ANNUAL REPORT 2018

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Administrative Structure

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Fernando Hernández

GENOMICS IN EVOLUTION AND DISEASE

Genome Integrity and Instability

Comparative and Functional Genomics

Bioinformatics of Genomics Diversity

Group Leader: Ignasi Roig

Group Leader: Aurora Ruiz-Herrera

The research activity of the research group has as a main objective to study of the mechanism(s) that are responsible for the origin and maintenance of mammalian genome integrity. We reach our main goal through a multidisciplinary approach, combining computational analysis and whole-genome comparisons with cutting-edge experimental technologies in both somatic and meiotic cells.

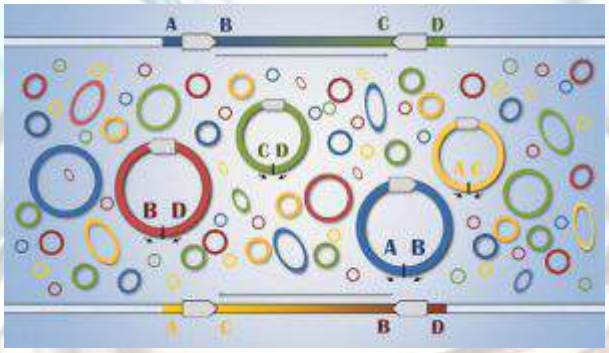
More specifically, the group is currently working in the following research lines:

- Investigate the conservation and functionality of the high-structural organization of mammalian genomes, both in the somatic and the germ line.
- Analysis of the signaling pathway that controls the progression of meiotic recombination in mammalian meiocytes.
- Identification of the role of the DNA damage response machinery in the DSB repair occurring during the meiotic prophase.
- Study how the DNA damage response mechanism controls the oocyte pool in mammals.
- Identification of non-annotated genes in the mammalian genome required to complete meiosis.
- Identification of the genetic basis of reproductive isolation and barriers of gene flow in mammalian natural populations.
- Development of a cell line repository of endangered mammalian species.
- Implementation of integrative bioinformatics and informatic tools for the analysis of the conservation and function of vertebrate genomes.
- Analysis of the mechanisms implicated in the origin of chromosome instability associated to solid tumors, in particular to colon and bladder cancer.

Altogether, these research lines address the interconnections between key cell biology processes, such as meiosis, and how these are involved in the origin of mammalian infertility and genomic disorders. Thus, these studies may help to better diagnose human infertility as well as, in the long term, they may aid the establishment of personalized medical strategies to revert male infertility in humans. Moreover, we expect that our results will provide the basis for the detection and isolation of therapeutic targets in complex human disorders and aid the design of future directional treatments.

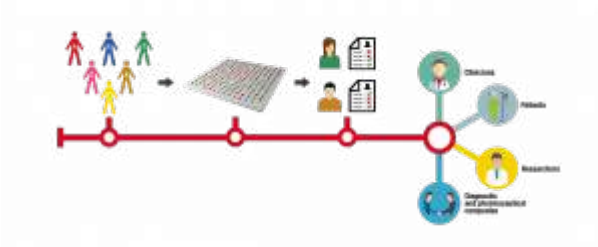
Group Leader: Mario Caceres

Our laboratory is focused in the study of genome evolution and the genetic changes associated with individual and species differences, applying the newest genomic techniques and the great wealth of genomic data available. In particular, a great degree of structural variation, including hundreds of copy number variants (insertions, duplications and deletions) and inversions have been discovered in multiple organisms. In addition, we now have the information of the variation of expression levels of thousands of genes in different tissues and individuals of many species. However, we still know very little about the functional consequences of these changes and the role that might have played during evolution. To address these questions, we use humans as a model and take a multidisciplinary approach that combines experimental and bioinformatic analysis, generating results of interest to diverse fields.



Functional and evolutionary analysis of polymorphic inversions in the human genome.

Despite being one of the first types of genetic changes characterized, the difficulty in the study of inversions is a big challenge to current structural variation analysis. Therefore, we are developing new experimental and bioinformatic methods to obtain a reliable catalogue of polymorphic inversions in the human genome, determine their distribution in world-wide human populations, and assess their functional and evolutionary impact, both with regard to their effect on gene expression and on nucleotide variation patterns.

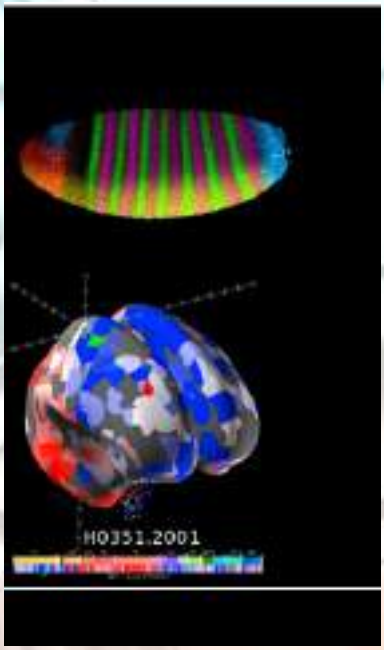


Genomic determinants of gene-expression changes in humans.

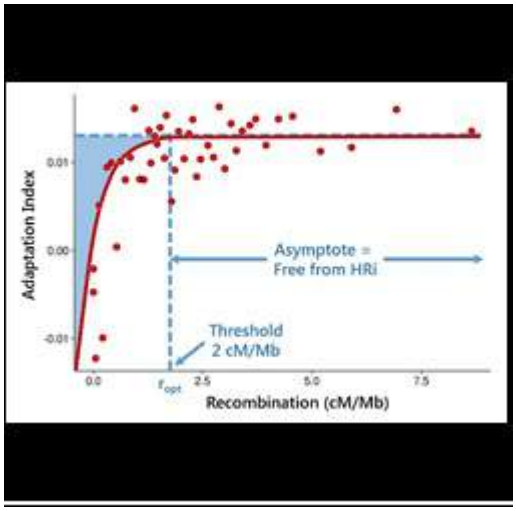
What makes us humans is a question that has attracted considerable interest for many years. Several research groups, including our own, have identified hundreds of genes with expression changes in the brain of humans and our closest primate relatives. However, due to the complexity of gene expression regulation, as the next step we need a better understanding of the molecular causes and the effects of these differences and their potential association to selective processes. This research could provide important information on the regulatory mechanisms of gene-expression evolution and interesting candidates of being involved in human brain characteristics for further analysis

Group Leader: Antonio Barbadilla

The Bioinformatics of Genome Diversity group is aimed to explain the nature of genome variation and its relationship with phenotypic variation and fitness. A new dimension of genetic variation studies is provided by the complete genomes that are increasingly being deciphered (e.g. 1000 Genomes Project), as well as new high-throughput data coming from other omics layers, such as transcriptomic and epigenomic data from the ENCyclopedia Of Dna Elements (ENCODE/modENCODE) or the International Human Epigenome Consortium (IHEC). We follow an interdisciplinary approach, merging methods and knowhow from genomics, population genetics, data science, systems biology and bioinformatics, to address, both in Drosophila and humans, the following objectives:



Mapping selection onto (a) embryo development in Drosophila and (B) human brain. Integrate information from population genomics data with recent knowledge on developmental genetics (Drosophila), single cell genomics and brain transcriptomics (humans) to get evidence of the evolution of embryonic development and human brain evolution at the microevolutionary level and test the selective importance of hierarchy in gene networks, pleiotropic interactions or preferential evolution of regulatory vs coding sequences.



Define parameters that measure the adaptive potential of a genome. Recent evidence based on the patterns of genome diversity shows that many loci and genome regions are affected by recurrent linked selection (genetic draft). We aim to develop a new general statistical approach to estimate the fraction of adaptive substitutions of any genome region regardless of whether or not they are undergoing recurrent linked selective events.

PopFly and PopHuman, the reference population genomics browsers of Drosophila and humans. Update our browsers with new genomic data that has been generated after the publication of the PopFly and PopHuman genome browsers and complement them with data from other species to become the reference population genomics browsers for eucaryotes.

RESPONSE MECHANISMS TO STRESS AND DISEASE

Molecular Immunology

Applied Immunology

Celular Immunology

Bacterial Molecular Genetics

Evolutive Immunology

Yeast Molecular Biology

Group Leader: Raul Castaño

Our group is interested in studying the recognition of CD1d by iNKT lymphocytes from a molecular and structural point of view in order to understand and manipulate the essential function of these lymphocytes in the regulation of the immune response, with especial focus in immune tumor surveillance.

CD1d presents glycolipids that are recognized by iNKT cells, inducing the production of cytokines and the activation of effector cells, depending on the structural characteristics of the antigen, thus determining the development of the immune response. Different glycolipids and molecular analogs recognized by iNKT cells, modify, modulate and regulate their function and the subsequent activation of the immune response and may be used as immunotherapeutic reagents with anti-tumor, adjuvant or immune-modulator capabilities with application to cancer, microbial infections or autoimmune diseases. We are currently performing preclinical animal studies analyzing several synthetic analogs that induce potent anti-tumor immune responses able to control metastases establishment and tumor growth in different tumor models in order to dissect their mechanism of action and asses their therapeutic possibilities.

Group Leader: Paz Martínez

Alguns del projectes de recerca en que està implicat el grups són :

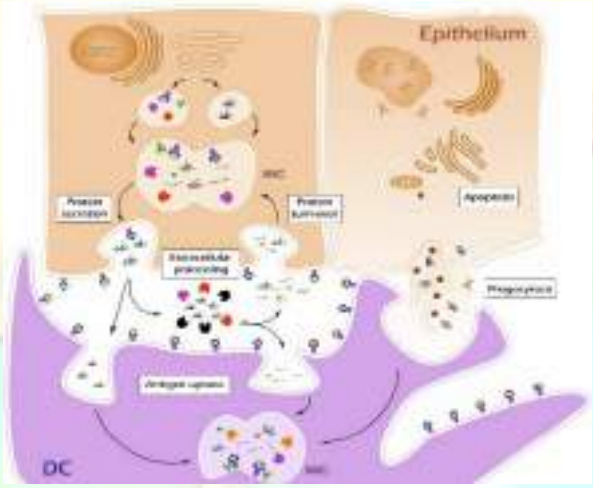
- Papel de los autoantígenos del espermatozoide humano en la fecundación y en patologías autoimmunes causantes de infertilidad
- Posible implicación de infecciones de transmisión sexual en el desarrollo de procesos autoinmunitarios en mujeres estériles
- Preparation of new monoclonal antibodies against human sperm pathology and assisted reproduction.
- Producción de anticuerpos monoclonales para su utilización en el diagnóstico de la infertilidad. Aplicación a las nuevas tecnologías de reproducción asistida.
- Factores de estrés celular implicados en el establecimiento y desarrollo de implantes ectópicos en endometriosis.
- Kit de diagnóstico para la valoración de patologías del espermatozoide. Aplicación en reproducción humana y animal.

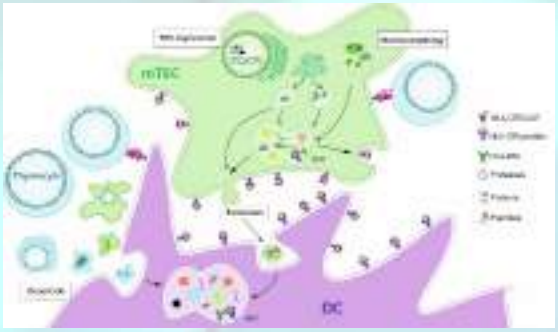
Group Leader: Dolores Jaraquemada

Protein autoantigens in Type 1 Diabetes

Respect to the recognition of proteins by T cells, our approach, following our previous experience with T1D and other autoinmune diseases, is to find T cell ligands that are present in the periphery but are not found in the thymus. Thus, we seek to identify CD4+ and CD8+ T cell epitopes for which there is a deficient central tolerance. Our approach includes two steps:

Peptidome of pancreatic b cells. Comparison with thymic natural peptide repertoires. We are aiming at the ex vivo identification of peptides presented by MHC class I and class II molecules from pancreatic b cells and thymus from donors matching relevant MHC class I and II alleles. We will also analyze the peptides presented by dendritic cells from healthy donors expressing T1D-associated HLA alleles pulsed with β-cells protein extracts and/or soluble autoantigens. T cell reactivity to the identified natural ligands will be screened.





Is there a differential peptide repertoire presented by MHC-II molecules in the cortex and the medulla of the thymus? Immunoproteomic analysis of the peptide repertoire participating in positive and negative selection in the thymus upon tissue microdissection. Searching for the β cell-specific peptides identified in the thymic medulla.

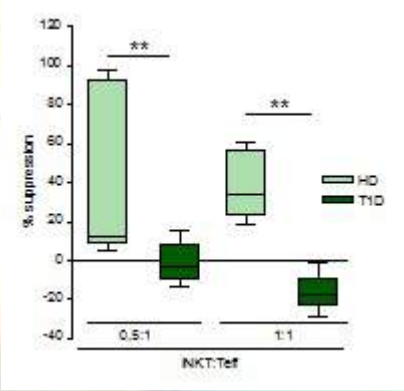
Research lines of Dr. Carme Roura

Lipid autoantigens in human type I Diabetes

Insulin-specific autoreactive CD8+ and CD4+ T cells are key at driving the autoimmune response in Type 1 Diabetes. Other antigenic specificities can be equally important along disease development or maintenance. Most of these proteins reside in the insulin secretory granules or the crinophagic bodies of β cells. There are a few reports on MHC class I presented peptides in human T1D. Much less is known on CD4+ effector or regulatory T cell recognized peptides in human T1D.

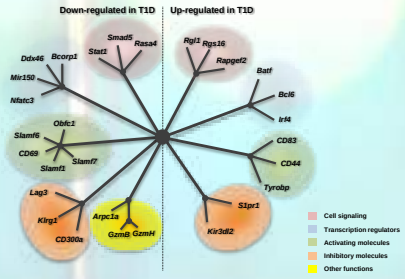
Apart from proteins, lipid-based antigens can load on MHC-I non-classical CD1 molecules and be recognized by NKT cells. Both exogenous and endogenous lipids have been shown to gain access to intracellular compartments and intersect CD1 molecules. However, the target ligands recognized by these cells in the autoimmune context are barely known. Further, little is known about local lipid ligands for NKT cells that may be influencing the disease outcome. The group is working on two different aspects:

- The regulatory role of iNKT cells in Type 1 Diabetes



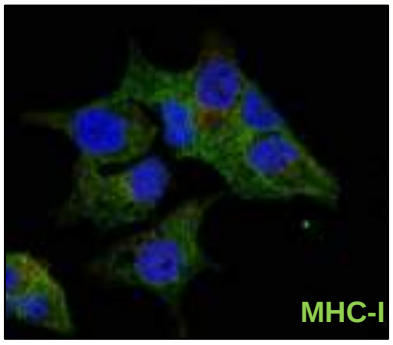
NKT cells regulate effector T cells in an IL13 dependent manner. In T1D patients NKT cells seem to lose their regulatory capacity which can be associated to a poor IL13 production at disease onset. Usero et al. Diabetes 2016;65:2356–66.

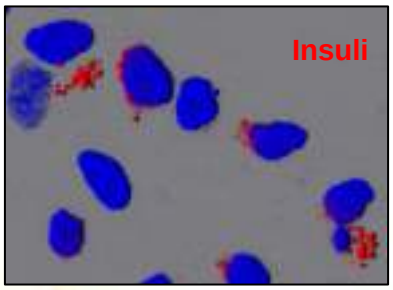
The regulatory deficiency of NKT cells in T1D patients can be related to a differentiated gene expression pattern compared to NKT cells from healthy controls (ongoing research).



- Lipid-based autoantigens recognized by iNKT cells in T1D

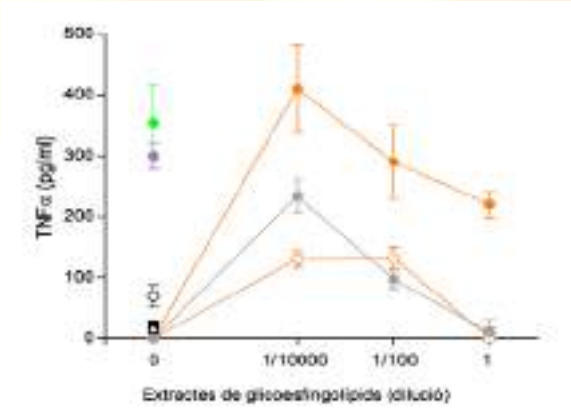
Because of their secretory function, b cells have a highly developed ER and are highly susceptible to ER stress. The group studies if cellular stress alters b cells lipid content generating lipid antigens that activate iNKT cells.





Insulin granules in pancreatic β cells. Immunofluorescence microscopy

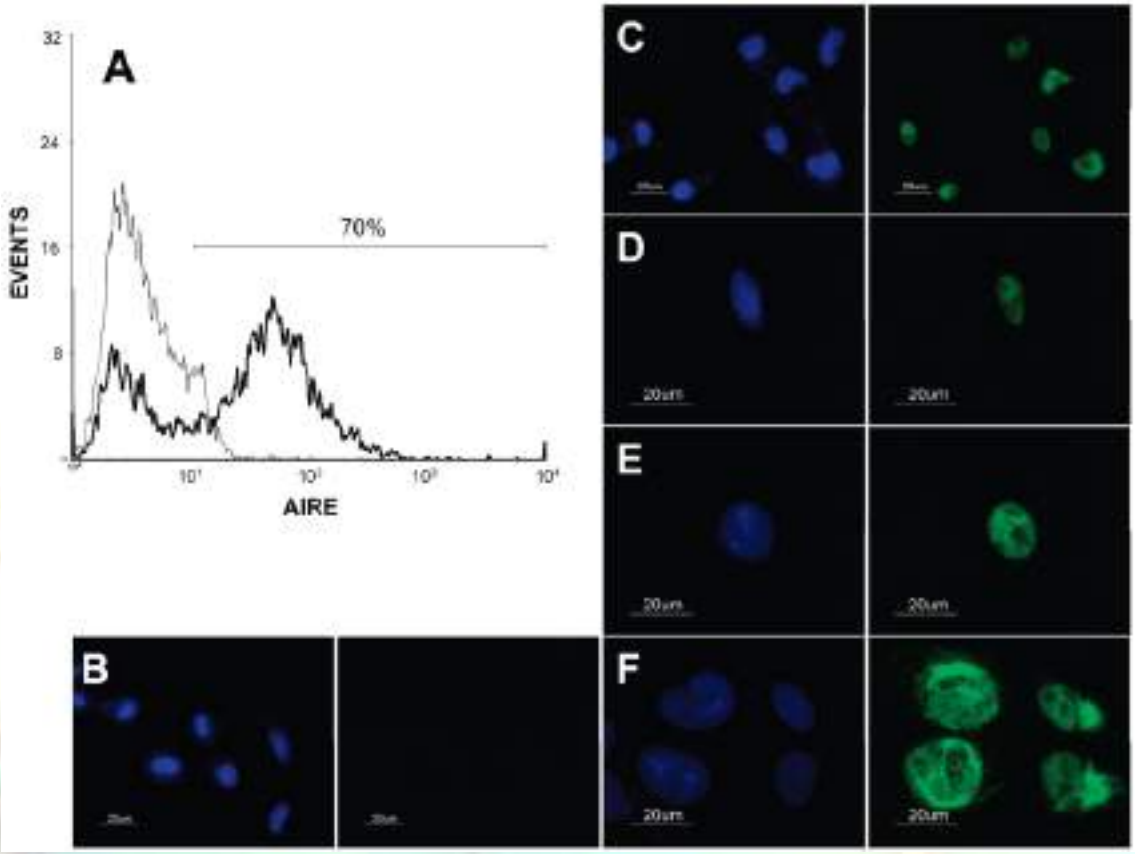
Response to b cell lipid extracts



Research lines of Dr.Iñaki Alvarez

The current lines of Iñaki Alvarez are:

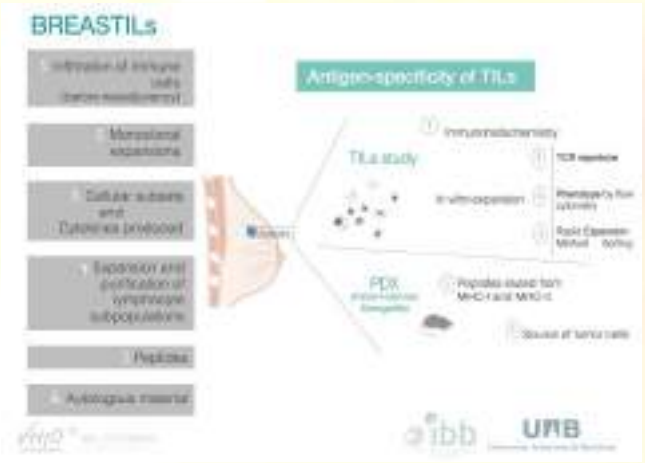
- Study of the specificity and contribution on the HLA peptide repertoires of different proteasomes and its role in tolerance and disease.
- Analysis of the role of the autoimmune regulator (AIRE) in antigen expression, processing and presentation.
- Study of standard and post-translational modificated HLA ligands in tolerance and disease.



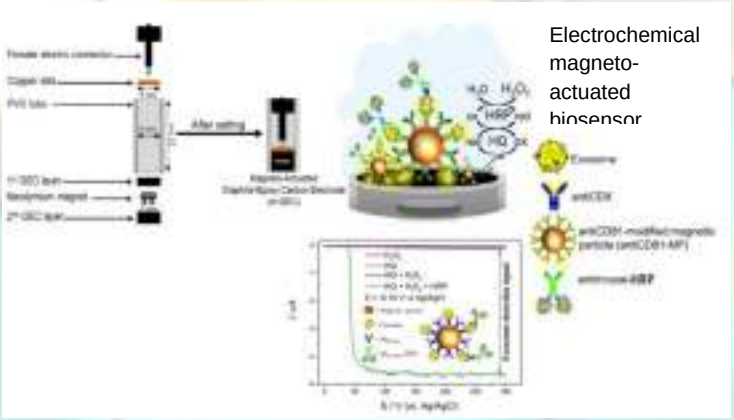
Research lines of Dr. Mercè Martí

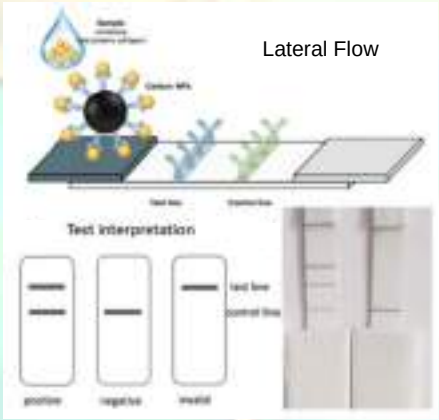
Dr. Mercè Martí is running two parallel lines of research.

Characterization of infiltrating T lymphocytes in samples of breast cancer (BREASTILs). T-cells are studied by i) molecular and functional level, ii) TCR diversity and clonality and iii) peptide repertoire presented by dendritic cells pulsed with tumor tissue. This project is in collaboration with Dr. Javier Cortés VHIO researcher.



Design of biosensors in the field of biomedicine (EXOSENS). This project is in collaboration with Dra. Maria Isabel Pividori of the Dp. of Chemistry at the UAB. We have designed a magnetoELISA and an electrochemical ELISA for the detection of exosomes from serum or plasma samples from breast cancer patients (doi: 10.1016/j.talanta.2019.120657; doi: 10.1016/j.bios.2019.111882) and from Alzheimer patients (in collaboration with ACE Foundation). We are also interested in biosensors for immunological biomarkers as cytokines. We have developed a genosensor (doi: 10.1016/j.bios.2018.05.030) and a rapid flow test (lateral flow) for the detection of proinflammatory cytokines in the context of infectious diseases as tuberculosis or COVID 19.

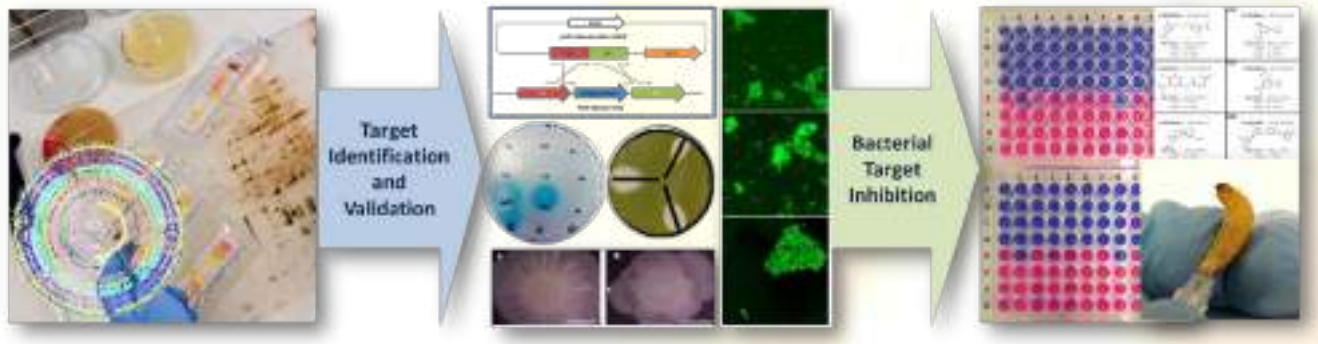




Group Leader: Isidre Gibert

Overview

The group's research lines fall within the field of bacterial pathogenesis and antimicrobial resistance (PatoBAnt). Antibiotic resistance is one of the most challenging problems in medicine and biology, and in particular, healthcare-associated infections caused by multidrug-resistant (MDR) bacteria are becoming a main cause of public health concern. Our group has been working at the IBB since 2000 and our main activity is the development of new strategies to try to solve this problem of marked socio-sanitary character. Thus, our research have been focused on the study of virulence and resistance determinants in different human pathogens such as Stenotrophomonas maltophilia, Pseudomonas aeruginosa, Burkholderia sp., Acinetobacter baumannii, Staphylococcus aureus and Mycobacterium tuberculosis among others. We try to unveil the genomic and molecular bases, from a genetic and functional point of view, of processes involved in pathogenesis, virulence and drug resistance. In recent years we have focused much of our efforts on S. maltophilia, as a model of an emerging nosocomial MDR microorganism. Thus, we aim to deepen the functional knowledge of its pathogenesis processes and exploit this knowledge to identify new targets for the development of novel drugs or alternative strategies to current treatments. In particular, we focus on the study of non-essential physiological processes such as the quorum sensing system and regulatory elements of gene expression as intrinsic determinants of virulence and resistance. The design of drugs against non-essential processes circumvents the selection of resistant strains and is therefore expected to result in a decrease in resistance development. In collaboration with groups at IBB and other outside groups, we apply a multidisciplinary approach, ranging from classical microbiology and bacterial molecular genetics to genomics, proteomics, and bioinformatics that should end with a selection of validated targets and drugs to suppress bacterial virulence and/or resistance phenotypes.



Currently we have four research lines:

Molecular and genomic bases of bacterial pathogenesis and antimicrobial agent resistance.

This project concerns the search and characterization of targets involved in the modulation of virulence and resistance in MDR Gram-negative pathogens. To address this general work plan we combine methods from microbial genetics, comparative genomics, transcriptomic analysis, structural biology and bioinformatics within a pan-genomic strategy. The main objectives that are addressed are: i) selection of "type strains" based on phenotypic and genotypic data and subsequent sequencing and annotation of their genomes when not available; ii) comparative genomics and determination of shared proteomes and exclusive proteomes of the most extreme strains in terms of virulence and/or drug resistance (in collaboration with the Computational Biology group led by Xavier Daura); iii) molecular epidemiology and genotype-phenotype correlations; iv) study of intrinsic physiological mechanisms involved in virulence/resistance by generation of specific mutants and evaluation of their phenotypes and virulence in different alternative animal models (Caenorhabditis elegans and Galleria mellonella, and zebrafish in collaboration with the Evolutive Immunology group led by Nerea Roher); and v) final selection and validation of candidate targets on the basis of the previous results.

Quorum sensing signal-response systems in Stenotrophomonas maltophilia.

In nosocomial settings, although with moderate incidence, S. maltophilia can cause severe infections, mainly in immunocompromised patients. Once in a human host, S. maltophila is difficult to eradicate due to its ability to form biofilm and its natural antibiotic resistance arsenal. Cell-to-cell signalling processes in S. maltophilia, controlled by the quorum-sensing (QS) systems, are thought to be pivotal in the regulation of several of these virulence and resistance factors. Our group aims at deepening the understanding of the QS networks of S. maltophilia at functional and molecular levels and exploiting this knowledge for the identification of targets for the development of an antimicrobial strategy based on the quenching of quorum

sensing. Antimicrobial compounds against these targets could be potentially used to reduce the pathogenic capacity of the bacteria and/or potentiate the activity of current antibiotics.

Study of the mechanisms of resistance to colistin in Gram-negative bacteria.

One of the antibiotics the group has focused on in recent years has been colistin. Colistin (polymyxin E) is an antibiotic used as a last-resort for MDR Gram-negative pathogens. Colistin is a polycationic peptide that interacts with the bacterial lipopolysaccharide (LPS) in the outer membrane and through its hydrophobic portion disrupts bacterial cell membranes causing cell lysis. The emergence of colistin-resistant isolates, as for other antibiotics, is considered a serious problem that requires special attention as it is a drug of restricted use. Our group has recently alerted about the existence of adaptive resistance and heteroresistance to colistin in S. maltophilia. We are currently identifying the genetic determinants of colistin resistance and applying genomic sequencing and transcriptome-based analyses to reveal the mechanisms governing these phenomena of heterogeneous resistance. In addition, and in collaboration with Uwe Mamat´s and Nicolas Gisch´s labs at the Research Center Borstel (RCB, Germany), we are studying LPS modifications as a mechanism of colistin resistance in S. maltophilia.

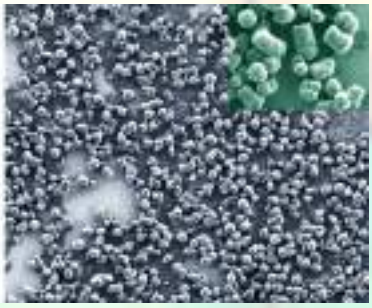
Validation of novel hit compounds as potential antibacterial drugs against Gram-negative pathogens.

In collaboration with the Computational Biology group at IBB led by Xavier Daura, we work on the design of antibacterial hits identified by virtual screening of chemical compounds against key targets of the pathogenesis and virulence processes. The drug discovery process and experimental validation of hit compounds includes: i) target proposal based on experimental evidences; ii) analysis of the intrinsic antimicrobial activity of selected compounds against and extended panel of MDR Gram-negative organisms; iii) enhancer activity of the hit compounds in combination with known antibiotics; iv) determination of the inhibitory effect of the compounds on biofilm formation; v) efficacy assays based on the analysis of antimicrobial or antivirulence activity in vivo in different animal models; and vi) in vitro assessment of the induction of drug resistance. Furthermore, we are evaluating, in collaboration with Timothy O'Sullivan at University College Cork (Ireland), molecules that interfere with the bacteria's native QS communication system and prevent them from producing biofilm.

Group Leader: Nerea Roher

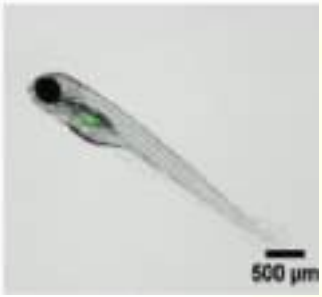
Using a combination of molecular, *in vitro* and *in vivo* methodologies we aim to understand host-pathogen interactions and how we can modulate the host immune system to have a good performance against pathogens. We develop our research using zebrafish as a model organism due to its high versatility and the availability of mutants. We do both basic and translational research on fish immunology in three main areas:

Development of vaccines for animal health



A central focus of our work has been the development of vaccines for fish species of commercial interest. We are searching for non-toxic, non-stressful and effective systems to protect commercial fish from diverse pathogenic challenges. The development of sustainable aquaculture is a strategic sector to feed the ever-increasing human population and disease prevention is mainly achieved through the implementation of preventive immunostimulation and effective vaccination strategies. Taking into account the particularities of the fish immune system, fish immunologists faced now a major challenge trying to prevent the massive economic losses caused by viral diseases. Our approach is based on protein nanoparticles made with relevant viral antigens that will induce a good and sustained immunization through the intestinal mucosa.

Evolution of pathogen recognition in vertebrates



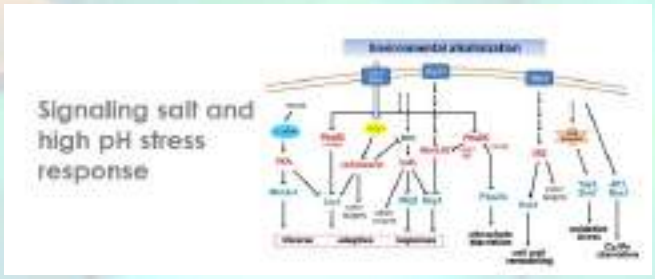
The evolution of pathogen recognition in vertebrates is also matter of interest of our research. In the last years we have been investigating the molecular basis of the fish and cephalochordates immune system, and we have been trying to decipher the particularities of its innate immune response. We are interested on Pathogen Recognition Receptors (PRRs) and specifically on Toll-like Receptors (TLRs) and in the role and biology of macrophages after pathogen exposure.

Development of diagnostic tools: biosensors for fish skin mucus

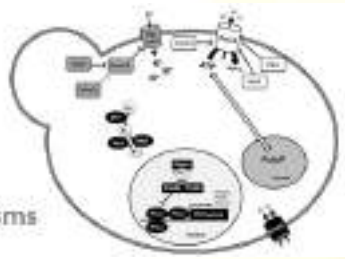
Mucosal immunity in fish has been shown to be a central part of the host response. In the context of the fish mucosal immunity the gut and the skin mucosa are extremely important. We take advantage of the high production of mucus by the fish skin to use mucus to monitorize fish health. Mucus composition is a direct reflex of fish internal physiological status and we develop biosensors based on lateral flow approach to test different metabolites in skin mucus.

Group Leader: Joaquin Ariño

Our group is interested in several topics concerning the biochemistry, the molecular biology and the genomics of the yeast *Saccharomyces cerevisiae*, specifically those that are related to cell signaling trough processes of phospho-dephosphorylation of proteins. For this purpose, we investigate issues such as ion homeostasis, the response to various stresses or the cell cycle regulation and how these circumstances affect specific protein kinases and/or phosphatases (activity, localization, binding to other proteins, postraductional modifications,...). The main objective is to obtain an overview on the yeast response to perturbations in its environment, so that we can both understand in deep the biology of this organism and to guide us towards new biotechnological applications or the identification of novel antifungal drugs targets.

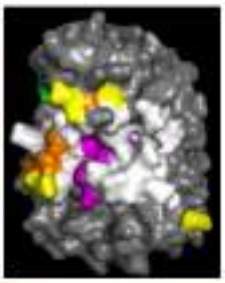


Saline and high pH responses are widely regulated by phosphorylation mechanisms. We have characterized the role of diverse protein phosphatases, such as calcineurin, PP1, Ppz1, or members of the PP2C family in this processes by combination of classical and molecular genetics and biochemistry. In the case of high pH response, our group has been pivotal in the understanding of the complex signaling network at the basis of the strong pH-induced transcriptional remodeling, which involves protein kinases (such as PKA, Snf1, Slt2 or Pho85), protein phosphatases (such as calcineurin), and a multitude of transcription factors.



Interactions between nutritional and cation homeostatic mechanisms

Maintenance of proper gradients of protons and monovalent cations and uptake of nutrients are tightly linked in yeasts, and alteration in the former process affects the latter. We have investigated how changes in potassium availability or increase in the pH of the medium alters the uptake of diverse nutrients, from sugars to phosphate, forces remodeling of metabolic pathways, and growth rate and behavior of the yeast cells, promoting even invasive growth.



The Ppz protein phosphatase as potential drug target: understanding its regulation and structure

Yeast Ppz1 is a type 1-like protein phosphatase that is found only in fungi, including pathogenic ones. In some cases, such as in *C. albicans* or *A. fumigatus*, ppz1 has been identified as a virulence factor. In *S. cerevisiae* this phosphatase is involved in several relevant functions such as the maintenance of cell wall integrity, cell-cycle regulation and the regulation of cation. It has been reported that, when overexpressed, Ppz1 is the most toxic yeast protein, pointing to the possibility that deregulation of Ppz1 activity in pathogenic fungi could become an antifungal drug target. We have demonstrated that Ppz1 toxicity derives from its phosphatase activity and is aggravated in less preferred carbon sources or under limiting glucose conditions. We are applying proteomics, transcriptomics, and classical genetic methods to elucidate the molecular basis of this toxicity in S. cerevisiae and in other pathogenic fungi.

APPLIED PROTEOMICS AND PROTEIN ENGINEERING

Computational Biology

Theoretical Molecular Biology

Nanobiotechnology

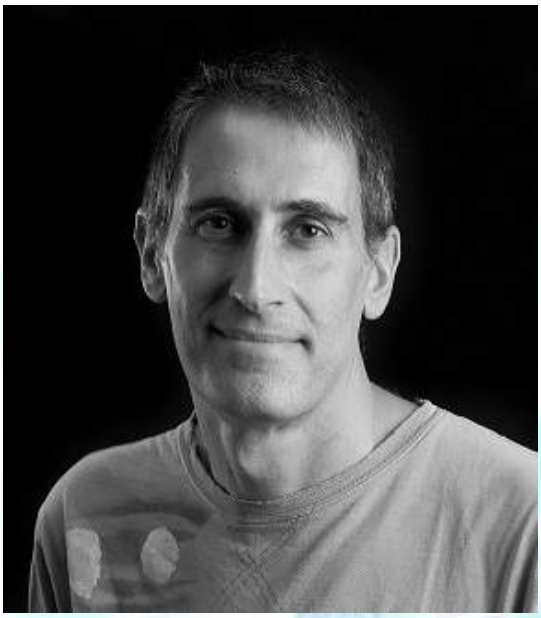
Molecular Biology

Protein Engineering and Proteomics

Protein Folding and Conformational Diseases

Protein Structure

Grup dAplicacions Biomèdiques de la Ressonància Magnètica Nuclear GABRMN



Group Leader: Xavier Daura

The main objective of our research group is the development of new strategies to combat infections by multidrug-resistant (MDR) bacteria, in particular of the gram-negative (GN) group. The increasing emergence and spread of MDR pathogens constitutes at present one of the major threats to public health worldwide. The shortage of effective antimicrobials for the treatment of infections by multiresistant gram-negative bacteria is particularly critical as cases of pan-resistance (i.e. to all drugs) accumulate. The discovery of new targets and modes of action (MoA), less propitious to the evolution of resistance, has therefore become a pressing need. In parallel, the development of effective vaccines is expected to offer a solution for high-risk population groups. Our team combines a range of computational and experimental techniques for the identification of vaccine-antigen and antimicrobial-target candidates with new modes of action in gram-negative bacteria. Much of this research is done in collaboration with the group of Bacterial Molecular Genetics of IBB, led by Dr. Isidre Gibert. On the antimicrobial side we aim to exploit conserved virulence factors as novel drug targets, reducing the pathogenic capacity of the bacteria as well as the selection pressure for drug-resistant phenotypes and preventing the devastating effect of the treatment with antibiotics on the patient's microbiota. In these areas our group has coordinated two European projects within FP6 (BacAbs, identification of new antigens) and FP7 (AntiPathoGN, identification of new targets and antibacterials).

Specifically, we are engaged in the following types of activities:

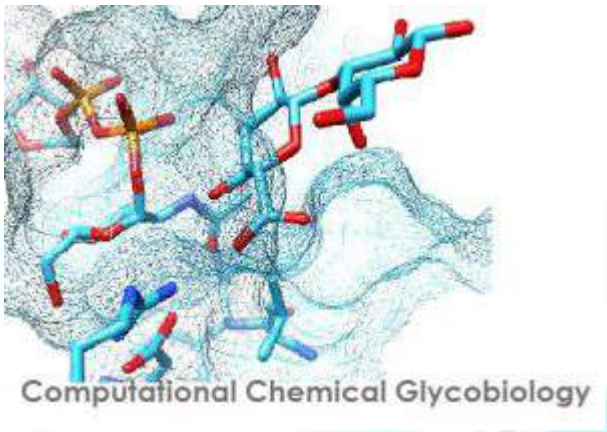
- Development of bioinformatic methods for the identification of novel antimicrobial-drug targets, antigens and their epitopes in pathogenic bacteria.
- Experimental validation and characterisation of identified antigens and antimicrobial-drug targets (in collaboration).
- Biomolecular modelling and simulation for the design of synthetic vaccines.
- Target-based virtual screening for antimicrobial-drug discovery.
- Experimental validation of hit antimicrobial compounds (in collaboration).

Group Leader: Josep M. Lluch

Our group works in the field of Theoretical Molecular Biology, encompassing a large path ranging from Theoretical Chemistry (at the borderline with Molecular Physics) to Biology (at the borderline with Medicine and Pharmacology). We use mainly Quantum Mechanics/Molecular Mechanics and Molecular Dynamics methods to carry out Biomolecular Simulations in silico for the study of enzyme activity: substrate binding, enzyme-substrate interactions, enzyme catalysis... The main purpose of our work is the understanding of these phenomena at a detailed molecular-level, and then the design/modification of the proteins/enzymes under study (using inhibitors, alosteric effects, mutations, radiation, electric fields or a combination of them) with the aim to control/modify their activity and/or function in a predefined direction, always with important biomedical and biotechnological applications. Progress in this direction can be relevant for the understanding and control, for instance, of inflammatory processes, in biocatalysis and in photopharmacology.

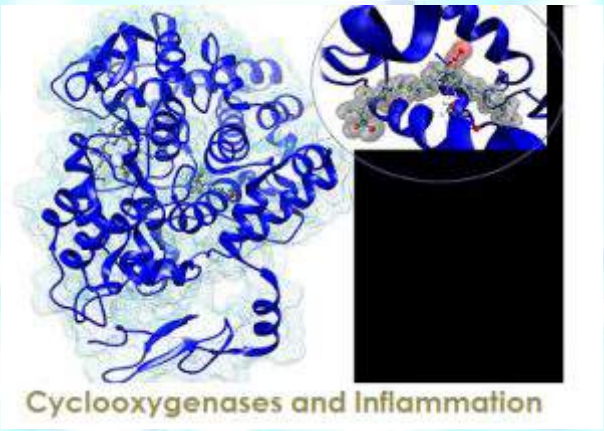
We not only apply the existing methods in Theoretical Chemistry, but we also develop other methods conveniently adapted to solve the challenges raised by the biological systems we study. Our purpose is to open new venues of experimental research starting from our theoretical results. We believe that Biomedicine and Theoretical Chemistry are connected disciplines that can work toguether to enhance the broad spectrum of human knowledge. With our research, we hope we can contribute to the rational design of new methods and drugs to act on human illnesses with as few undesirable secondary effects to human health as possible, thus, yielding contributions to practical advancements in Biomedicine and Pharmacology.

In the field of Biotechnology, we intend to design new enzymes as engineered biomolecular catalysts for the preparation of relevant organic molecules with better, faster, cheaper and with more selective synthetic processes than the ones currently available.


Computational Chemical Glycobiology

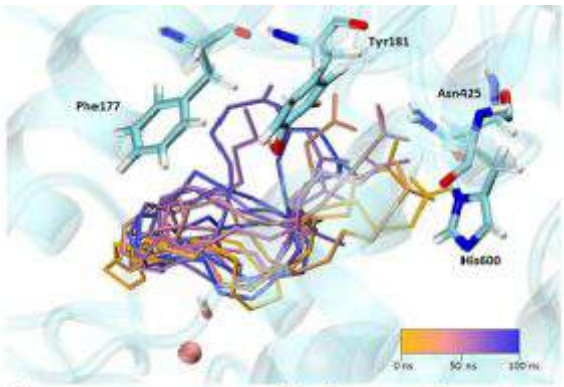
We are interested on the study of **carbohydrate-acting enzymes** (CAZy) and of **recognition processes involving glycans** and carbohydrate derivatives:

Reaction mechanism of CAZy enzymes.
Enzyme engineering for the synthesis of glycans.
Enzyme inhibition.
Carbohydrate – lectin interactions.


Cyclooxygenases and Inflammation

Prostaglandin endoperoxide H synthase (PGHS) is a bifunctional hemoprotein endowed with both cyclooxygenase and peroxidase activities; since the former constitutes the first committed step on the biosynthetic pathway leading from arachidonic acid (AA) to prostaglandins (PGs), this enzyme is often referred to as cyclooxygenase (COX). Two isoforms of COX exist; while COX-1 is constitutive, the expression of COX-2 is induced during inflammatory states. PGG2 is the main product generated by COX upon dioxygenation of AA, with minor amounts of monooxygenated 11- and 15-hydroperoxyeicosatetraenoic (HPETE) acids. COX activity is substantially altered as a consequence of aspirin treatment. While acetylated COX-1 fails to generate any oxygenated products, in the case of COX-2 only PG generation is blocked, while the production of 11R- and 15-HETE is maintained. This switch in lipid mediator production by COX-2 has important therapeutic implications: metabolites of 15RHETE are endowed with potent pro-resolving activity, which sums up to the anti-inflammatory activity consequent to the blockade of PGG2 biosynthesis, making aspirin a unique, dual-acting irreversible COX inhibitor.

Neither the mechanisms enforcing stereospecificity in AA oxygenation by native COX-2 nor the changes induced by aspirin treatment have been completely clarified so far. Our current goal is to reveal the molecular origin of aspirin effects by means of Molecular Dynamics and Quantum Mechanics/Molecular Mechanics calculations on the catalytic mechanism in wild type and acetylated COX-2 and COX-1, and the design of new inhibitors, especially molecular photoswitches with inhibiting properties of COX-2 specific to each isomer.



Lipoxygenases and Inflammationy

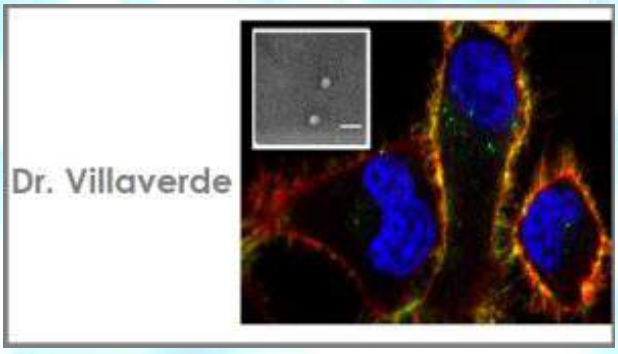
Lipoxygenases (LOXs) form a family of lipid peroxidizing enzymes which have been implicated in a number of physiological processes and in the pathogenesis of inflammatory, hyperproliferative and neurodegenerative diseases. The LOX reaction constitutes a special type of lipid peroxidation and differs from non-enzymatic reactions in several respects, such as higher reaction rate, limited substrate selectivity, mechanisms of regulatory interference and the high product specificity. Non-enzymatic lipid peroxidation converts a given substrate to a complex array of primary oxygenation products whereas LOXs usually generate a single product isomer.

Over the last years our group has been studying the catalytic mechanism of several LOX isoforms (rabbit ALOX15, pig ALOX15, coral ALOX15b, ALOX5) with linoleic and arachidonic acids as substrates by means of Docking, Molecular Dynamics and QM/MM calculations. Those studies have revealed the molecular origin of the exquisite regiospecificity of LOX catalysis that leads to the formation of inflammatory or anti-inflammatory agents. At present our main target is ALOX5, the most important human LOX, that catalyzes the hydroperoxidation of arachidonic acid leading either to the pro-inflammatory agents known as leukotrienes or, in combination with ALOX15, leading to the formation of lipoxins, anti-inflammatory molecules. In addition we will focus on the 5-lipoxygenase-activating protein (FLAP).

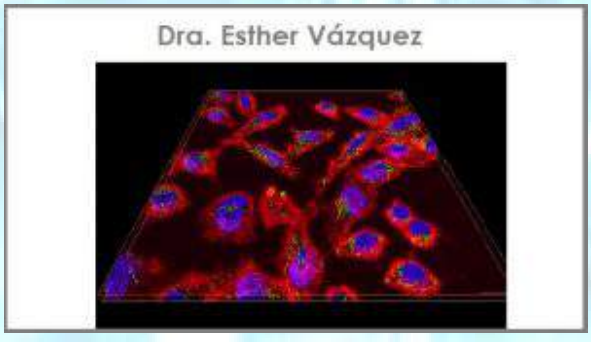
Group Leader: Antoni Villaverde

The Nanobiotechnology Unit is committed to develop biomaterials, mostly based on recombinant proteins, for application in different therapeutic situations, as either drug carriers or therapeutic materials themselves. The team is member of the Centro de Investigación Biomédica en Red (CIBER) in the subject area of Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN, (http://www.ciber-bbn.es/en), devoted to perform research and translation into these areas. The team holds the Protein

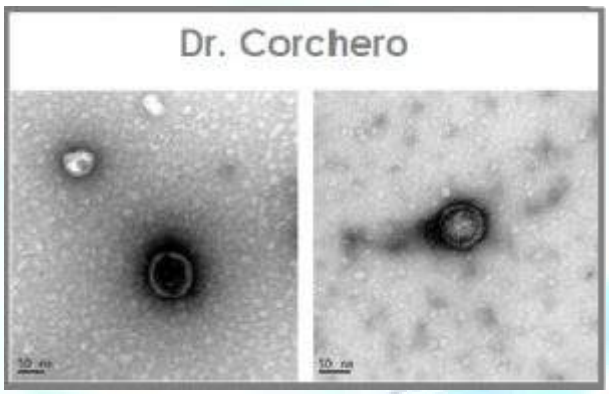
Production Platform (PPP, http://www.nanbiosis.es/portfolio/u1-protein-production-platform-ppp/), that is the Unit 1 (PPP) of the Singular Scientific and Technological Infrastructures (ICTS) NANBIOSIS and the Scientific and Technological Servive sePBioEs (SCT) of the UAB, directed by Dr Neus Ferrer Miralles. PPP is offering services to both public and private sectors in protein production, technical advice and formation.



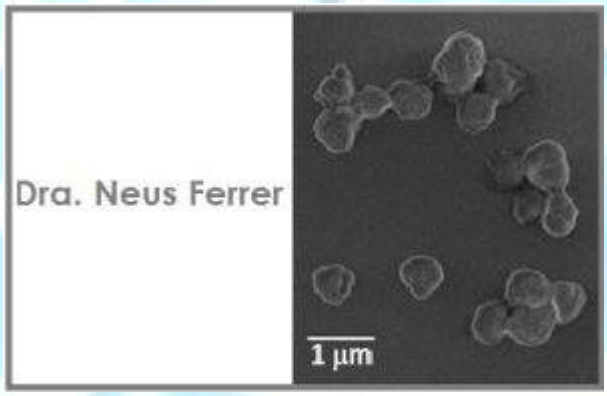
Dr. A. Villaverde designs nanostructured protein-only antitumoral drugs for application in colorectal cancer, using intrinsically cytotoxic proteins and nanoarchitectonic peptide motives. In collaboration with Dr. E. Vázquez and with Prof. R. Mangues, from Hospital de Sant Pau, he generates tumor-targeted vehicle-free drugs with applicability in colorectal cancer and other relevant human neoplasias.



Dr. Esther Vázquez develops tumor targeted protein nanoparticles as drug carriers, and smart nanoconjugates, for the treatment of colorectal cancer and triple negative breast cancer. These studies are performed in collaboration with Profs Simó Schwartz from Hospital Vall d'Hebron and Ramon Mangues, from Hospital de Sant Pau.



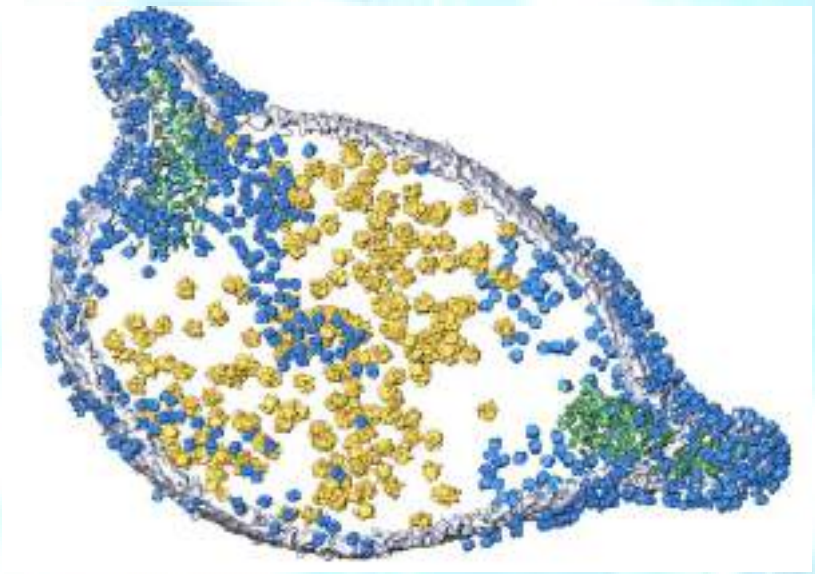
Dr. Corchero current research mainly deals with the production, in mammalian cells as expression system, of recombinant human proteins for their use as therapeutics in the treatment of rare diseases (Fabry disease and Sanfilippo syndrome). In this context, he is also involved in the development of new drug delivery systems for the targeted delivery of therapeutic molecules. These nanovehicles are based either on liposomal formulations or in protein nanocages derived from eukaryotic vaults.



Dr. Neus Ferrer is developing protein-based nanomaterials as substitutes of antibiotics in animal medicine. The dry period of dairy cows is addressed to achieve a cellular regeneration of the mammary gland aiming at optimize milk production in the subsequent lactation. The preventive use of antibiotics in this period has become questionable. Therefore, the aim of the project is to develop non-antibiotic preventive alternatives based on the administration of protein-only nanoparticles or encapsulated proteins to improve cow dry period tissue regeneration and immunomodulation. The project is performed in collaboration with Dr. Elena García Fruitós and Anna Arís from the IRTA.

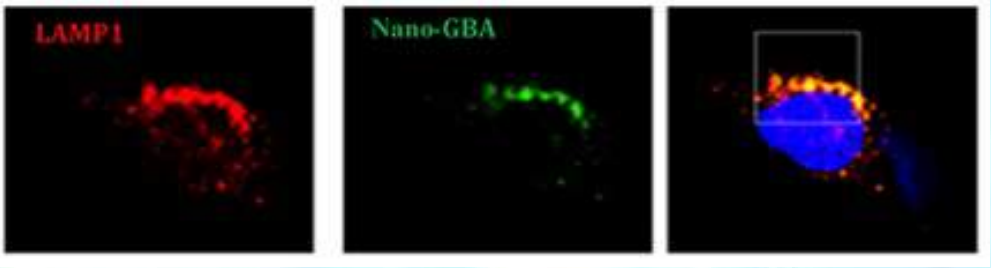
- *Mycoplasma genitalium* as a model of minimal cell and genome. Molecular mechanisms of pathogenicity and virulence.
- Reverse vaccinology
- Bioinformatics analysis of protein structure and function. Moonlighting proteins

Group Leader: Enrique Querol



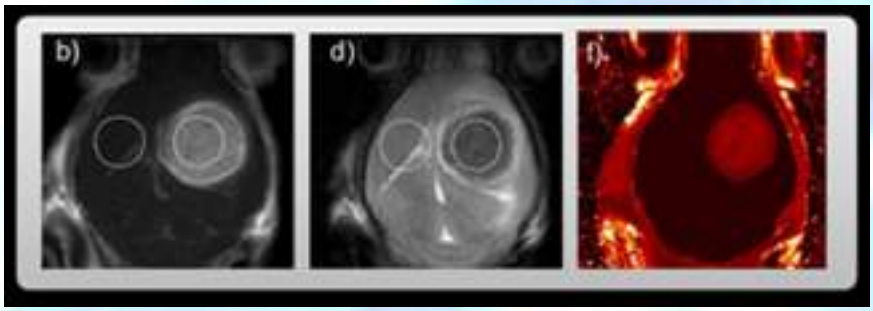
Group Leader: Francesc Xavier Avilés

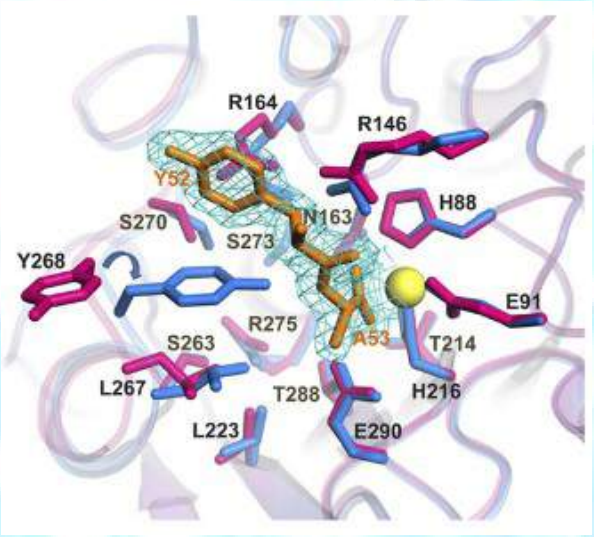
Our group, mid-between IBB and the Biochemistry and Molecular Biology Unit of the Faculty of BioSciences of UAB, devotes our best efforts to the application of molecular/structural biology, protein engineering, proteomics biotechnology on proteases (in particular metallo-carboxypeptidases) as well us on their inhibitors. In the last years, the group has also specialized in the development of biocompatible nanomaterials and the study of their biological properties and interactions.



Thus, we try to characterize and redesign proteins that naturally control such proteases in nature: i.e. in animals or invertebrates or in plants, or synthesize organopeptidic molecules, to unveil its properties and develop and use them, or derivatives, for potential biomedical or biotechnological uses. Metallo-carboxypeptidases pancreatic-like or regulatory (M14 family, as A1, A2, A3, B, O, D, Z ...) and their small protein inhibitors, as the ones from potato or the marine snail Nerita v., are among the best studied models by us. The experimental approaches used, directly on extracts or on purified molecules, are HPLC, Mass spectrometry, protein & cDNA sequencing & cloning, proteomics, NMR, Xray crystallography and computer-based approaches. We also work in the development of nanomaterials for specific delivery, encapsulation, or

nanoconjugation of enzymes/inhibitors and small compounds for biomedical purposes as well as in the assays in cell cultures and in animal models to test their efficacy and safety.

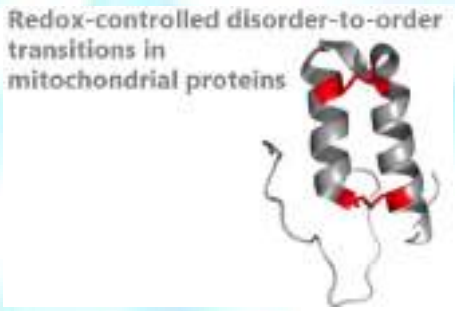




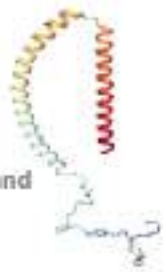
We also intend to develop our own methodologies for affinity proteomics, protein modelling, rational design of ligands and drugs, protein/peptide engineering and in the development and characterization of nanomaterials with biomed/biotech purposes. To efficiently do so and the former goals, we have established collaborations with research groups well recognized at the Catalonia, Spain and international level (i.e. Synchroton Alba, CSIC, ICN2, UCM, PRINCIPE Felipe Res. Inst., MPI-Munich, IJS-Slovenia, Univ. Uppsala, Univ. Cambridge, Univ. Notre-Dame, A. Einstein-NY, Univ. Habana, Univ. LaPlata, Univ. Concepción, UNAM-CostaRica, Universidad Nova de Lisboa), and with the firms CHEMIPOL, ABD Biodesing and Nanonica Europe, ...etc.), with fruitful exchanges. Noteworthy is the formative task, spirit and aims of our group at the Master and PhD levels, with national and foreign students.

Group Leader: Salvador Ventura

Our lab uses a multidisciplinary approach to address fundamental aspects of protein folding, misfolding and aggregation. In addition to define the basic mechanistic principles underlying these processes, we aim to understand how their deregulation leads to the onset of human conformational diseases and to develop innovative therapeutics to target these pathologies. Moreover, this knowledge should allow us to design and produce novel and better protein-based biopharmaceuticals as well as the development of new self-assembled materials for nanotechnology applications.



For most proteins, biological function requires folding into a unique structure, in which they remain during their lifetime. There is, however, an emerging class of proteins that adopt a specific structure to function, but are otherwise disordered, the so-called conditionally disordered proteins (CDPs). The structure and activity of CDPs is tightly regulated by the environment. Some CDPs, use oxidation of their redox-sensitive cysteines to reversibly convert large disordered regions into defined structural domains. This is the case of proteins synthesized on cytosolic ribosomes and targeted to the intermembrane space (IMS) of mitochondria as reduced and disordered species. They become oxidized and folded into their functional forms only after entering this organelle. This redox-controlled folding, acts as a folding-trap that drives their translocation to the IMS. We use an integrated structural approach to decipher the molecular determinants of these massive structural rearrangements, which determine the function of mitochondrial proteins linked to diseases like Parkinson's, Huntington's or cardiomyopathies.



Towards early diagnostic of Parkinson's disease and its prevention using pharmacological chaperones

Parkinson's disease (PD) is the second most common neurodegenerative disorder and is still incurable. PD is associated with the death of dopaminergic neurons in the brain. There is substantial evidence supporting the aggregation of the protein a-Synuclein (a-Syn) as a key event in pathogenesis of PD, emerging thus as a privileged therapeutic target. We have recently identified and designed small compounds and peptides able to inhibit a-Syn aggregation with extremely high potency in vitro and in animal models. We aim to develop these molecules into lead compounds for the therapeutics of PD.

Early detection of PD is a long pursued objective. A predictive test would revolutionize clinical care, research and treatment. Biochemical analysis evidenced an elevation of a-Syn aggregates in the biofluids of patients, suggesting that this feature might be used as a diagnostic biomarker for PD. We aim to develop an orthogonal approach towards the development of a sensitive automated diagnostic assay based on the specific detection of early a-Syn aggregates in biofluids.

Transthyretin amyloidosis: Pharmacological chaperones as a therapeutic approach

Transthyretin amyloidosis (ATTR) is the most common form of familial amyloidosis. In ATTR, destabilizing mutations in the protein transthyretin (TTR) causes amyloid fibres to build up, which, depending on the mutation, are deposited in different organs, such as the brain, the nerves or the myocardium, causing them to malfunction and bringing the various forms of the disease. To prevent disease progress, a liver transplant or heart transplant is needed. However, the use of pharmacologic chaperones that stabilize the structure of TTR is emerging as a non-invasive therapeutic means to halt the disease. In this context, we have repurposed a molecule originally intended to treat Parkinson's, as perhaps, the most effective drug for these diseases, already in clinical trials. We pursue both to test its efficacy for previously unaddressed forms of ATTR, with special emphasis of those occurring in the brain, and to use structure based design to generate second generation, more powerful, drugs.

Prion-like functional proteins and their link to disease

Amyloids become infectious in prion diseases. Nevertheless, not all prion proteins are disease-related; in yeast, they help for environmental adaptation. Most yeast prions contain a low complexity (LC) prion domain responsible for their self-assembly and propagation. Proteins from other organisms such as bacteria, plants and humans do also bear prion-like domains indicating that their aggregated state might also be beneficial for the cell. Human prion-like proteins are involved in the formation of membraneless intracellular compartments through liquid-liquid phase separation using their LC domains to favor functional interactions between specific partners. However, these proteins are inherently aggregation-prone and the liquid state can revert into an aberrant solid state responsible for several pathologies including inflammatory and neurodegenerative disorders and cancer. We have recently developed a set of novel algorithms aimed to uncover novel proteins with prion-like behavior in order to characterize the functional pathways in which they are involved as well as their association to disease.

Amyloid assemblies for nanotechnology purposes

The extraordinary stability and tunable assembly of amyloid fibrils make them very attractive targets in nanotechnology. Most efforts so far have been focused on the use of short synthetic peptides as the bioactive components of such materials, and an analogous approach for inducing globular proteins to assemble into functional nanofibres has been much less explored. The main limitations to create mono- or multi-component nanofibres that contain functional globular proteins come from the requirement to prevent their aggregation during expression, to maintain them in a soluble state during purification and storage, and to be able to induce their assembly at a desired time and place. We aim to exploit our combined computational/experimental expertise to design and produce new molecules fulfilling these properties for a range of biomedical and biotechnological applications, including enzyme catalysis, biosensors, electronics, tissue engineering, drug delivery and immunotherapy.

Towards the design and production of improved protein therapeutics

The fast development of protein therapeutics- monoclonal antibodies, replacement enzymes and hormones- is providing improved therapies for a wide range of human diseases, taking advantage of their high specificity towards their targets. One of the major challenges that one should face during the development of protein-based biopharmaceuticals is their inherent propensity to aggregate. Indeed, protein therapeutic agents are both stored and typically administered at very high concentrations. Under these conditions they can easily aggregate, impacting the product's developability, stability, formulation, and immunogenicity. Traditionally, attempts to improve protein solubility have exploited experimental trial and error approaches. However, they are expensive, difficult to perform and time consuming. We have overcome these limitations developing AGGRESCAN3D, a very efficient computational tool for the automated design of protein structures displaying improved solubility, without compromising their thermodynamic stability and function. We aim to use this approach to assist the production of novel and better protein therapeutics.

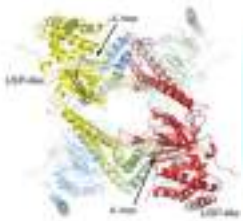
Group Leader: David Reverter

Our lab uses protein crystallography with synchrotron radiation as a major procedure to decipher the molecular mechanisms that lay behind the atomic structure of proteins and protein complexes. In our lab we combine this powerful structural technique with a functional and biochemical characterization using either in vitro or in vivo methods. In the last decades protein-function characterization of proteins and protein complexes have shed light into the most relevant discoveries in biochemistry and molecular biology.

SUMO and ubiquitin are small protein modifiers that can be attached via an iso-peptidic bond to lysine residues of target proteins. This type of post-translational modification is very common and regulate almost all processes of cell life, including cell division, DNA repair or gene expression. For example, ubiquitin modification through Lys48 regulates the half-life of many proteins by degradation with the proteasome system and is essential for the protein homeostasis in the cell.

The conjugation of *ubiquitin* and *SUMO* (*Ubl*) to target proteins is conducted via a conserved multistep enzymatic cascade through *E1* (activating enzyme), *E2* (conjugating enzyme), and *E3* (ligase enzyme). Reversely, deubiquitinating enzymes (*DUBs*) can remove ubiquitin by catalyzing the hydrolysis of the isopeptide bond. Therefore, ubiquitin and *SUMO* conjugation and deconjugation are balanced and tightly regulated by *E3* ligases conjugation and *DUBs* deconjugation.

Structural/Functional Characterization of the USP25 deubiquitinase enzyme



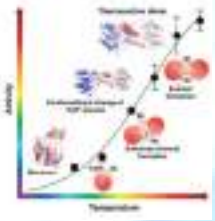
Human *USP25* (and *USP28*) are deubiuquitinating proteases that control the levels of important targets in the cell and are regulated, among other systems, by *SUMO* conjugaiton on the N-terminal domain. *USP25* (and *USP28*) are modular proteins composed by three domains: a N-terminal regulatory domain that interact with the ubiquitin chains; a central USP-like domain with the catalytic residues and including a long insertion in the middle of the domain; and a C-terminal domain that interacts with specific substrates, such as the recently reported Tankyrases involved in the Wnt/β-catenin pathway. We have recently solved the crystal structure of *USP25*, which reveals the presence of a homotetrameric structure which is involved in a novel regulatory mechanism of the deubiquitinating activity.

Structural/Functional Characterization of the SMC5/6 complex, a multimeric SUMO E3 ligase enzyme

SMC (Structural Maintenance of Chromosomes) complexes are topologically closed molecules formed by two elongated SMC subunits and by a distinct number of associated non-SMC elements (NSE). SMC proteins contain three different domains: an ATPase head structurally related to that of ABC transporters (hereafter named "HEAD"), an extended coiled coil region ("ARM") and a heterodimerization or hinge domain ("HINGE"). Each SMC complex has specific and essential roles: cohesin maintains connections between sister chromatids, condensin compacts chromosomes and Smc5/6 promotes chromosome disjunction. Despite these seemingly disparate functions, all SMC complexes share a common property, which is to organize chromosomes by topologically embracing DNA inside their ring-shaped structure.

We have recently shown that the Nse2 SUMO E3 ligase in the Smc5/6 complex, a critical player during recombinational DNA repair, is directly stimulated by binding to DNA. Activation of SUMOylation requires the electrostatic interaction between DNA and a positively-charged patch in the ARM domain of the Smc5 subunit, which acts as a DNA sensor that subsequently promotes an stimulation of the Nse2 ligase activity. These results reveal a novel mechanism to enhance a SUMO E3 ligase activity by direct DNA-binding and to restrict SUMOylation in the vicinity of those Smc5/6-Nse2 molecules engaged on DNA.

Structural mechanism for the temperature-dependent activation of the hyperthermophilic Pf2001 esterase



Esterases and *lipases* are very important biocatalysts for industrial purposes, since they catalyze reactions of synthesis or hydrolysis of lipidic ester bonds. In general agreement, esterases (E.C. 3.1.1.1) prefer short to medium chains up to C10 of monoesters, whereas lipases (E.C. 3.1.1.3) can hydrolyze water-insoluble long-chain triglycerides. The Pf2001 esterase from ***Pyrococcus furiosus*** reaches its optimal activity between 70 and 80°C.

We have recently solved the crystal structure of the *Pf2001 esterase*, which shows two different conformations: monomer and dimer. The structures reveal important rearrangements in the "cap" subdomain between monomer and dimer, by the formation of an extensive intertwined helical interface. Moreover, the dimer interface is essential for the formation of the hydrophobic channel for substrate selectivity, as confirmed by mutagenesis and kinetic analysis. We propose a novel temperature-dependent activation mechanism of the *Pf2001 esterase* by dimerization.

Group Leader: Carles Arús

The aim of our group - the GABRMN - is to improve the diagnostic and prognostic evaluation of patients bearing abnormal brain masses. We use magnetic resonance spectroscopy (MRS), which can be performed concominantly to a conventional magnetic resonance imaging (MRI) study.

The information provided by MRS allows us to characterise the metabolic profile of these abnormal brain masses without the need to perform a biopsy.

Our group is distributed between the Department of Biochemistry and Molecular Biology of the Bioscience Faculty, where we perform the preclinical studies in animal models, and the IBB. What the IBB subgroup does is to analyse all clinical patient data from our collaborating hospitals. We also work in the improvement of current processing and analysis tools for analysing MRS Data.

Publications

Year	Publications	Impact Factor	Average IF
2011	64	241,49	3,77
2012	105	473,86	4,51
2013	84	418,86	4,99
2014	75	360,66	4,81
2015	89	462,45	5,20
2016	79	355,33	4,50
2017	53	190,10	3,59
2018	72	438,89	6,10

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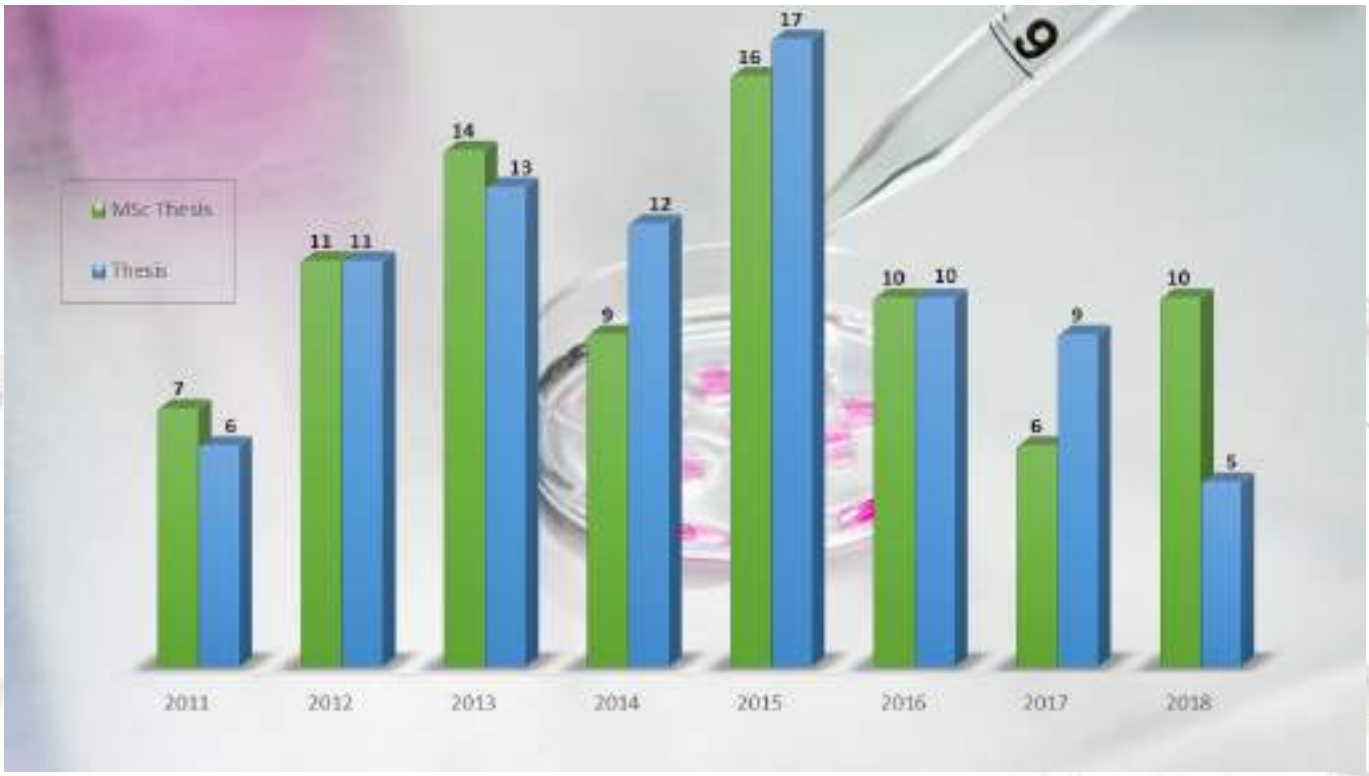
THESIS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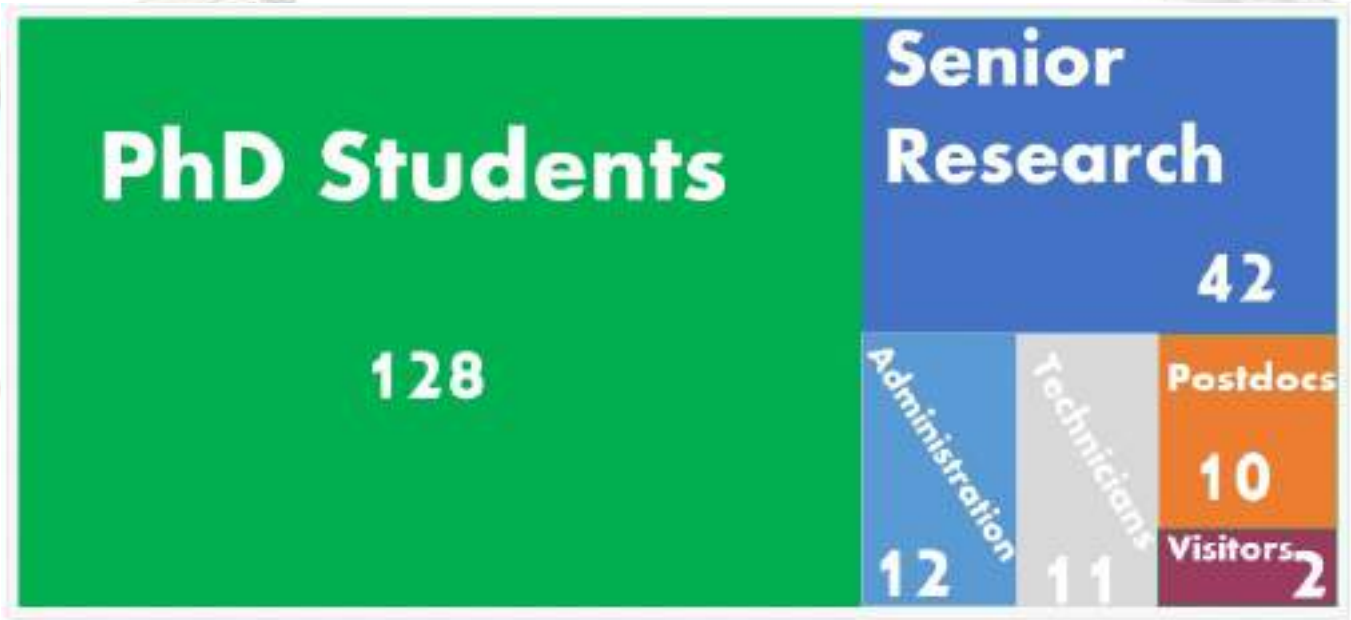

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