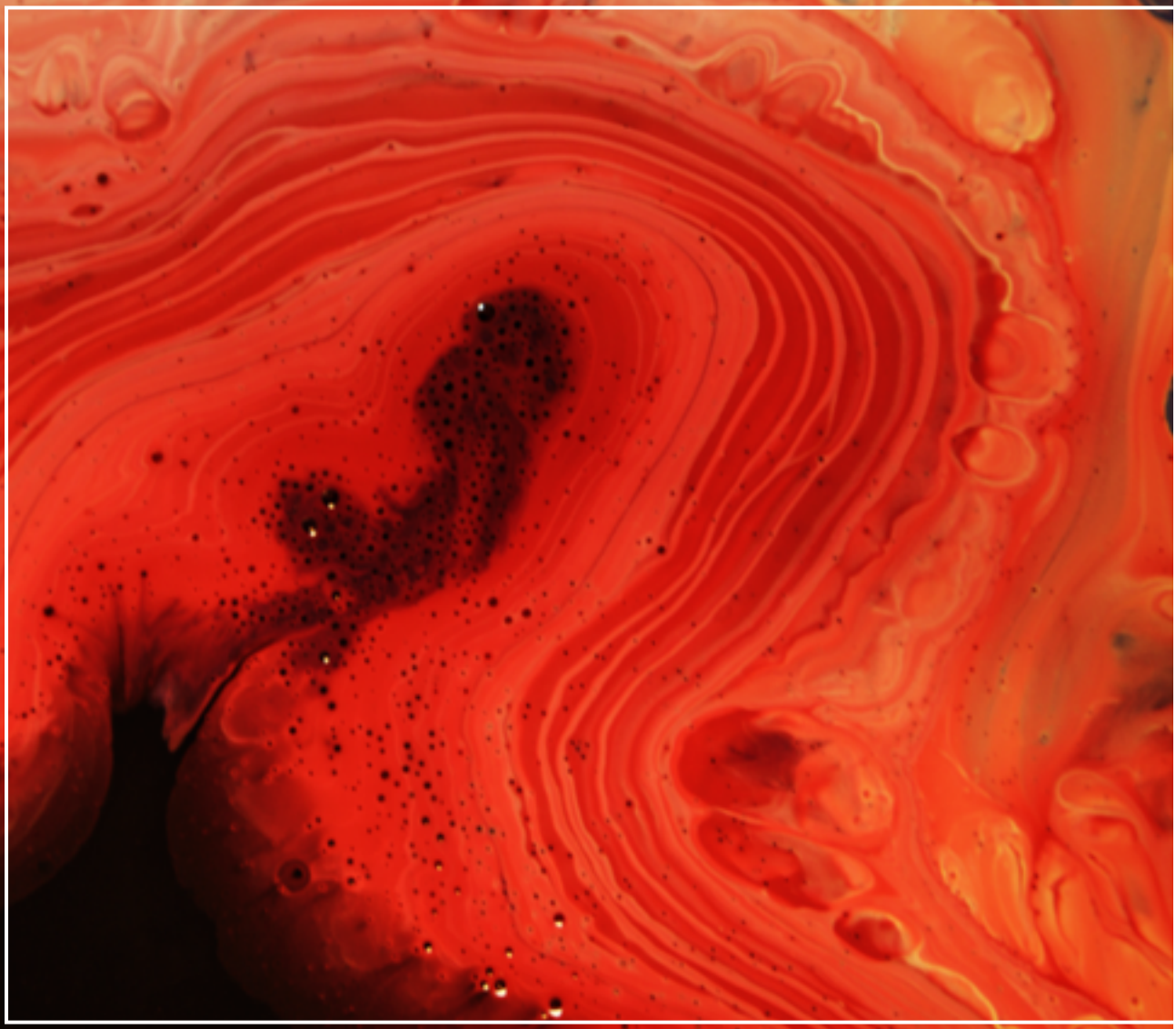
UNIVERSITAT DE BARCELONA

CATALOGUE OF

Preclinical models in biomedical research



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Preclinical models in biomedical research

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The classification of preclinical models is based on the WHO International Statistical Classification of Diseases and Related Health Problems, 10th Revision.

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Preclinical models in biomedical research

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The classification of preclinical models is based on the WHO International Statistical Classification of Diseases and Related Health Problems, 10th Revision.

INTRODUCTION

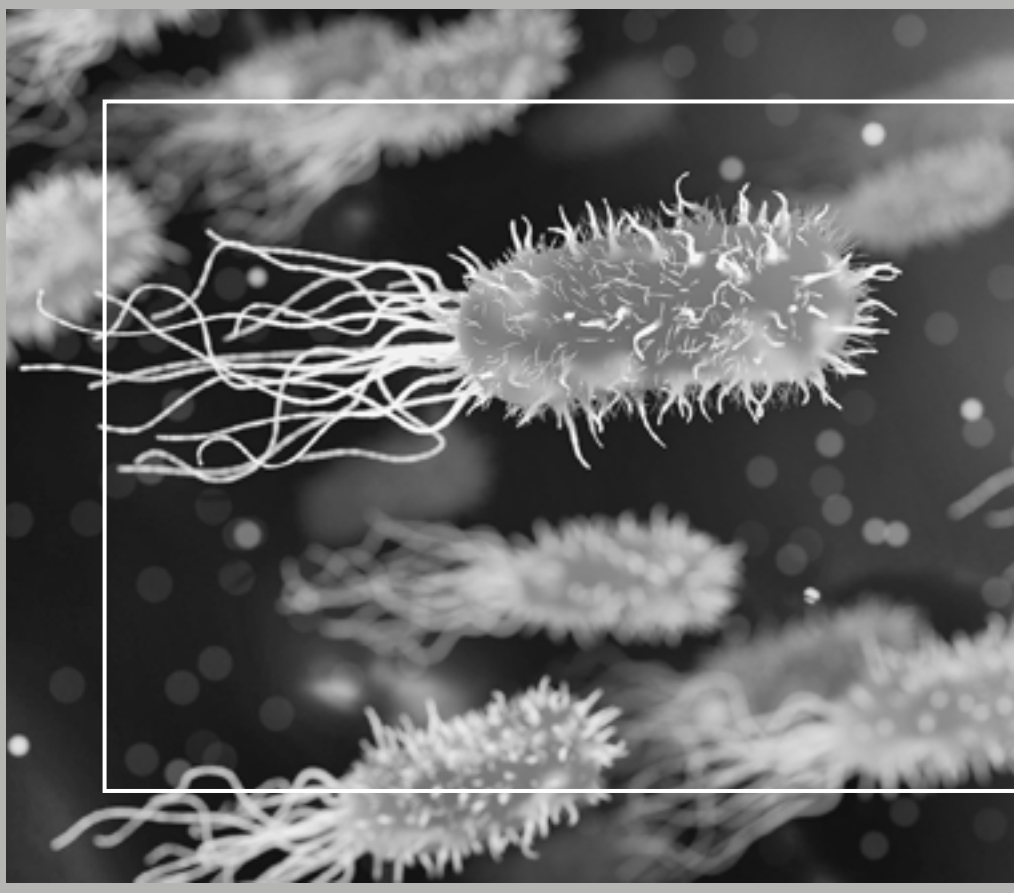
Experimental models in biomedicine, also known as preclinical models, are nowadays widely used by most R&D laboratories in universities and companies around the world. These models make possible to study a disease, a biological condition or an organic system to an extent that would be impossible to achieve in humans. Despite their limitations, there is no doubt that they offer many advantages, allowing the study of genes and therapies with high predictive values which avoid posing an initial risk to humans. The most standardized models used are those based on cell lines (*in vitro* and *ex vivo* models) and animal models (*in vivo* models), in which rodents are the main subjects. The use of these species is justified because they share 95% of their genes with humans. Moreover, they have a shorter life expectancy, a faster capacity to develop the disease (compare with humans) and are easy to handle thanks to their small size. The applications that preclinical models offer are many:

- Neurobiological and behavioural studies.
- Environmental studies: study of factors that contribute to the development of a disease.
- Studies of the different phases and evolution of a disease.
- Search and validation of diagnostic and prognostic markers and treatment selection.
- Search and validation of new therapeutic targets.
- Search and validation of new therapeutic routes.
- Search and validation of new molecular mechanisms of action of therapeutic targets.
- Proofs of Concept of efficacy and safety of compounds (new compounds and reformulations).

This catalogue was created with the aim of unifying the great variety of experimental models that the University of Barcelona is currently developing in the biomedical field in order to make them known both to researchers from this or other universities and, to companies and other institutions. The final goal is to be able to work together to generate knowledge about the diseases that affect our society and to be one step closer each day to finding a cure for all of them.

CHAPTER 0

Generation of new experimental models



0

0. Generation of new experimental models

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: New cellular models based on the required approach.

EXPERTISE: The CELLTEC-UB team is a consolidated group specialized in the development, transfer and application of cellular and molecular technology at different levels: cellular, morphological and molecular.

APPLICATIONS:

- Development and validation of therapeutic targets.
- Development and validation of functional targets (cosmetics, smart tissues).
- Screening of compounds.
- Toxicity, metabolism and safety studies of molecules.
- Efficacy and safety studies of compounds and products for regulatory or commercial dossiers.

EXAMPLES:

- Models to study of anti-oxidant effects.

- Models to study anti-aging effects.

- Models to study skin repair effects.

PRINCIPAL INVESTIGATORS:
Manuel Reina.

OTHER GROUP PUBLICATIONS AND WEBSITE:

PubMed Publications.

Group website.

SYSTEM: *In vivo - Ex vivo*

EXPERIMENTAL MODEL: New animal models based on the required approach-mouse and rat (rabbit, hamster and guinea pig are also possible).

EXPERTISE: The group CEREMET, with a highly qualified team, offers its knowledge in generating new models in the fields of biochemistry, physiology and metabolism. The services are conducted under the ISO 9001 certification of quality.

APPLICATIONS:

- Proof of concept.
- Pharmacokinetics and local tolerance.
- Pre-clinical studies.
- Monitoring of blood parameters.
- Metabolism regulation.
- Feeding with different diets.
- Genetic expression.
- Different routes administration.
- Surgery procedures.
- Tissue perfusion (liver, heart and white adipose tissue).
- Blood and tissue samples obtaining.
- Development of animal models on request.

EXAMPLES:

- Fructose feeding model for hypertriglyceridemia.

- Diet induced obesity model for obesity and its comorbidities.

- Hepatic punch model for hepatic regeneration and hemostasis.

- Hepatectomy model for hepatic regeneration.

PRINCIPAL INVESTIGATORS:
David Ricart.

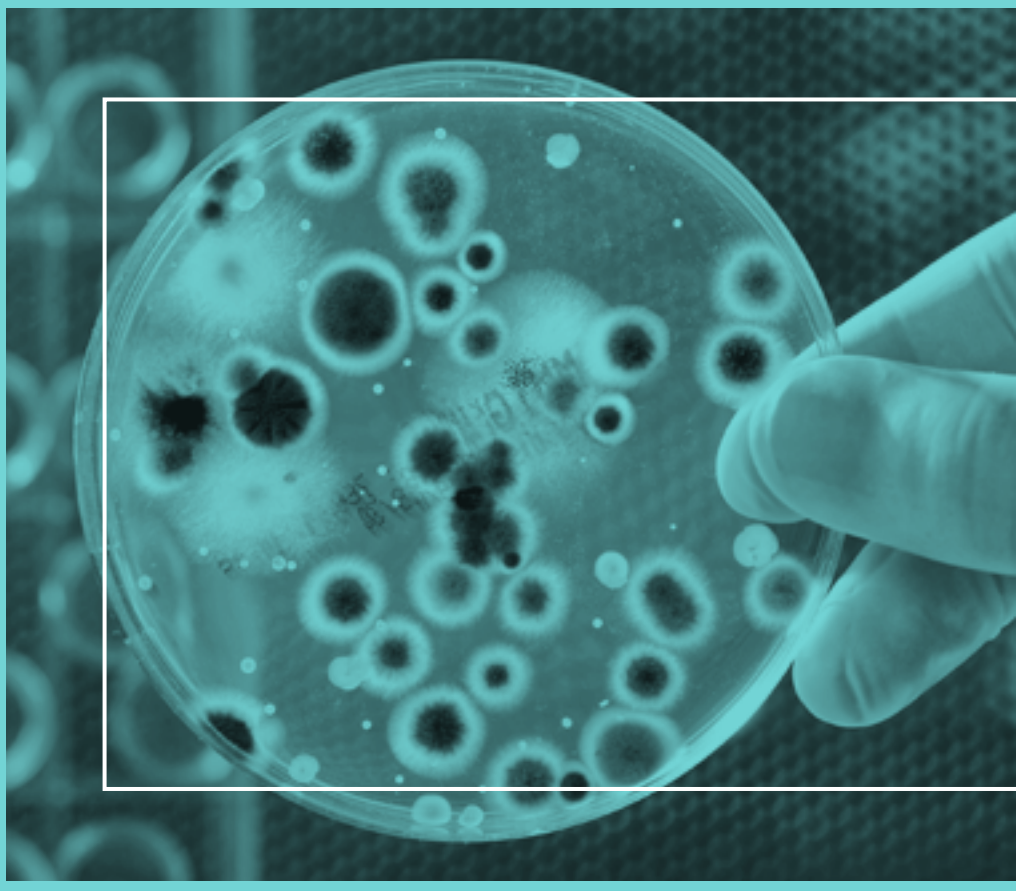
OTHER GROUP PUBLICATIONS AND WEBSITE:

PubMed Publications.

Group website.

CHAPTER 1

Certain Infectious and Parasitic Diseases



01

1.1. Intestinal Infectious Diseases (A00-A09)

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: Gastroenteritis associated to rotavirus infection in newborn rat. (***Pediatric Research*** *2007; 62 (6), pp. 658-663).*

APPLICATIONS:

- Testing the effect of bioactive compounds.
- Disease indicators and biomarkers: pathogen shedding, incidence, duration and severity of the disease.
- Host immune response evaluation: specific humoral and cellular immune response, microbiota composition, intestinal barrier function.

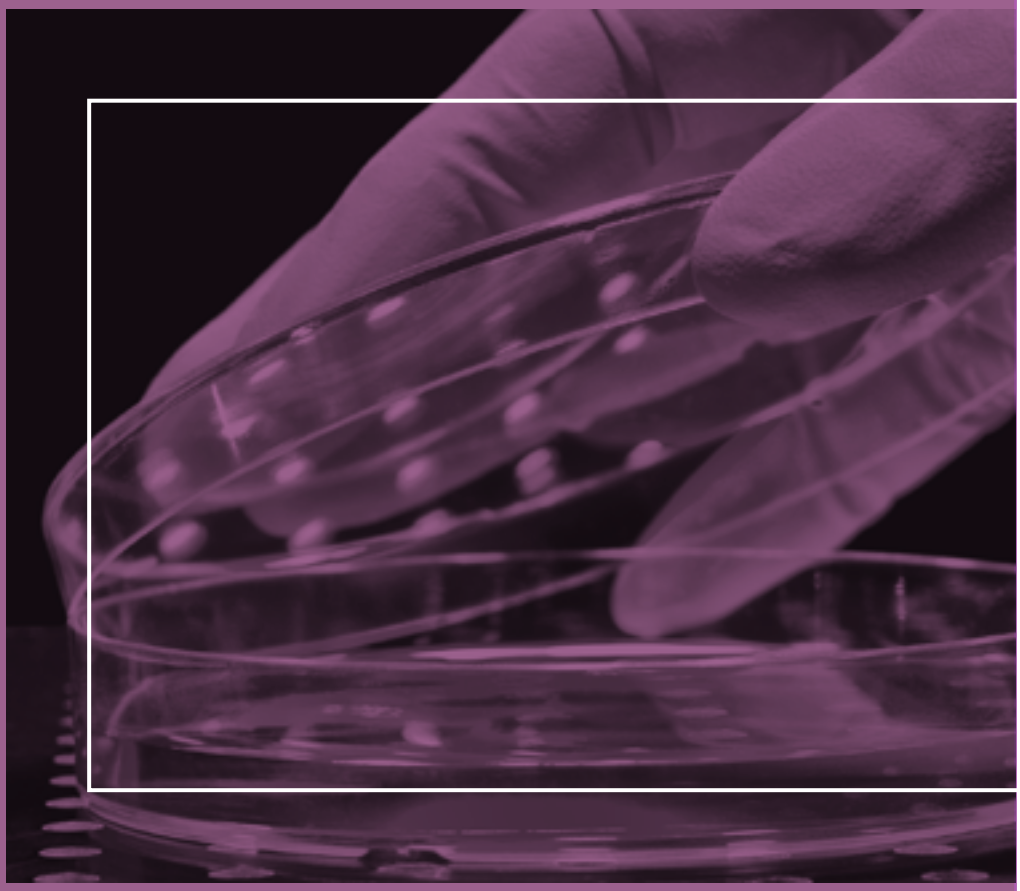
PRINCIPAL INVESTIGATORS:
Francisco J. Pérez-Cano, Àngels Franch, Margarida Castell, M. José Rodríguez-Lagunas, Malén Massot-Cladera.

OTHER GROUP PUBLICATIONS:

PubMed publications.

CHAPTER 2

Neoplasms



02

2.1. Malignant neoplasms of respiratory and intrathoracic organs (C30 - C39)

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Primary cultures of lung cancer patient derived fibroblasts. (***Oncotarget.*** *2016 Dec 13; 7 (50):82324-82337).*

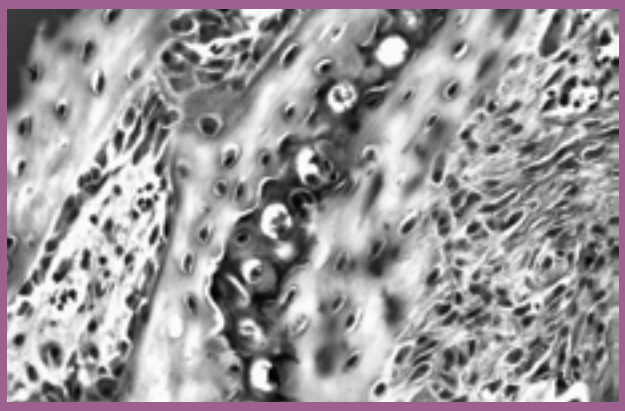
APPLICATIONS:

- Normal vs pathologic studies.
- Mechanisms of drug action.
- Potential targets identification.
- Therapeutic effects validation.
- Drug combinations and reproval from preexisting treatments.
- Drug resistance mechanisms.

PRINCIPAL INVESTIGATORS:
Jordi Alcaraz.

OTHER GROUP PUBLICATIONS:

PubMed publications.



SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Biomechanical models of lung cancer and fibrosis. 2D and 3D hydrogels with fibroblasts culture systems. (***Mol Cancer Res.*** *2015 Jan;13 (1):161-73).*

APPLICATIONS:

- Mechanistic studies.
- Cell stiffness.
- Novel mechanoregulatory pathways.
- Cell-to-cell, cell-to-matrix interactions.
- Predictive data in normal and pathologic situation.
- Mechanisms of drug action.
- Potential targets identification.
- Therapeutic effects validation.
- Drug combinations and reproval from preexisting treatments.
- Drug resistance mechanisms.
- Personalized treatment.

MODEL ADVANTAGES:
This model allows the modulation of matrix rigidity and other culture conditions to reproduce the desired pathologic stage or condition, obtaining physiologically relevant information.

PRINCIPAL INVESTIGATORS:
Jordi Alcaraz.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Stablished cancer cell lines cultures and cocultures with patient derived fibroblasts. (***Mol Cancer Res.*** *2015 Jan; 13 (1):161-73).*

APPLICATIONS:

- Mechanisms of drug action.
- Tissue organization.
- Candidate targets identification.
- Therapeutic effects validation.
- Drug combinations and reproval from preexisting treatments.
- Drug resistance mechanisms.

PRINCIPAL INVESTIGATORS:
Jordi Alcaraz.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: Tumor dissemination mouse models (tail vein, heart injection).

APPLICATIONS:

- Cancer metastases studies (tumor cells dissemination and progression).
- Drug distribution.
- Toxicity studies.
- Molecular targets validation.

PRINCIPAL INVESTIGATORS:
Jordi Alcaraz.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: Tumor xenografts into immunocompromised mice.

APPLICATIONS:

- Cancer progression.
- Effectivity and toxicity of candidate compounds.
- Therapeutic effects validation.
- Drug combinations and resistance mechanisms.

PRINCIPAL INVESTIGATORS:
Jordi Alcaraz.

OTHER GROUP PUBLICATIONS:

PubMed publications.

2.2. Malignant Cachexia (C80 - C80.9)

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Cell cultures of muscle C2C12 cell line (mouse) and mouse adipose 3T3 L1 cell line. *(**Nutr Metab (Lond).** 2012 Aug 21; 9 (1):76; **J Lipid Res.** 2013 Nov; 54 (11):3045-51).*

APPLICATIONS:

- Disease evolution.
- Drug test.
- Molecular disease markers.
- Molecular biology techniques: WB, cytometry, RT-PCR.

PRINCIPAL INVESTIGATORS:
Josep Maria Argilés, Silvia Busquets, Francisco López-Soriano.

OTHER GROUP PUBLICATIONS:

F. López-Soriano at PubMed.

S. Busquets at PubMed.

JM. Argilés at PubMed.

SYSTEM: *Ex vivo*

EXPERIMENTAL MODEL: Incubation of muscle and adipose tissue. *(**Oncol Rep.** 2008 Jan; 19 (1):253-6).*

APPLICATIONS:

- Measuring muscle strength and physical activity in experimental models.

PRINCIPAL INVESTIGATORS:
Josep Maria Argilés, Silvia Busquets, Francisco López-Soriano.

OTHER GROUP PUBLICATIONS:

F. López-Soriano at PubMed.

S. Busquets at PubMed.

JM. Argilés at PubMed.

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: Ascites hepatoma Yoshida AH-130: model of cancer cachexia in rats of the Wistar strain. (***Biochimie.*** *2018 Jun; 149:79-91;* ***Oncotarget.*** *2015 Dec 22; 6 (41):43202-15).*

APPLICATIONS:

- Normal vs pathologic studies.
- Therapies effectiveness of cancer cachexia.
- Discovery and validation of targets and pathways involved in the pathology and syndrome evolution.
- Molecular disease markers validation.
- Molecular biology techniques: WB, RT-PCR, optical and electron microscopy, IB, TUNEL.
- Tumor weight measurement.
- Strength measurement (Grip strength test).
- Locomotor activity measurement (IR actimeter System with ACTITRAK software).
- Tapes to train animals.
- Blood tests.

PRINCIPAL INVESTIGATORS:
Josep Maria Argilés, Silvia Busquets, Francisco López-Soriano.

OTHER GROUP PUBLICATIONS:

F. López-Soriano at PubMed.

S. Busquets at PubMed.

JM. Argilés at PubMed.

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: Lewis lung carcinoma: model of cancer cachexia in mice of the strain C57BL6. (***Int J Cancer.*** *2016 Apr 15; 138(8):2021-9;* ***Oncotarget.*** *2015 Dec 22; 6 (41):43202-15).*

APPLICATIONS:

- Normal vs pathologic studies.
- Therapies effectiveness of cancer cachexia.
- Discovery and validation of targets and pathways involved in the pathology and syndrome evolution.
- Molecular disease markers validation.
- Molecular biology techniques: WB, RT-PCR, optical and electron microscopy, IB, TUNEL.
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- Tapes to train animals.
- Blood tests.

PRINCIPAL INVESTIGATORS:
Josep Maria Argilés, Silvia Busquets, Francisco López-Soriano

OTHER GROUP PUBLICATIONS:

F. López-Soriano at PubMed.

S. Busquets at PubMed.

JM. Argilés at PubMed.

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: C26 colon adenocarcinoma: model of cancer cachexia in mice of the Balb strain. (***J Cachexia Sarcopenia Muscle.*** *2015 Mar; 6 (1):84-94;* ***Oncotarget.*** *2015 Dec 22; 6 (41):43202-15).*

APPLICATIONS:

- Normal vs pathologic studies.
- Therapies effectiveness of cancer cachexia.
- Discovery and validation of targets and pathways involved in the pathology and syndrome evolution.
- Molecular disease markers validation.
- Molecular biology techniques: WB, RT-PCR, optical and electron microscopy, IB, TUNEL.
- Tumor weight measurement.
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- Blood tests.

PRINCIPAL INVESTIGATORS:
Josep Maria Argilés, Silvia Busquets, Francisco López-Soriano.

OTHER GROUP PUBLICATIONS:

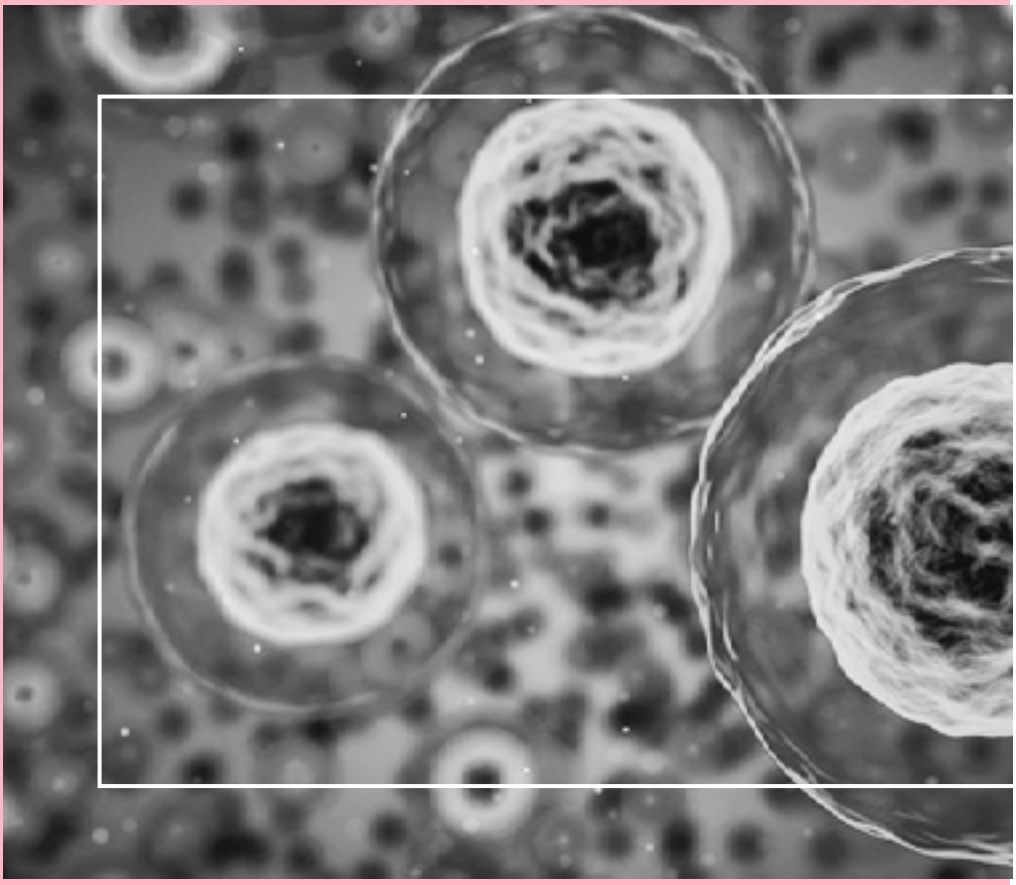
F. López-Soriano at PubMed.

S. Busquets at PubMed.

JM. Argilés at PubMed.

CHAPTER 3

Immune System



03

3.1. Programming and development of the immune system

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: Immune development in prematurity. *(**Nutrients** 2019; 11 (5), art. no. 999).*

APPLICATIONS:

- Testing the effect of bioactive compounds.
- Diets design and ingredient incorporation into feed.
- Host immune development: humoral and cellular immune response, composition of lymphoid tissues.
- Intestinal immune system: microbiota composition, intestinal barrier.
- Immune functions: phagocytosis, cytotoxic activity, lymphocyte composition and functionality.

PRINCIPAL INVESTIGATORS:
Àngels Franch, Francisco J. Pérez-Cano, Margarida Castell, M. José Rodríguez-Lagunas, Malén Massot-Cladera.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: Immune development during gestation and sucking period. *(**Developmental and Comparative Immunology** 2007; 31 (12), pp, 1264-1277; **Pediatric Research** 2005; 58 (5), pp. 885-891; **Pediatric Research** 2005; 58 (1), pp. 164-169).*

APPLICATIONS:

- Testing the effect of bioactive compounds.
- Diets design and ingredient incorporation into feed.
- Host immune development: humoral and cellular immune response, composition of lymphoid tissues.
- Intestinal immune system: microbiota composition, intestinal barrier.
- Immune functions: phagocytosis, cytotoxic activity, lymphocyte composition and functionality.

PRINCIPAL INVESTIGATORS:
Àngels Franch, Francisco J. Pérez-Cano, Margarida Castell, M. José Rodríguez-Lagunas, Malén Massot-Cladera.

OTHER GROUP PUBLICATIONS:

PubMed publications.

3.2 Microbiota and intestinal immune system

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: Rat model for evaluation of intestine microbiota and immunity modulators. *(**Journal of Functional Foods** 2015; 19, pp. 341-352; **Archives of Biochemistry and Biophysics** 2012; 527 (2), pp. 105-112).*

APPLICATIONS:

- Testing the effect of bioactive compounds (pro-, pre-, postbiotics).
- Host immune development: humoral and cellular immune response, composition of lymphoid tissues.
- Intestinal immune system: microbiota composition, intestinal barrier.

PRINCIPAL INVESTIGATORS:
Francisco J. Pérez-Cano, Margarida Castell, Àngels Franch, M. José Rodríguez-Lagunas, Malén Massot-Cladera.

OTHER GROUP PUBLICATIONS:

PubMed publications.

3.3 Exercise and immune system

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: Effect of running in immune system. *(**Nutrients** 2019 11(4). pii: E78).*

APPLICATIONS:

- Testing the effect of bioactive compounds.
- Host immune development: humoral and cellular immune response, composition of lymphoid tissues.
- Intestinal immune system: microbiota composition, intestinal barrier.

PRINCIPAL INVESTIGATORS:
Francisco J. Pérez-Cano, Margarida Castell, Àngels Franch, M. José Rodríguez-Lagunas, Malén Massot-Cladera.

OTHER GROUP PUBLICATIONS:

PubMed publications.

CHAPTER 4

Endocrine, Nutritional and Metabolic Diseases

04

4.1. Type 1 Diabetes Mellitus (E10)

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Cellular models for T and B cell activation and analysis. (***PLoS One.*** *2015 Jun 3;10(6):e0127057;* ***Eur J Immunol.*** *2013 Nov; 43 (11): 10.1002/eji.201343633;* ***Sci Rep.*** *2018 May 25; 8 (1):8106;* ***Nature.*** *2016 Feb 25;530(7591):434-40).*

APPLICATIONS:

- Contribution of T and B cells and mechanism of action to diabetes type I.

PRINCIPAL INVESTIGATORS:
Thomas Stratmann.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Generation of T cell hybridomas and monoclonal antibodies. (***Eur J Immunol.*** *2013 Nov; 43 (11): 10.1002/eji.201343633).*

APPLICATIONS:

- In vitro and in vivo multiple testing (diagnostic tool).
- Vaccine development.

PRINCIPAL INVESTIGATORS:
Thomas Stratmann.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Design and generation of recombinant proteins in *E. coli* and *D. melanogaster* SC2 cells recombinant IL-2 containing a side-specific biotinisation sequence. (***Eur J Immunol.*** *2013 Nov; 43 (11): 10.1002/eji.201343633;* ***J Immunol*** *September 15, 2000, 165 (6) 3214-3225).*

APPLICATIONS:

- Function analysis and modulation of autoreactive T and B cells.
- Laboratory escalation for therapeutic studies in prokaryotes and eukaryotes models.

PRINCIPAL INVESTIGATORS:
Thomas Stratmann.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Generation of DNA vaccines that contain CTLA4 fused to the peptide's sequence of interest. *(**J Immunol.** 2011 Apr 1;186 (7):4078-87).*

APPLICATIONS:

- T regs activation.
- Autoimmunity.

PRINCIPAL INVESTIGATORS:
Thomas Stratmann.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: NOD mouse + BDC-2.5T Cell: transgenic TCR. *(**J Immunol.** 2011 Apr 1;186 (7):4078-87).*

MODEL ADVANTAGES:
Model based on BDC-2.5 mimotope, accele rates diabetic process in the animal T.

PRINCIPAL INVESTIGATORS:
Thomas Stratmann.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: NOD mouse: human-like diabetes model. *(**PLoS One.** 2015 Jun 3;10 (6): e0127057; **Eur J Immunol.** 2011 May; 41(5): 1344–1351; **Sci Rep.** 2018 May 25; 8 (1):8106; **Nature.** 2016 Feb 25;530(7591):434-40).*

APPLICATIONS:

- Transgenic mice generation (diabetes-related genes).
- New drugs and compounds test.
- Diabetes reversal and disease development studies.

PRINCIPAL INVESTIGATORS:
Thomas Stratmann.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: NOD mouse + FOX-P3EGFP. *(**Eur J Immunol.** 2013 Nov; 43 (11):10.1002/eji.201343633*; ***Sci Rep.** 2018 May 25; 8 (1):8106).*

APPLICATIONS:

- New drugs and compounds testing.
- Useful model for T cell studies.
- Modulation of FOXP3 T reg for diabetes prevention.

PRINCIPAL INVESTIGATORS:
Thomas Stratmann.

OTHER GROUP PUBLICATIONS:

PubMed publications.

4.2. Type 2 Diabetes Mellitus (E11)

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Human LHCN-M2 myoblasts (***Metabolism.*** *2018 Aug; 85:59-75).*

APPLICATIONS:

- Gene silencing (siRNA).
- Gene expression (RT-PCR).
- Protein levels (WB).
- EMSA: transcription factors assessment.
- Fatty Acid Oxidation Assay.
- Lipid accumulation in hepatocytes (Oil Red O Staining).
- Deoxy-D-glucose,2-[1,2-3H(N)] Uptake Experiments.

PRINCIPAL INVESTIGATORS:
Manuel Vázquez-Carrera.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *Ex vivo*

EXPERIMENTAL MODEL: Mouse C2C12 myoblasts-myotubes (***Diabetes.*** *2016 Oct; 65 (10):3185-99).*

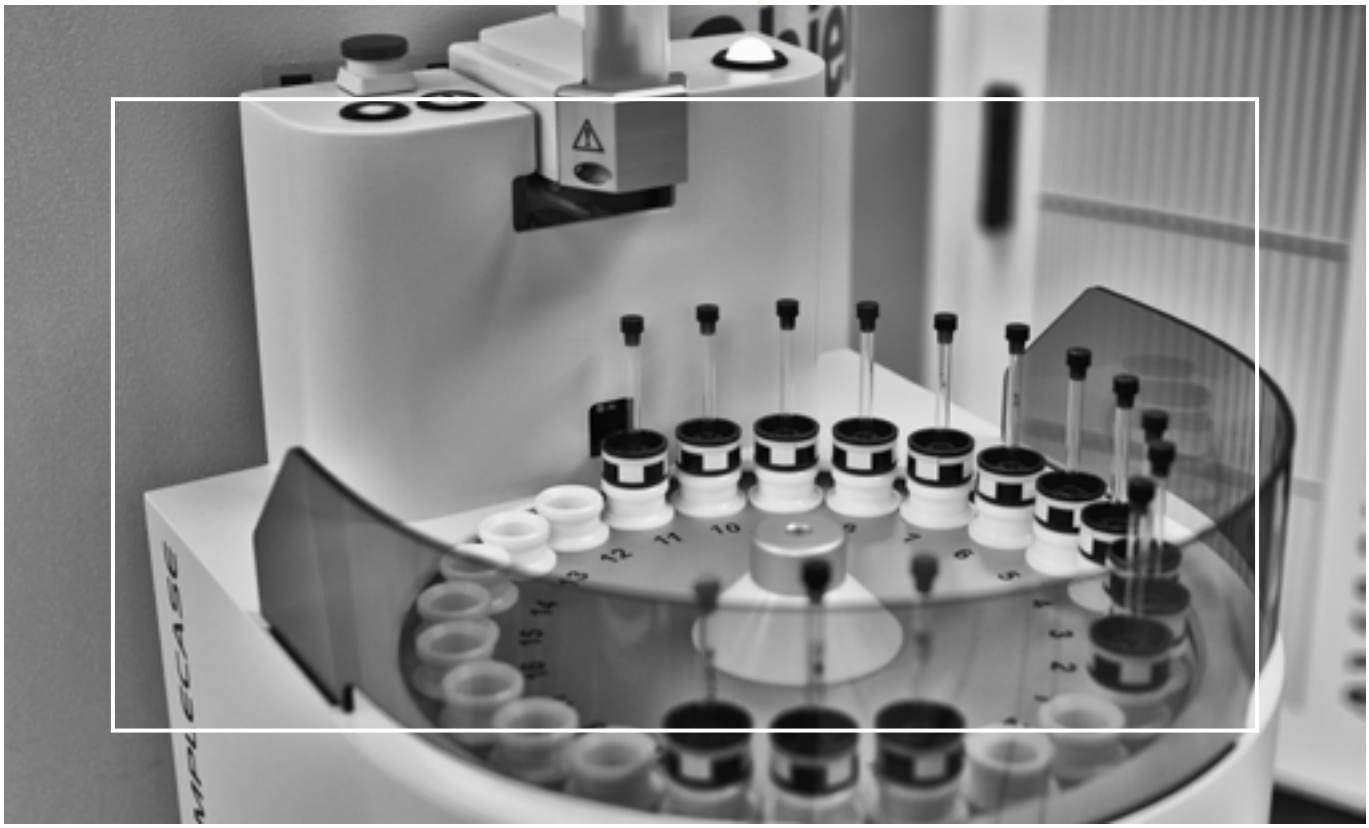
APPLICATIONS:

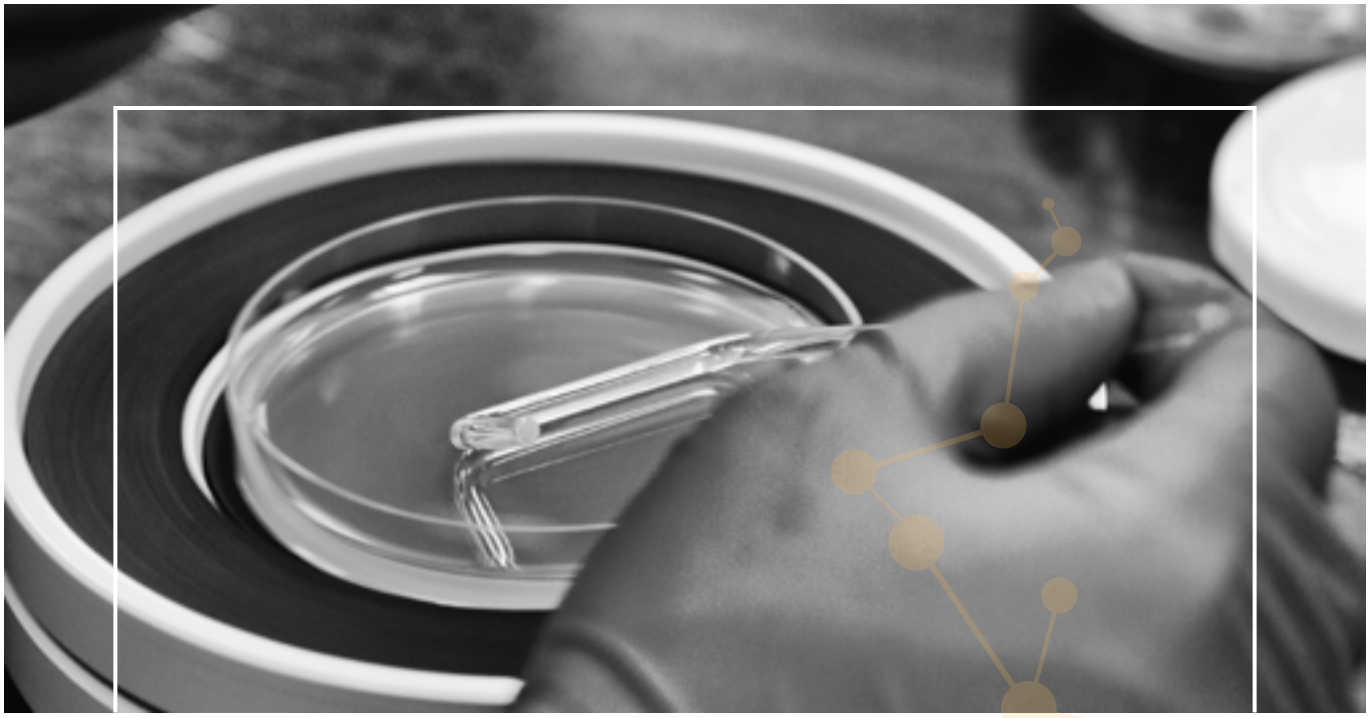
- Gene silencing (siRNA).
- Gene expression (RT-PCR).
- Protein levels (WB).
- EMSA: transcription factors assessment.
- Fatty Acid Oxidation Assay.
- Lipid accumulation in hepatocytes (Oil Red O Staining).
- Deoxy-D-glucose,2-[1,2-3H(N)] Uptake Experiments.

PRINCIPAL INVESTIGATORS:
Manuel Vázquez-Carrera.

OTHER GROUP PUBLICATIONS:

PubMed publications.





SYSTEM: *In vivo*

EXPERIMENTAL MODEL: High fat diet induced type 2 diabetes (palmitate diet). (***Diabetes.*** *2016 Oct; 65 (10):3185-99;* ***Metabolism.*** *2018 Aug; 85:59-75).*

- Male PPAR ß/σ knockout mice and wildtype (PPAR ß/σ $^{+/+}$) littermates.

APPLICATIONS:

- Fatty acids, glucose and specific markers measurement in serum and tissues (white adipose tissue, blood, hepatocytes).
- Glucose Tolerance Test (GTT).
- Insulin Tolerance Test (ITT).
- Piruvate Tolerance Test (PTT).
- Biochemical and biomolecular techniques.
- EMSA: transcription factors assessment.

PRINCIPAL INVESTIGATORS:
Manuel Vázquez-Carrera.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: High fat diet induced ER stress model (under development).

- Male ATF3$^{-/-}$ mice and wildtype littermates (ATF3$^{+/+}$).
- GADD45a $^{-/-}$ mice and wildtype littermates (GADD45a $^{+/+}$).

APPLICATIONS:

- Fatty acids, glucose and specific markers measurement in serum and tissues (white adipose tissue, blood, hepatocytes).
- Glucose Tolerance Test (GTT).
- Insulin Tolerance Test (ITT).
- Piruvate Tolerance Test (PTT).
- Biochemical and biomolecular techniques.
- EMSA: transcription factors assessment.

PRINCIPAL INVESTIGATORS:
Manuel Vázquez-Carrera.

OTHER GROUP PUBLICATIONS:

PubMed publications.

4.3. Cystinuria (E72)

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: Mouse model of type I and non-type I cystinuria: Slc7a9 null KO (stones) and wt in C57BL6/J-129Sv mice. *(**Am J Physiol Renal Physiol.** 2007 Sep; 293 (3):F732-40; **Hum Mol Genet**. 2003 Sep 1;12 (17):2097-108).*

APPLICATIONS:

- Aminoaciduria studies.
- Renal transporters study.
- Molecular basis of renal reabsorption on different experimental diets.
- Phenotypic studies.
- Urinary bladder calculi quantification by X- ray analysis.
- Metabolites studies from urine and blood.
- Molecular Biology techniques from animal tissue: WB, PCR, IP, IC.
- High throughput techniques (omic studies, proteomics, transcriptomics) from mouse tissue.
- Test of drug candidates.

PRINCIPAL INVESTIGATORS:
Virginia Nunes Martínez, Manuel Palacín, Antonio Zorzano.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: Double KO LAT2-TAT1 mice: DKO Slc7a8/Slc3a2 model. *(**J Am Soc Nephrol.** 2018 Jun; 29 (6):1624-1635).*

APPLICATIONS:

- Aminoaciduria studies.
- Renal transporters study.
- Molecular basis of renal reabsorption on different experimental diets.
- Phenotypic studies.
- Urinary bladder calculi quantification by X- ray analysis.
- Metabolites studies from urine and blood.
- Molecular Biology techniques from animal tissue: WB, PCR, IP, IC.
- High throughput techniques (omic studies, proteomics, transcriptomics) from mouse tissue.
- Test of drug candidates.

PRINCIPAL INVESTIGATORS:
Virginia Nunes Martínez, Manuel Palacín, Antonio Zorzano.

OTHER GROUP PUBLICATIONS:

PubMed publications.

4.4. Sanfilippo Syndrome B and C (E76)

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Sanfilippo C IPSC neurons and astrocytes: patient-derived IPCs fibroblasts of Sanfilippo C syndrome patients differentiation into neurons. (***Stem Cell Reports.*** *2015; 5: 546-57).*

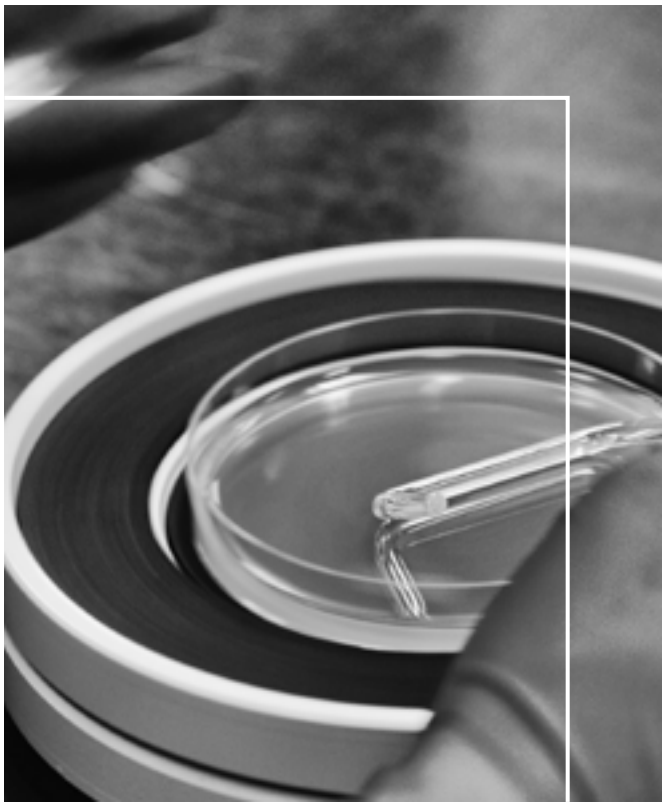
APPLICATIONS:

- Cell reprogramming.
- Mutant alleles characterization and expression.
- Study of mechanisms that generate recombinant alleles traffic.
- Nonsense mediated decay genotype-phenotype correlation gene silencing.
- New therapeutic strategies research.
- Splicing analysis (microexon).

PRINCIPAL INVESTIGATORS:
Daniel-Raul Grinberg, Mª Lluïsa Vilageliu.

OTHER GROUP PUBLICATIONS:

PubMed publications.



SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Sanfilippo B and C Neurons and Astrocytes (using CRISPR/Cas9). (***Stem Cell Res,*** *under review)*.

APPLICATIONS:

- Cell reprogramming.
- Mutant alleles characterization and expression.
- Study of mechanisms that generate recombinant alleles traffic.
- Nonsense mediated decay genotype-phenotype correlation gene silencing.
- New therapeutic strategies research.
- Splicing analysis (microexon).

PRINCIPAL INVESTIGATORS:
Daniel-Raul Grinberg, Mª Lluïsa Vilageliu.

CLINICAL RELEVANCE: These models allow deciphering and classifying pre-symptomatic stages of Sanfilippo Syndrome, to describe a disease progression model and results in a drug screening platform for new therapeutic approaches (i.e. aminoglycoside antibiotics, antisense oligonucleotides, chaperones).

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Patients' fibroblasts as therapeutic model of Heparan Sulphate substracts reduction through shRNA. (***PLoS One.*** *2015;10: e0135873).*

APPLICATIONS:

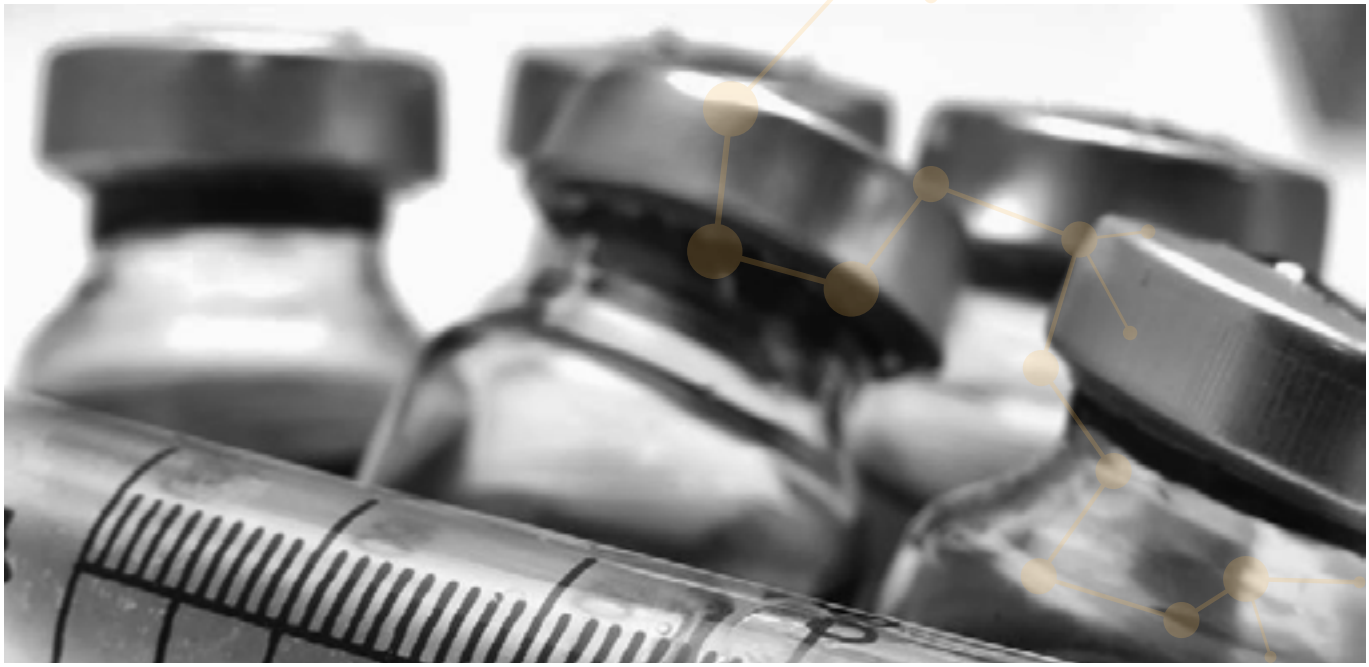
- Cell reprogramming.
- Splicing analysis (microexon).
- Study of mechanisms that generate recombinant alleles traffic.
- Nonsense mediated decay genotype-phenotype correlation gene silencing.
- New therapeutic strategies research.
- Mutant alleles characterization and expression.

PRINCIPAL INVESTIGATORS:
Daniel-Raul Grinberg, Mª Lluïsa Vilageliu.

CLINICAL RELEVANCE: These models allow deciphering and classifying pre-symptomatic stages of Sanfilippo Syndrome, to describe a disease progression model and results in a drug screening platform for new therapeutic approaches (i.e. aminoglycoside antibiotics, antisense oligonucleotides, chaperones).

OTHER GROUP PUBLICATIONS:

PubMed publications.



4.5. Niemann-Pick Disease C (E75)

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Niemann-Pick type C (NPC) mutant cell lines and patient fibroblasts. *(**JIMD Rep.** 2012;4:29-37; **Cell Rep.** 2014 May 8;7(3):883-97; **Hum Mutat.** 2009 Jul; 30(7): 1117–1122).*

APPLICATIONS:

- New therapeutic strategies.
- Construction of transient and stable NPC gene silencing model.
- Functional studies.

PRINCIPAL INVESTIGATORS:
Daniel-Raul Grinberg, Mª Lluïsa Vilageliu.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: Niemann-Pick disease type C animal (Sp: Mouse) models bearing pseudoexon-generating mutations (Npc1^{imagine} and Npc1^{pioneer} homozygous models). *(**Hum Mutat.** 2009 Nov30(11):E993-E1001; **Sci Rep.** 2017; 7: 41931).*

APPLICATIONS:

- Mutation roles in the disease progression.
- Molecular and behavioral disease characterization.
- New therapeutic approaches.
- Cell reprogramming.
- Mutant alleles expression and characterization.
- Origin of mutations and splicing analysis study of mechanisms that generate recombinant alleles.
- Protein traffic.
- Protein structure.
- Nonsense mediated decay (NMD) genotype-phenotype correlation.
- Gene silencing.
- New therapeutic strategies research.

PRINCIPAL INVESTIGATORS:
Daniel-Raul Grinberg, Mª Lluïsa Vilageliu.

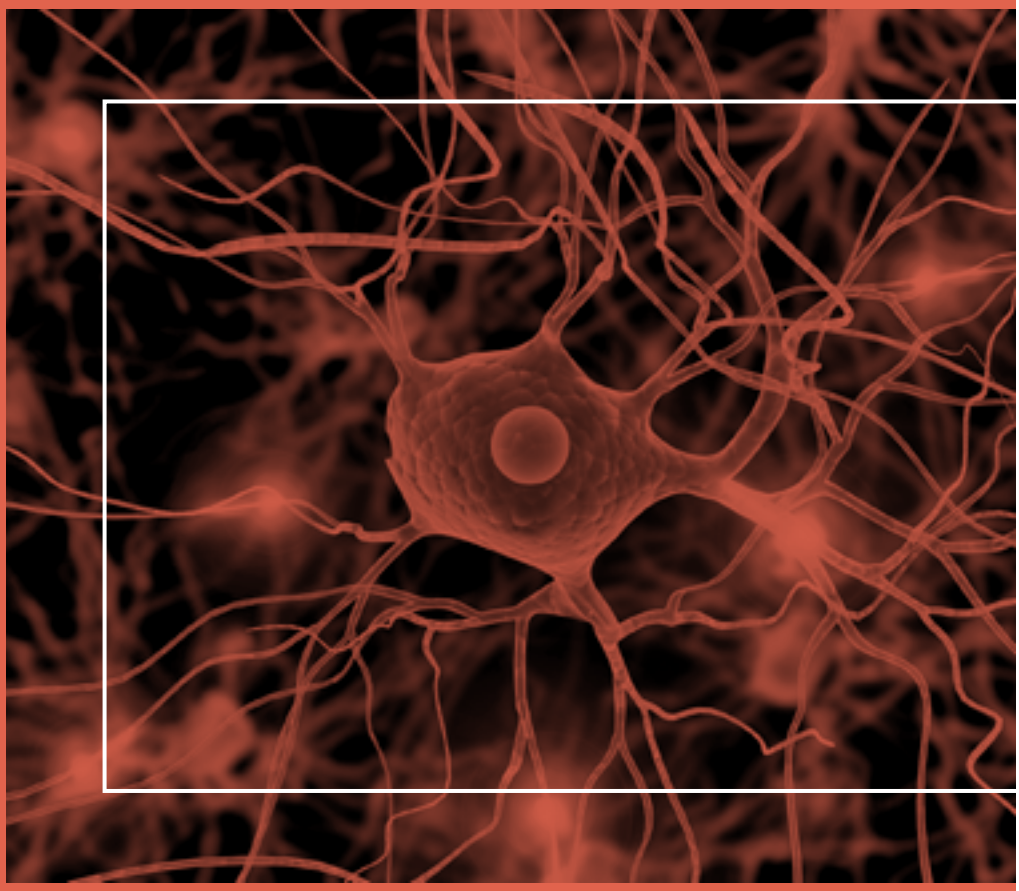
CLINICAL RELEVANCE: These models allow deciphering and classifying pre-symptomatic stages of Niemann-Pick disease, to describe a disease progression model and results in a drug screening platform for new therapeutic approaches.

OTHER GROUP PUBLICATIONS:

PubMed publications.

CHAPTER 6

Diseases of the Nervous System



06

6.1. Leukodystrophies

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Primary quiescent astrocytes (rat, mouse) and human stablished cell lines. *(**J Physiol.** 2017 Nov 15;595(22):6993-7008; **Human Molecular Genetics,** 2017, Vol. 26, No. 13; **J Physiol.** 2015 Sep, 15; 593(18):4165-80).*

APPLICATIONS:

- Site-directed mutagenesis.
- TALEN nucleases.
- CRISPR.
- RNAi, Adenoviruses and Lentiviruses.
- Transduction.
- Electrophysiology tests (patch-clamp).
- Biochemical tests: image techniques to study cell-cell junction and subcellular localization.
- Biotinilation.
- *In vitro* transcription.
- Membrane protein biochemistry.
- Protein-protein interactions.
- SPLIT-TEV method.

PRINCIPAL INVESTIGATORS:
Raul Estevez Povedano, Virginia Nunes.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Xenopus oocytes expressing Ion channel proteins. *(**J Physiol.** 2017 Nov 15;595(22):6993-7008; **J Physiol.** 2015 Sep 15;593(18):4165-80; **Neuron**. 2012 Mar 8;73 (5):951-61).*

APPLICATIONS:

- Electrophysiology tests (patch clamp).
- Membrane protein biochemistry.
- Proteins expression.
- Surface protein expression.
- Protein-protein interactions.

PRINCIPAL INVESTIGATORS:
Raul Estevez Povedano, Virginia Nunes.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: Clc2/Glial *CAM* $^{-/-}$ mouse model. *(**Human Molecular Genetics,** 2017, Vol. 26, No.13; **Nat Commun,** 2014 Mar 19; (5):3475).*

APPLICATIONS:

- Channel studies.
- Phenotypic studies.
- Molecular biology techniques from animal tissue.
- High throughput techniques.
- Test of drug candidates.

MODEL RELEVANCE:
Recapitulates phenotypic features of Leukodystrophy, CLCN2-related leukoencephalopathy (CC2L) and Megalencephalic leukoencephalopathy.

PRINCIPAL INVESTIGATORS:
Raul Estevez Povedano, Virginia Nunes.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: Mlc1 $^{-/-}$ mouse model. *(**Nat Commun.** 2014 Mar 19; (5):3475).*

APPLICATIONS:

- Channel studies.
- Phenotypic studies.
- Molecular biology techniques from animal tissue.
- High throughput techniques.
- Test of drug candidates.

PRINCIPAL INVESTIGATORS:
Raul Estevez Povedano, Virginia Nunes

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: Chloride channels zebrafish models: KO model in zebrafish. *(**Hum Mol Genet.** 2014 Oct 1; 23 (19):5069-86).*

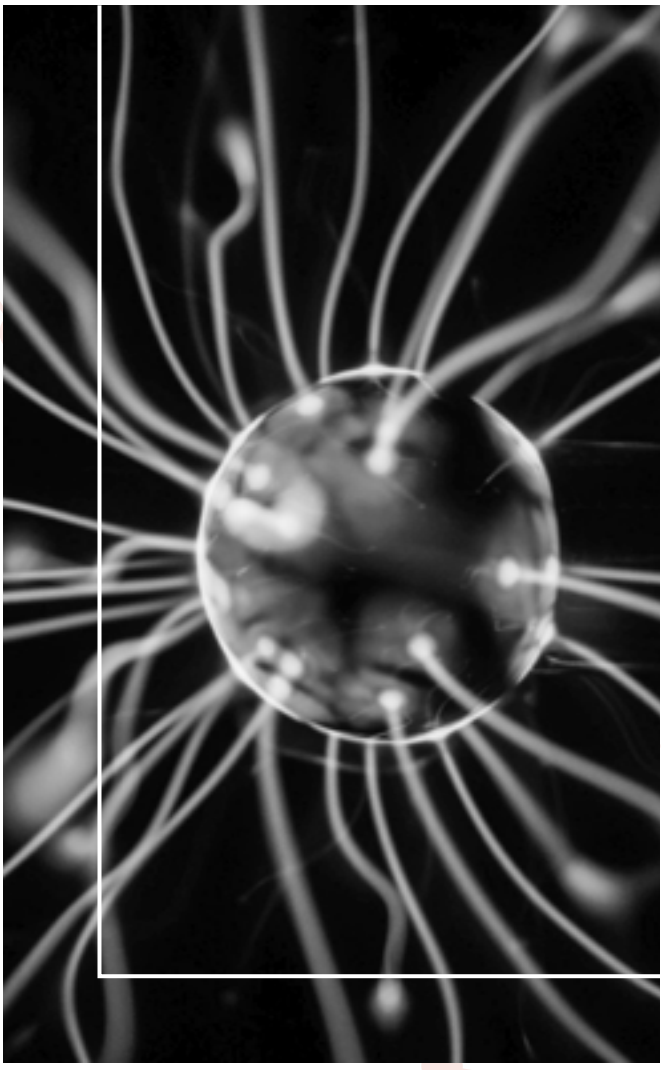
APPLICATIONS:

- Embryonic development and phylogeny studies.
- Adaptive physiology.
- Ion channels identification.
- Biochemical studies.
- Gene mapping.
- Transfection and co-transfection.

PRINCIPAL INVESTIGATORS:
Raul Estevez Povedano, Virginia Nunes.

OTHER GROUP PUBLICATIONS:

PubMed publications.



6.2. Epilepsy (G40)

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Primary cultures of striatal, cortical and hippocampal neurons. *(**Prog Neuropsychopharmacol Biol Psychiatry.** 2014 Oct 3; 54:231-42; **Pharmacol Res.** 2013 Apr;70(1):116-25).*

APPLICATIONS:

- Calcium level and calcium binding proteins.
- Potential therapeutic targets detection.
- Biochemical tests: western blot, microarrays, gene expression, targets activity assays, cytotoxicity, flow cytometry.
- Candidate drugs effects.

PRINCIPAL INVESTIGATORS:
Antoni Camins.

OTHER GROUP PUBLICATIONS:

A. Camins & Epilepsy at PubMed.

A. Camins at PubMed.

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: Chemically-induced epilepsy rodent model: Kainic Acid (KA) administration mainly induces neuronal loss in the hippocampus. *(**Mol Neurobiol.** 2018 May; 55(5):4437-4452; **Neuropharmacology.** 2018 Mar 15;131:440-452; **Front Biosci**. 2017 Jan 1;22:795-814; **J Neurochem.** 2010 Sep 1;114(5):1315-22).*

APPLICATIONS:

- KO mice models.
- Epilepsy disease molecular.
- Mechanisms and physiologic studies.
- Evaluation of epilepsy inductors and neuroprotectant drugs.
- Seizure-related behavioural studies.
- Biomolecular experimentation: cytotoxicity tests, inflammation tests, immunolocalization, ELISA.

PRINCIPAL INVESTIGATORS:
Antoni Camins.

OTHER GROUP PUBLICATIONS:

A. Camins & Epilepsy at PubMed.

A. Camins at PubMed.

6.3. Trigeminal Neuralgia and Peripheral Neuropathy (G90)

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Primary cell culture of sensory neurons, cortical and hippocampal neurons. (***Pain*** *2018 Jan 159(1): 92-105;* ***Sci Rep.*** *2016; 6 35775;* ***Mol Pain*** 2011; 7: 30; ***J. Neurosci*** *20 April 2011, 31 (16) 6059-6066;* ***Sci Signal****. 2019 Jun 18;12(586)).*

APPLICATIONS:

- Transient and stable expression of ion channels genes.
- Intracellular calcium effects and other ion fluxes (by imaging and electrophysiological techniques).
- Signaling pathways.
- Drugs testing.
- Molecular biology: Protein and gene expression techniques (western blot, immunoprecipitation, biotinylation, protein expression in yeast).

PRINCIPAL INVESTIGATORS:
Xavier Gasull, David Soto.

OTHER GROUP PUBLICATIONS:

X. Gasull at PubMed.

D. Soto at PubMed.

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Stablished cell lines (Hippocampus, cerebral cortex).(***Sci Signal.*** *2019 Jun 18; 12 (586);* ***J Physiol.*** *2017 Nov 15;595(22):6993-7008;* ***Front Mol Neurosci.*** *2018 Aug 8;11:275).*

APPLICATIONS:

- Transient and stable expression of ion channels genes.
- Intracellular calcium effects and other ion fluxes (by imaging and electrophysiological techniques).
- Signaling pathways.
- Drugs testing.
- Molecular biology: Protein and gene expression techniques (western blot, immunoprecipitation, biotinylation, protein expression in yeast).

PRINCIPAL INVESTIGATORS:
Xavier Gasull, David Soto.

OTHER GROUP PUBLICATIONS:

X. Gasull at PubMed.

D. Soto at PubMed.

SYSTEM: *In vitro - In vivo*

EXPERIMENTAL MODEL: Neuronal excitability models. Imaging techniques: intracellular calcium imaging and live-cell functionality imaging with fluorescent dyes. *(**Pain.** 2016 Feb; 157 (2): 399–417; **Mol Pain.** 2011; 7: 30).*

APPLICATIONS:

- Direct measurement of the calcium fluxes within neurons.
- Study of roles of calcium ions in different physiological and pathological situations.
- Intracellular signaling that control pain pathways.
- Sensory neurons response to drugs compounds and gene modifications cell volume, nitric oxide.

PRINCIPAL INVESTIGATORS:
Xavier Gasull, David Soto.

OTHER GROUP PUBLICATIONS:

X. Gasull at PubMed.

D. Soto at PubMed.

SYSTEM: *In vitro - In vivo*

EXPERIMENTAL MODEL: Neuronal excitability models. Current/voltatge-clamp techniques. (***Sci Rep.** 2016 Oct 21; 6:35775; **Sci Signal.** 2019 Jun 18;12(586); **Brain.** 2018 Nov 1;141(11):3144-3159; **Front Cell Neurosci.** 2015 Feb 2; 8:469).*

APPLICATIONS:

- Measurement of membrane voltage and neuronal excitability.
- Measurement of ion channel currents expressed in various cell types.
- Measurement of synaptic transmission and long-term potentiation (LTP) in hippocampal slices.
- Synaptic excitability functions.
- Measurament of membrane currents (whole-cell, single-channel, inside-out, outside-out configuration).

PRINCIPAL INVESTIGATORS:
Xavier Gasull, David Soto.

OTHER GROUP PUBLICATIONS:

X. Gasull at PubMed.

D. Soto at PubMed.

6.4. Muscular Dystrophy (G71)

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Model of Xenopus oocytes expressing and/or coexpressing CLCN1 and VRAC (wt and mutations) and CLC1 chloride channel proteins. (***Muscle Nerve.*** *2018 Feb 9;* ***Hum Mutat.*** *2016 Jan;37(1):74-83).*

APPLICATIONS:

- Channel osmosensitivity.
- Functional expression, modification and characterization of voltage channels, related subunits and regulatory proteins.
- Voltage channel activators and inhibitors analysis.
- 3D studies of voltage channels structure, binging molecules and mechanisms.

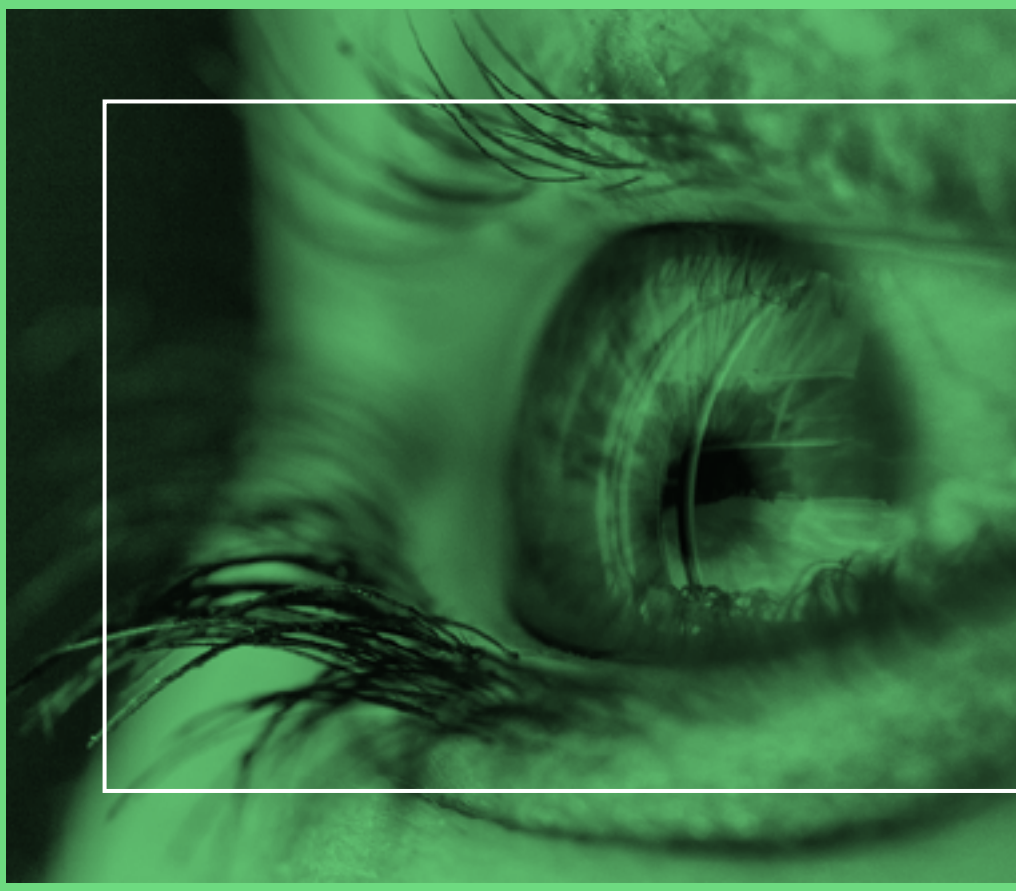
PRINCIPAL INVESTIGATORS:
Raul Estevez Povedano.

OTHER GROUP PUBLICATIONS:

PubMed publications.

CHAPTER 7

Diseases of the Eye and Adnexa



07

7.1. Dry Eye, Keratoconjuctivitis, glaucoma and ocular hypertension, ocular pain (H00 - H59)

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Ocular cell lines: Trabecular Meshwork (TM) cells and Schlemm's canal endothelial cells (SC) derived from a human normotensive patient. *(TM cells:* ***Sci Rep.*** *2017 Mar 28;7(1):452; SC cells:* ***Prog Retin Eye Res.*** *2015 Jan;44:86-98;* ***Exp Eye Res.*** *2014 Oct; 127:224-35;* ***Sci Rep.*** *2019 Apr 1; 9 (1):5392).*

APPLICATIONS:

- To study cellular aspects of these cells participating and regulating the passage of aqueous humor through the conventional route.
- To decipher molecular mechanisms of Schlemm's Canal Pore formation and its relationship with glaucoma disease.
- Molecular biology techniques: western blot, calcium free measurement, immunofluorescence (subcellular localization studies), gene expression analysis.

PRINCIPAL INVESTIGATORS:
Xavier Gasull, David Soto, Nuria Comes.

OTHER GROUP PUBLICATIONS:

X. Gasull at PubMed.

D. Soto at PubMed.

Nuria Comes at PubMed.

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: Animal models (mouse, rat and rabbit) of ocular pain by applying painful or pruritic substances in the ocular surface. *(****Pain.*** *2015 Mar;156(3):483-95;* ***Pain.*** *2016 Feb;157(2):399-417;* ***Eur J Pharmacol.*** *2007 Jul 12; 567 (1-2):145-8;* ***Exp Eye Res.*** *2011 Mar; 92 (3):221-6).*

Ocular pain tests

- Blinking test.

- Thermal / mechanical sensitivity.

- Lacrimation (tear secretion measurement).

APPLICATIONS:

- To study ocular pain after inflammation, injury or dry eye diseases.
- Topical application of substances to decipher neural mechanisms regulating intraocular pressure and ion K+ and Cl– channels that regulate contraction, shape and cell volume in trabecular cells that control aqueous humor flow and intraocular pressure in the eye.
- Understand the sensory ocular pathophysiology.

PRINCIPAL INVESTIGATORS:
Xavier Gasull, David Soto, Nuria Comes.

OTHER GROUP PUBLICATIONS:

X. Gasull at PubMed.

D. Soto at PubMed.

Nuria Comes at PubMed.

CHAPTER 8

Diseases of the Ear and Mastoid Process

08

8.1. Diseases of the Inner Ear (H80 - H83): Disorders of vestibular function, vertiginous syndromes

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: Animal model of auditive and vestibular dysfunction: 3,3'-iminodipropionitrile (IDPN) and streptomycin ototoxic exposure in mouse and rat. (***Arch Toxicol.*** *2019 Feb; 93 (2):417-434;* ***J Assoc***. ***Res Otolaryngol.*** *2019 Jul 11*; ***Toxicol Sci.*** *2017 Mar 1;156(1):109-122;* ***Dis Model Mech.*** *2015 Oct 1;8(10):1323-37;* ***Neurotoxicology.*** *2017 May;60:1-9).*

APPLICATIONS:

- Neurotoxicity assessment.
- Regeneration studies.
- Behavioral evaluation of auditive and vestibular dysfunction.
- Drugs and chemicals testing.
- Histopathologic analysis of vestibular system: identification of molecular targets in the vestibular periphery.
- Vestibular toxicology and pharmacology.
- Histology and gene expression studies of the sensory epithelia of the inner ear: RT-PCR, RNA-seq, inmuno-histochemistry and confocal microscopy, scanning electron microscopy, transmission electron microscopy, light microscopy in semi-thin sections.

PRINCIPAL INVESTIGATORS:
Jordi Llorens.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: Animal models of sensory neurotoxicity auditory, visual, olfactory, dorsal root ganglia (mouse, rat). (***Arch Toxicol.*** *2019 Feb;93 (2):417-434;* ***J Assoc.Res Otolaryngol.*** *2019 Jul 11;* ***Neurotoxicology****. 2018 Jul; 67:270-278).*

APPLICATIONS:

- Neurotoxicity assessment.
- Regeneration studies.
- Behavioral evaluation of auditive and vestibular dysfunction.
- Drugs and chemicals testing.
- Histopathologic analysis of vestibular system: identification of molecular targets in the vestibular periphery.
- Vestibular toxicology and pharmacology.
- Histology and gene expression studies of the sensory epithelia of the inner ear: RT-PCR, RNA-seq, inmuno-histochemistry and confocal microscopy, scanning electron microscopy, transmission electron microscopy, light microscopy in semi-thin sections.

PRINCIPAL INVESTIGATORS:
Jordi Llorens.

OTHER GROUP PUBLICATIONS:

PubMed publications.

8.2. Other disorders of the ear (H91.1): Presbycusis (Age-Related Hearing Loss)

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: Model of age-related hearing loss in C57BL6/J-129Sv mice: Slc7a8 $^{-/-}$ KO, Slc7a8 $^{+/-}$. (***Elife.*** *2018 Jan 22;7. pii: e31511).*

APPLICATIONS:

- Molecular basis of ARHL.
- Disease development and stages.
- Phenotypic studies of auditory system.
- Cytoarchitecture of inner ear.
- Cell type specific biomarkers study.
- Syte-directed mutagenesis studies.
- Molecular biology techniques from animal tissue: WB, PCR, cellular localization studies.
- High throughput techniques (omic studies, proteomics, transcriptomics) from mouse tissue.

PRINCIPAL INVESTIGATORS:
Virginia Nunes, Manuel Palacín.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: Double KO LAT2-TAT1 mice: dKO Slc7a8/Slc3a2 $^{-/-}$. (***J Am Soc Nephrol.*** *2018 Jun; 29 (6):1624-1635).*

APPLICATIONS:

- Molecular basis of ARHL.
- Disease development and stages.
- Phenotypic studies of auditory system.
- Cytoarchitecture of inner ear.
- Cell type specific biomarkers study.
- Syte-directed mutagenesis studies.
- Molecular biology techniques from animal tissue: WB, PCR, cellular localization studies.
- High throughput techniques (omic studies, proteomics, transcriptomics) from mouse tissue.

PRINCIPAL INVESTIGATORS:
Virginia Nunes, Manuel Palacín.

OTHER GROUP PUBLICATIONS:

PubMed publications.

CHAPTER 9

Diseases of the Circulatory System

09

9.1. Cardiomyopathy (I42)

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Human cardiac AC16 cell line: Fusion of primary ventricular cells with SV-40 transformed fibroblasts (not transferable cell line). *(**Int J Cardiol.** 2014 Jun 1; 174(1):110-8; **Dis Model Mech.** 2015 Sep;8(9):1081-91).*

APPLICATIONS:

- Deciphering molecular markers of cardiac disorders.
- Test of therapeutic candidates.
- Gene transfection.
- Biochemical and biomolecular tests from cells and supernatants: gene expression (RT-PCR, qPCR), nuclear fractionation, protein expression and protein phosphorylation (WB), enzyme activity.
- Cell viability studies.

PRINCIPAL INVESTIGATORS:
Manuel Vázquez-Carrera.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *Ex vivo*

EXPERIMENTAL MODEL: Neonatal rat cardiomyocytes from 1 to 2 old day Sprague-Dawley rats. *(**Dis Model Mech.** 2015 Sep; 8 (9):1081-91).*

APPLICATIONS:

- Deciphering molecular markers of cardiac disorders.
- Test of therapeutic candidates.
- Gene transfection.
- Biochemical and biomolecular tests from cells and supernatants: gene expression (RT-PCR, qPCR), nuclear fractionation, protein expression and protein phosphorylation (WB), enzyme activity.
- Cell viability studies.

PRINCIPAL INVESTIGATORS:
Manuel Vázquez-Carrera.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: Male PPAR ß/σ-nullmice and their wild-type littermates PPAR ß/σ $^{+/+}$. (***Int J Cardiol.*** *2014 Jun 1;174(1):110-8).*

APPLICATIONS:

- Validation of molecular markers of cardiac disorders.
- Test of therapeutic cardiomyopaties candidates.
- Biochemical and biomolecular tests: gene expression (RT-PCR, qPCR), nuclear fractionation, protein expression and protein phosphorylation (WB).
- Cell viability studies.
- EMSA.

PRINCIPAL INVESTIGATORS:
Manuel Vázquez-Carrera.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: Mice models of Endoplasmatic Reticulum Stress: Male ATF3 $^{-/-}$ and ATF3$^{+/+}$ mice and male GADD45a $^{-/-}$ and ATF3 $^{+/+}$ mice model (under development).

APPLICATIONS:

- Validation of molecular markers of cardiac disorders.
- Test of therapeutic cardiomyopaties candidates.
- Biochemical and biomolecular tests: gene expression (RT-PCR, qPCR), nuclear fractionation, protein expression and protein phosphorylation (WB).
- Cell viability studies.
- EMSA.

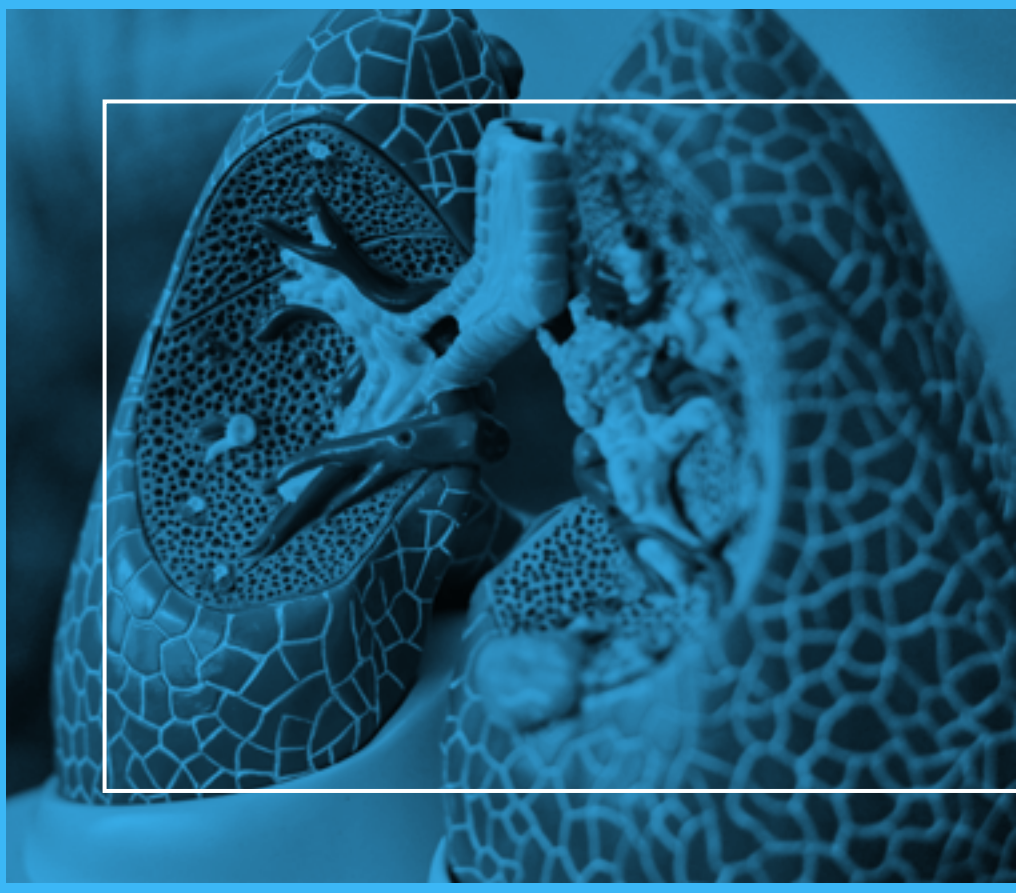
PRINCIPAL INVESTIGATORS:
Manuel Vázquez-Carrera.

OTHER GROUP PUBLICATIONS:

PubMed publications.

CHAPTER 10

Diseases of the Respiratory System



10

10.1. Other interstitial pulmonary diseases with fibrosis (J84.1)

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Primary fibroblasts (normal/pathologic) cultures from human tissue explants: cell lines culture of mesenchymal/epithelial origin. *(**Mol Biol Cell.** 2017 Dec 15; 28 (26): 3741–3755).*

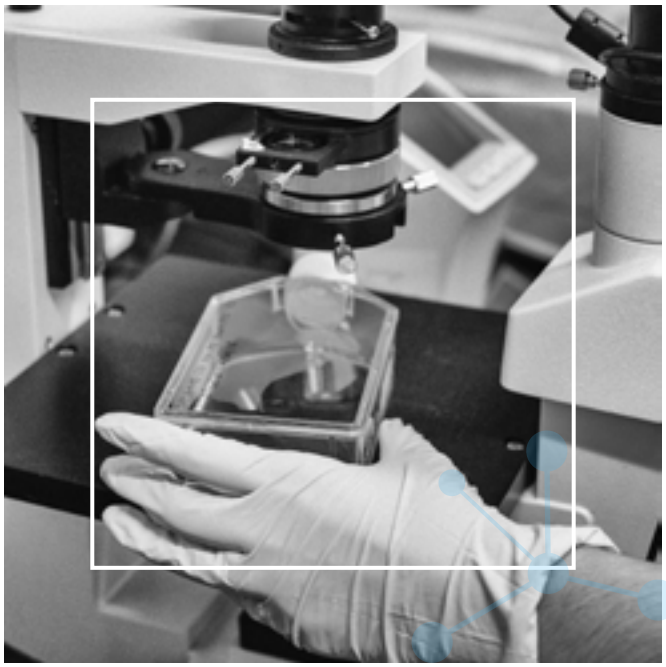
APPLICATIONS:

- Normal vs pathologic studies.
- Mechanisms of drug action.
- Potential targets identification.
- Therapeutic effects validation.
- Drug combinations and reproval from preexisting treatments.
- Drug resistance mechanisms.

PRINCIPAL INVESTIGATORS:
Jordi Alcaraz.

OTHER GROUP PUBLICATIONS:

PubMed publications.



SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Biomechanical models of fibrosis: 2D and 3D hydrogels with fibroblasts culture systems. *(**Mol Cancer Res.** 2015 Jan;13 (1):161-73).*

APPLICATIONS:

- Mechanistic studies.
- Cell stiffness.
- Novel mechanoregulatory pathways.
- Cell-to-cell, cell-to-matrix interactions.
- Predictive data in normal and pathologic situation.
- Mechanisms of drug action.
- Potential targets identification.
- Therapeutic effects validation.
- Drug combinations and reproval from preexisting treatments.
- Drug resistance mechanisms.
- Personalized treatment.

MODEL ADVANTAGES:
This model allows the modulation of matrix rigidity and other culture conditions to reproduce the desired pathologic stage or condition, obtaining physiologically relevant information.

PRINCIPAL INVESTIGATORS:
Jordi Alcaraz.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: Bleomycin model of pulmonary fibrosis.

APPLICATIONS:

- Disease progression.
- Biomarkers study.
- Drugs reproval, new drugs effectivity test and combinations.

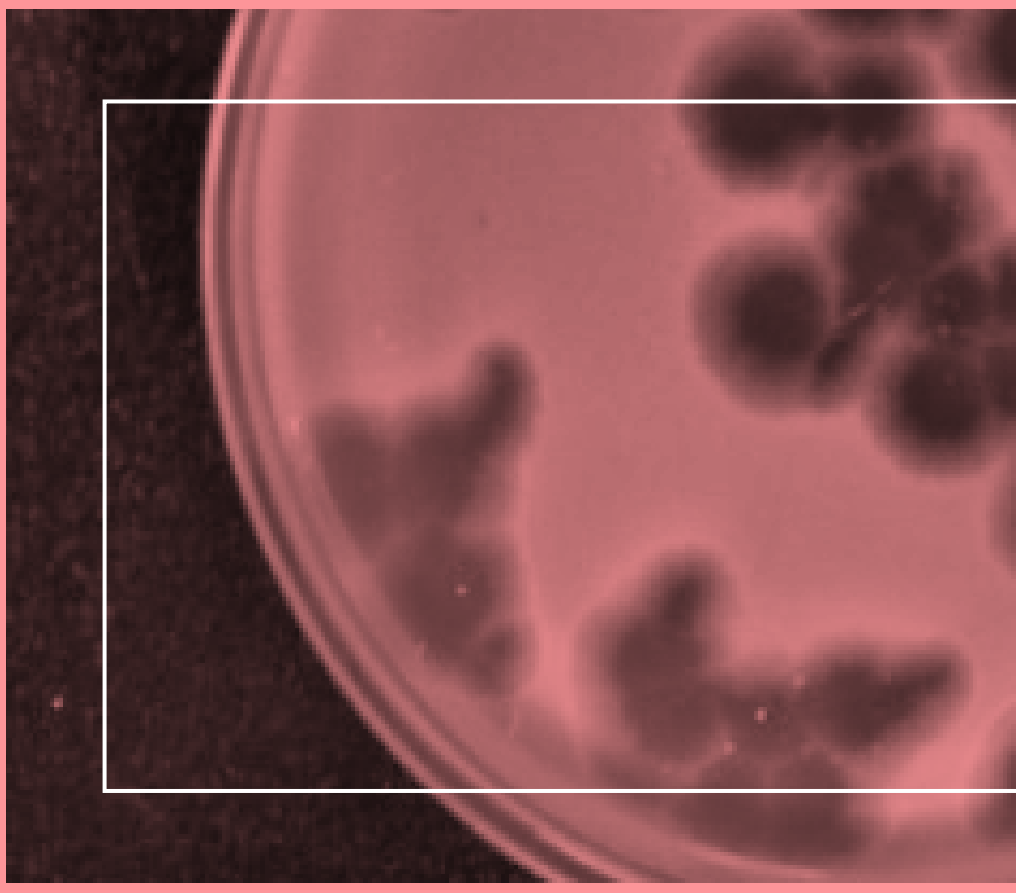
PRINCIPAL INVESTIGATORS:
Jordi Alcaraz.

OTHER GROUP PUBLICATIONS:

PubMed publications.

CHAPTER 11

Diseases of the Digestive System



11

11.1 Noninfective enteritis and colitis

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: Intestinal inflammation model in rats. (***Experimental Biology and Medicine*** *2012; 237 (10), pp. 1181-1188).*

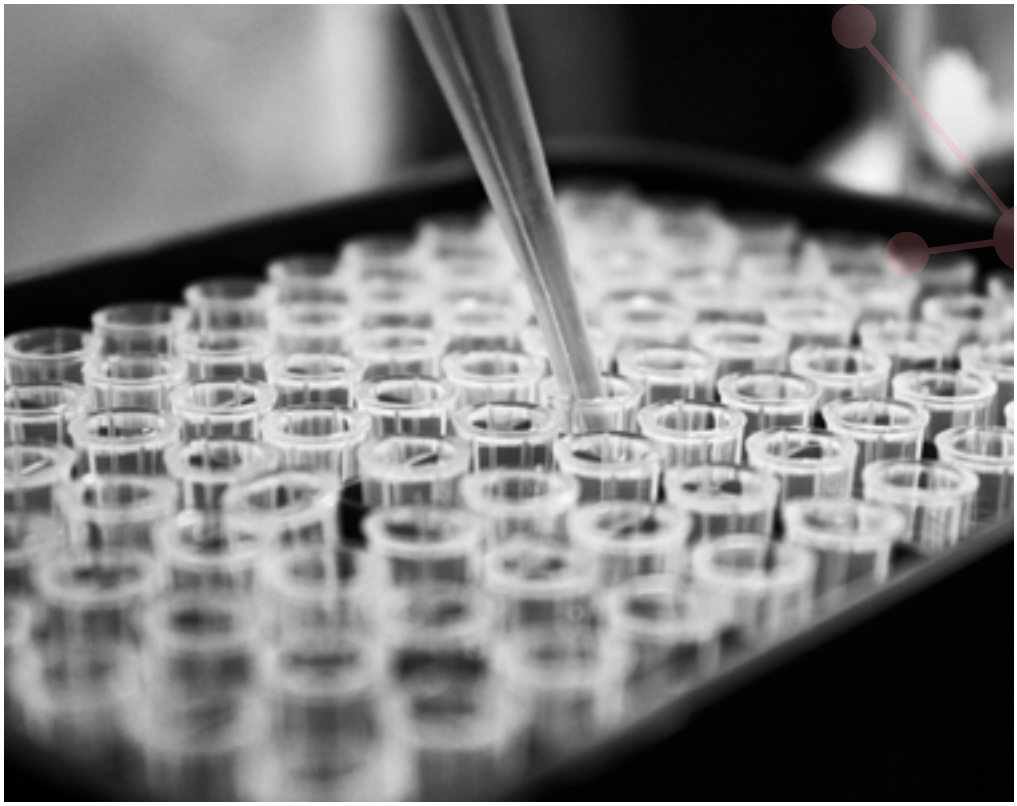
APPLICATIONS:

- Screening of new drugs.
- Testing the effect of bioactive compounds.
- Biomarkers: disease severity and duration.
- Host immune response and intestinal barrier evaluation.
- Role of the microbiota.
- Diets design and ingredients incorporation into feed.

PRINCIPAL INVESTIGATORS:
Margarida Castell, Francisco J. Pérez-Cano, Àngels Franch, M. José Rodríguez-Lagunas, Malén Massot-Cladera.

OTHER GROUP PUBLICATIONS:

PubMed publications.



11.2. Nonalcoholic Steatohepatitis (NASH) and Nonalcoholic Fatty Liver disease (NAFLD) (K75.8 - K76)

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Human derived hepatocellular carcinoma cell lines: HepG2, Huh7. (***Biochim Biophys Acta.*** *2015 May;1852(5):1049-58).*

APPLICATIONS:

- Validation of molecular markers of hepatic disorders and inflammation.
- Screeening of potential therapeutic compounds for liver diseases.
- Fatty Acid Oxidation Assay.
- Oil red O Staining.
- Cell viability studies.
- EMSA.
- Biochemical and biomolecular tests: gene expression (RT-PCR, qPCR), nuclear fractionation, protein expression and protein phosphorylation (WB).

PRINCIPAL INVESTIGATORS:
Manuel Vázquez-Carrera.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *Ex vivo*

EXPERIMENTAL MODEL: Mouse derived primary hepatocytes. (***Diabetes.*** *2016 Oct; 65 (10):3185-99).*

APPLICATIONS:

- Validation of molecular markers of hepatic disorders and inflammation.
- Screeening of potential therapeutic compounds for liver diseases.
- Fatty Acid Oxidation Assay.
- Oil red O Staining.
- Cell viability studies.
- EMSA.
- Biochemical and biomolecular tests: gene expression (RT-PCR, qPCR), nuclear fractionation, protein expression and protein phosphorylation (WB).

PRINCIPAL INVESTIGATORS:
Manuel Vázquez-Carrera.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: NAFLD and NASH mouse models. High fat diet and high fructose diet in: male PPAR ß/σ-KO mice and their wild-type littermates PPAR ß/σ, male ATF3 $^{-/-}$ and ATF3$^{+/+}$ mice, male GADD45a $^{-/-}$ and ATF3$^{+/+}$ mice model (***Biochim Biophys Acta.*** *2015 May;1852(5):1049-58;* ***Metabolism.*** *2018 Aug;85: 59-75;* ***Diabetes.*** *2016 Oct; 65 (10):3185-99).*

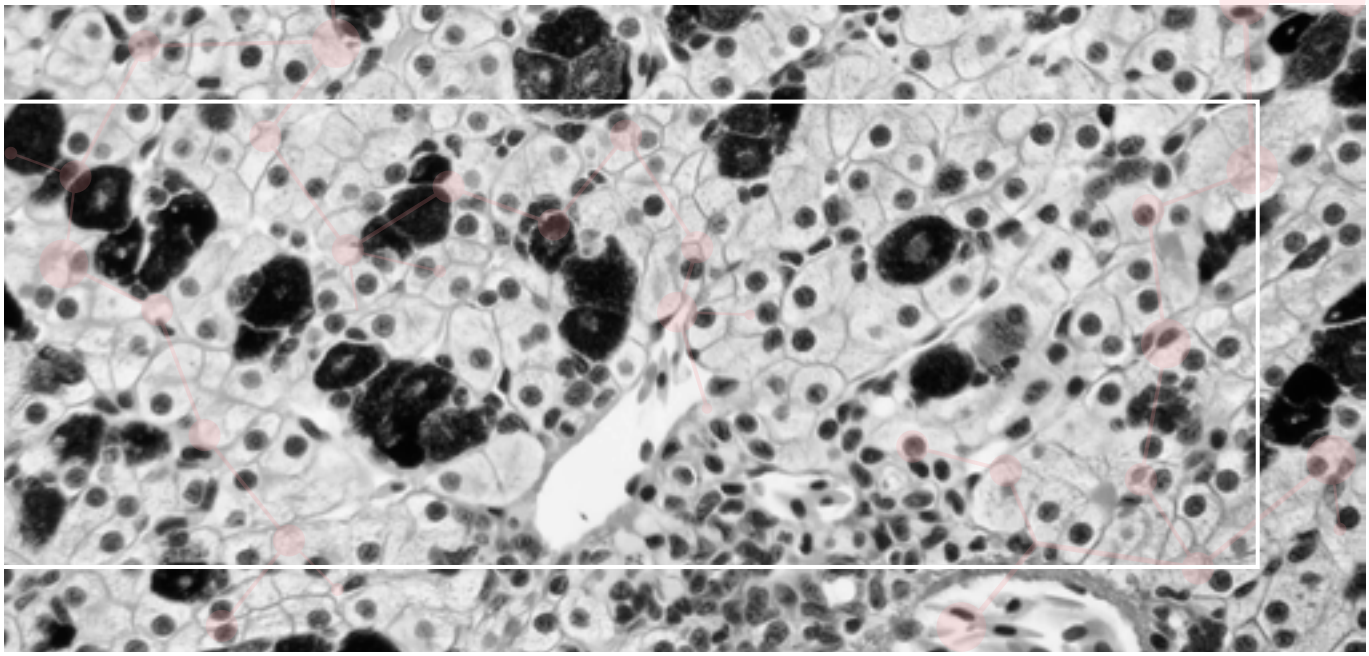
APPLICATIONS:

- Validation of molecular markers of hepatic disorders and inflammation.
- Screeening of potential therapeutic compounds for liver diseases.
- Fatty Acid Oxidation Assay.
- Oil red O Staining.
- Cell viability studies.
- EMSA.
- Biochemical and biomolecular tests: gene expression (RT-PCR, qPCR), nuclear fractionation, protein expression and protein phosphorylation (WB).

PRINCIPAL INVESTIGATORS:
Manuel Vázquez-Carrera.

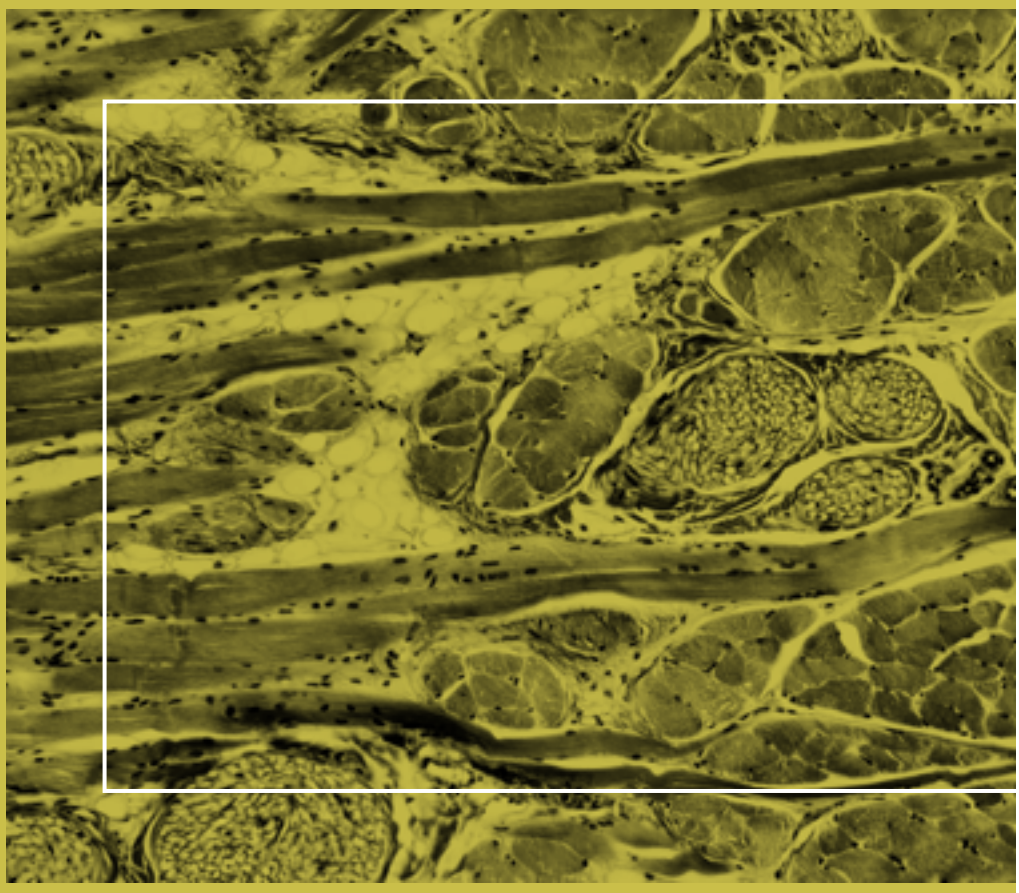
OTHER GROUP PUBLICATIONS:

PubMed publications.



CHAPTER 13

Diseases of the Musculoskeletal System and Connective Tissue



13

13.1 Arthopathies (M00 - M25)

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: Chronic and autoimmune inflammation model in rats. (***British Journal of Nutrition*** *2012; 107 (4), pp. 523-532;* ***Journal of Rheumatology*** *2006; 33 (1), pp. 110-118;* ***Clinical and Experimental Immunology*** *2001; 125 (3), pp. 470-477).*

APPLICATIONS:

- Screening of new drugs.
- Testing the effect of bioactive compounds.
- Diets design and ingredient incorporation into feed.
- Biomarkers: disease severity, oxidative stress.
- Host immune response evaluation: specific humoral and cellular immune response, cytokines.

PRINCIPAL INVESTIGATORS:
Margarida Castell, Àngels Franch, Francisco J. Pérez-Cano, M. José Rodríguez-Lagunas, Malén Massot-Cladera.

OTHER GROUP PUBLICATIONS:

PubMed publications.

13.2. Systemic connective tissue disorders (M00 - M25): Giant cell arteritis with polymyalgia rheumatic and other giant cell arteritis

SYSTEM: *Ex vivo - In vitro*

EXPERIMENTAL MODEL: Giant cell artheritis: model from epicraneal artery (10-15 cm control/disease pair). *(**Front Immunol.** 2018 Apr 20;9:809;* ***Ann Rheum Dis.*** *2017 Sep;76(9):1624-1634;* ***Ann Rheum Dis.*** *2016 Jun; 75 (6):1177-86).*

APPLICATIONS:

- Translatable model to other vasculitis and vasculopathies.
- Disease vs Control comparison studies.
- Drugs, compounds and treatment combinations test.
- Molecular biology studies and biochemical tests: Proliferation, migration, regeneration, matrix constriction, microenvironment studies, gene and protein expression, histopathology, immunofluorescence, optical and confocal microscopy, cytometry.

MODEL ADVANTAGES:
Innovative and non-invasive model.

PRINCIPAL INVESTIGATORS:
Maria Cinta Cid.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *Ex vivo - In vitro*

EXPERIMENTAL MODEL: Coculture models of peripheral blood mononuclear cells (PBMCs), lymphocytes, monocytes and vascular smooth muscle cells. (***Ann Rheum Dis.*** *2017 Sep; 76 (9):1624-1634).*

APPLICATIONS:

- Translatable model to other vasculitis and vasculopathies.
- Disease vs Control comparison studies.
- Drugs, compounds and treatment combinations test.
- Molecular biology studies and biochemical tests: Proliferation, migration, regeneration, matrix constriction, microenvironment studies, gene and protein expression, histopathology, immunofluorescence, optical and confocal microscopy, cytometry.

MODEL ADVANTAGES:
Innovative and non-invasive model.

PRINCIPAL INVESTIGATORS:
Maria Cinta Cid.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *Ex vivo - In vitro*

EXPERIMENTAL MODEL: Vasculopathies patient samples bank (serum, DNA and RNA).

APPLICATIONS:

- Study of pathogenic processes.
- Molecular pathways and regulators.
- Prognostic and predictive disease biomarkers.
- Therapeutic targets (current and novel biomolecules, chemical compounds).

MODEL ADVANTAGES:
Innovative and non-invasive model.

PRINCIPAL INVESTIGATORS:
Maria Cinta Cid.

OTHER GROUP PUBLICATIONS:

PubMed publications.

CHAPTER 18

Symptoms, Signs and Abnormal Clinical and Laboratory Findings, not elsewhere classified

18

18.1. Pain, not elsewhere classified

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: Behavioral animal models of pain and itch by applying painful or pruritic substances in the ocular surface and other measurements. *(**Pain.** 2018 Jan; 159(1): 92–105); **Mol Pain.** 2011; 7: 30).*

Nociceptive pain

- Mechanical sensitivity: Von Frey filaments.

- Thermal Sensitivity: Radiant heat, hot/cold plate, cold plantar assay, thermal place preference.

- Chemical sensitivity: Flinching test.

Inflammatory pain

- Peripheral inflammation CFA.

- Formaline test.

Neuropathic pain

- Cuff model of nerve injury (sciatic nerve).

Itch

- Cheek test (distinguishes pain and itch).

APPLICATIONS:

- Evaluation of nociceptive pain in chronic diseases as chronic inflammation, chronic nerve injury, dry skin, psoriasis, allergic conjunctivitis, dry eye or allergic dermatitis.

PRINCIPAL INVESTIGATORS:
Xavier Gasull, David Soto.

OTHER GROUP PUBLICATIONS:

PubMed publications.

18.2 Systemic Inflammatory Response Syndrome (R65)

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Macrophage culture. *(**Cellular Immunology** 2003; 226 (2), pp. 86-94; **Journal of Agricultural and Food Chemistry** 2005; 53 (22), pp. 8506-8511).*

APPLICATIONS:

- Screening of new drugs.
- Testing the effect of bioactive compounds.
- Biomarkers: cytokine synthesis and release.

PRINCIPAL INVESTIGATORS:
Margarida Castell, Francisco J. Pérez-Cano, Àngels Franch, M. José Rodríguez-Lagunas, Malén Massot-Cladera.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *in vivo*

EXPERIMENTAL MODEL: Local inflammation model in rats (carrageenin). *(**Flavonoids: Biosynthesis, Biological Effects and Dietary Sources** 2009 pp. 213-230; **Proceedings of the Nutrition Society** 2008; 67 (OCE), pp. E65).*

APPLICATIONS:

- Screening of new drugs.
- Testing the effect of bioactive compounds.
- Diets design and ingredient incorporation into feed.
- Biomarkers: swelling, oxidative stress.

PRINCIPAL INVESTIGATORS:
Margarida Castell, Francisco J. Pérez-Cano, Àngels Franch, M. José Rodríguez-Lagunas, Malén Massot-Cladera.

OTHER GROUP PUBLICATIONS:

PubMed publications.

CHAPTER 19

Injury, Poisoning and certain other consequences of External Causes

19

19.1 Allergy, unspecified (T78.4)

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: Allergy models (systemic, food, respiratory) in rats. *(**Experimental Biology and Medicine** 2015; 240 (10), pp. 1373-1377; **PLoS ONE** 2015; 10 (4), art. no. 0125314; **Clinical Immunology, Endocrine and Metabolic Drugs** 2014; 1 (2), pp. 89-101).*

APPLICATIONS:

- Screening of new drugs.
- Testing the effect of bioactive compounds.
- Diets design and ingredient incorporation into feed.
- Biomarkers: disease severity and duration.
- Host immune response evaluation: IgE and other specific antibodies, anaphylactic shock.
- Role of the microbiota.

PRINCIPAL INVESTIGATORS:
Margarida Castell, Francisco J. Pérez-Cano, Àngels Franch, M. José Rodríguez-Lagunas, Malén Massot-Cladera.

OTHER GROUP PUBLICATIONS:

PubMed publications.

CHAPTER 20

Translational models: Dermatology and Translational Toxicology

20

20.1. Ocular irritation

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Ocular *in vitro* irritation models. Hemolysis and hemoglobin denaturation (protocol Invittox 37), 3D models. *(**Toxicology.** 2004 May 3; 197(3):229-37).*

APPLICATIONS:

- Safety assessment.
- Developing measurement methods preclinical *in vitro.*
- Ocular irritation of cosmetics and other products.

PRINCIPAL INVESTIGATORS:
Mª Pilar Vinardell, Montserrat Mitjans.

OTHER GROUP PUBLICATIONS:

PubMed publications.

20.2. Skin irritation

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Skin irritation models. Monolayer cell line models: THP 1, 3T3 mouse fibroblasts and HaCaT cell lines. *(**Nanomaterials (Basel).** 2017 Mar 4;7(3):56; **J Photochem Photobiol B.** 2015 Dec;153:127-36).*

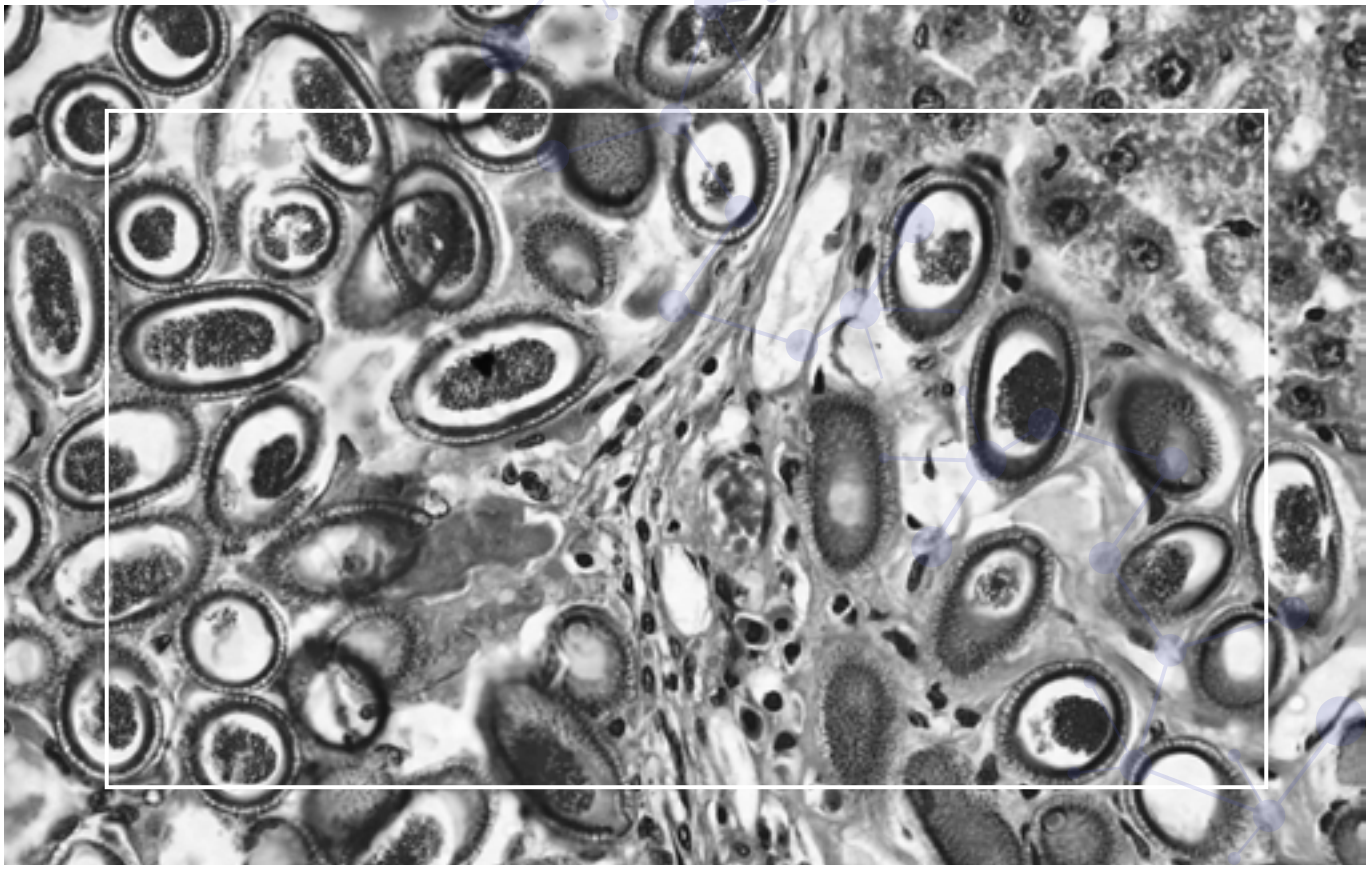
APPLICATIONS:

- Cutaneous irritation.
- Skin (photo contact) and sensitization.
- NRU Phototoxicity tests.
- Cytotoxicity and genotoxicity tests (MTT and others).
- Model system for Vitamin D metabolism in the skin.
- Nanotoxicology.

PRINCIPAL INVESTIGATORS:
Mª Pilar Vinardell, Montserrat Mitjans.

OTHER GROUP PUBLICATIONS:

PubMed publications.



SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Skin irritation 3D models. 3D Epidermis commercial models (EpiSkinTM), new 3D models development (HaCat, HEK). *(**Nanomaterials (Basel).** 2017 Mar 4;7(3):56).*

APPLICATIONS:

- Skin irritation and corrosion of chemicals and cosmetic ingredients.

PRINCIPAL INVESTIGATORS:
Mª Pilar Vinardell, Montserrat Mitjans.

OTHER GROUP PUBLICATIONS:

PubMed publications.

20.3. Skin sensitization

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Skin sensitization and photosensitivity models. Dendritic cells model: h-CLAT, IL-8 and IL-18 production. *(**Toxicol In Vitro.** 2013 Sep;27(6):1920-7; **JImmunotoxicol.** 2010 Oct-Dec;7(4):255-67; **Toxicol In Vitro.** 2008 Mar;22(2):386-95).*

APPLICATIONS:

- Allergenic potential (irritants, respiratory and contact) of chemical compounds.
- Molecular markers of skin sensitivity and photosensitivity.

PRINCIPAL INVESTIGATORS:
Mª Pilar Vinardell, Montserrat Mitjans.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Skin sensitization and photosensitivity models. Keratinocites model: NCTC, HaCaT cell lines, IL-18 production (***J Immunotoxicol.*** *2010 Oct-Dec; 7 (4):255-67;* ***J Photochem Photobiol B.*** *2015 Dec;153:127-36;* ***Toxicol In Vitro.*** *2009 Aug;23(5):789-96).*

APPLICATIONS:

- Allergenic potential of chemicals.
- Immunotoxicity tests.
- Discrimination between contact vs respiratory allergens and/or irritants.
- Molecular markers of skin sensitization.
- 3T3 NRU test.
- UV induced DNA damage.

PRINCIPAL INVESTIGATORS:
Mª Pilar Vinardell, Montserrat Mitjans.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Skin sensitization and photosensitivity models. Skin irritation 3D models: 3D epidermis commercial models (EpiSkinTM), new 3D models development (HaCat, HEK) (***Nanomaterials (Basel).*** *2017 Mar 4;7(3):56).*

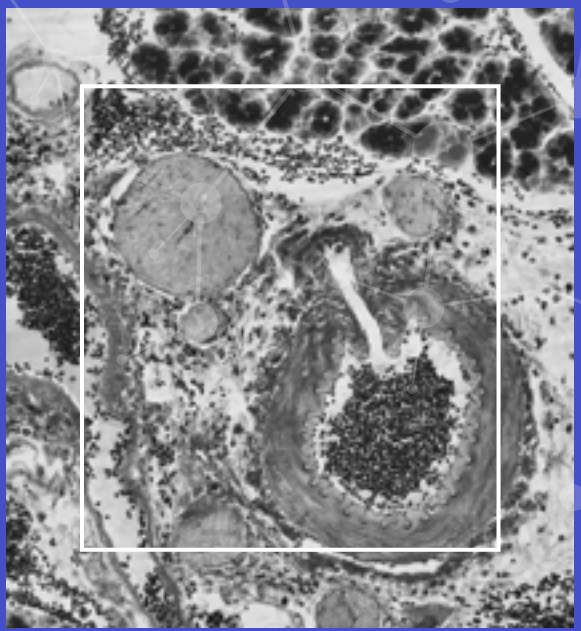
APPLICATIONS:

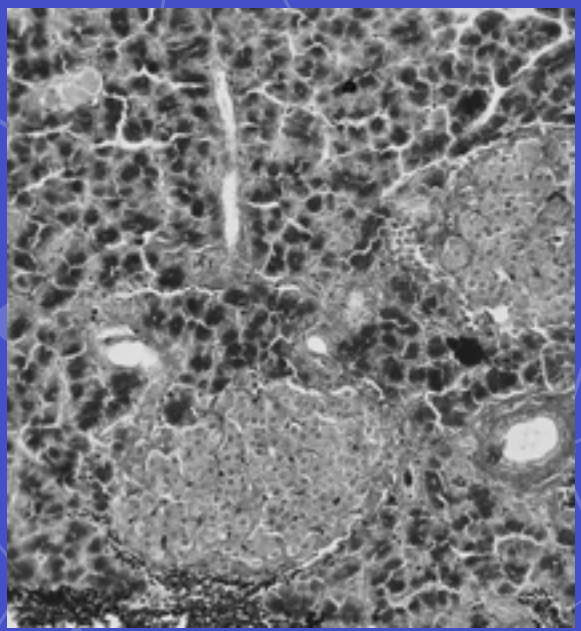
- UV exposure.

PRINCIPAL INVESTIGATORS:
Mª Pilar Vinardell, Montserrat Mitjans.

OTHER GROUP PUBLICATIONS:

PubMed publications.





SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Skin sensitization and photosensitivity models. Photo Toxicology. *(**Toxicology.** 2004 Sep 1;201(1-3):87-93; **Toxicol In Vitro.** 2015 Dec 25;30(1 Pt B):421-8; **Food Chem Toxicol.** 2010 Jan;48(1):70-5).*

APPLICATIONS:

- Sensitization studies (membrane CD54/CD86).
- 3T3 NRU Photohaemolysis assay.
- Phototoxicity and photoprotection *in vitro* assays.
- Genotoxicity tests.

PRINCIPAL INVESTIGATORS:
Mª Pilar Vinardell, Montserrat Mitjans.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Other *in vitro* models A549 Alveolar model; red blood cells, serum coagulation.

APPLICATIONS:

- Respiratory system/airways' studies.
- Hemocompatibility and cytotoxicity studies.

PRINCIPAL INVESTIGATORS:
Mª Pilar Vinardell, Montserrat Mitjans.

OTHER GROUP PUBLICATIONS:

PubMed publications.

20.4. Antiox tests and other model

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Antioxidants tests and antioxidant activity. Keratinocytes and erythrocytes in suspension and other cell lines. *(**J Agric Food Chem.** 2009 May 27;57(10):4459-65; **Toxicol In Vitro.** 2014 Feb;28(1):120-4).*

APPLICATIONS:

- Antioxidant effect analysis after adding reactive species such as hydrogen peroxide (H2O2).
- Lipid Peroxidation Inhibition Assay (H2O2).
- Cytotoxicity Protection Assay (H2O2).
- Hemolysis Inhibition Assay.
- Antioxidants from natural and chemical origin.

PRINCIPAL INVESTIGATORS:
Mª Pilar Vinardell, Montserrat Mitjans.

OTHER GROUP PUBLICATIONS:

PubMed publications.

SYSTEM: *In vitro*

EXPERIMENTAL MODEL: Antioxidants tests and other *in vitro* models. Antitumoral model: HepG2 (Hepatoblastoma) and other cancer cells as HeLa and MCF-7. *(**Int J Pharm.** 2011 Nov 25;420(1):51-(8); **Nanomaterials (Basel)**. 2015 Jun 9;5(2):1004-1021; **Biomaterials.** 2013 Apr;34(11):2758-72).*

APPLICATIONS:

- Massive screening of compounds.
- Proliferation and toxicity tests.
- Chemotherapy sensitivity assays.
- Nanotoxicology.

PRINCIPAL INVESTIGATORS:
Mª Pilar Vinardell, Montserrat Mitjans.

OTHER GROUP PUBLICATIONS:

PubMed publications.

20.5. In vivo models: HET-CAM eggs

SYSTEM: *In vivo*

EXPERIMENTAL MODEL: HET-CAM fertilized chicken eggs: before the 10th day which is when the embrio develops the nervous system. *(**Toxicol In Vitro.** 2006 Sep;20(6):1066-70; **Food Chem Toxicol.** 2004 Aug;42 (8):1287-90).*

APPLICATIONS:

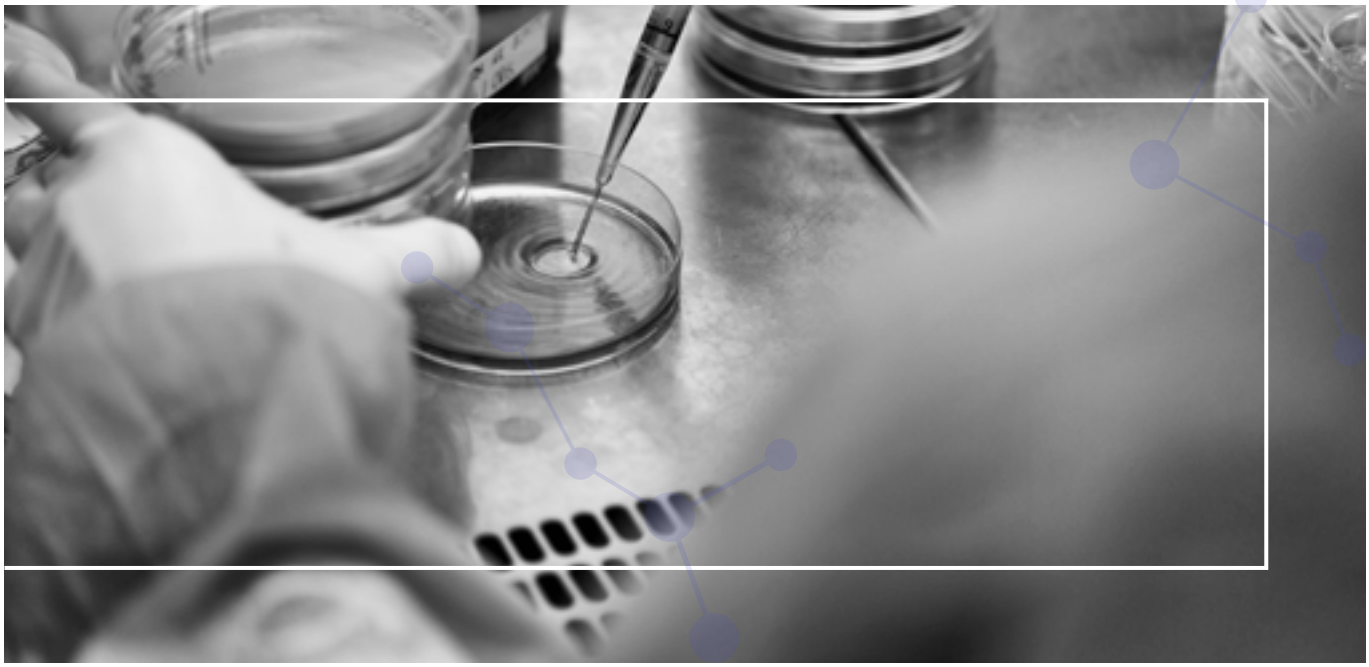
- Alternative eye and mucoses irritation testing: The chorioallantoic membrane is used to simulate the effect of cosmetics at ocular level.

MODEL ADVANTAGES:
This system can also be used to evaluate anti-tumor treatments or angiogenesis studies.

PRINCIPAL INVESTIGATORS:
Mª Pilar Vinardell, Montserrat Mitjans.

OTHER GROUP PUBLICATIONS:

PubMed publications.



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