liege, Belgica). Duración: Abril 2012- Abril2022. Investigador Principal: Dra. M.-Pilar Marco (CSIC)/Dr. Benoit Granier (UNISENSOR SA)

4. Acuerdo de Explotación de Immunoreactivos para Sulfonamidas. Empresa/Administración financiadora: UNISENSOR (Liege, Belgica). Duración: Junio 2016- Junio 2026. Investigador Principal: Dra. M.-Pilar Marco (CSIC)/Dr. Benoit Granier (UNISENSOR SA)

5. Acuerdo de Explotación de Immunoreactivos para Sulfonamidas. Empresa/Administración financiadora: BIOO Scientific Corporation (Texas, USA). Entidades participantes: IQAC-CSIC/ BIOO Scientific Corporation. Duración: Julio 2012-Julio 2022. Presupuesto: based on royalties. Investigador Principal: Dra. M.-Pilar Marco (CSIC).

NUCLEIC ACIDS CHEMISTRY GROUP

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 2016-2017 deal with 1) conjugation of small molecules to DNA and RNA for a potential use in DNA/ RNA therapeutics, 2) the effect of modified nucleosides 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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MARIA DELLAFIORE
CLAUDIA RICCARDI
JESUS GARCIA CHICA
MARC ERES OLIVARES
ISMAIL AMGHAR
JESSICA ZABALA

ARTICLES

The influence of the polar head-group of synthetic cationic lipids on the transfection efficiency mediated by niosomes in rat retina and brain

Ojeda, E., Puras, G., Agirre, M., Zarate, J., Grijalvo, S., Eritja, R., Martínez-Navarrete, G., Soto-Sánchez, C., Diaz-Tahoces, A., Aviles-Trigueros, M., Fernández, E., Pedraz, J.L.

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Aviñó, A., Huertas, C. S., Lechuga, L. M., Eritja, R.

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Alagia, A., Eritja, R.

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Biodegradable liposome-encapsulated hydrogels for biomedical applications: A marriage of convenience

Grijalvo, S., Mayr, J., Eritja, R., Díaz Díaz, D.

Biomater. Sci., 4, 555-574, **2016**.

The effect of small cosolutes that mimic molecular crowding conditions on the stability of triplexes involving duplex DNA

Aviñó, A., Mazzini, S., Gargallo, R., Eritja R.

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Benabou, S., Garavís, M., Lyonnais, S., Eritja, R., González, C., Gargallo, R.

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The role of helper lipids in the intracellular disposition and transfection efficiency of niosome formulations for gene delivery to retinal pigment epithelial cells

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Int. J. Pharm., 503(1-2), 115-126, **2016**.

Nioplexes encapsulated in supramolecular hybrid biohydrogels as versatile drug delivery platforms for nucleic acids

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Glucose-nucleobase pseudo base pairs as a new biomolecular interaction in a DNA context

Vengut-Climent, E., Gómez-Pinto, I., Lucas, R., Peñalver, P., Aviñó, A., Fonseca-Guerra, C, Bickelhaupt, F.M.., Eritja, R., González, C., Morales, J.C.

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Controlling the reversible assembly of liposomes through a multi-stimuli responsive anchored DNA

Hernández-Ainsa, S., Ricci, M., Hilton, L., Aviñó, A., Eritja, R., Keyser, U. F.

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RESEARCH PROJECTS

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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

Genotoxic nanoparticles targeting colorrectal cancer stem cells.

Fundació La Marato 2012 (416/C/2013)

2014-2016

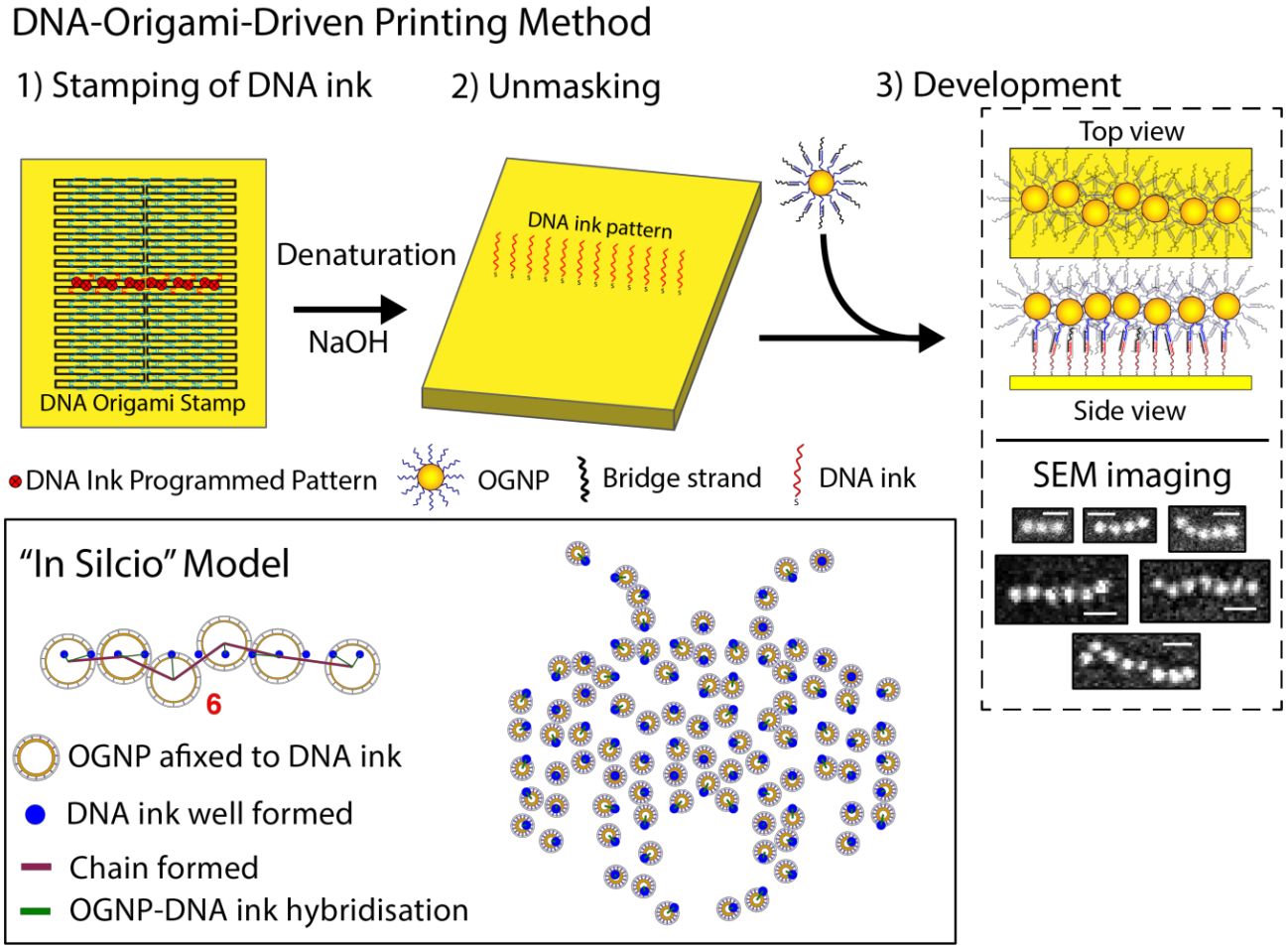
RESEARCH HIGHLIGHTS

Alignment of gold nanoparticles on gold surfaces using DNA origami technology. Integrating nature's bottom up assembly mechanisms with technologically relevant fabrication techniques has the potential to advance science and future technologies. While top down methodologies such as photolithography have successfully been used to generate features on the nanometer scale, the nuanced programmability of biomolecules offers advantages in generating complex assemblies with multiple materials.

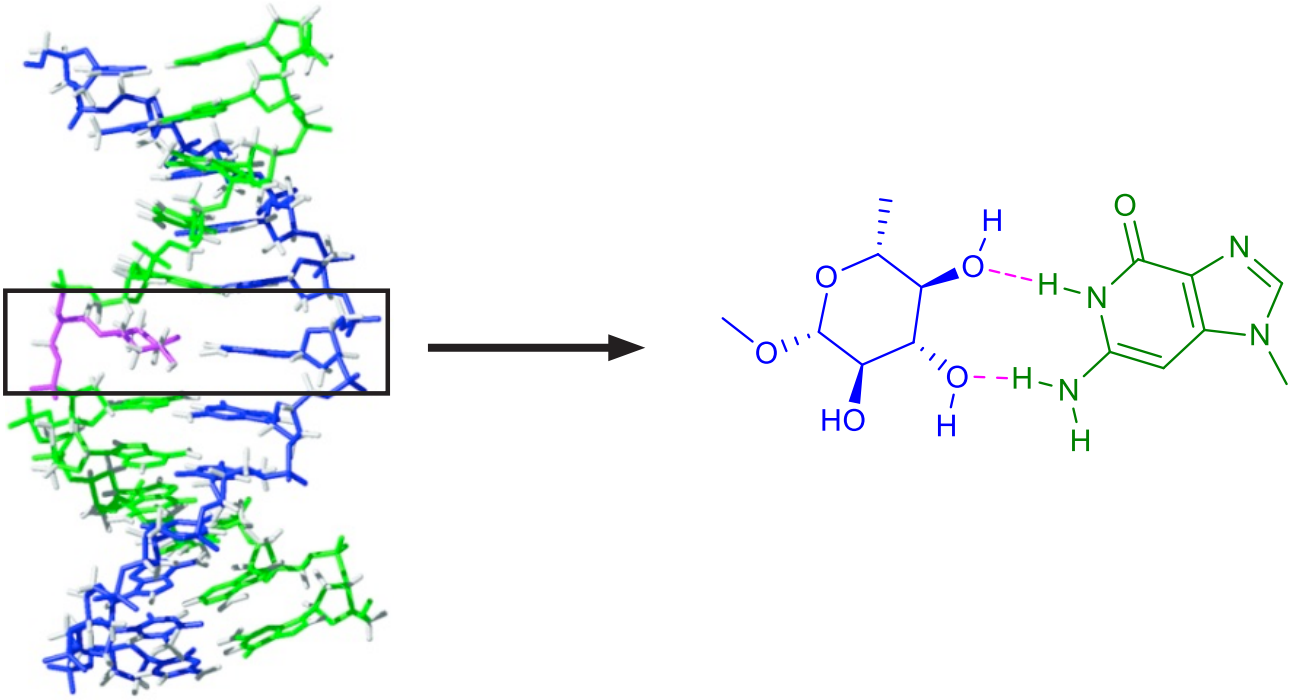
DNA is the molecule responsible of the transmission of genetic heritage but in recent years, has become the biomolecule of choice for organizing nanomaterials both in solution and on surfaces. Small molecules of DNA can be produced synthetically at low cost and the DNA double helix structure has been extensively used for the design of well-defined nanostructures. One of

the more promising DNA structures is the so called DNA origami developed by Paul Rothemund in 2006. These DNA structures are formed by folding the genetic material of a virus with hundreds of small synthetic oligonucleotides into a predesigned shape.

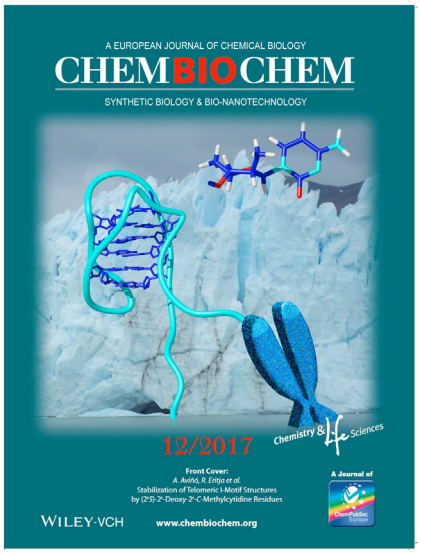
In a recent study, the Nucleic Acids Chemistry group at IQAC succeeded for the first time in the alignment of a discrete number of gold nanoparticles in gold surfaces using DNA origami. The method described introduces chemically modified synthetic oligonucleotides to form a pattern inside the origami. Once the origami structure is formed, the chemically modified pattern contained therein can chemically react with a suitable surface, allowing pattern transfer. Following the transfer of the pattern, the origami structure is no longer needed and can be removed by washing. The chemically bound oligonucleotide pattern directs the alignment of gold nanoparticles by using the binding properties of DNA. Future applications of this technology include the formation of hybrid bio nanoelectronic devices or the fabrication of well-defined active surfaces for highly sensitive multiplexed detection of analytes.



Base-Pairing between carbohydrates and nucleobases. The double-helical structure of DNA is maintained by the formation of non-covalent bonds between adenine and thymine on the one hand and guanine and cytosine on the other. In a recent study carried out in collaboration within several groups of CSIC (IIQ, IPB, IQFR, IQAC) it is demonstrated that other non-covalent interactions are possible, even without having the natural bases. In this way, researchers describe for the first time the formation of double helix structures in which carbohydrates participate in the establishment of non-covalent bonds with natural bases.



Enhancing the stability of non-canonical DNA structures in cytidine-rich oligonucleotides. Nucleic acids can adopt secondary structures that play important roles in several cellular functions. Among them, i-motifs are present in oncogenic regions as well as in human telomeric DNA regions indicating their possible role during the regulation of oncogene expression at the transcription level. These i-motifs are intercalated tetraplex structures formed by the association of a hemiprotonated cytosine base pair, and close sugar-sugar contacts in C-rich sequences. In addition, i-motif structures have the possibility of producing nanodevices with pH-sensitive functions. These facts have triggered the interest for modified oligonucleotides with improved structural properties. In a recent study carried out in collaboration within several groups of CSIC (IQFR, IQAC), University of Barcelona and two Universities of Buenos Aires it is demonstrated that artificial nucleosides may produce more stable i-motif structures. To this end, researchers have synthesized C-rich oligonucleotides carrying conformationally restricted (2'S)-2'-deoxy-2'-C-methyl-cytidine units. The effect of this modified nucleoside on the stability of intramolecular i-motifs related to vertebrate telomere was investigated by means of spectroscopic methods. The replacement of selected positions of the C-core by the appropriate C-modified residues induces the formation of stable intercalated tetraplexes at pHs near neutrality. The study demonstrates the possibility of enhancing the stability of i-motif by chemical modifications.



COLLOID AND INTERFACIAL CHEMISTRY GROUP

Our group is focused on molecular self-assembly and colloid chemistry as tools for the formulation and bottom-up fabrication of nanomaterials. We are interested in nanostructured colloidal systems such as surfactants, polymers, micelles, gels, liquid crystals, foams, microemulsions and nano-emulsions; they can find direct applications (e.g. as nanocarriers) or used as templates, structure directing agents or nanoreactors for the synthesis of nanoparticles, nanocomposites or nanoporous solids. Through state-of-the-art techniques, we intend to understand the fundamentals mechanisms of aggregation, phase behavior, and interfacial interactions and their impact on material domain size, structure, stability and other properties. We aim to use molecular information and physicochemical parameters to predict, control and program hierarchical self-organization at multiple scales and with increasing complexity, for materials with new or improved properties and applications.

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ARTICLES

Nano-emulsions as vehicles for topical delivery of forskolin.

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Studies on the formation of polymeric nano-emulsions obtained via low-energy emulsification and their use as templates for drug-delivery nanoparticle dispersions.

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Self-Assembly and Formation of Chromonic Liquid Crystals from the Dyes Quinaldine Red Acetate and Pyronin Y.

Magaña, J. R.; Homs, M.; Solans, C.; Obiols-Rabasa, M.; Salonen, L. M.; Rodríguez-Abreu, C.

Journal of Physical Chemistry B, 120, 250-258, **2016**.

Hybrid hierarchical porous silica templated in nano-emulsions for drug release.

Riachy, P.; Roig, F.; García-Celma, M.J.; Stébé, M.J.; Pasc, A.; Esquena, J.; Solans, C.; Blin, J.L.

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

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BOOK CHAPTERS

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RESEARCH PROJECTS

PROYECTOS DE INVESTIGACIÓN FINANCIADOS CON CARGO A CONVOCATORIAS PÚBLICAS

PROYECTOS FINANCIADOS POR ORGANISMOS NACIONALES

Estudio de sistemas nanoestructurados para aplicaciones tecnológicamente avanzadas: Formulación y textiles inteligentes (CTQ2005-09063-C03-02/PPQ), MEC. Inv. Responsable: C. Solans (2005-2008)

PROYECTOS EUROPEOS

Theranostic Magnetic Nanoparticles For Cancer Diagnosis and Treatment: Magnetic Properties and Controlled Release of Anticancer Drugs (TheraMag-Nano) (TECSPR14-2-0033). Programa TecnioSpring, ACCIÓ. Inv. Responsable: C. Solans (2015-2017)

AYUDAS RECIBIDAS DE APOYO A LA INVESTIGACIÓN

Ayudas para grupos de Investigación Consolidados de Catalunya, 2014SGR1655 Generalitat de Catalunya Inv. Responsable: J. Esquena (2014-2016)

Pla d'actuació al Centre QCI IQAC-CSIC (TECCIT16-1-0049). ACCIÓ Generalitat de Catalunya. Inv. Responsable: J. Esquena (2016-2017)

Asignación del CIBER-BBN para el desarrollo de los proyectos intramurales y los programas horizontales, y Programa Plataformas CIBER-BBN. Inv. Responsible: C. Solans, C. Rodríguez-Abreu (2016-2017)

RESEARCH HIGHLIGHTS

Molecular self-assembly by π-π stacking and derived applications

Molecular self-assembly is driven by various types of non-covalent interactions; π-π stacking is one of them. We studied several polyaromatic systems that form molecular stacks. In particular, we focused on cationic dyes that display lyotropic (chromonic) liquid crystal behavior in water. They form nematic and hexagonal liquid crystals but also other mesophases (**Self-Assembly and Formation of Chromonic Liquid Crystals from the Dyes Quinaldine Red Acetate and Pyronin Y.** Journal of Physical Chemistry B, 120, 250-258, **2016**). We found that the chromonic nematic phase can serve as a soft template for the formation of silica nanofibers by the sol-gel method with alkoxysilanes as precursors (**From Chromonic Self-Assembly to Hollow Carbon Nanofibers: Efficient Materials in Supercapacitor and Vapor-Sensing Applications.** ACS Applied Materials & Interfaces, 8, 31231-31238, **2016**). These silica nanofibers contain mesopores in a hexagonal array and oriented along the fiber´s axis. The silica nanofibers were in turn used as hard templates for the formation of carbon nanofibers (CNFs) upon impregnation with a carbon precursor followed by carbonization (Figure 1). The obtained nanofibers are hollow and contain randomly oriented graphitic layers and show outstanding electrochemical supercapacitance performance. The high capacitance of CNFs comes from their porous structure, high pore volume, and electrolyte-accessible high surface area. CNFs with ordered graphitic layers were also obtained upon treatment at high temperatures (>1500 °C). High-surface-area CNFs can also be used in sensing applications; in particular, they showed selective differential adsorption of volatile organic compounds, which is attributed to the free diffusion of these volatile aromatic molecules into the pores of CNFs accompanied by interactions with sp2 carbon structures and other chemical groups on the surface of the fibers.

Covalent organic frameworks (COFs) are another class of π-π stacking systems. A water-stable covalent organic framework (COF) was evaluated as adsorbent for the hydrophobic toxin okadaic acid, one of the most relevant marine toxins and the parental compound of the most common group of toxins responsible for shellfish poisoning (**Adsorption of Marine Phycotoxin Okadaic Acid on a Covalent Organic Framework.** Journal of Chromatography A, 1525, 17-22, **2017**). The adsorption kinetics of okadaic acid onto the COF in seawater is fast and the equilibrium concentration is reached quickly. Moreover, okadaic acid can be desorbed from COF using ethanol and acetonitrile as solvents, and the COF material can be reused with minor losses in adsorption capacity for three cycles. The results demonstrate that COF materials are promising candidates for solid-phase adsorption in water monitoring devices.

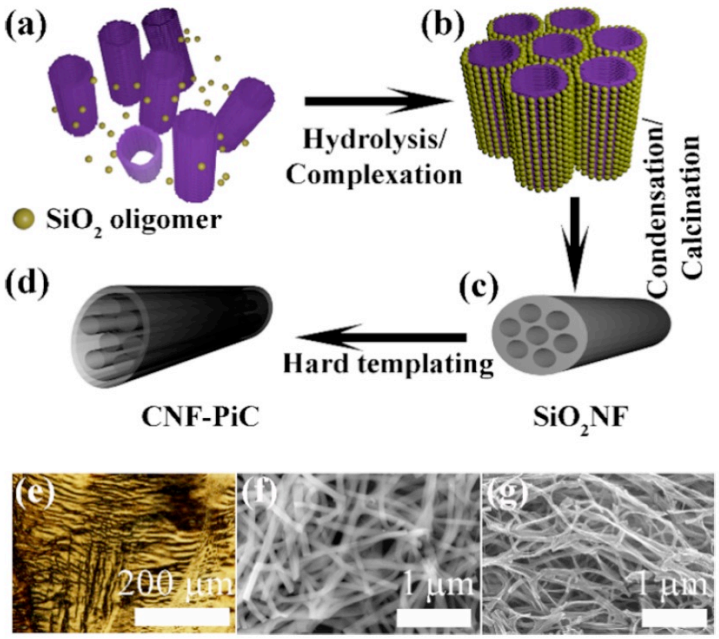

Figure 1. Schematic Mechanism for the synthesis of silica and carbon nanofibers from dye liquid crystals (a) Dye aggregates (nematic liquid crystal), (b) SiO_2– dye complex (hexagonal liquid crystal), (c) SiO_2 nanofiber (SiO_2 NF), (d) carbon nanofiber (CNF), (e) Optical microscope image of a dye nematic phase in concentrated ammonia, (f) SEM image of SiO_2 NF, and (g) an SEM image of CNF (adapted from ACS Applied Materials & Interfaces, 8, 31231-31238, **2016)**

Nano-emulsions: formulation, properties and applications

We have carried out comprehensive research on the formulation and preparation of nano-emulsion by low-energy (bottom-up) methods in order to establish the most important physicochemical parameters to tune nano-emulsion properties such as droplet size, content of dispersed phase, colloidal stability and interfacial properties. In our research, nano-emulsions have been used as soft templates for the preparation of polymer nanoparticles with potential theranostic applications.

Ethylcellulose nanoparticles for drug encapsulation were obtained from O/W nano-emulsions by low-energy emulsification (Figure 2). Our experiments have evidenced for the first time that both the polymer and the drug play a role on the structure of the aggregates formed along the emulsification path. Nano-emulsion formation may take place by both, phase inversion and self-emulsification. Spherical ethylcellulose nanoparticles with sizes below 160 nm were obtained from the nano-emulsions by organic solvent evaporation. Loading of a model drug (dexamethasone) in the nanoparticles was high (>90%). Drug release from the nanoparticle dispersions was slower than from the aqueous solution. A coupled diffusion/relaxation model fitted the results very well, suggesting that polymer chains undergo conformational changes that induce drug release. (**Studies on the formation of polymeric nano-emulsions obtained via low-energy emulsification and their use as templates for drug-delivery nanoparticle dispersions**. Colloids and Surfaces B: Biointerfaces 145, 922-931, **2016**)

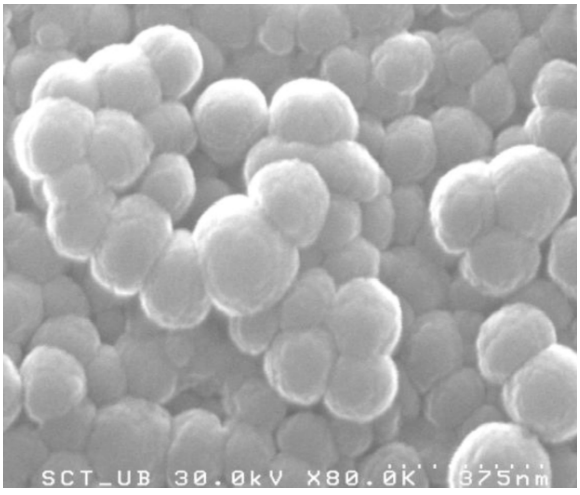

Figure 2. Ethylcellulose particles prepared from nano-emulsions by solvent evaporation (adapted from Colloids and Surfaces B: Biointerfaces 145, 922-931, **2016)**

We have established that the addition of increasing concentrations of electrolytes in the aqueous phase of nano-emulsions produce a decrease on droplet size by almost an order of magnitude (Figure 3). In consequence, the size of polymer poly(lactic-co-glycolic acid (PLGA) nanoparticles produced from nano-emulsions can also be controlled by only varying the electrolyte concentration (**Electrolytes as a tuning parameter to control nano-emulsion and nanoparticle size.** RSC Advances, 6, 58203-58211, **2016**).

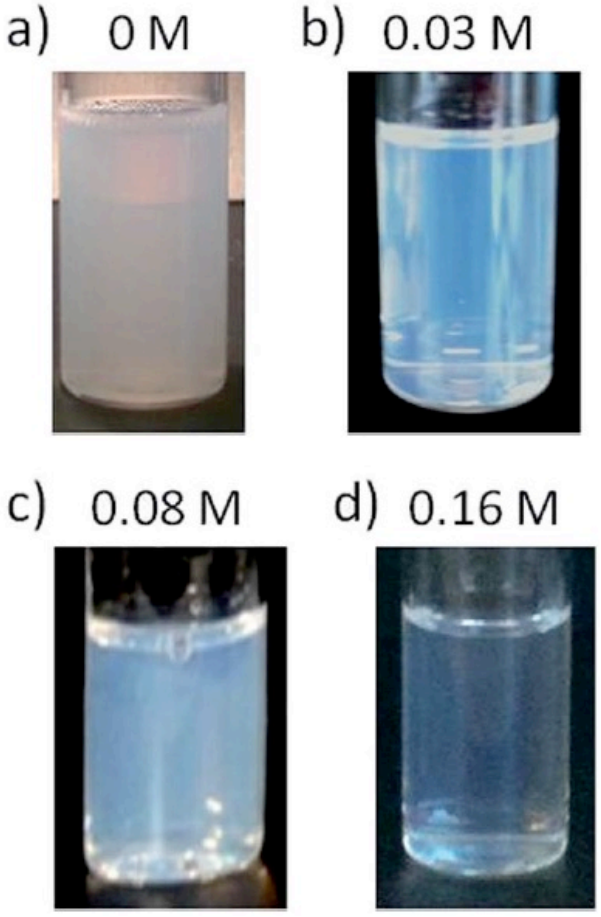

Figure 3. Effect of electrolyte concentration (indicated on the top of the pictures) on nano-emulsions with 90 wt% aqueous phase and an Oil/Surfactant ratio of 70/30. Note the increase of transmittance (decrease in droplet size) when the electrolyte concentration is increased (adapted from RSC Advances, 6, 58203-58211, **2016**)

Encapsulation of iron oxide magnetic nanoparticles (MNP) into PLGA nanoparticles has also been achieved via nano-emulsion templates produced by low-energy methods (**Design of parenteral MNP-loaded PLGA nanoparticles by a low-energy emulsification approach as theragnostic platforms for intravenous or intratumoral administration.** Colloids and Surfaces B: Biointerfaces 160, 535-542, **2017**). PLGA

nanoparticles with an average size of 50 nm were able to encapsulate MNPs of about 10 nm (Figure 4). Physical-chemical properties suggest that the obtained MNP-loaded PLGA nanoparticles are good candidates for intravenous or intratumoral administration.

A similar nano-emulsion-based strategy was followed for the encapsulation of gold-nanoparticles in PLGA particles **(Versatile Methodology to Encapsulate Gold Nanoparticles in PLGA Nanoparticles Obtained by Nano-Emulsion Templating** Pharmaceutical Research 34, 1093-1103, **2017**). Firstly, gold nanoparticles were transferred from water to ethyl acetate. Next, the formation of nano-emulsions loaded with gold nanoparticles was carried out using a phase inversion composition (PIC) emulsification (low energy) method, followed by solvent evaporation to produce Au-loaded PLGA nanoparticles.

Another representative case is the preparation of hybrid nanocarriers by combining oil-in-water (O/W) nanoemulsions contanining solubilized drug with mesostructured silica (**Hybrid hierarchical porous silica templated in nano-emulsions for drug release.**European Journal of Inorganic Chemistry, 2016, 1989-1997, **2016**). The hybrid nanocarriers showed pH-dependent controlled release. The drug solubility and release increase strongly by the addition of block copolymer micelles to the receptor phase; this suggests a micelle-promoted release mechanism.

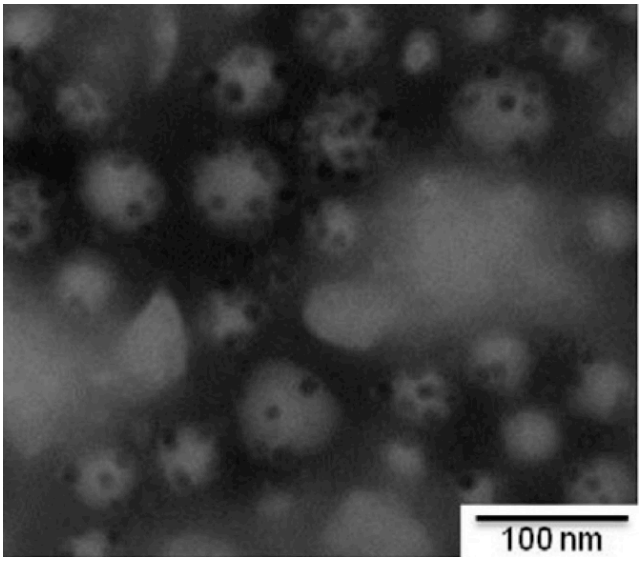

Figure 4. Nano-emulsion-derived PLGA particles loaded with magnetic (iron oxide) nanoparticles (adapted from Colloids and Surfaces B: Biointerfaces 160, 535-542, **2017**)

CELL THERAPY

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MARTA GUERRA REBOLLO
ÓSCAR MECA CORTÉS
LOURDES SÁNCHEZ-CID PÉREZ

ARTICLES

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. 2016; 11(1):104-12.

Real-Time Bioluminescence Imaging of Cell Distribution, Growth, and Differentiation in a Three-Dimensional Scaffold Under Interstitial Perfusion for Tissue Engineering. Vila OF, Garrido C, Cano I, Guerra-Rebollo M, Navarro M, Meca-Cortés O, Ma SP, Engel E, Rubio N, Blanco J. Tissue Eng Part C Methods. 2016; 22(9):864-72.

Development of near-infrared photoactivable phthalocyanine-loaded nanoparticles to kill tumor cells: An improved tool for photodynamic therapy of solid cancers. Duchi S, Ramos-Romero S, Dozza B, Guerra-Rebollo M, Cattini L, Ballestri M, Dambruoso P, Guerrini A, Sotgiu G, Varchi G, Lucarelli E, Blanco J. Nanomedicine. 2016; 12(7):1885-1897.

CRISPR/Cas9-Mediated Knockin Application in Cell Therapy: A Non-viral Procedure for Bystander Treatment of Glioma in Mice. Meca-Cortés O, Guerra-Rebollo M, Garrido C, Borrós S, Rubio N, Blanco J. Mol Ther Nucleic Acids. 2017; 8:395-403.

MicroRNA-200, associated with metastatic breast cancer, promotes traits of mammary luminal progenitor cells. Sánchez-Cid L, Pons M, Lozano JJ, Rubio N, Guerra-Rebollo M, Soriano A, Paris-Coderch L, Segura MF, Fueyo R, Arguimbau J, Zodda E, Bermudo R, Alonso I, Caparrós X, Cascante M, Rafii A, Kang Y, Martínez-Balbás M, Weiss SJ, Blanco J, Muñoz M, Fernández PL, Thomson TM. Oncotarget. 2017; 8(48):83384-83406.

RESEARCH PROJECTS

NUEVO TRATAMIENTO PARA EL GLIOBLASTOMA MULTIFORME BASADO EN TERAPIA GENICA NO INVASIVA (RTC 2014-2077-1)

RETOS COLABORACION

Coordinador:
Sagetis Biotech

Participantes:
Grupo de Ingeniería de Materiales (IQS-Universidad Ramón Llull) I.P. S. Borrós

Grupo de Terapia Celular (IQAC-CSIC) I.P. J. Blanco

MULTIFUNCIONAL NANOPARTICULAS FOR GLIOMA CELL THERAPY (TRANSMAG)

Proyectos de transferencia CIBER-BBN 2016-2017

Coordinador:
J. Blanco

Participantes:
J. Santamaria
Sagetis Biotech

ESTRATEGIA COMBINADA CONTRA LAS CELULAS MADRE DEL GLIOBLASTOMA RESISTENTES A TERAPIA (SAF 2015-64927-C2)

Coordinador:
J. Blanco

Participante:
S. Borrós

RESEARCH HIGHLIGHTS

The Cell Therapy group has continued working in the area of cell therapy against tumors. Random introduction of DNA sequences in the human genome is inherently dangerous due to the possibility of mutating antioncogenes. To avoid this, we have used the CRISPR/Cas9 to generate therapeutic mesenchymal stem cells (MSCsTer) bearing the thymidine kinase gene in a specific location of the genome. Moreover, we have demonstrated that such cells have antiglioma therapeutic capacity, equivalent to the virally modified ones.

Since discovering that MSCsTer used against gliomas are not killed in vivo by the Ganciclovir treatment, we were forced to assume that their therapeutic effect was mediated by an exosome or exosome-like based mechanism. Therefore, during the past year we have initiated a project to facilitate large scale purification of extracellular vesicles for therapy.

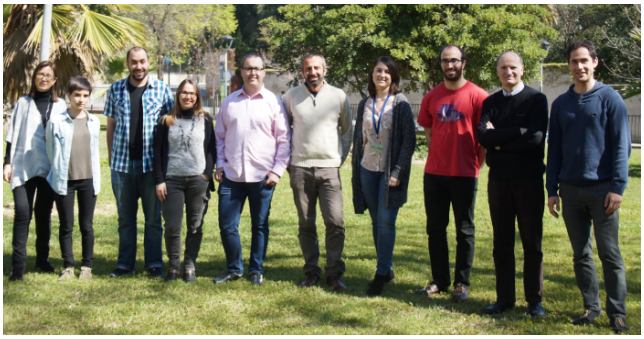
A consequence of anti-replication therapy against tumors is the appearance of a pool of therapy resistant glioma stem cells, that we can detect and quantify by bioluminescence imaging, capable of recapitulating tumors upon release from therapy. We believe that these cells are the last resource of therapy resistance and, in consequence, have aimed the project on their eradication.

The team has been funded by: a MINECO project, a Retos Collaboration project with Instituto Químico de Sarria (Barcelona) and SAGETIS, the Cell Therapy Network (TERCEL) and by a CIBER "Transference" project.

The group has collaborated with CIBER groups for Biomaterials for Regenerative Therapy (IBEC); Bioengineering and Tissue Regeneration (UMA-Bionand) and Nanostructured Surfaces and Nanoparticle (NFP-INA), as well as with the Cardiac Insuficiency and Regeneration group Hospital Germans Trias i Pujol.

SURFACE CHEMISTRY

The main objective is studying the formation and characterization of novel nanostructured systems, and evaluating their applications in novel technological processes. The main reasearch lines include: (a) Study of the formation and stabilization of novel water-in-water (W/W) dispersions; (b) Formation and study of hydrogels and microgels, with stimuli-sensitive properties; (c) Development of novel advanced textiles, by incorporation of nanostructured systems, and (d) Preparation and characterization of organic and inorganic complex porous materials.



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NÉSTOR SALINAS GONZÁLEZ
LAURA CORVO ALGUACIL

INDEXED ARTICLES

Hybrid hierarchical porous silica templated in nano-emulsions for drug release.

P. Riachy, F. Roig, M.J. García-Celma, M.J. Stébé, A. Pasc, J. Esquena, C. Solans and J.L. Blin. *European Journal of Inorganic Chemistry*, 1989–1997 (2016).

Dynamic vapour sorption and thermoporometry of polyamide fabricscoated with chitosan hydrogels

S. Vílchez, A.M. Manich, J. Miras, R. Molina, P. Erra, J. Esquena.

Thermochimica Acta, 639, 47–52 (2016).

Synthesis and properties of TiO_2-P_2O_5 and SiO_2-TiO_2-P_2O_5 porous hybrids obtained by templating in highly concentrated emulsions.

L.A. Pérez-Carrillo, S. Vílchez, J. Mosa, M. Aparicio, Y. Castro, A. Duran, J.M.D. Tascón, J. Esquena. *Ceramics International* 42, 18965–18973 (2016).

Supramolecular metallogel that imparts self-healing properties to other gel networks.

T. Feldner, M. Haring, S. Saha, J. Esquena, R. Banerjee and D. Diaz Diaz.

Chem. Mater.28 (9), 3210–3217 (2016).

Investigation of the elastic and adhesion properties of adsorbed hydrophobically modified inulin films on latex particles using atomic force microscopy (AFM).

M. Obiols-Rabasa, G. Oncins, F. Sanz, Th.F. Tadros, C. Solans, B. Levecke, K. Booten, J. Esquena.

Colloids and Surfaces A 524, 185–192 (2017).

DHA and L-carnitine loaded chitosan hydrogels as delivery systems for topical applications.

I. Sole, S. Vılchez, J. Miras, N. Montanya, M.J. Garcıa-Celma, J. Esquena.

Colloids and Surfaces A: Physicochem. Eng. Aspects (2017).

Comparative study of surface chemical composition and oxide layer modification upon oxygen plasma cleaning and piranha etching on a novel low elastic modulus $Ti_{25}Nb_{21}Hf$ alloy.

Virginia Paredes, Emiliano Salvagni, Enrique Rodríguez-Castellón, José María Manero. *Metallurgical and Materials Transactions A*, 48 (8), 3770–3776 (2017).

Water-in-Water (W/W) emulsions

J. Esquena.

Current Opinion in Colloid & Interface Science, 25, 109–119, (2016).

BOOK CHAPTERS

J. Nestor, J. Esquena. SILICA AND TITANIA NANODISPERSIONS (CHAPTER 5). 'Nanocolloids. A Meeting Point for Scientists and Technologists. Edited by M. Sánchez-Domínguez and C. Rodríguez-Abreu (2016)

NON-INDEXED ARTICLES

Procesos de estampación con un menor impacto mediambiental

J. Miras, S. Vilchez, N. Puigventós, J. Esquena. *Revista Química e Industria textil*, nº 18, pags. 19-27 (2016)

RESEARCH PROJECTS AND CONTRACTS

Biopolymer Based Food Delivery Systems (BIBAFOODS). FP7-PEOPLE-2013-ITN, 606713.

European Union FP7, Marie Curie Action.

2014-2018.

Diseño y aplicaciones de nuevos micro/nanogeles biocompatibles obtenidos mediante métodos de condensación avanzados (MICRONANOGELES). CTQ2014-52687-C3-1-P

Programa estatal de investigación, desarrollo e innovación orientada a los retos de la sociedad.

2015-2017.

Novel antimicrobial hydrogels for contact lenses (HYDROLENSES) TECSPR14-2-0044

TECNIOSPRING Program, ACC1Ó – European Commission (COFUND Program)

2015–2017.

Apoyo Tecnológico a la Obtención de emulsiones de simeticona estables

Laboratorio Estedi S.L.

From 2012.

Prácticas de un Máster en Cosmética y Dermofarmacia.

Centro de Estudios de la Industria Farmacéutica (CESIF)

From 2008.

RESEARCH SUPPORT GRANTS (Coordinated by the Surface chemistry Group)

Ajuts per donar suport a les activitats dels grups de recerca (SGR)

2014SGR1655 and 2017SGR1778, AGAUR, Generalitat de Catalunya. (2014-2016 and 2017-2019, respectively)

Ajuts als plans d'actuació dels centres reconeguts i candidats TECNIO

TECCIT15-1-0009 and TECCIT16-1-0049, ACCIÓ, Generalitat de Catalunya (2015-2016 and 2016-2017, respectively)

RESEARCH HIGHLIGHTS

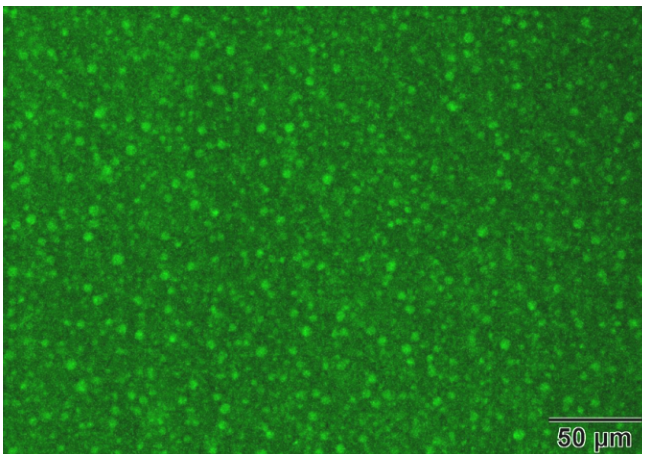
STUDY OF NOVEL WATER-IN-WATER (W/W) EMULSIONS

Water-in-water (W/W) emulsions are colloidal dispersions of an aqueous solution into another aqueous phase. These emulsions can be formed in mixtures of at least two hydrophilic macromolecules, which are thermodynamically incompatible in solution, producing two immiscible aqueous phases. Consequently, water-in-water emulsions can be obtained without oil and without surfactant, with water as the only solvent. Recent advances and successful results in the stabilization of these emulsions have triggered a renewed interest, opening a wide range of novel possibilities for practical applications.

Our research in water-in-water emulsions focuses on systems with fully biocompatible and edible components, mainly consisting of proteins and polysaccharides. Some examples include Gelatin in Maltodextrin, Carboxymethyl cellulose in Bovine Serum Albumin, and BSA in alginate emulsions. We study the formation of W/W emulsions by low-energy methods based on phase transitions, which allow forming emulsions with smaller and controlled droplet size. Other studies deal about the formation and estabilization of multiple wa-

ter-in-water-in-water (W/W/W) emulsions, prepared by two consecutive emulsification steps. The main objective for the future is studying these systems as carriers for the release of active components.

Example of a protein-in-polysaccharide emulsion, labeled with isothiofluorescein.

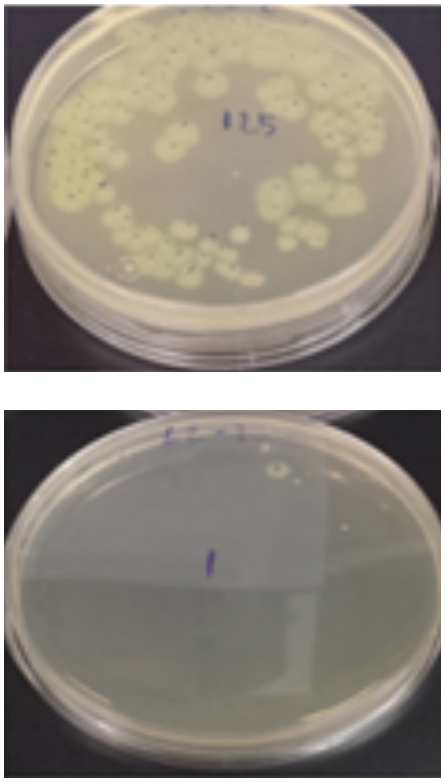


SURFACE FUNCTIONALIZATION OF CONTACT LENSES WITH ANTIMICROBIAL PEPTIDES

The main objective is developing novel surface coated materials bearing antimicrobial molecules with the aim to achieve contact lenses that minimize the risk of corneal infections. It is well known that eye microbial infection is one of the most common problems related to contact lenses. However, current contact lenses do not exhibit anti-bacterial properties.

In order to improve the safety of contact lenses, we propose the functionalization of its surface with antimicrobial peptides (AMPs). These peptides are known to be effective against a wide range of microorganisms. AMPs molecules have been covalently bonded to the surface of contact lenses, and thus, these molecules remain strongly anchored to its surface.

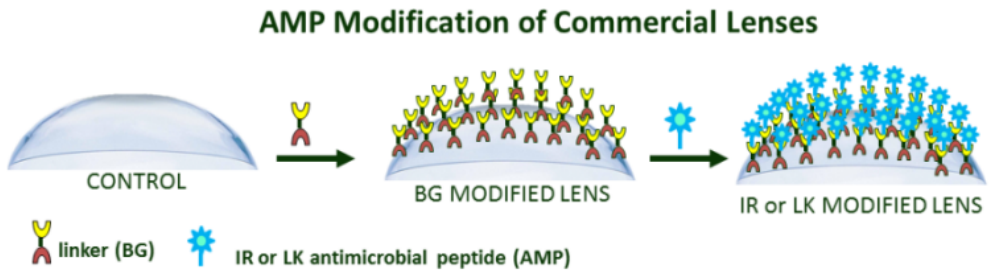
Recently, we have demonstrated that AMP-functionalized contact lenses are highly effective against two model bacteria: Pseudomonas aeruginosa and klebsiella pneumoniae. Our present research focuses on determining the efficacy of AMP-functionalized contact lenses against a wider range of microorganisms; and studying the possible toxicity of AMP-functionalized contact lenses on corneal cells, by in vitro testing with cells from corneal origin.



Examples of bacterial cultures, with many forming-colony units (left) in the positive control sample, and very few colonies (right) in contact with AMP-functionalized contact lenses.

FORMATION AND PROPERTIES OF MICROGELS AS CARRIERS FOR DRUG DELIVERY

Hydrogels are usually defined as three-dimensional networks of highly hydrated polymer materials. They have very high water content, often above 90wt%, but nevertheless they behave as predominantly elastic soft



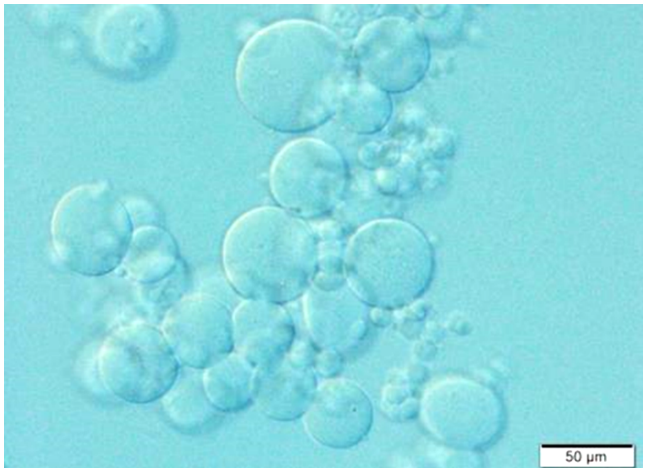
Schematic representation of surface functionalization of contact lenses with AMPs.

materials. Chemical hydrogels, which are cross-linked with covalent bonds, can greatly swell and shrink reversibly, as a response to external stimuli, without dissolving or losing their structural integrity.

This research line focuses on preparation and characterization of microgel particles, with the final aim of studying the microgels as carriers for the delivery of active components. We have prepared biocompatible microgels in mild conditions (neutral pH, low temperature, without oil and without surfactant) by cross-linking in the disperse phase of protein-in-polysaccharide water-in-water (W/W) emulsions. The microgel particles were obtained by adding genipin as a crosslinker, which reacts with amino groups of proteins mainly located inside the droplets.

The enzyme β-galactosidase (known as lactase) has been loaded into cross-linked gelatin microgel particles, and the efficiency of encapsulation and delivery to various receptor solutions has been studied. The results have shown that gelatin microgels are indeed appropriate carriers for the protection and delivery of the enzyme.

Example of a gelatin microgel, observed by optical microscopy.



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 have 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 highly hydrophilic and contain a large amount of water, which allows proteins to be incorporated into the microgels with only moderate conformational changes, preserving the protein activity.

5

CHEMICAL AND SURFACTANTS TECHNOLOGY

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

- Biocompatible Surfactants
- Environmental Chemistry of Surfactants and Ionic Liquids
- Physical Chemistry of Surfactant Systems
- Biophysics of Lipids and Interphases
- Plasma Chemistry
- Textiles and Cosmetic Innovations
- Sustainable processes and materials characterization

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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TERESA PARADELL GIL (University of Barcelona)

ARTICLES

New cationic vesicles prepared with double chain surfactants from arginine: Role of the hydrophobic group on the antimicrobial activity and cytotoxicity.

Pinazo, A; Petrizelli, V; Bustelo, M; Pons, R; Vinardell, M P; Mitjans, M; Manresa, A; Perez, L.

Colloids and Surfaces B, 2016, 141, 19-27

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Amino acid-based surfactants: New antimicrobial agents

Pinazo, A.; Manresa, M. A.; Marques, A. M.; Pérez, L.

Advances in Colloid and Interface Science, 2016, 228, 17-39

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Lichenysin-geminal amino acid-based surfactants: Synergistic action of an unconventional antimicrobial mixture.

J. Coronel-León, A. Pinazo, L. Pérez, M.J. Espuny, A.Marqués, A. Manresa

Colloids and Surfaces B: Biointerfaces, 2017, 149, 38-47.

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Green Catanionic Gemini Surfactant–Lichenysin Mixture: Improved Surface, Antimicrobial, and Physiological Properties.

Ruiz A.; A. Pinazo, L. Pérez, A. Manresa, A. Marquez. ACS Appl. Mater. Interfaces, 2017, 9, 22121-22131.

.....

Monocatenary histidine-based surfactants: Role of the alkyl chain length in antimicrobial activity and their selectivity over red blood cells

Bustelo, M; Pinazo, A.; Manresa, M.A.; Vinardell, M.P.; Pérez, L.

Colloids and Surfaces A, 2017, 532, 501-509.

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Pharmaceutical versatility of cationic niosomes derived from amino acid-based surfactants: Skin penetration behavior and controlled drug release.

R. Muzzalupo, L. Pérez, A. Pinazo, L. Tavano

International Journal of Pharmaceutics, 2017, 529, 245-252.

.....

Self- Aggregation and Emulsifying Properties of Methyl Ester Sulfonate Surfactants

Asselah A.; A. Pinazo, A. Mezei, L. Pérez, A. Tazerouti

J. Surfactant and Detergents, 2017, 20, 1453-1465.

.....

Micellization and Antimicrobial Properties of Surface-Active Ionic Liquids Containing Cleavable Carbonate Linkages

Garcia, MT; Ribosa, I; Perez, L; Manresa, A ; Comelles, F.

Langmuir, 33, 6511-6520, 2017.

.....

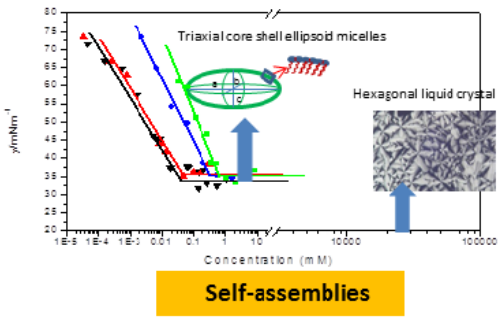
Protein-repellent and antimicrobial nanoparticle coatings from hyaluronic acid and a lysine-derived biocompatible surfactant.

Bracic, M; Fras-Zemljic, L; Perez, L; Kogej, K; Stana-Kleinschek, K; Kargl, R; Mohan, T,

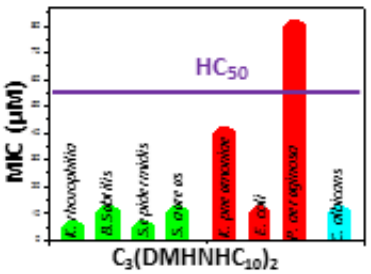
J. of Materials Chemistry B, 2017, 5, 3888-3897.

RESEARCH HIGHLIGHTS

Synthesis of new biocompatible surfactants from natural renewable materials such as amino acids and fatty acids or fatty amines: study of their micellization process, phase behavior, antimicrobial activity and cellular toxicity.



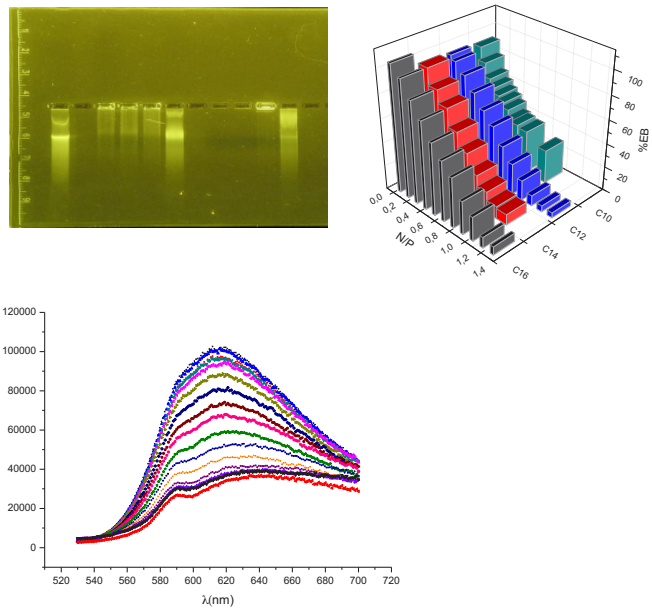
Self-assemblies



New monocatenary and gemini cationic surfactants bearing imidazolium groups as polar heads and alkyl chains of various lengths were prepared using the amino acid histidine as starting material. The surface properties of these surfactants were assessed by measuring their conductance and surface tension, and the morphology of aggregates formed in aqueous solution was determined by SAXS. Several physicochemical parameters were calculated from the surface tension measurement, including the surface tension at the cmc (γcmc), adsorption efficiency (pC20), effectiveness of surface tension reduction (γcmc), and the standard molar Gibbs energy of micellization. The surfactants were found to have very low cmc values and reduced the surface tension of water solutions with high efficiency.

The minimum inhibitory concentration values against representative Gram-positive and Gram-negative bacteria as well as the hemolytic activity depended on the alkyl chain length, the C10 homologue being the most active compound against all strains tested and the least toxic against erythrocytes. These surfactants are active against methicillin-resistant Staphylococcus aureus (MRSA), microorganism often resistant to several widely used antibiotics. Their extraordinary interfacial properties as well as biological activity suggest these new surfactants have potential use in biomedical applications

The use of gemini cationic lipids based on amino acid as cationic groups in a vesicles to improve their transfection activity and biocompatibility.



Electrophoresis mobility in agarose gel for DNA (**A**) and gemini surfactant/ DNA mixtures at different charge ratios and Displacement of ethidium bromide from DNA-EB complex by a gemini histidine surfactants at different charge ratios

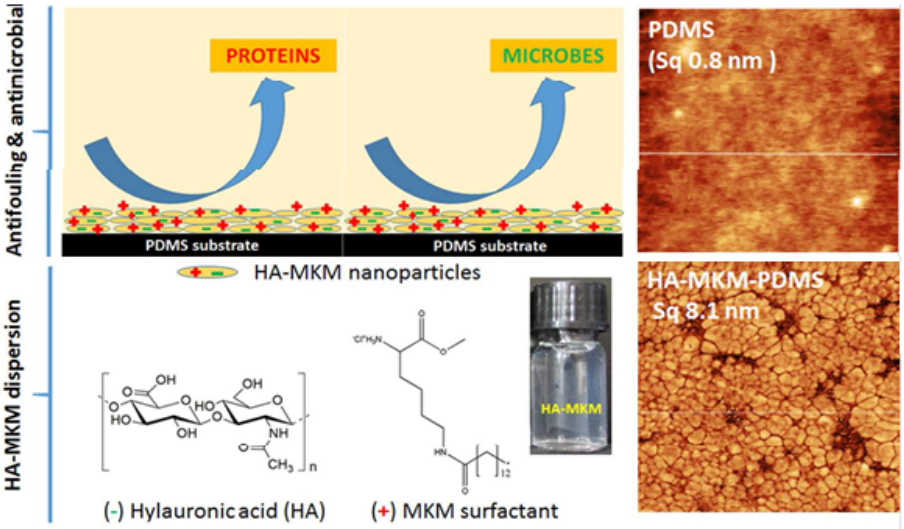
In vivo and in vitro evaluation of the transfection activity of gemini cationic lipids based on amino acids have been evaluated. The gemini cationic lipids were mixed with a fusogenic helper lipid and the physicochemical characterization of the gemini surfactant/fusogenic-pDNA lipoplexes with two different DNA plasmids was carried out. Agarose gel electrophoresis and zeta potential was used to evaluate the compaction of plasmids whilst their structure was characterized by small-angle X-ray scattering (SAXS) and the bilayer fluidity by fluorescence anisotropy. For gemini surfactants from histidine the transfection efficiency was evaluated *in vitro* using COS-7 cells line through fluorescence assisted cell sorting (FACS) and luminometry. Interestingly, the Gemini histidine/DOPE-pDNA lipoplexes have shown few cytotoxicity for all the formulations analyzed. Moreover, *in vitro* experiments with a therapeutic plasmid (IL-12) and *in vivo* assays with plasmid pCMV-Luc in mice were also accomplished. Biological *in vitro* and *in vivo* results conclude that the gemini histidine based surfactant/DOPE-pDNA lipoplexes are highly efficient and biocompatible as nucleic acids nanocarriers and are potential candidates as therapeutic vectors.

Preparation of vesicles using amino acid based surfactants: physicochemical characterization (size, z-potential and stability), drug encapsulation, drug realise and citotoxicity.

Cationic vesicles present important pharmacological advantages including the selective targeting of the tumour vasculature, the promotion of permeation across cell membranes, as well as the influence of cationic vesicles on drug delivery. Cationic amphiphiles derived from amino acids may represent an alternative to traditional synthetic cationic surfactants due to their lower cytotoxicity. The importance lysine-based gemini surfactants was evaluated in drug delivery by designing cationic niosomes as usable pharmaceutical tools of chemotherapeutics and antibiotics, respectively like methotrexate and tetracycline. The influence of formulation factors on the vesicles' physical-chemical properties, drug entrapment efficiency, *in vitro* release and *ex-vivo* skin permeation were investigated. Moreover niosomal gels containing the gemini surfactant were also tested as a viable multi-component topical formulation. It has been observed that in the presence of cholesterol, gemini surfactants from lysine were able to form stable and nanosized niosomes, loading hydrophilic or hydrophobic molecules. Furthermore, *in vitro* release studies and *ex-vivo* permeation profiles showed that these vesicles behave as sustained and controlled delivery systems in the case of parenteral administration, and as drug percutaneous permeation enhancers after topical application. Finally, the gemini surfactant from lysine act as carrier constituents, conferring peculiar and interesting functionality to the final formulations.

Preparation of antimicrobial advanced materials: design of advanced materials with antimicrobial and antibiofilm properties

The biofilm formation triggered by uncontrolled protein adsorption, on medical devices is the leading cause of catheter-associated urinary tract infections (CAUTI) during implantation. We have developed a water-based, green and one-step strategy to functionalize surfaces of silicone catheters, poly(dimethylsiloxane)



(PDMS), with antifouling and antimicrobial substances to avoid uncontrolled protein adsorption and microbial attachment. A novel synergetic formulation

consisting of an anionic glycosaminoglycan (hyaluronic acid, HA) and a lysine-derived biocompatible cationic surfactant (Nε -myristoyl-lysine methyl ester, MKM) was prepared, resulting in the formation of nanoparticles (NPs, *ca.* 100 - 250 nm). Besides their high stability

and long-lasting hydrophilicity in ambient and aqueous environments for 60 days, the nanometric layers of HA-MKM NPs on PDMS showed no adsorption of BSA and lysozyme and substantially lower adsorption of fibrinogen as revealed by a quartz crystal microbalance with dissipation (QCM-D). *In-vitro* antimicrobial test with *S. Aureus*, *E. Coli*, *P. Aeruginosa*, *P, Mirabilis C. Albicans* microbes under dynamic conditions revealed that the microbial growth was hampered by 85% compared with unmodified PDMS. Given the multiple functionalities, charges and diverse physiochemical properties of polysaccharide-lysine-based surfactant mixtures, this approach can be easily extended to the development of novel coatings on other silicone-based materials, thereby broadening potential applicability of PDMS-based biomaterials/devices in microfluidics, diagnostic biosensors and others.

Green Catanionic Gemini Surfactant-Lichenysin Mixture improved Surface, Antimicrobial, and Physiological Properties

Catanionic surfactant mixtures form a wide variety of organized assemblies and aggregates with improved physicochemical and biological properties. Zeta potential and Monolayer results showed that one of the cationic charges of the gemini surfactant $C_3(CA)_2$ is neutralised by Lichenysin biosurfactant forming stable aggregates. The **catanionic** aggregate was able to interact with bacterial phospholipids showing antimicrobial synergies against *Yersinia enterocolitica*, *Bacillus subtilis*, *Escherichia coli* O157:H7 and *Candida albicans*. According to the therapeutic index, the $C_3(CA)_2$:Lichenysin mixture was the formulation least toxic to eukaryotic cells. Partial neutralisation of $C_3(CA)_2$ by lichenysin modified the mode of action that enhances the transition of bacterial cells into a viable but nonculturable state (VBNC) and improved the cell selectivity.

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 efficient and environmentally friendly compounds. Our research activities are mainly focused on the bioavailability, biodegradability and toxicity of surfactants and ionic liquids in the aquatic environment.

STAFF

MARÍA TERESA GARCÍA RAMÓN, Group leader
FRANCESC COMELLES FOLCH

TECHNICIANS

JUAN JOSÉ GONZÁLEZ CHAPARRO
JOSÉ JAVIER PEINADO ROBLES
MARTA ANDRÉS NIETO

Ph.D.

ISABEL RIBOSA FORNOVI

STUDENTS

JUDITH LLENA SOPENA
RAQUEL RODRÍGUEZ ROMERO
IGNACIO VICTORIA SANTACOLOMA
KAINA ASTIER
AURELIE LAROCHE
AURORE BOURGUIGNON

ARTICLES

Biodegradability and aquatic toxicity of quaternary ammonium-based gemini surfactants: Effect of the spacer on their ecological properties

Garcia, M. Teresa; Kaczerewska, Olga; Ribosa, Isabel; Brycki, Bogumil; Materna, Paulina; Drgas, Malgorzata

Chemosphere, 154, 155-160, **2016**

.....

Supramolecular Arrangement of Molybdenum Carbonyl Metallosurfactants with CO-Releasing Properties

Parera, Elisabet; Marin-Garcia, Maribel; Pons, Ramon; Comelles, Francesc; Suades, Joan; Barnadas-Rodriguez, Ramon

Organometallics, 35, 484-493, **2016.**

.....

Hydrophilicity and flexibility of the spacer as critical parameters on the aggregation behavior of long alkyl chain cationic gemini surfactants in aqueous solution

Garcia, M. Teresa; Kaczerewska, Olga; Ribosa, Isabel; Brycki, Bogumil; Materna, Paulina; Drgas, Malgorzata

Journal of Molecular Liquids, 230, 453-460, **2017**

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Hexadecyltrimethylammonium bromide (CTA-Br) and 1-butyl-3-methylimidazolium tetrafluoroborate (bmim-BF4) in aqueous solution: An ephemeral binary system

Comelles, Francesc; Ribosa, Isabel; Gonzalez, Juan Jose; Garcia, M. Teresa

Journal of Colloid and Interface Science, 490, 119-128, **2017**

.....

Micellization and Antimicrobial Properties of Surface-Active Ionic Liquids Containing Cleavable Carbonate Linkages

Garcia, M. Teresa; Ribosa, Isabel; Perez, Lourdes; Manresa, Angeles; Comelles, Francesc

Langmuir 33, 6511-6520, **2017**

.....

Cationic gemini surfactants containing an O-substituted spacer and hydroxyethyl moiety in the polar heads: Self-assembly, biodegradability and aquatic toxicity

Kaczerewska, O.; Brycki, B.; Ribosa, Isabel; Comelles, Francesc; Garcia, M. Teresa

Journal of Industrial and Engineering Chemistry, Ahead of print **2017.**

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

.....

Participación en programas de formación de personal técnico.

Promoción del Empleo Joven e Implemantación de la Garantía Juvenil (MINECO)

.....

Participación en programas internacionales de prácticas (undergraduated students)

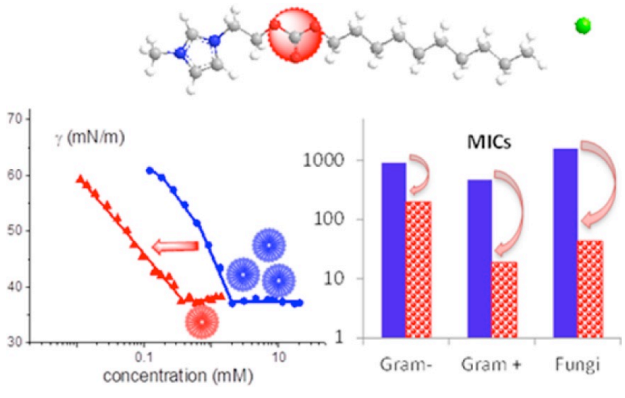
Under-graduated students. Convenio Ecole Superieure de Chimie-Lille (Francia)

RESEARCH HIGHLIGHTS

Self-aggregation and antimicrobial activity of functionalized ionic liquids

The study of ionic liquids (ILs) as a new class of non-molecular, ionic solvents for use in sustainable processes as solvents, catalysts and electrolytes has increased exponentially during the last years. Most widely studied ILs are comprised of bulky, asymmetric N-containing organic cations in combination with any wide variety of anions, ranging from simple inorganic anions to complex organic species. One of the main aspects gaining attention in ILs research is the enormous range of cation-anion combinations, which results in a large potential for adjustability of structure-properties. ILs are often considered "task-specific" because of their possibility to be tailored to fulfill the technological demands of a variety of applications.

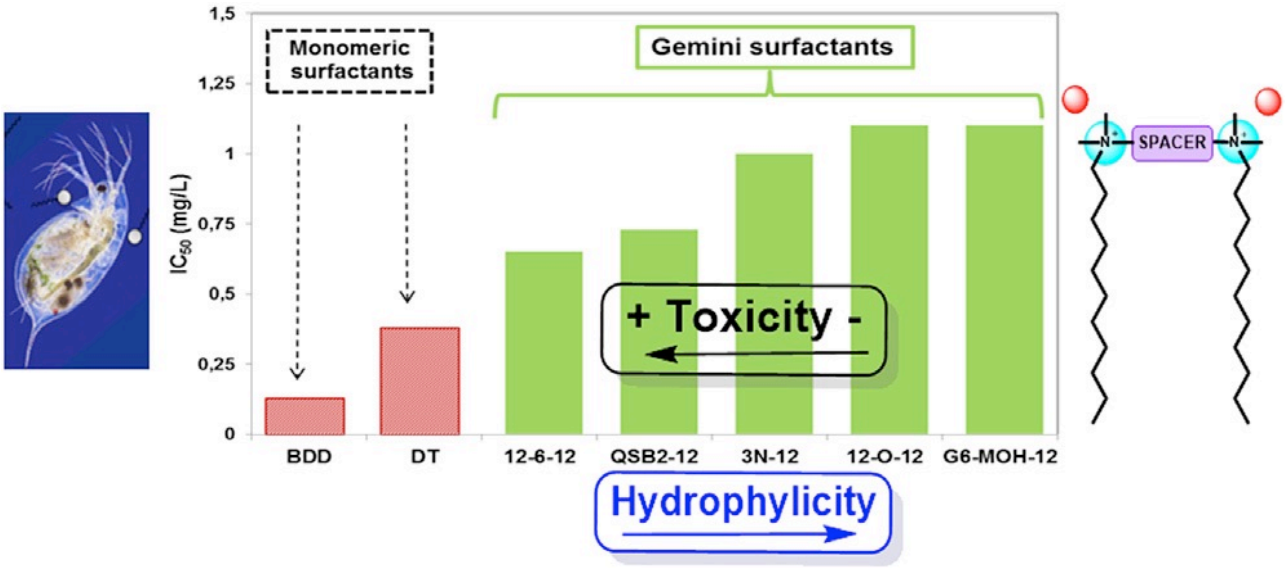
Long chain imidazolium-based ILs possess an inherent amphiphilic nature and exhibit interfacial and aggregation behavior analogous to conventional surfactants as we previously showed. Besides, to interfacial activity they can exhibit significant biological activity against bacteria and fungi. However, despite the promising activity of surface-active ionic liquids in a wide range of biotechnological applications, the lack of biodegradability of commonly used imidazolium based ionic liquids poses a threat to the environment. This fact prompted us to design and synthetize a series of ionic liquids containing a primary biodegradation site in the molecule in order to investigate the physicochemical and biological properties of these novel functionalized compounds in relation to non-functionalized imidazolium salts. Therefore, aimed at improving the physicochemical and biological properties of amphiphilic ionic liquids, we disclosed the synthesis, aggregation behavior and antimicrobial activity of a series of novel imidazolium-based surface active ionic liquids containing hydrolysable carbonate linkages. Carbonate-functionalized ionic liquids display high thermal stability and form stable thermotropic smectic liquid crystalline phases in a wide range of temperatures. The ILs investigated exhibit higher adsorption efficiency and better aggregation behavior as they form micellar aggregates at lower concentrations than non-functionalized ILs. These novel compounds present a broad spectrum of antimicrobial activity and are more efficient and selective as antimicrobial agents than simple alkyl chain substituted ILs. Our findings demonstrate the ability of the carbonate ester functionality to modify the parameters affecting self-aggregation and biological activity of imidazolium-based ILs. This work contributes to a better understanding of the structural factors governing the aggregation behavior and biological activity of functionalized ionic liquids, and can aid in the design and selection of ionic liquids with enhanced biodegradability and improved physicochemical properties for biotechnological applications, biocatalysis and preparation of nanostructured materials.



Biodegradability and aquatic toxicity of gemini surfactants: effect of structural parameters on their ecological properties

Gemini surfactants show biological and surface activities much higher than conventional monomeric cationic surfactants. Because of the current increasing use of these compounds as antimicrobials or corrosion inhibitors, detailed knowledge is required to prevent or reduce the potential risk to the aquatic environment. However, scarce information is available on the ecological properties of gemini surfactants. In this context, the aerobic biodegradability and aquatic toxicity of five types of quaternary ammonium-based gemini surfactants that in a previous work showed better surface activity than common single chain cationic surfactants was evaluated. The effect of the spacer structure and the head group polarity on the ecological properties of such dimeric cationic surfactants was investigated. Standard tests for ready biodegradability assessment (OECD 310) were conducted for dodecyl alkyl chain gemini surfactants containing oxygen, nitrogen or a benzene ring in the spacer linkage and/or a hydroxyethyl group attached to the nitrogen atom of the head groups. According to the results obtained, the dimeric surfactants examined cannot be considered as readily biodegradable compounds. The negligible biotransformation of gemini surfactants can be attributed to the toxic effects of these compounds on the aerobic microorganisms responsible for biodegradation under the standard test conditions. Aquatic toxicity of gemini surfactants was evaluated against Daphnia magna. The acute toxicity values to Daphnia magna, IC_{50} at 48 h exposure, ranged from 0.6 to 1 mg/L. Based on these values, the gemini surfactants tested should be classified as toxic or very toxic to the aquatic environment. However, the dimeric quaternary ammonium-based surfactants examined result to be less toxic than their corresponding monomeric analogs. Furthermore, the aquatic toxicity of these gemini surfactants can be reduced by increasing the molecule hydrophilicity by adding an heteroatom to the spacer or a hydroxyethyl group to the polar head groups.

Our study provides reference data about the environmental behavior of quaternary ammonium-based gemini surfactants and the relationship between the hydrophilicity of the dimeric surfactant molecule and its ecological properties and can aid in the design and selection of surfactants for surface protection applications with a lower impact on the aquatic environment.



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.

STAFF

RAMON PONS PONS
JAUME CAELLES BALCELLS
IMMA CARRERA ALTARRIBA

ARTICLES

Cross-linked chitosan/liposome hybrid system for the intestinal delivery of quercetin

Caddeo,C.; Díez-Sales, O.; Pons, R.; Carbone, C.; Ennas, G.; Puglisi, G.; Fadda, A.M[a].; Manconi, M.

J. of Colloid and Interface Sci., 461, 69-78, **2016**

New cationic vesicles prepared with double chain surfactants from arginine: role of the hydrophobic group on the antimicrobial activity and cytotoxicity

A. Pinazo, A.; Petrizelli, V.; Bustelo, M.; Pons, R.; Vinardell, M.P.; itjans, M.; Manresa, A.; Perez, L.

Colloids and Surfaces B, 141, 19-27, **2016**

Supramolecular arrangement of molybdenum carbonyl metallosurfactants with CO releasing properties

Elisabet Parera, Maribel Marín-García, Ramon Pons, Francesc Comelles, Joan Suades, Ramon Barnadas-Rodríguez

Organometallics, 35, 484-493, **2016**

Nioplexes Encapsulated in Supramolecular Hybrid Biohydrogels as Versatile Delivery Platforms for Nucleic Acids

Grijalvo, S.; Puras, G.; Zárate, J.; Pons, R.; Pedraz, J.L. Eritja, R.; Díaz Díaz, D.

RSC Advances, 6, 39688-39688, **2016**

Santosomes as natural and efficient carriers for the improvement of phycocyanin reepithelising ability in vitro and in vivo

Castangia, I.; Manca, M.L.; Caddeo, C.; Bacchetta, G.; Pons, R.; Demurtas, D.; Diez-Sales, O.; Fadda, A.M[a]; Manconi, M.

European Journal of Pharmaceutics and Biopharmaceutics, 103, 149-158, **2016**

Chiral Cyclobutane β-Amino Acid-Based Amphiphiles: Influence of Cis/Trans Stereochemistry on Condensed Phase and Monolayer Structure

Sorrenti, A.; Illa, O.; Ortuño, R.; Pons, R.

Langmuir, 32, 6977-6984, **2016**

Effect of quercetin and resveratrol co-incorporated in liposomes against inflammatory/oxidative response associated with skin cancer

Caddeo, C.; Nacher, A.; Vassallo, A.; Armentano, M.F.; Pons, R.; Fernàndez-Busquets, X.; Claudia Carbone, Valenti, D.; Fadda, A.M[a]; Manconi, M.

International Journal of Pharmaceutics, 513, 153-163, **2016**

Physico-chemical characterization of succinyl chitosan-stabilized liposomes for the oral co-delivery of quercetin and resveratrol

Caddeo, C.; Pons, R.; Carbone, C.; Fernàndez-Busquets, X.; Cardia, M.C.; Maccioni, A.M[a]; Fadda, A.M[a]; Manconi, M.

CarbohydratePolymers, 157, 1853-1861, **2017**

Transfection of antisense oligonucleotides mediated by cationic vesicles based on non-ionic surfactant and polycations bearing quaternary ammonium moieties

J. Mayr, S. Grijalvo, J. Bachl, R. Pons, R. Eritja, D.D. Díaz

International Journal of Molecular Sciences, 18, 1139, 1-13, **2017**

RESEARCH PROJECTS

Aplicaciones no convencionales de tensioactivos y liquidos ionicos derivados de aminoacidos naturales en nanotecnologia y quimica sostenible.

MINECO- CTQ2013-41514-P

2014-2016

.....

Colaboración, asesoramiento científico y uso de las instalaciones del CSIC, para del desarrollo del proyecto " reducción de contaminantes en fuel"

Investigación y desarrollo

SYNTHIOS SL

2015-2017

Determinación de azufre y otros metales en fueles recuperado

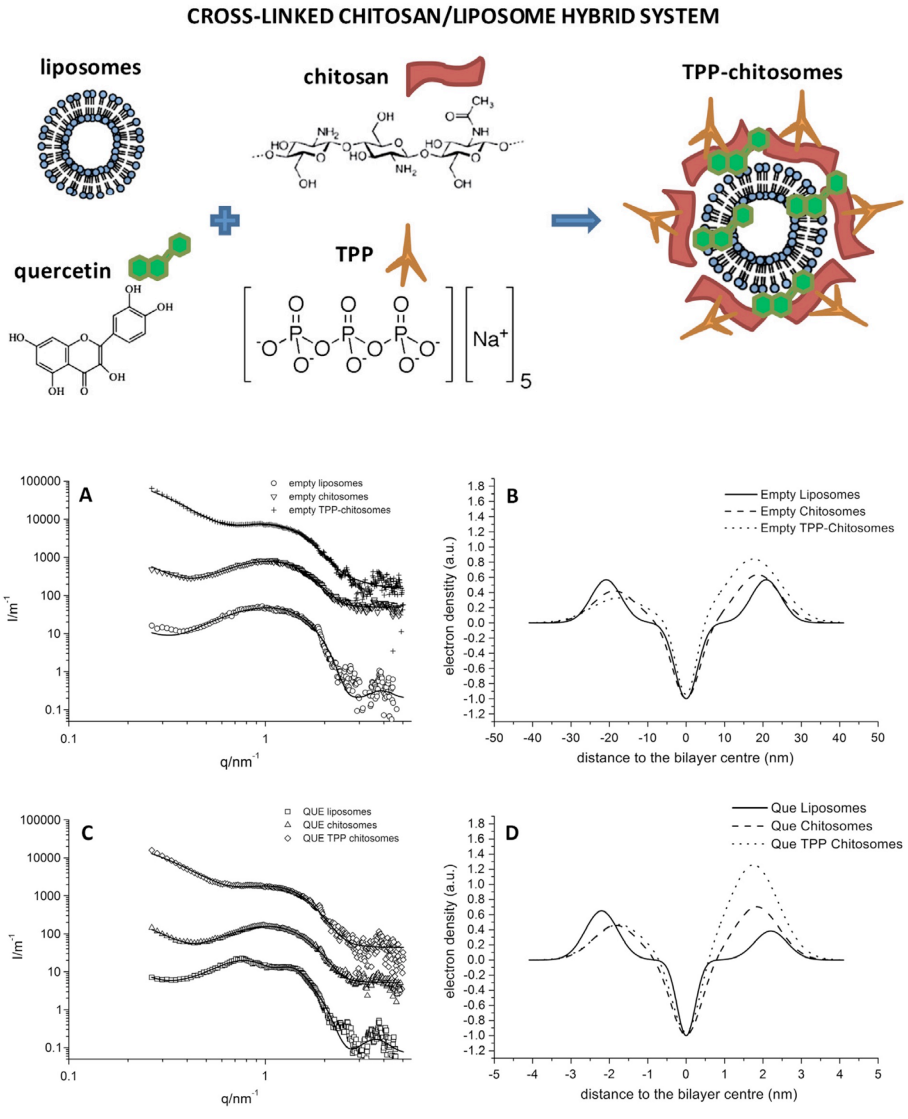
Apoyo tecnológico

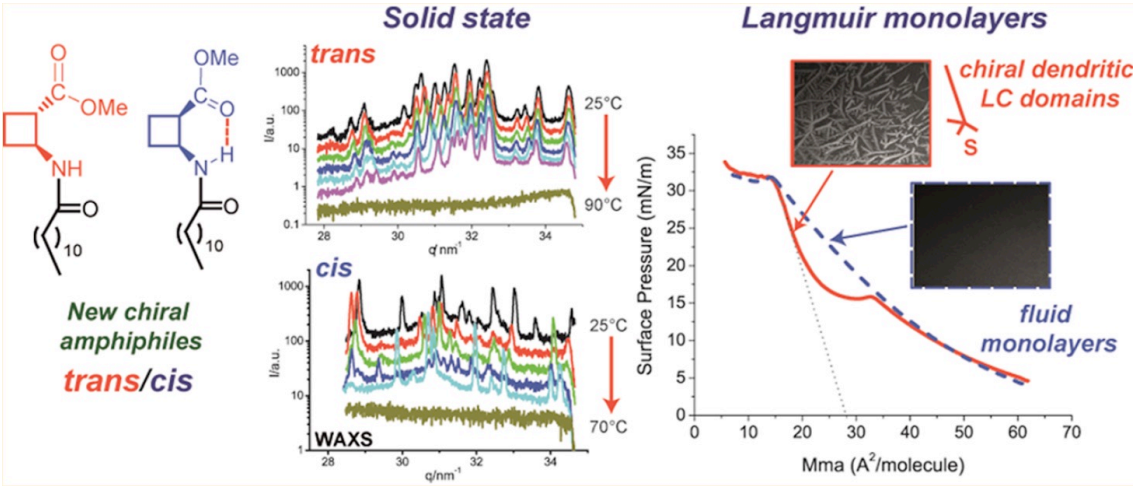
Energía SA

2015 - 2017

RESEARCH HIGHLIGHTS

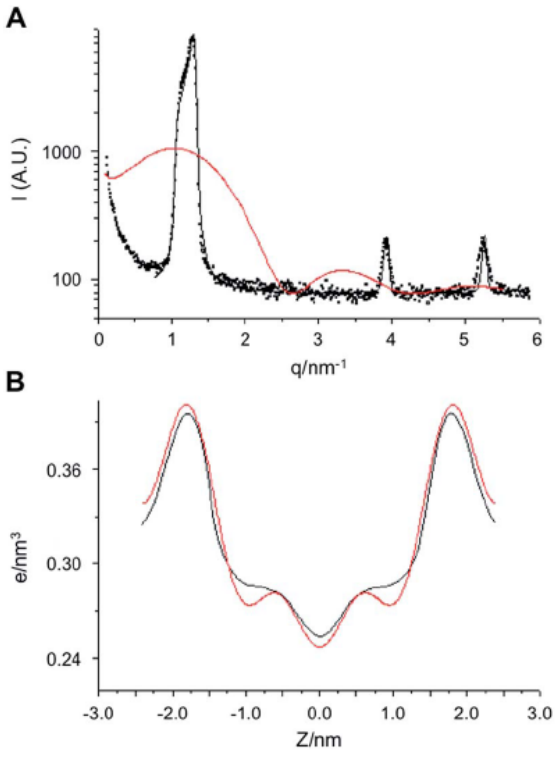
Effort has been made to determine the characteristics of liposome's bilayers for drug delivery. Systematic comparison of empty and loaded liposomes allows determining specific site location in the bilayer. For this purpose the bilayers have been modeled allowing for asymmetric electronic profiles, taking into account the maximum number of restrictions possible. This is exemplified in the figure below where liposomes were





loaded a drug and the liposome protected by precipitation of chitosan crosslinked with tripolyphosphate. The symmetry of the bilayers is lost when chitosan is added to the liposomes showing the effective coating of the liposomes. The release of quercetin in simulated gastric and intestinal pH was investigated, the results showing that the system provided resistance to acidic conditions, and promoted the release in alkaline pH, mimicking the intestinal environment

New diastereomeric nonionic amphiphiles, cis- and trans-, based on an optically pure cyclobutane β-amino ester moiety have been investigated to gain insight into the influence exerted by cis/trans stereochemistry and stereochemical constraints on the physicochemical behavior, molecular organization, and morphology of their Langmuir monolayers and dry solid states. All these features are relevant to the rational design of functional materials. trans showed a higher thermal stability than cis. For the latter, a higher fluidity of its monolayers was observed when compared with the films formed by trans whose BAM images revealed the formation of condensed phase domains with a dendritic shape, which are chiral, and all of them feature the same chiral sign. Although the formation of LC phase domains was not observed by BAM for cis-1, compact dendritic crystals floating on a fluid subphase were observed beyond the collapse, which are attributable to multilayered 3D structures. These differences can be explained by the formation of hydrogen bonds between the amide groups of consecutive molecules allowing the formation of extended chains for trans-1 giving ordered arrangements. However, for cis-1, this alignment coexists with another one that allows the simultaneous formation of two hydrogen bonds between the amide and the ester groups of adjacent molecules. In addition, the propensity to form intramolecular hydrogen bonds must be considered to justify the formation of different patterns of hydrogen bonding and, consequently, the formation of less ordered phases. Those characteristics are congruent also with the results obtained from SAXS–WAXS experiments which suggest a more bent configuration for cis-1 than for trans-1.



Small-angle X-ray scattering (SAXS) measurements showed the formation of lamellar structures for glycerol-based lipid- which remained practically constant in a temperature range between 25 _C and 45 _C. Furthermore, the strong correlation and low flexibility of the bilayers deduced from the SAXS curves supported the stability of nioplexes. It is worth mentioning that a complete fusion of the lipid-1 was observed in the SAXS pattern when the temperature was increased at 55 _C.

BIOPHYSICS OF LIPIDS AND INTERPHASES

The group of Biophysics of Lipids and Interfaces addresses scientific objectives that consider biophysical, biochemical, physical-chemical and technological aspects related to biological membranes and complex tissues. The research of the group is based on the study and biomedical application of colloidal systems in which lipids and other amphiphiles have a relevant role such as liposomes, micelles, bicelles, bicosomes and other arrangements. In addition, research related to the knowledge, behavior and treatment of tissues such as the skin, mucosal membranes and the hair are also among our objectives.

During recent years, within the framework of our projects, the group has proposed different phospholipid systems for the treatment of the skin, with special emphasis on the use of these systems for the transport and delivery of antioxidants. A new strategy based on lipid systems that mimic epidermal biological structures has been proposed for the treatment of skin diseases. Lipid systems have been developed for the transport and improvement of antibiotic efficacy and efforts have been made to obtain adequate membrane models where certain proteins and peptides maintain or even improve their activity. All this is addressed through the application of high resolution technologies such as cryoelectron microscopy and techniques based on Synchrotron radiation.

We emphasize that the purpose of the group's activities is to have a medium-term impact in the industry and to solve society's problems. Due to the novelty of the topics that are addressed, we need to undertake basic research in order to obtain knowledge that allows adequate applicability.

STAFF

ALFONS DE LA MAZA RIBERA
OLGA LÓPEZ SERRANO

Ph.D.

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MERCEDES CÓCERA NÚÑEZ
GELEN RODRÍGUEZ DELGADO

Ph.D. STUDENTS

VERÓNICA MONER DEL MORAL
KIRIAN TALLÓ DOMÍNGUEZ

ARTICLES

SORPTION–DESORPTION TEST FOR FUNCTIONAL ASSESSMENT OF SKIN TREATED WITH A LIPID SYSTEM THAT MIMICS EPIDERMAL LAMELLAR BODIES

V. Moner, E. Fernández, A. del Pozo, G. Rodríguez, M. Cócera. A. de la Maza, O. López.

Contact Dermatitis, 77, 25-34 (2017)

THE FIRST FLUOROGENIC SENSOR FOR SPHINGOSINE-1-PHOSPHATE LYASE ACTIVITY IN INTACT CELLS

P. Sanllehí, M. Casasampere, J-L. Abad, G. Fabriàs, O. López, J. Bujons, J. Casas, A. Delgado.

Chem. Commun., 53, 5441-5444 (2017)

MONITORING BICOSOMES CONTAINING ANTIOXIDANTS IN NORMAL AND IRRADIATED SKIN.

E. Fernández, S. Hostachy, C. Sandt, G. Rodriguez, HC Bertrand, S. Clède, M. Cócera, A. de la Maza, F. Lambert, C. Policar, O. López.

RSC Advances, 6: 72559-72567 (2016).

LAMELLAR BODY MIMETIC SYSTEM: AN UP-TO-DOWN REPAIRING STRATEGY OF THE STRATUM CORNEUM LIPID STRUCTURE.

V. Moner, E. Fernández, G. Rodriguez, M. Cócera,L. Barbosa-Barros, A. de la Maza, O. López.

Int J Pharmaceutics, 510: 135-143 (2016).

REDUCING THE HARMFUL EFFECTS OF INFRARED RADIATION ON THE SKIN USING BICOSOMES INCORPORATING B-CAROTENE

E. Fernández, L Fajari, M. Cócera, V. Moner, ,L. Barbosa-Barros, Kamma-Lorger CS, A. de la Maza, O. López.

Skin Pharmacol Physiol, 29(4): 169-177 (2016).

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ESTUDIAR LA PIEL CON LUZ SINCROTRON.

I. Yousef, N. Benseny, M. Kreuzer, T. Ducic, AB Martinez, M Ávila, M Cocera, G Rodriguez, R Saldaña, L Barbosa-Barros, E Fernandez, V Moner, O. López.

Pharmatech, 24: 28-34 (2016).

.....

TECNOLOGIA BICOSOME CON CAROTENOS: REFORZANDO LA FOTOPROTECCIÓN BIOLÓGICA DE LA PIEL.

G Rodriguez, M Cocera, R Saldaña, L Barbosa-Barros, E Fernandez, A de la maza, O. López.

Industria Cosmetica, 001: 36-43 (2016).

.....

ADVANCED LIPID DELIVERY SYSTEM FOR ANTIOXIDANTS

G Rodriguez, M Cocera, L Barbosa-Barros, E Fernandez, O. López.

Personal Care, June: 50-54 (2016).

RESEARCH PROJECTS

DESARROLLO DE UNA FORMULACIÓN QUE ESTABILICE LA FOSFOMICINA Y AUMENTE LA BIODISPONIBILIDAD DEL ANTIBIÓTICO

Tipo de contrato:N

Empresa/Administración financiadora: LABIANA SA

Entidades participantes: LABIANA y IQAC

Duración: 2013-2016

Investigador responsable: Dr. O. López

.....

PREPARACIÓN Y CARACTERIZACIÓN DE BICOSOMAS QUE CONTENGAN PRINCIPIOS ACTIVOS COSMÉTICOS

Tipo de contrato:N,

Empresa/Administración financiadora: BICOSOME SL

Entidades participantes: BICOSOME SL y IQAC-CSIC

Duración: 2015-2017

Investigador responsable: Dr. O. López

.....

FISICOQUIMICA I ESTRUCTRUACIÓN VESICULAR DE LIPIDS I BIOPOLÍMERS BACTERIANS. (2014 SGR 1325)

ENTIDAD FINANCIADORA: Generalitat de Catalunya

ENTIDADES PARTICIPANTES: C.S.I.C. y Univ. Barcelona

DURACION: 2014-2016

INVESTIGADOR PRINCIPAL: Dra. Olga López

.....

NANOESTRUCTURACIÓ FÍSICO-QUÍMICA I APLICACIONS DE LÍPIDS I POLÍMERS D'ORIGEN BIOLÒGIC (2017 SGR 986)

ENTIDAD FINANCIADORA: Generalitat de Catalunya

ENTIDADES PARTICIPANTES: C.S.I.C. y Univ. Barcelona

DURACION: 2017-2019

INVESTIGADOR PRINCIPAL: Dra. Olga López

.....

INVESTIGACIÓN DE TERAPIAS ANGIOGÉNICAS BASADAS EN FACTOR TISULAR (RTC-2016-4957-1)

ENTIDAD FINANCIADORA: Ministerio de Economía, Industria y Competitividad

ENTIDADES PARTICIPANTES: C.S.I.C., Hospital Universitario de la Fe, Thrombotargets S.L.

DURACION: 2016-2019

INVESTIGADOR PRINCIPAL: Dra. Olga López, Dra Pilar Sepulveda, Dr. Ignasi Miguel

.....

SISTEMAS LIPIDICOS AVANZADOS PARA LA VEHICULIZACION DE ANTIOXIDANTES

EN APLICACIONES DERMATOLOGICAS (CTQ2013-44998-P)

ENTIDAD FINANCIADORA: Ministerio de Economía y Competitividad

ENTIDADES PARTICIPANTES: C.S.I.C.

DURACION: 2014-2017
INVESTIGADOR PRINCIPAL: Dras Luisa Coderch y Olga López

MONITORING DIFFERENT LIPID SYSTEMS INTO THE SKIN BY FTIR MICROSPECTROSCOPY

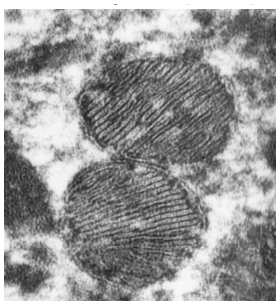
ENTIDAD FINANCIADORA: MINECO y Generalitat de Cataluña

ENTIDADES PARTICIPANTES: C.S.I.C. y Sincrotron Alba
DURACION: 2016
INVESTIGADOR PRINCIPAL: Dr. Olga López

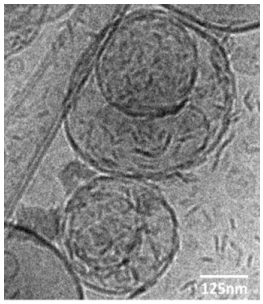
RESEARCH HIGHLIGHTS

Development of a lipid system that mimics the composition and structure of the epidermal lamellar bodies for the treatment of the skin.

Epidermal lamellar bodies are organelles that secrete their content, mainly lipids and enzymes, into the intercorneocyte space of the stratum corneum (SC) to form the lamellar structure of this tissue. Thus, these organelles have a key role in permeability and the microbial cutaneous barrier. The group has designed a complex lipid system that mimics the morphology, structure and composition of epidermal lamellar bodies, the lamellar body mimetic system (LBms).



TEM image of epidermal lamellar bodies.



Cryo-TEM image our lamellar body mimetic system (LBms).

In vitro experiments using porcine skin were performed using freeze substitution transmission electron microscopy (FSTEM) and grazing-incidence small-angle X-ray

scattering (GISAXS). These results demonstrated a strong effect of the treatment in repairing part of the lipid lamellar structure of the SC. In vivo studies in human volunteers also demonstrated that the treatment with this system reinforces the barrier function in both healthy and irritated human skin.

Lipid systems to improve the effectiveness of antibiotics and antifungals.

Bicelles and bicosomes have been used as carriers for antibiotic and antifungal molecules. The effectiveness of these systems was assessed by determination of the amount of drug released, by evaluation of their antimicrobiological efficacy and by assessment of the transmucosal or transcutaneous absorption *in vitro* and/or *in vivo*. When the drug was included in the phospholipid systems, the minimum inhibitory concentration was lower than that of the drug included in the commercial product. Additionally, the amount of drug that was retained in the tissues was higher when the tissue was treated with these new systems. Electron microscopy analysis of the tissues after treatment with the lipid systems containing antimicrobial molecules showed the preservation of the microstructural tissue integrity and the presence of new vesicle-like structures. Thus, these lipid systems offered the following benefits over the use of current formulations: a prolonged delivery of drug, the lack of permeation enhancers that could damage the tissue and a decrease in the amount of drug needed to obtain the same benefits. The bicosomes were the only formulation that remained into the tissue, even after *in vivo* treatment. These systems may even act as a lipid reservoir to alleviate the damaged tissues.

Lipid systems to improve the stability of antioxidants and to increase their free radical scavenging effect on the skin in front of UV-vis and IR radiation.

Different antioxidants were vehiculized into normal skin and skin exposed to ultraviolet-visible radiation (UV-VIS) using in liposomes, bicelles and bicosomes. Using Fourier-transform infrared microspectroscopy (FT-IR) and synchrotron radiation, a higher and deeper penetration of the antioxidants into the skin was observed when vehiculized in the lipid systems. The penetration of the systems in irradiated skin was lower in comparison with the normal skin. This fact could be a consequence of the alteration of water transport in the skin during the irradiation process. These results indicated the effectiveness of bicosome systems as skin carriers, and provide information to protect skin under radiation using antioxidants. Additionally, the stability of the antioxidants improved when incorporated in the lipid systems.

Lipid membrane models for insertion of tissue factor (TF)

We have designed and developed lipid nanostructures such as liposomes and bicelles able to incorporate tissue factor (TF). TF as an integral membrane protein must be incorporated into the proper lipid environment to preserve its optimal activity. The objective has been to evaluate its efficacy in the treatment of conditions mediated by angiogenesis in cardiac and peripheral ischemic disease.

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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TECHNICIANS
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ARTICLES

Synthesis of Thermo-Sensitive Hydrogels from Free Radical Copolymerization of NIPAAm with MBA Initiated by Atmospheric Plasma Treatment.

Jovančić, P.; Vílchez, A.; Molina, R.

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Dynamic vapour sorption and thermoporometry of polyamide fabrics coated with chitosan hydrogels.

Vílchez, S.; Manich, A.M.; Miras, J.; Molina, R.; Erra, P.; Esquena, J.

Thermochimica Acta, 639, 47-52, 2016.

Hydrophobic Coatings on Cotton Obtained by in Situ Plasma Polymerization of a Fluorinated Monomer in Ethanol Solutions

Molina, R.; Teixidó, J.M.; Kan, C.-W.; Jovančić, P.

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Surface chemistry and germination improvement of Quinoa seeds subjected to plasma activation

Gómez-Ramírez, A.; López-Santos, C.; Cantos, M.; García, J.L.; Molina, R.; Cotrino, J.; Espinós, J.P.; González-Elipe, A.R.

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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.

Nuevas nanoestructuras 1d-hibridas multifuncionales para el desarrollo de nanosistemas autoalimentados.

Development of stimuli sensitive textile coatings using plasma in liquids (PLASMABIOGELS).

Nanostructured multilayered architectures for the development of optofluidic responsive devices, smart labels and advanced surface functionalization

RESEARCH HIGHLIGHTS

The research in Plasma Chemistry Group is focused on the technological applications of non-thermal plasmas (low and atmospheric pressure). 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.

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.

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.

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

Fig. 1. Plasma configurations for advances technologies.

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.

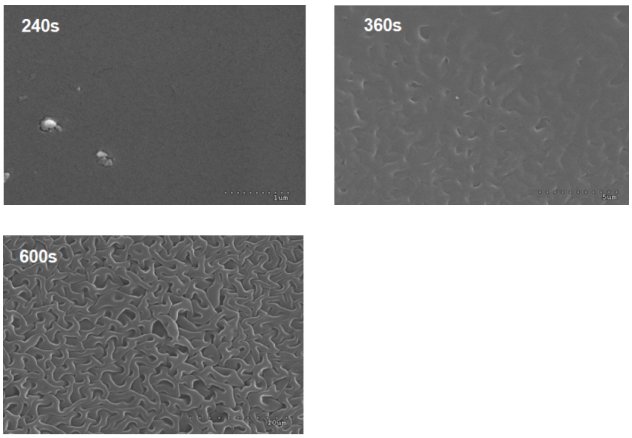

Figure 2. SEM images of N-isopropylacrylamide (NIPAAm) solution (1%) as a function of plasma treatment time.

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.

TEXTILES AND COSMETIC INNOVATIONS

The main scientific activity of this group focuses on the study of physicochemical properties of keratinized tissues such as hair and human stratum corneum. In particular, our main interest is based on the lipid role in the barrier function of these fibers. Besides, much work is being performed on 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.

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MARC ADRIÀ OLIVER NICOLAU

ARTICLES

THE INFLUENCE OF HAIR LIPIDS IN ETHNIC HAIR PROPERTIES

M Martí, C Barba, A M Manich, L Rubio, C Alonso, L Coderch

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SKIN PENETRATION AND ANTIOXIDANT EFFECT OF COSMETO-TEXTILES WITH GALLIC ACID

C. Alonso, M. Martí, C. Barba, M. Lis, L. Rubio and L. Coderch

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THE EFFECT OF INTERNAL LIPIDS ON THE WATER SORPTION KINETICS OF KERATINIZED TISSUES

C. Barba, M. Martí, J. Carilla, A. Manich and L. Coderch

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IN VITRO DVS APPROACH TO EVALUATE SKIN REPARATION

C. Barba, C. Alonso, A. Semenzato, G. Baratto and L. Coderch

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INFLUENCE OF VEHICLES ON ANTIOXIDANT EFFICACY IN HAIR

L. Rubio, C. Alonso, M. Martí, V. Martínez and L. Coderch

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EFECTO ANTIOXIDANTE DE COSMETO-TEXTILES CON ÁCIDO GÁLICO ENCAPSULADO EN MICROESFERAS

C. Alonso, C. Barba, M. Lis, L. Rubio and L. Coderch, M. Martí.

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C. Barba, C. Alonso, M. Martí, A. Manich and L. Coderch

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SOYBEAN-FRAGMENTED PROTEOGLYCANS AGAINST SKIN AGING

C. Barba, C. Alonso, I. Sánchez, E. Suñer, L.C. Sáez and L. Coderch

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L. Coderch, M. Oliver, V. Martínez, A.M. Manich and M. Martí

Skin Research an Technology 23 (2017) 479-485

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SKIN PERMEATION AND ANTIOXIDANT EFFICAY OF TOPICALLY APPLIED RESVERATROL

C. Alonso, M. Martí, C. Barba, M. V. Carrer, L. Rubio and L. Coderch

Archives of Dermatological Research 309, (2017) 423-431

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DEVELOPING TRANSDERMAL APPLICATIONS OF KETOROLAC TROMETHAMINE ENTRAPPED IN STIMULI SENSITIVE BLOCK COPOLYMER HYDROGELS

M. Mallandrich, F. Fernández –Campos, B. Clarer, L. Halbaut, C. Alonso, L. Coderch, M.L. Garduño-Ramirez, B. Andrade, A. Del Pozo, M. E. Lane and A. Calpena

Pharm Res 34 (2017) 1728-1740

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SURFACE DETERMINATION OF 3D CONFOCAL RAMAN MICROSCOPY IMAGING OF THE SKIN

J. Schleusener, V. Carrer, A. Patzelt, J. Lademann and M.E. Darvin

Laser Phys. Lett. 14 (2017) 125601-125608

CONTRACTS

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

.....

Título del contrato/proyecto: Análisis cuantitativo de un principio activo por HPLC SED/15/09

Bicosome
11/2015 – 1/2017

.....

Estudio comparativo de la liberación "in vitro" de tres sistemas conteniendo un principio activo SED/15/17

Bicosome
11/2015-1/2017

.....

Análisis cuantitativo de nucleopure por HPLC SED/15/19

Bicosome
11/2015-1/2017

.....

Evaluación Receding Contact angle SED/16/03

Beautyge-Revlon
2/2016 – 3/2016

.....

Hidration of Hairs SED/15/18

Beautyge-Revlon
2/2016 – 3/2016

.....

Estudio comparativo de la liberación "in vitro" de tres sistemas conteniendo principio activo Nucleopore. SED/16/04

Bicosome
2/2016 – 4/2016

.....

Cabello étnico tratado e irradiado SED/16/05

Provital
3/2016 – 4/2016

Repairing formulations on hair SES/16/06

UNIFARCO (S. Giustina, Italia)
6/2016 - 5/2017

Análisis cuantitativo de Treonina por HPLC/DA. SED/16/11

Bicosome
5/2016 – 7/2016

Cabello asiático pretratado e irradiado SED/16/13

Provital
5/2016 – 7/2016

Estudio de Absorción Percutánea "in vitro" de 4 formulaciones sobre piel porcina. SED/16/12

Bicosome
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Almirall S.A.
6/2016 – 12/2016

Contenido en cisteína de cabellos decolorados. SED/16/17

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11/2016 -3/2017

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Bicosome
11/2016 – 1/2017

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MartíDerm
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Beautyge-Revlon
2/2017- 4/2017

Water permeability of Toppik hair building fibers. SES/17/04

Church & Dwight
5/2017- 9/2017

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Centro de Edafología y Biología Aplicada del Segura (CEBAS)
10/2017 - 12/2017

Bradford analyses of treated hair samples SEC/16/23

Laboratoires Lea
11/2017 - 2/2018

RESEARCH PROJECTS

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

Mitigation of environmental impact caused by Flame Retardant textile finishing Chemicals

LIFE-FLAREX. LIFE16 ENV/ES/000374

2017-2020

RESEARCH HIGHLIGHT

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

Skin permeability

Water has a large influence on the properties of keratinized tissues. 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 being fully studied. The water diffusion properties of keratinized tissues are known to be mainly governed by their lipid bilayers. Characterization of hair and stratum corneum of skin water sorption behavior both with and without internal lipids was performed. The role of intercellular lipids in the SC is more marked than in the hair. Lipid structures in the SC are essential to prevent changes in water-holding capacity of the skin and to maintain the water permeability.

Skin lipids intimately involved in maintaining the barrier function were disrupted with organic solvents to study the lipid role in the skin barrier. SC lipid modifications were evaluated by lipid analysis, water sorption/desorption, confocal-Raman visualization and FSTEM images. A preferential solubilization of acetone to fluid lipids was envisaged, this could explain the decrease on the SC permeability. Therefore their preferential depletion could diminish water or drug penetration with an increase of the barrier properties contrary to the chloroform/methanol treated sample. Select lipid solubilization with different organic solvents can modulate SC permeabilization.

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. Biophysical measurements "in vivo" such as TEWL or hydration were carried out to evaluate protecting and repairing effect of different barrier repair cosmetic formulations. Freeze-substitution transmission electron microscopy (FSTEM) also demonstrates lipid bilayer reconstitution due to applied formulations:

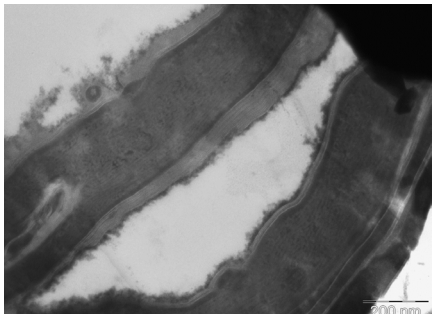
Antioxidants on skin and hair

The permeation of resveratrol on skin was assessed by in vitro by Raman spectroscopy and in vivo experiments by the tape stripping method. Moreover, the free radical scavenging activity of the antioxidant was determined by the DPPH assay. The Raman spectra indicated that the topically applied resveratrol penetrates deep into the skin. After topical application resveratrol maintained its antiradical activity and reinforces the antioxidant system of stratum corneum, providing an efficient means of increasing the tissue levels of antioxidants in human epidermis.

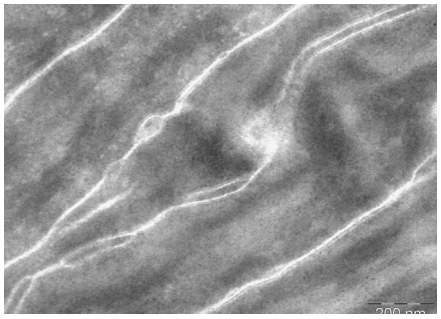
The UV radiation of sunlight is known to damage human hair, causing fibre degradation. Gallic acid loaded in PCL microspheres, in PC liposomes were prepared to study their effectiveness as antioxidants when applied to human hair compared with free GA. Efficacy was increase when gallic acid was encapsulated, moreover the efficacy was preserve for more than two months when GA is loaded into microspheres. Encapsulation technologies, such as polymer-based and lipid-based systems are being studied to enhance and prolong the effectiveness of ingredients, in our case antioxioxidants.

Hair lipids

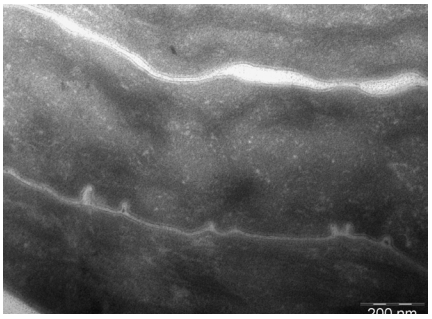
Even the small presence of lipids in hair, some works reported ethnic differences in their chemical and physical properties possible associated with differences in lipid



Non Treated Stratum Corneum



Lipid Depleted Stratum Corneum



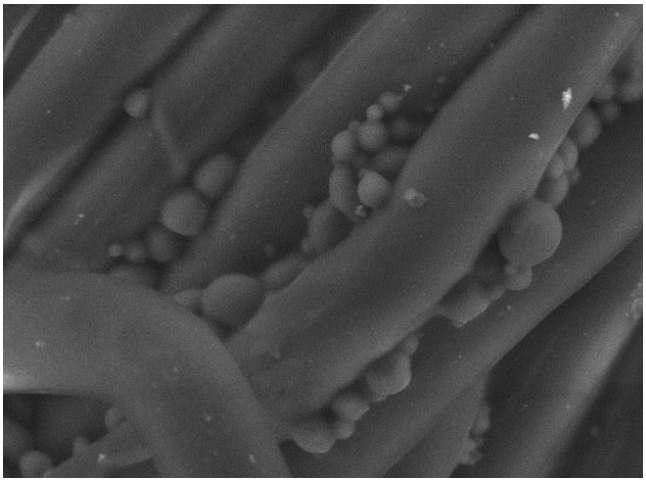
Lipid Treated Depleted Stratum Corneum

content. The main aim of our work consists in the lipid characterization of different ethnic hairs (Caucasian, African and African) and the study of the influence of these lipids on hair characteristics such as mechanical properties, contact angle and water sorption and desorption mainly to determine permeation changes. Highest amount of total lipids were found for African hair and its extraction ameliorates the fibre structure decreasing its permeability to water. Caucasian is the most hydrated fibre and together with the Asian one present the lower diffusion coefficients. The ethnic hairs were assessed related to their lipid composition, and some differences between them were found in terms of water uptake and mechanical properties.

Hair lipids are categorized as exogenous and endogenous depending on whether they originate from sebaceous glands or hair matrix cells. Their role was studied to determine their influence on physicochemical properties, in particular, the fluid/solid state of the lipids to be related with the water permeability. External and internal lipids were extracted from Caucasian hair and characterized. Extraction of internal lipids, which have higher unsaturated lipid content than external lipids, leads to a lower permeability of the fibre. On the capillary formulations should be considered the importance of lipid fluidity to modify the permeability of the fibre.

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.



Polyamide fabric treated with gallic acid microspheres.

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. The antioxidant efficacy of a cosmeto-textile containing microsphere-encapsulated gallic acid was explored. Lipoperoxide formation was evaluated by a non-invasive ex vivo method and a clear inhibition was found demonstrating the effectiveness of the cosmeto-textiles. Besides lipoperoxidation methodology was demosnstrated to its capacity to be used to verify the antioxidant capacity of encapsulated substances transferred into human skin by cosmetotextiles that can deliver specific doses of active ingredients.

SUSTAINABLE PROCESSES AND MATERIALS CHARACTERIZATION

The analysis of future trends in leather production emphasizes the introduction of cleaner leather processing technologies. One of the expected results includes avoiding the presence in the leather of substances from the Restricted Substances Lists (RSL) due to its proven impact on human health and ecosystems as well as its use in leather processing. Due to its carcinogenic character, formaldehyde is one of these substances and its presence in leather should be avoided or kept below allowable limits

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ARTICLES

Reduction of the formaldehyde content in leathers treated with formaldehyde resins by means of plant polyphenols

Marsal, A.; Cuadros, S.; Manich, A.M.; Izquierdo, F.; Font, J.

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Effect of fatliquoring on leather comfort. Part III: Moisture absorption-desorption of leather

Manich, A. M.; Barenys, J.; Martínez, L.; Lloria, J.; Carilla, J.; Marsal, A.

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Manich, A. M.; Cuadros, S.; Font, J.; Bacardit, A.; Combalia, F.; Marsal, A.

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Exogenous and endogenous lipids of human hair

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Cayuela, D.; Cot, M.; Algaba, I.; Manich, A.M.

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Barba, C.; Alonso, C.; Martí, M.; Manich, A.; Coderch, L.

Biochimica et Biophysica Acta – Biomembranes 1858(8), 1935-1943, **2016**

RESEARCH HIGHLIGHT

The analysis of future trends in leather production emphasizes the introduction of cleaner leather processing technologies. One of the expected results includes avoiding the presence in the leather of substances from the Restricted Substances Lists (RSL) due to its proven impact on human health and ecosystems as well as its use in leather processing. Due to its carcinogenic character, formaldehyde is one of these substances and its presence in leather should be avoided or kept below allowable limits. Therefore, it is essential to have analytical methods to determine, reliably, the content of formaldehyde in leather. In one of the research lines and given that the currently existing Standard for the determination of formaldehyde content in leather (EN ISO 17226) has certain ambiguities in the wording of some operations, a revision has been carried out in order to improve it. It has been found that sodium dodecyl sulphate (surfactant less expensive) can be used as alternative to sodium dodecyl sulphonate (suggested by the Standard) in the extraction of formaldehyde from leathers since both surfactants provide similar results. On the other hand, magnetic agitation gives higher results of formaldehyde content than linear reciprocal agitation when used in the extraction of formaldehyde from leather. Therefore, the EN ISO 17226 Standard should establish more clearly the type of agitation. Another objective of the research is to look for measures to reduce the formaldehyde content in leather when its presence is suspected. The influence of plant polyphenols on the reduction of the formaldehyde content in leathers treated with formaldehyde resins has been studied. It has been found, that the formaldehyde content of leathers treated only with resins increased with ageing indicating a partial hydrolysis of the resins. Among the three vegetable compounds considered (mimosa, quebracho and tara), mimosa exhibited the highest ability to reduce the formaldehyde content, which may be probably attributed to the reactivity of formaldehyde with the phloroglucinol A-rings and resorcinol A-rings present in mimosa tannins. Likewise, it has been confirmed that gallic acid (used in the final washing of leather processing or as a fixing agent) is suitable as a formaldehyde scavenger in the leather industry. Other chemicals such as hydroxylamine sulphate and pyrogallol, although show good ability to reduce the formaldehyde content, present certain drawbacks. Pyrogallol gives rise to darkening of the leather and hydroxylamine sulphate is toxic to the aquatic environment and its reaction with formaldehyde is partially reversible with ageing. When studying the influence of the dyeing process on the formaldehyde content in split leathers treated with formaldehyde resins, it has been found that the ability

of dyes in reducing the formaldehyde content depends on the amount of amino groups amenable to reaction with formaldehyde. Those amino groups that in their vicinity have other functionalities, with which to form relatively stable structures, have a reduced reactivity with formaldehyde.

The effect of the more sustainable industrial processing on the structure and properties of processed materials is also considered. In this field the modified leather and the other fibrous materials have been characterized from the point of view of sorption-desorption characteristics, thermal stability, viscoelastic behaviour and mechanical properties. The influence of ceramic micro and nano particles on PET composites has been considered and the effect of titania in their different configurations and size has been determined. Chemical and enzymatic processing of hemp has been undertaken to get spinnable hemp fibres able to be mixed with cotton and other synthetic fibres to get more sustainable products with better comfort properties for the user.

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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M. SC. STUDENTS

ALEX ABRAMOV
TING LI
MARKUS TAUTZ

VISITING SCIENTISTS (3-6 MONTHS)

CÉSAR SALDÍAS (POSTDOC)
ELAINE ARMELIN (POSTDOC)
SANTIAGO GRIJALVO TORRIJO (POSTDOC)
MAR PÉREZ MADRIGAL (Ph.D. STUDENT)
DANIELA GUZMÁN ÁNGEL (Ph.D. STUDENT)
JUAN VICENTE ALEGRE REQUENA (Ph.D. STUDENT)
ASJA PETTIGNANO (Ph.D. STUDENT)
SUSHMA KUMARI (Ph.D. STUDENT)

PUBLICATIONS (ARTICLES)

Towards sustainable solid-state supercapacitors: Electroactive conducting polymers combined with biohydrogels

Pérez-Madrigal, M. M.; Estrany, F.; Armelin, E.; Díaz, D. D.; Alemán, C.

J. Mater. Chem. A, 4, 1792-1805, **2016**

Biodegradable liposome-encapsulated hydrogels for biomedical applications: A marriage of convenience

Grijalvo, S.; Mayr, J.; Eritja, R.; Díaz, D. D.

Biomater. Sci., 4, 555-574, **2016**

Metal-organic frameworks (MOFs) bring new life to hydrogen-bonding organocatalysts in confined spaces

Alegre-Requena, J. V.; Marqués-López, E.; Herrera, R. P.; Díaz, D. D.
CrystEngComm, 18, 3985-3995, **2016**

Kleben mit Klick

Díaz, D. D.
Nach. Chem., 64, 122-126, **2016**

Nioplexes encapsulated in supramolecular hybrid biohydrogels as versatile delivery platforms for nucleic acids

Grijalvo, S.; Puras, G.; Zárate, J.; Pons, R.; Pedraz, J. L.; Eritja, R.; Díaz, D. D.

RSC Adv., 6, 39688-39699, **2016**

Self-assembled fibrillar networks of a multifaceted chiral squaramide: Supramolecular multistimuli-responsive alcogels

Schiller, J.; Alegre-Requena, J. V.; Marqués-López, E.; Herrera, R. P.; Casanovas, J.; Alemán, C.; Díaz, D. D.

Soft Matter, 12, 4361-4374, **2016**

Supramolecular metallogel that impart self-healing properties to other gel networks

Feldner,T.; Häring,M.; Esquena,J.; Subhadeep,S.; Banerjee,R.; Díaz, D. D.

Chem. Mater., 28, 3210-3217, **2016**

Fluoride anion recognition by a multifunctional urea: An experimental and theoretical study

Schiller, J.; Pérez-Ruiz, R.; Sampedro, D.; Marqués-López, E.; Herrera, Díaz, D. D.

Sensors, 16, 658, **2016**

Protonenleitende und selbstheilende weiche Gelmaterialien

Häring, M.; Díaz, D. D.

Praxis der Naturwissenschaften, 6/65, 5-9, **2016**

Current status and challenges of biohydrogels for applications as supercapacitors and secondary batteries

Armelin, E.; Pérez-Madrigal, M. M.; Alemán, C.; Díaz, D. D.

J. Mater. Chem., A 4, 8952-8968, **2016**

Gd(III)-based porous luminescent metal-organic frameworks (MOFs) for bimodal imaging

Kundu, T.; Mitra, S. D.; Díaz, D. D.; Banerjee, R.

ChemPlusChem, 81, 728-732, **2016**

Non-covalent incorporation of some substituted metal phthalocyanines into different gel networks and the effects on the gel properties

Keseberg, P.; Bachl, J.; Díaz, D. D.

J. Porphyr. Phthalocyanines, 20, 1390-1400, **2016**

Regulatory parameters of self-healing alginate hydrogel networks prepared via mussel-inspired dynamic chemistry

Alegre-Requena, J. V.; Häring, M.; Herrera, R. P.; Díaz, D. D.

New J. Chem., 8493-8501, **2016**

Keratin protein-catalyzed nitroaldol (Henry) reaction and comparison with other biopolymers

Häring, M.; Pettignano, A.; Quignard, F.; Tanchoux, N.; Díaz, D. D.

Molecules, 21, 1122, **2016**

Phase-transfer catalysis with ionene polymers

Tiffner, M.; Zielke, K.; Mayr, J.; Häring, M.; Díaz, D. D.; Waser, M.

ChemistrySelect, 1, 4030-4033, **2016**

Supramolecular metallogels with bulk self-healing properties prepared by *in situ* metal complexation

Häring, M.; Díaz, D. D.

Chem. Commun., 52, 13068-13081, **2016**

Spectroscopic characterization of azo dyes aggregation induced by DABCO-based ionene polymers and dye removal efficiency as a funcion of ionene structure

Dragan, E. S.; Mayr, J.; Häring, M.; Irina, A.; Díaz, D. D.

ACS Appl. Mater. Interfaces, 8, 30908-30919, **2016**

Self-healing alginate-gelatin biohydrogels based on dynamic covalent chemistry: Elucidation of key parameters

Pettignano, A.; Häring, M.; Bernardi, L.; Tanchoux, N.; Quignard, F.; Díaz, D. D.

Mater. Chem. Front., 1, 73-79, **2017**

Catalytic macroporous biohydrogels made of ferritin-encapsulated gold nanoparticles

Kumari, S.; Häring, M.; Gupta, S. S.; Díaz, D. D.

ChemPlusChem, 82, 225-232, **2017**

Antimicrobial and hemolytic studies of a series of polycations bearing quaternary ammonium moieties: Structural and topological effects

Mayr, J.; Bachl, J.; Schlossmann, J.; Díaz, D. D.

Int. J. Mol. Sci., 18, 303, **2017**

Protective coatings for aluminum alloy based on hyperbranched 1,4-polytriazoles

Armelin, E.; Whelan, R.; Martínez-Triana, Y.; Alemán, C.; Finn, M. G.; Díaz, D. D.

ACS Appl. Mater. Interfaces, 9, 4231-4243, **2017**

Glass-metal adhesive polymers from copper(I)-catalyzed azide-alkyne cycloaddition

Martínez-Triana, Y.; Whelan, R.; Finn, M. G.; Díaz, D. D.

Macromol. Chem. Phys., 218, 1600579, **2017**

Anregen und tauschen

Häring, M.; Abramov, A.; Díaz, D. D.

Macromol. Symp., 372, 87-101, **2017**

Interplaying anions in a supramolecular metallohydrogel to form metal organic frameworks

Karak, S; Kumar, S.; Bera, S.; Díaz, D. D.; Banerjee, R.

Chem. Commun., 53, 3705-3708, **2017**

On-site synthesis

Díaz, D. D.

European Coatings Journal, 6, 30-34, **2017**

Supramolekulare Gele als räumlich eingrenzende Reaktionsmedien für die Photonen-Hochkonversion

Abramov, A.; Häring, M.; Díaz, D. D.

Nach. Chem., 65, 1100-1105, **2017**

Boronic acid-modified alginate enables direct formation of injectable, self-healing and multistimuli-responsive hydrogel

Pettignano, A.; Grijalvo, S.; Häring, M.; Eritja, R.; Tanchoux, N.; Quignard, F.; Díaz, D. D.

Chem. Commun., 53, 3350-3353, **2017**

Targeted drug delivery in covalent organic nanosheets (CONs) via sequential postsynthesis

Mitra, S.; Sasmal, H. S.; Kundu, T.; Kandabeth, S.; Illath, K. S.; Díaz, D. D.; Banerjee, R.

J. Am. Chem. Soc., 139, 4513-4520, **2017**

Aromatic ionene topology and counterion-tuned gelation of acidic aqueous solutions

Bachl, J.; Bertran, O.; Mayr, J.; Alemán, C.; Díaz, D. D.

Soft Matter, 13, 3031-3041, **2017**

Transfection of antisense oligonucleotides mediated by cationic vesicles based on non-ionic surfactant and polycations bearing quaternary ammonium moieties

Mayr, J.; Grijalvo, S.; Bachl, J.; Pons, R.; Eritja, R.; Díaz, D. D.

Int. J. Mol. Sci., 18, 1139, **2017**

An experimental and theoretical comparative study of the entrapment and release of dexamethasone from micellar and vesicular aggregates of PAMAM-PCL dendrimers

Avila-Salas, F.; Pereira, A.; Rojas, M. A.; Saavedra-Torres, M.; Montecinos, R.; Bonardd, S.; Quezada, C.; Saldías, S.; Díaz, D. D.; Leiva, A.; Rodic, D.; Saldías, C.

Eur. Polym. J., 93, 507-520, **2017**

Ultrasonication-enhanced gelation properties of a versatile amphiphilic formamidine-based gelator exhibiting both organogelation and hydrogelation abilities

Bachl, J.; Sampedro, D.; Mayr, J.; Díaz, D. D.

Phys. Chem. Chem. Phys., 19, 22981-22994, **2017**

A paradigm shift for preparing versatile M2+-free gels from unmodified sodium alginate

Pérez-Madrigal, M.; Torras, J.; Casanovas, J.; Häring, M.; Aleman, C.; Díaz, D. D.

Biomacromolecules, 18, 2967-2979, **2017**

Cationic nioplexes-*in*-polysaccharide-based hydrogels as versatile biodegradable hybrid materials to deliver nucleic acids

Grijalvo, S.; Alagia, A.; Puras, G.; Zárate, J.; Mayr, J.; Pedraz, J. L.; Eritja, R.; Díaz, D. D.

J. Mater. Chem. B, 5, 7756-7767, **2017**

***In situ* preparation of film and hydrogel bio-nanocomposites of chitosan/fluorescein-copper with catalytic activity**

Saldías, C.; Díaz, D. D.; Bonardd, S.; Soto-Martull, C.; Cordoba, A.; Saldías, S.; Quezada, C.; Radic, D.; Leiva, A.

Carbohydr. Polym., 180, 200-208, **2017**

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. Among different applications of these materials, we have special interest in their use as nanoreactors, controlled drug delivery systems, contaminant removal agents, semi-solid supercapacitor, neural regeneration, etc.

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 nanoscale 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 also 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. In addition, from a chemical point of view we are interesting in performing reactions using gels as confining medium to achieve reactions that are otherwise unaffordable under mild conditions in solution.

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, antifouling coatings, anticorrosion coatings and superhydrophobic surfaces.

NANOPARTICLES-CONTAINING MATERIALS

In collaboration with several groups, 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, microextraction, 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 for 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.

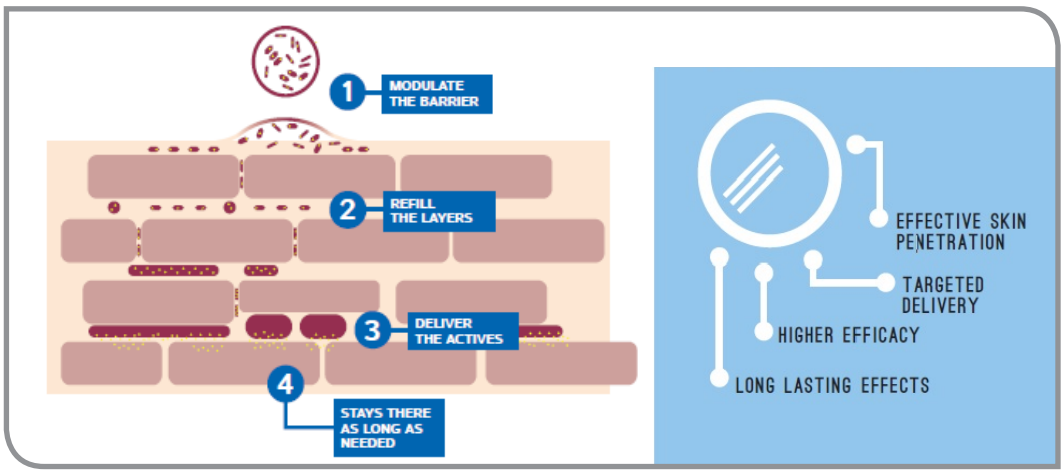
Bicosome company develops high performance skin care ingredients based on the patented Bicosome® Technology that are commercialized mainly to the dermocosmetic and pharmaceutical industries.

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 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 sun repair system that stabilises and delivers carotene molecules in the epidermis, providing biological sun protection. The supply of carotenes by Bicotene® Antiox reinforces the skin's defense 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 multitarget delivery system that works blocking the different processes involved in the skin hyperpigmentation. The system incorporates five actives: 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.

bicomide® by bicosome®

Bicomide® Sebum Control is a Bicosome system that targets the epidermis and follicles to effectively control sebum production, prevents the development of acne and reduces the irritation of acneic skin.

bicohair® up by bicosome®

Bicohair® Anti Urban Pollution system protects the hair from urban pollution. Bicohair® UP adheres to the hair cuticle by electrostatic interactions working as shield protector that repeals pollution particles avoiding deposition, protects structural proteins from degradation caused by sun exposure and decreases the color loss caused by UV exposure and daily washings.

bicohair® hp by bicosome®

Bicohair® Heat Protection system protects the hair against thermal damages. Bicohair® HP covers the hair fiber adding a barrier to the direct contact of the heat from tools or esthetic procedures. Additionally, its application recovers the hydration and mechanical properties of damaged hair.

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.

WWW.BICOSOME.COM

8

FACILITIES AND TECHNOLOGY TRANSFER

SERVICE FOR CHARACTERIZATION OF COLLOIDAL DISPERSIONS

SUPERVISING SCIENTISTS

JORDI ESQUENA MORET
CARLOS RODRÍGUEZ ABREU

TECHNICAL ASSISTANT

SUSANA VÍLCHEZ MALDONADO

RELEVANT TECHNIQUES

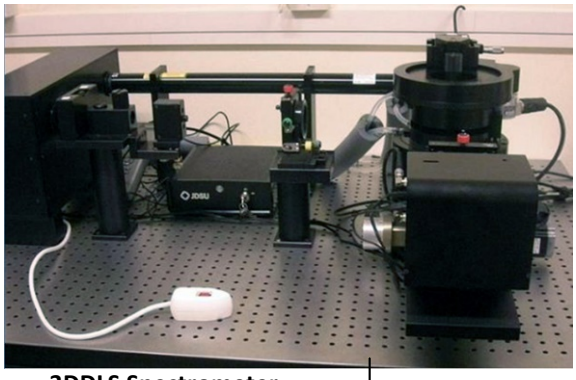
This service is dedicated to the characterization of nano-structured liquids (e.g. micelles, vesicles, liquid crystals, microemulsions, nano-emulsions etc.) and solid dispersions (e.g. organic inorganic or hybrid nanoparticle suspensions).

The characterization includes the determination of size, morphology, phase transitions, surface, interfacial and rheological properties.

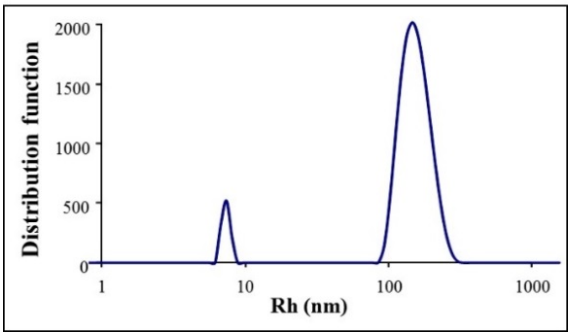
The group in charge of this service is a member of TECNIO and has been awarded a quality certificate (similar to ISO 9001) by ACC1Ó (Generalitat de Catalunya).

Static (SLS) and dynamic (DLS) light scattering

Determination of particle size distribution, shape, diffusion coefficient, aggregation number, molecular weight of colloidal dispersions



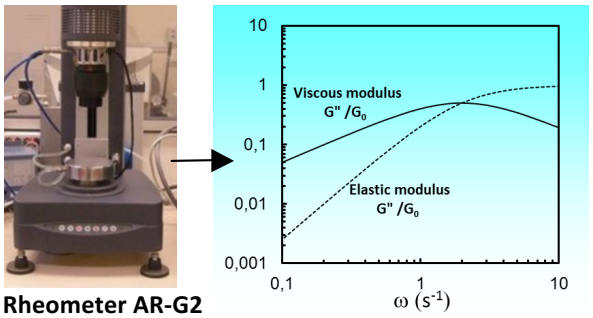
3DDLS Spectrometer



Size distribution of a mixed micelle and vesicle dispersion b
dynamic light scattering

Rheology

Determination of the rheological properties of fluids and soft materials in flow and deformation regimes by steady-state (viscosity, shear thinning, shear thickening) and dynamic (elastic and viscous moduli, relaxation time) measurements.

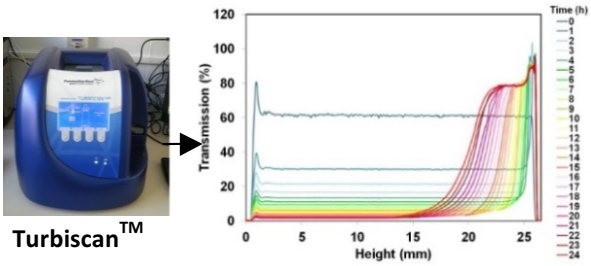


Rheometer AR-G2

Variation of elastic (G') and viscous (G'') moduli, as a function of frequency, for a viscoelastic fluid that follows Maxwell behaviour.

Turbidimetry

Time and position-resolved turbidimetry by back-light scattering for the characterization of dispersion stability



Turbiscan™

High resolution optical microscopy with spectral analysis

Imaging of nanosize objects (e.g. nanoparticles, nano-emulsions) and spectral mapping.

Other techniques:

Laser Light Diffraction
Differential Refractometry
Tensiometry
Optical Microscopy
Densimetry
Electrophoretic mobility and surface charge (Zeta Potential)
Osmometry
Fluorimetry

CUSTOM ANTIBODY SERVICE (CABS)

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

MARÍA PILAR MARCO COLÁS (Scientific Director)
NURIA PASCUAL DURAN (SCIENTIFIC COORDINATOR)
ANA GONZÁLEZ GONZÁLEZ
PABLO MARTÍNEZ VALERA

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: labelled 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.

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

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.
- Doble/Triple resonance experiments for peptides/small proteins.

STAFF

YOLANDA PÉREZ RUIZ (NMR Facility Manager)

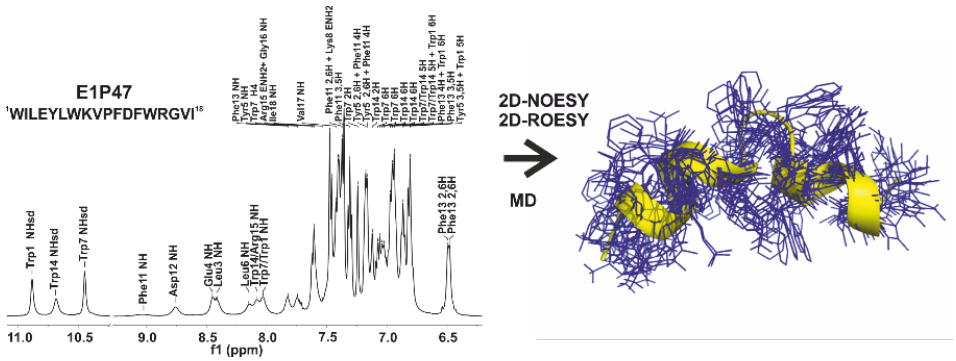
NAIARA SOLOZÁBAL MIRÓN
(Technician, Fondo Garantía Juvenil)

NMR EQUIPMENT

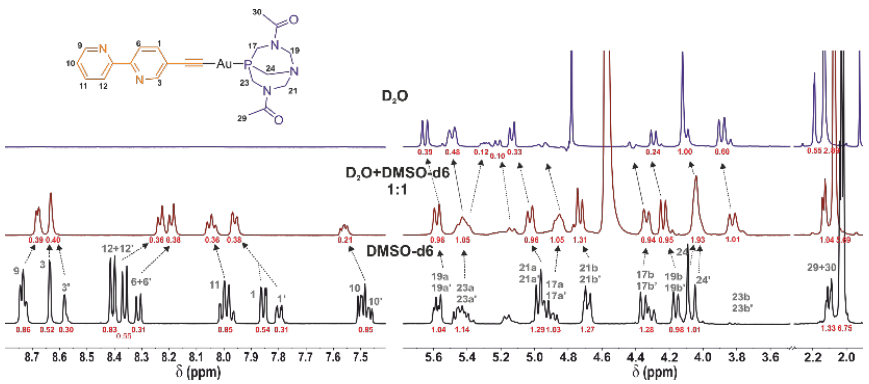
Varian Mercury 400 MHz (9.3950 T) is the walk-up instrument for automated heteronuclear NMR.

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. An automated 100-sample changer (for standard 8" long/5 mm Ø NMR tubes) and VnmrJ3.2 software allow performing acquisitions and quick access to spectra

Bruker AVANCEIIIHD 500 MHz (11.7440 T field strength) with TCI Cryoprobe and SampleXPressLite 18-charger. This system is the NMR spectrometer of choice for more demanding samples and 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 when tiny amounts of material are available. 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 and ^{13}C direct detection, ^{13}C and ^{15}N indirect-detection. The spectrometer uses Topspin 3.7 software on a Linux Workstation. *This NMR system was purchased with financial support from MINECO-FEDER CSIC13-4E-2076 grant.*



Y. Pérez, M. J. Gómara, E. Yuste, P. Gómez-Gutiérrez, J. J. Pérez, I. Haro. *Chem. Eur. J.* **2017**, 23, 11703.

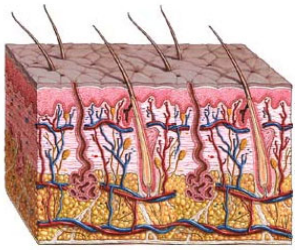


SERVICE OF DERMOCOSMETIC ASSESSMENT (SED-IQAC)

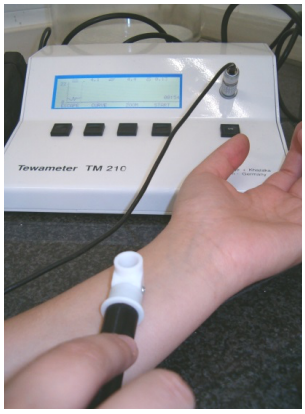
SED service is located on the premises of the Institute for Advanced Chemistry of Catalonia (IQAC) from the CSIC and it was constituted in 2002. SED service is divided in three groups: Skin Absorption group, Skin Efficacy group and Hair Efficacy group.

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.

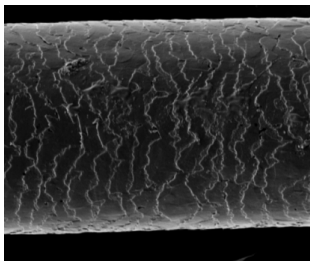
Service of Dermoscosmetic Assesment (SED) from the IQAC-CSIC, have since May 2012, a Quality System of Management in accordance with the UNE-EN ISO 9001:2008 certified by AENOR with the reference ER-0430/2012.



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.



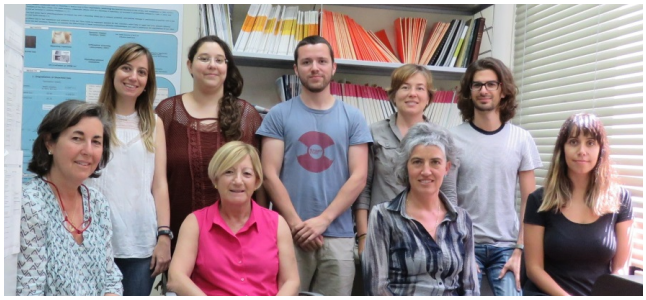
The **Skin Efficacy** group deals with the experimental design, evaluation and objective diagnostic of the skin efficacy and tolerance of cosmetic and dermatologic formulations topically applied by the use of non-invasive biophysical techniques. Evaluation and diagnosis of other keratinized tissues such 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

MARÍA LUISA CODERCH NEGRA (Supervising Scientist, Contacting person)
MERITXELL MARTÍ GELABERT (Ph.D.) (Technical Director)
ISABEL YUSTE HERNÁNDEZ
CRISTINA ALONSO MERINO (Ph.D.)
CLARA BARBA ALBANELL (Ph.D.)
VÍCTOR CARRER VIVES
MARC ADRIÀ OLIVER NICOLAU
VANESSA MARTÍNEZ RODRÍGUEZ
BEATRIZ GUZMÁN MONREAL



EQUIPMENT

- HPLC Merck Hitachi (L-6200 Intelligent pump, detector UV-visible (L-4250), AS-4000 Intelligent autosampler, D-6000 Interfase.) Detection and Quantification of active componds.
- HPLC VWR Hitachi Elite LaChrom (Pump L-2130, Autosampler L-2200, UV Detector L-2400, DAD detector Chromaster 5430, Organizer L-2000). Detection and Quantification of active compounds.
- Vertical diffusion FRANZ Cell. Classical and automatized cells to Percutaneous absorption.
- DERMATOMO GA 630 (Aesculap). Skin dermatome.
- TEWAMETER TM300-MDD4 (Courage + Khazaka). Skin assessment, in vitro or in vivo of transepidermal water loss.
- GLOSS-METER Micro-Tri-Gloss (BYK Gardner-Gmbtt). Hair gloss
- ZETASIZER Nano-ZS ZEN3600 (Malvern). Particle size and Z potential.
- THIN LAYER CHROMATOGRAPHY. FLAME IONIZATION DETECTOR (TLC-FID) (IATROSCAN MK-5, IATRON LabInc). Lipid quantifier.
- MEXAMETER MX16 (Courage + Khazaka). Skin color.
- CUTOMETER MPA580 (Courage + Khazaka). Skin elasticity.
- SEBUMETER SM810 (Courage + Khazaka). Skin lipid content.
- CORNEOMETER CM825 (Courage + Khazaka). Skin hydration.
- VISIOLINE VL 650 (Monaderm). Skin topography
- SKIN-pHMETER PH900 (Courage + Khazaka). Skin pH.

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

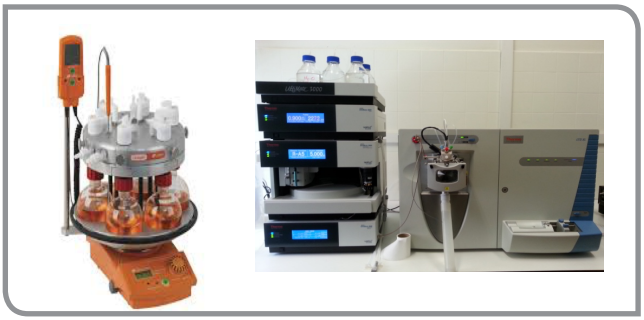
- MW
- Radleys
- Manifold

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)



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.

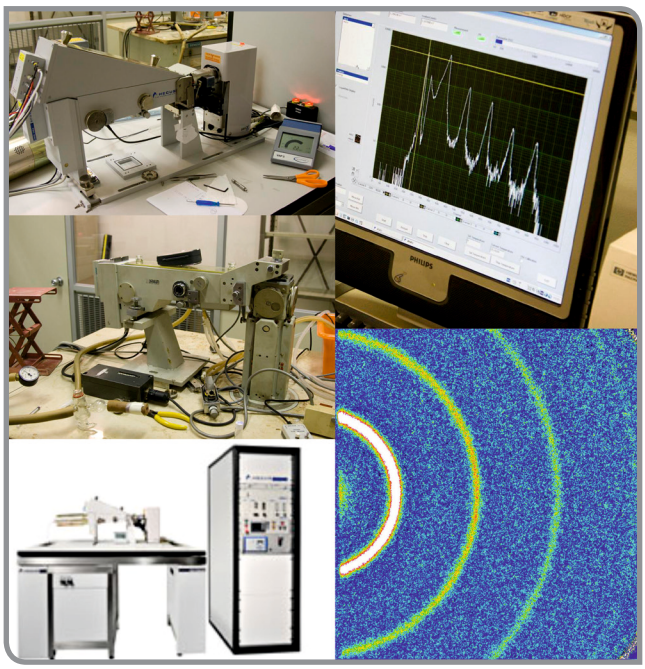
The range of distances of interest falls in the nanoscale domain (0.2-100 nm). It can allow determinations of size, space ordering, morphology, fractal dimension and total interfacial area. The materials comprise surfactant solutions and liquid crystals, mesoporous materials, macromolecules in solution 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



THERMAL ANALYSIS SERVICE

STAFF

ALBERT M. MANICH BOU (Supervising scientist)
SONIA PÉREZ 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

PROTEOMICS SERVICE

The IQAC-Proteomics Service is focused on the analysis of biomolecules (proteins, peptides, protein modifications, oligonucleotides, sugars, ...) and large organic molecules (such as polymers, dendrimers, polyphenols and other macromolecules) by **MALDI-TOF/TOF mass spectrometry**.

Most recently, the Service also offers **MALDI Imaging.** This technique allows direct measurement of these biomolecules as well as drugs and metabolites distribution **in tissues**. The great advantage of MALDI Imaging is that the distribution of the detected compounds can be visualized as images, which can be integrated with other imaging modalities. This method is label-free and allows multiplex analysis of several molecules in the same tissue section simultaneously.

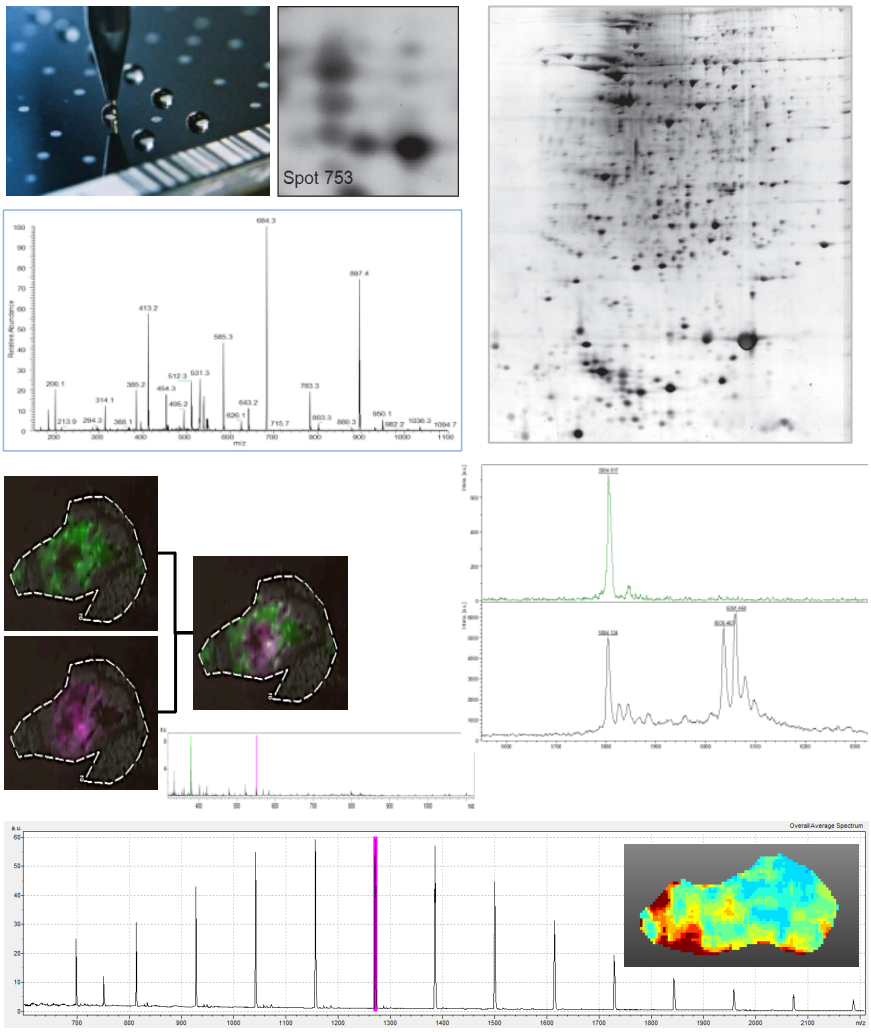
The Service offers additional services related to the analysis of other molecules and development of methods and protocols.

STAFF

CARME QUERO LÓPEZ (Supervising scientist)
EVA DALMAU ALSINA (Technician)

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. Separation of proteins by one- and two-dimensional electrophoresis.
5. Label-free measurement of biomolecules, drugs and metabolites distribution in tissues.
6. Determination of the molecular content of tissue sections by MALDI Imaging.

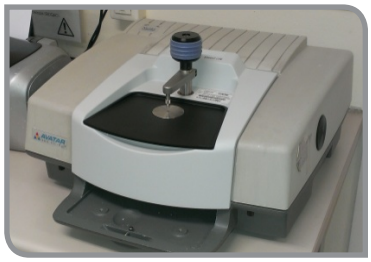


INFRARED AND UV-VISIBLE SPECTROSCOPY SERVICE

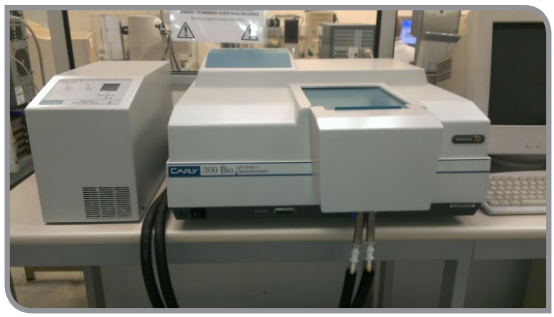
STAFF

RICARDO MOLINA MANSILLA (Supervising Scientist)
ALBERTO VÍLCHEZ GONZÁLEZ (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 solid, powdered 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 or chemical compounds.



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 BRUGULAT (Supervising Scientist)
EVA DALMAU ALSINA (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.

ELECTRONIC PARAMAGNETIC RESONANCE (EPR UNIT)

STAFF

LLUÍS JULIÁ BARGÉS (EPR UNIT SCIENTIFIC MANAGER)
LLUÍS FAJARÍ AGUDO (EPR UNIT TECHNICAL MANAGER)

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

KNOWLEDGE TRANSFER UNIT

STAFF

ISABEL MASIP 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_047*. Immunoassay for rapid diagnosis of infectious diseases caused by *Pseudomonas aeruginosa*.
- *IQAC_053*. Immunoassay for detection of infections caused by *Staphylococcus aureus*.
- *IQAC_059*. Immunoassay for detection of lipoprotein (a) to determine cardiovascular risk.

Cancer

- *IQAC_060*. Non-glycosidic analogues of α-GalCer as NKT cell activators.

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.
- *IQAC_059*. Multiplexing liquid system in biosensor microchambers

Surfactants

- *IQAC_054*. Biocompatible cationic aminoacid surfactants.

Biocatalysis

- *IQAC_056*. Enzymatic process to obtain L-Homoserine and other functionalized molecules.

- *IQAC_057*. Industrial (poly)hydroxylate compounds by enzymatic catalysis.

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.

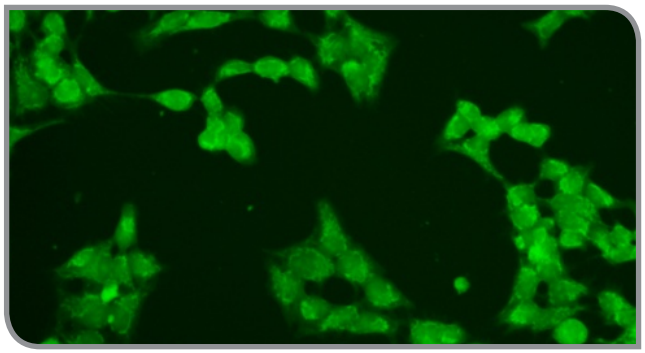
STAFF

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.



9

ANNEXES

SCIENTIFIC STAFF

Abad Saiz, José Luis	Tenured Scientist
Alfonso Rodríguez, Ignacio	Scientific Researcher
Anglada Rull, Josep Maria	Scientific Researcher
Arsequell Ruiz, Gemma	Scientific Researcher
Blanco Fernández, Jerónimo	Scientific Researcher
Bosch Verderol, Maria Pilar	Scientific Researcher
Bujons Vilàs, Jordi	Tenured Scientist
Caminal Saperas, Gloria	Scientific Researcher
Casas Brugulat, Josefina	Scientific Researcher
Clapés Saborit, Pere	Research Professor
Coderch Negra, Maria Luisa	Research Professor
Comelles Folch, Francesc	Research Professor
Crehuet Simon, Ramon	Tenured Scientist
Delgado Cirilo, Antonio	University professor
Díaz Díaz, David	Tenured Scientist
Eritja Casadellà, Ramon	Research Professor
Esquena Moret, Jordi	Tenured Scientist
Fabriàs Domingo, Gemma	Research Professor
Galve Bosch, Roger	Tenured Scientist
García Ramón, María Teresa	Tenured Scientist
Gómara Elena, María José	Tenured Scientist
Guerrero Pérez, Ángel	Research Professor
Haro Villar, Isabel	Scientific Researcher
Jimeno Mollet, Ciril	Tenured Scientist
Joglar Tamargo, Jesús	Tenured Scientist
Juliá Bargés, Luis	Scientific Researcher
Llebaria Soldevila, Amadeu	Scientific Researcher
López Serrano, Olga	Scientific Researcher
Manich Bou, Albert Maria	Scientific Researcher
Marco Colás, María Pilar	Research Professor
Marsal Monge, Agustí	Scientific Researcher
Maza Ribera, Alfons de la	Research Professor
Molina Mansilla, Ricardo	Tenured Scientist
Muñoz Rubio, Lourdes	Bacherol's degree
Pérez Muñoz, Lourdes	Tenured Scientist
Pinazo Gassol, Aurora	Tenured Scientist
Pons Pons, Ramon	Scientific Researcher
Rodríguez Abreu, Carlos	Scientific Researcher
Rosell Pellisé, Gloria	University professor
Solà i Oller, Jordi	Tenured Scientist
Solans Marsà, Conxita	Research Professor
Torres, Josep Lluís	Research Professor
Triola Guillem, Gemma	Tenured Scientist
Valencia Parera, Gregorio	Scientific Researcher

TECHNICAL STAFF

Barrera De Paz, Nuria	Research Assistant
Bleda Hernández, María José	Specialized technician
Carrera Altarriba, Imma	Research Assistant
Caelles Balcells, Jaume	Specialized technician
Dalmau Alsina, Eva	Advanced Technician
Fajarí Agudo, Lluís	Senior Specialized Technician
González Chaparro, Juan José	Research Assistant
Lloria Tolrà, Joan	Specialized Technician
Martí Gelabert, Meritxell	Research Assistant
Pascual Duran, Nuria	Senior Specialized Technician
Pérez Pomeda, Ignacio	Senior Specialized Technician
Pérez Ruiz, Yolanda	Senior Specialized Technician
Vila Terrades, Maria Teresa	Specialized Technician
Yuste Hernández, Isabel	Research Assistant

ADMINISTRATION STAFF

Beltrán Fabregat, Lídia	Administrative Assistant
Moliner Ferrer, Leonor	Administrative Assistant

POSTDOCTORAL FELLOWS

Alagia, Adele
Alonso Merino, Cristina
Aviñó Andrés, Anna Maria
Barba Albanell, Clara
Calderó Linnhoff, Gabriela
Carbajo López, Daniel
Casasampere Ferrer, Mireia
Catena Ruiz, Juanlo
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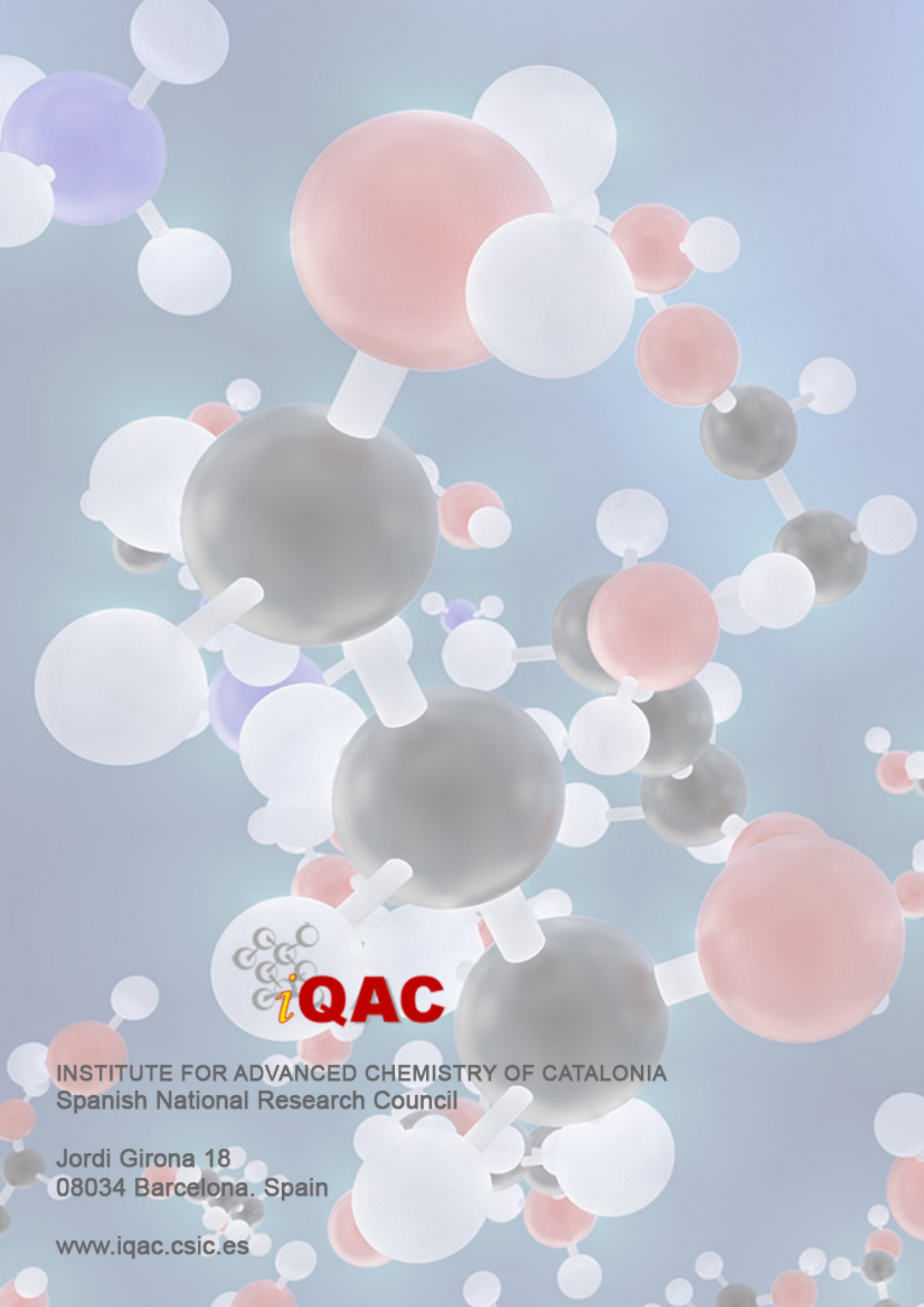

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