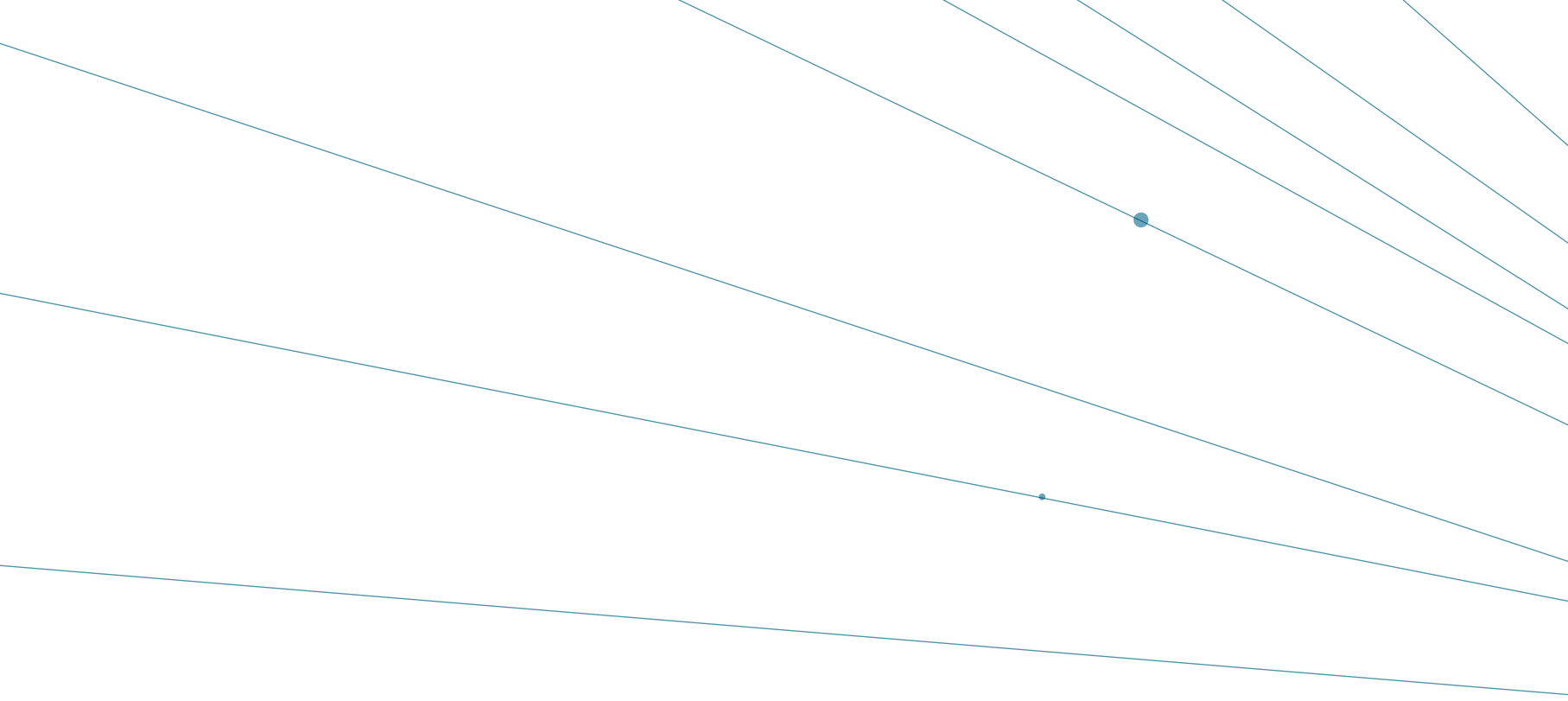
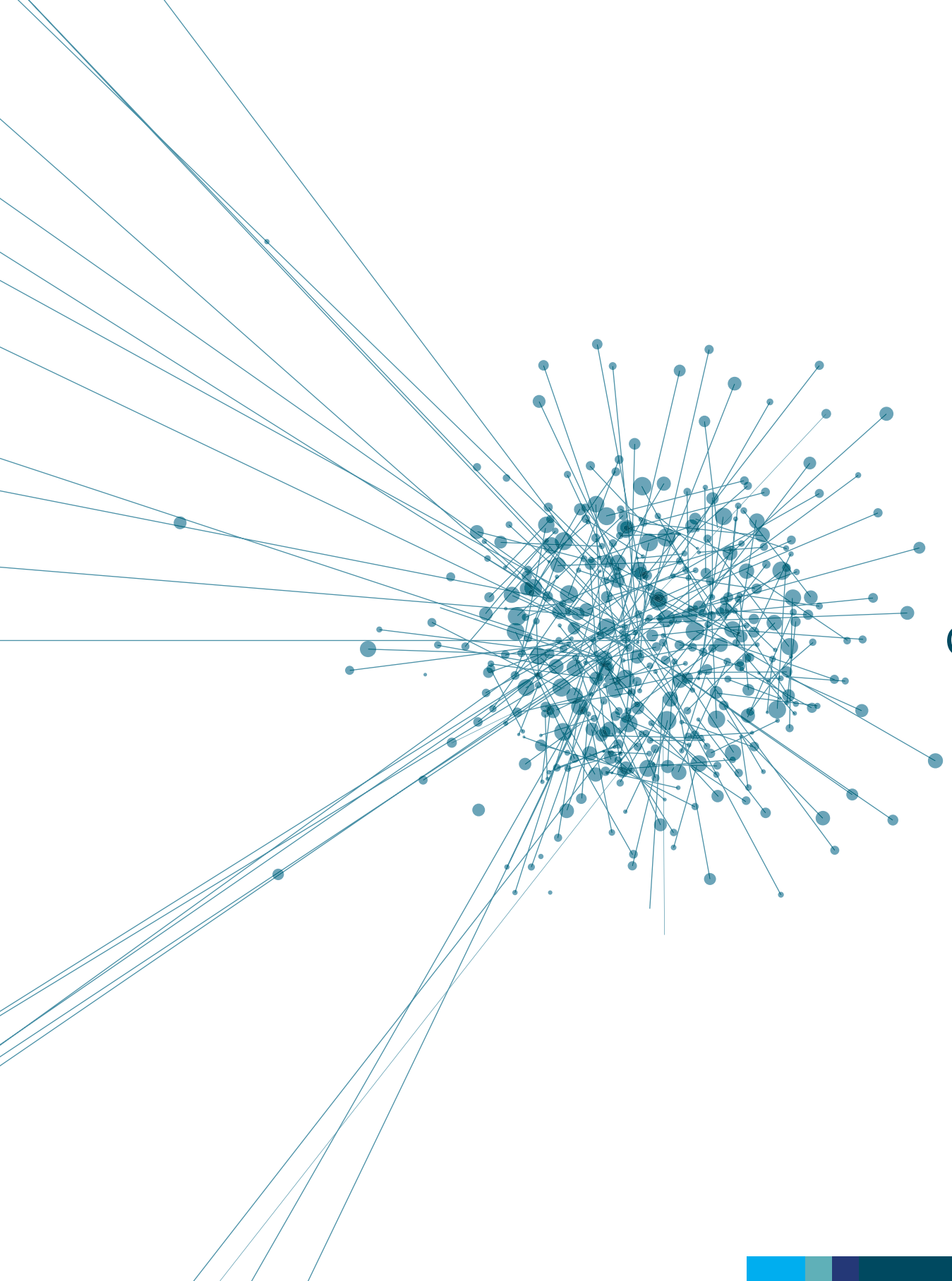
CIC bioGUNE



“The world looks so different after learning science” *Richard Feynman*



CIC bioGUNE

José M Mato
General Director
CIC bioGUNE and CIC biomaGUNE
Principal Investigator

Jesús Jiménez-Barbero
Scientific Director
CIC bioGUNE
Principal Investigator

ADVANCING BIOMEDICAL RESEARCH AND TECHNOLOGICAL INNOVATION IN THE BASQUE COUNTRY

OUR MISSIONS COVER DIFFERENT ASPECTS: THE DEVELOPMENT OF HIGH-LEVEL SCIENCE, INCLUDING FUNDAMENTAL RESEARCH, INDUSTRIAL RESEARCH AND EXPERIMENTAL DEVELOPMENT, HIGH-QUALITY TRAINING, INSTITUTIONAL COOPERATION, INTERNATIONALIZATION, AND DISSEMINATION.

CIC bioGUNE a non-profit biomedical research organization, founded in 2002 at the initiative of the Department of Industry of the Basque Government, opened its research facilities at the Technology Park of Bizkaia in January 2005. Since then, CIC bioGUNE has been playing a strong role in advancing biomedical research and technological innovation in the Basque Country. To support the research activities of the center's scientists and students, CIC bioGUNE initially made an investment of more than 35 million € in state-of-the-art research infrastructure - in genomics, proteomics, metabolomics, NMR, electron microscopy, X-ray diffraction, and computer and animal facilities, among others. Our missions cover different aspects: the development of high-level Science, including fundamental research, industrial research and experimental development, high-quality training, institutional cooperation, internationalization, and dissemination. Our researchers, recruited internationally, include fellows from Ikerbasque, Bizkaia: talent, and Ramón y Cajal and Juan de la Cierva programs. CIC bioGUNE currently employs over 150 people, including 20 research group leaders, ca. 100 postdocs, technicians and engineers, providing training opportunities to more than twenty Ph.D. students each year.

Extramural competitive funding from the Basque Country, Spain, International Institutions, including EU and ERC, and local and international Industries, combined with the generous support of the Basque Government and the Regional Government of Bizkaia, allowed our modern research projects to continuously grow and prosper. In 2015, CIC bioGUNE's researchers have authored over 100 scientific publications in peer-reviewed journals and licensed two patents.

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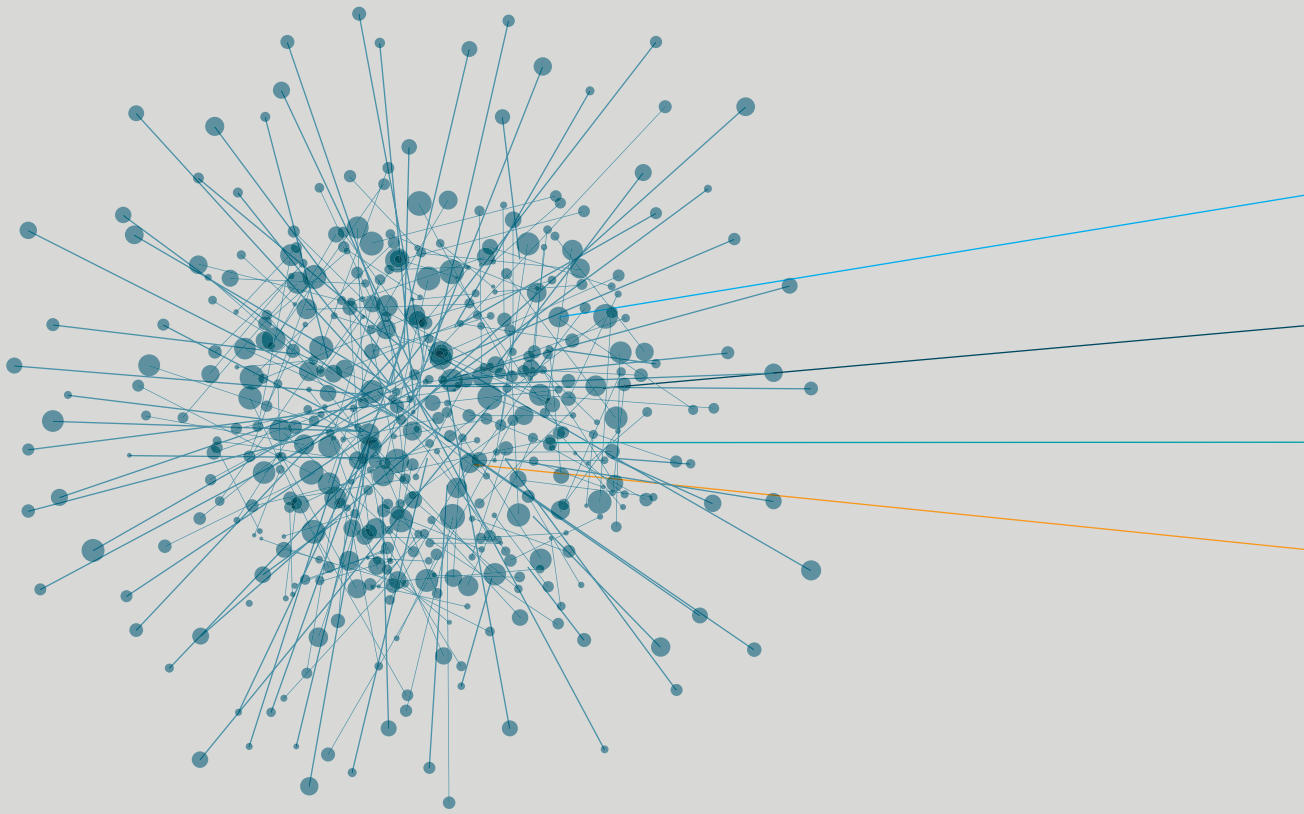

CIC bioGUNE

MOLECULAR RECOGNITION AND HOST-PATHOGEN INTERACTIONS

We study cellular processes controlling the pool and the life of proteins, from their synthesis on ribosomes to their modifications, to achieve their cellular functions in the organism context. We also elucidate the interaction of infectious microorganisms with mammalian cells at the structural and cellular levels, understanding the pathogenic mechanisms and the immune response against viruses, bacteria and prions.

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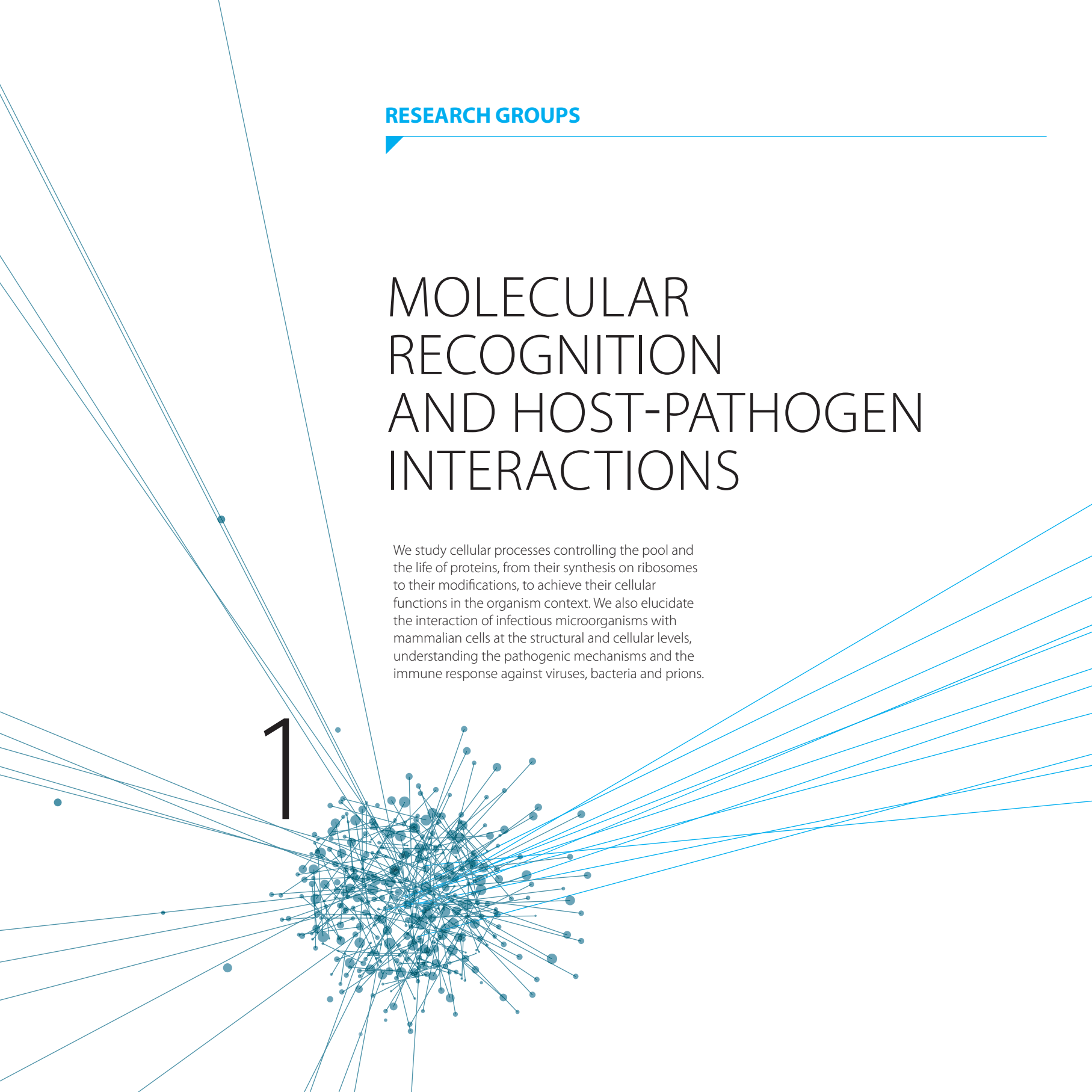

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Óscar Millet

Principal Investigator

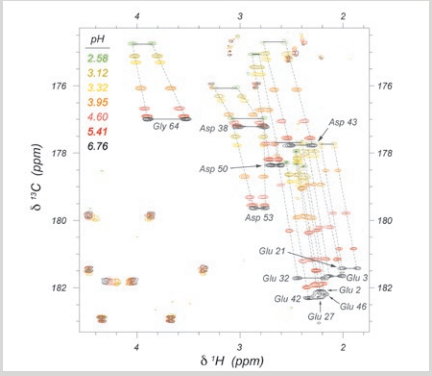
He holds degrees in Chemistry (Univ. Ramon Llull, 1994) and Chemical Engineering (IQS, 1995). After obtaining a Ph D in Organic Chemistry (University of Barcelona, 1999) he joined the group of Lewis Kay in Toronto for a post-doctoral stay (University of Toronto, 2000-2004). He was then recipient of a Ramón y Cajal reincorporation contract at the Parc Cientific de Barcelona (2004-2006) and he currently is group leader at the CIC bioGUNE. His research line focuses of the use of nuclear magnetic resonance (NMR) to the study of biologically relevant proteins and enzymes, paying special attention to the delicate balance existing between protein stability and dynamics. Such knowledge is applied for the development of new compounds with therapeutic activity, specifically in the field of rare diseases. He have published more than 55 papers with a total number of citations (1998-2015) of 2050 and an h-index of 17.
He was the Spanish delegate for the trans domain of the COST program (2009-2014). He was awarded the prize of the Real Sociedad Española de Química (2004) and the Spanish NMR group prize (2005). He currently is the president of the Spanish NMR group.

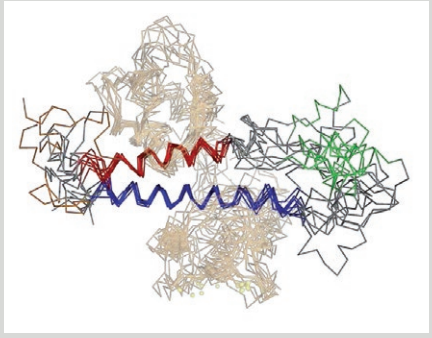
PROTEIN STABILITY AND INHERITED DISEASE LAB

Protein stability (thermodynamic and kinetic) drives the biophysical properties of the polypeptide chain (protein folding) and the protein's concentration in the cellular environment (protein homeostasis). It is the result of a delicate balance between inter- and intramolecular interactions, which can be easily altered by mutations and/or upon changes in the composition of the surrounding media. In this context, NMR spectroscopy offers a plethora of suitable experiments to investigate protein stability. The Protein Stability and Inherit Disease Lab is currently interested in the following topics:

1. Pharmacological chaperones.
Rare diseases (~7000 identified to date) are an area of significant medical need affecting an estimated 350 million people worldwide, with ~95% having no currently approved drug treatment. They are often produced by inherited mutations affecting the activity of a protein and It is becoming increasily clear that, most frequently, a mutation destabilizes the protein/enzyme, ultimately affecting its intracellular homeostasis. In this context, pharmacological chaperones (small molecules which bind to the protein, restoring stability and activity without affecting its function) can be applied to many diseases. The laboratory is investigating new methods (NMR, biophysical and biochemical) for the discovery and characterization of pharmacological chaperones against a set of diseases: congenital eryhtropoietic porphyria, tyrosianemia.

2. Environmental modulation of enzyme stability.
The high catalytic efficiency and the exquisite enantioselectivity of an enzyme has been employed in some industrial processes to upgrade their properties in order to make them more environmentally-friendly. However, large scale industrial implementation of biotechnological reactions is often limited by the marginal stability of the enzyme in the reactor conditions. The laboratory employs NMR and circular dichroism to investigate the effect of external crowding agents to improve the activity and stability of several enzymes. Specifically, the group is investigating the mechanism for protein haloadaptation by a combined use of site directed mutagenesis and high-resolution NMR spectroscopy.





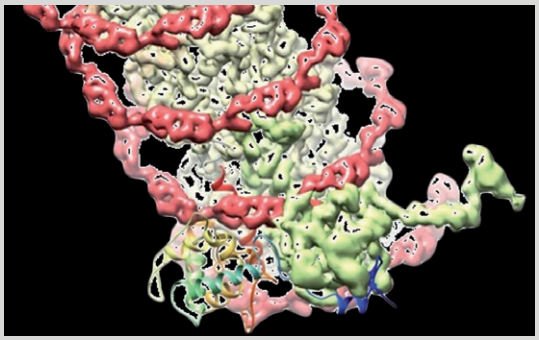
Mikel Valle

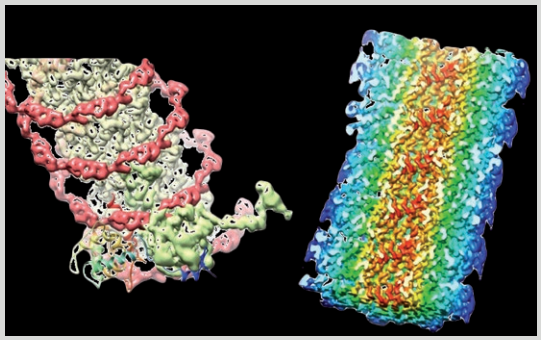
Principal Investigator

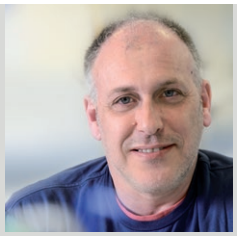
His research interest is focused on the structural characterization of macromolecular machines by cryo-electron microscopy (cryoEM). After his PhD in Madrid, he joined Prof. Joachim Frank in the USA, where Dr. Valle tasted the latest developments in cryoEM applied to the study of the ribosome. This period was really fruitful, and several classic articles revealed fundamental aspects of the ribosomal functioning during translation. After a short period as civil servant in the Spanish Research Council (CSIC), Mikel Valle joined CIC bioGUNE in 2006. Since then, Dr. Valle leads a team focused on several projects, from ribosomal structure to large metabolic enzymes, always by means of cryoEM, a powerful structural biology technique. His research has recently delivered the highest resolution structure for a plant flexible filamentous virus.

CRYOEM OF BIOLOGICAL MACROMOLECULES LAB

The structural study of biological macromolecules is key to understand their functioning. By means of cryo-electron microscopy we can obtain 3D maps biological complexes under nearly physiological conditions, and the latest developments in the field allow for near-atomic resolution, providing detailed observation of molecules. The aim of the team is to describe the structure and the conformational changes associated with the biological function. We focus on motors involved in universal biological functions where interactions between protein and nucleic acids are essential. Structural studies of ribosomes during translation allow the understanding of the mechanisms which govern protein synthesis. In this process, interactions with translation factors and interference by several antibiotics are especially important.
The group also analyzes the structure of flexible filamentous viruses, a group of plant pathogens, and large oligomeric enzymes such as pyruvate carboxylase.





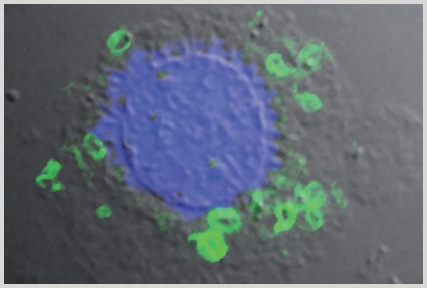


Juan Anguita

Principal Investigator
Ikerbasque Research Professor

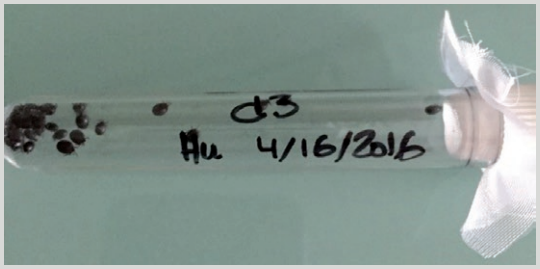
Juan Anguita joined CIC bioGUNE as an Ikerbasque Professor in 2012. He has a BS degree in Biochemistry and Molecular Biology from the University of the Basque Country, and a PhD degree in Animal Health from the University of Leon. After 5 years as a postdoctoral fellow at Yale University School of medicine followed by 2 years as Associate Research Scientist (non-tenure faculty position) at the same institution, Dr. Anguita started his independent career first as an Assistant Professor in the Department of Biology at the University of North Carolina at Charlotte, then as an Assistant and then Associate Professor with tenure in the Department of Veterinary and Animal Sciences at the University of Massachusetts at Amherst. Dr. Anguita´s laboratory is currently focused on the study of the mammalian host immune response to the spirochete that causes Lyme disease, Borrelia burgdorferi. His work is centered in the mechanisms of immune defense against infection, particularly focused on the phagocytosis of spirochetes and the activation of macrophages in the context of cardiac infection. His laboratory is also involved in the search of vaccine candidates to tick salivary antigens in order to prevent the transmission of several pathogens of medical importance, as part of international collaborative networks that include ANTIDotE, an European Commission funded consortium. Dr. Anguita's group performs extensive –omic analysis relevant to his research interests, including phosphoproteomics, transcriptomics, proteomics and metabolomics.

MACROPHAGE AND TICK VACCINE LAB



The macrophage and tick vaccine laboratory studies the interaction between athropod vectors, infectious microorganisms and their mammalian hosts. The laboratory is primarily focused on ticks of the genus Ixodes, which transmit several medically important pathogens, such as the causative agent of Lyme borreliosis, Borrelia burgdorferi. The lab participates in a large multicenter project funded by the EU (ANTIDotE) that seeks to identify tick salivary antigens that could be used as potential vaccine candidates against tick bites and therefore, prevent the transmission of pathogens. They are also interested in the pharmacological activities exerted by tick saliva proteins, especially those that can modulate the immune response and that can have therapeutic applications in immune disorders. Finally, the group is interested in understanding the regulation of the immune response pathways present in ticks that participate in the control of pathogens within the vector.

On the other hand, the laboratory seeks to understand the response of macrophages to infectious agents, from Lyme borreliosis to inflammatory bowel disease to tuberculosis. They are interested in understanding the metabolic control of macrophage responses through the specific mitochondrial complex I repressor, MCJ in different models of disease in which these cells participate, such as Lyme carditis and inflammatory bowel disease. Furthermore, the role of INFγ and other signals on the plasticity of the response of macrophages to infectious agents is another focus of the laboratory. Finally, the group is interested in defining the phagocytic 'ome' that mediates the uptake, elimination and initiation of proinflammatory responses by macrophages. In this context, the group described the Complement Receptor (CR) 3 as a phagocytic receptor involved in the elimination of B. burgdorferi by macrophages. CR3 cooperates with the GPI-anchored protein, CD14, in the internalization of the spirochete, a novel mechanism that is independent of MyD88 signals.



Francisco Blanco

Principal Investigator
Ikerbasque Research Professor

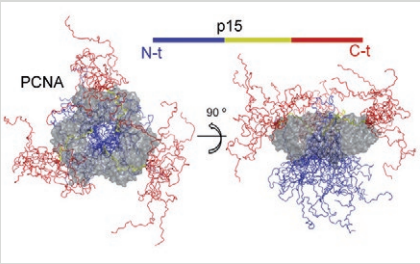
Francisco J Blanco obtained his Bachelor and Doctorate degrees in Chemistry at the Complutense University of Madrid, in years 1988 and 1992. His PhD thesis was supervised by JL Nieto at the Instituto de Estructura de la Materia-CSIC, Madrid. He used Nuclear Magnetic Resonance to characterize the first linear peptides able to fold as β-hairpins in solution. In 1993 he joined L Serrano's Group at the European Molecular Biology Laboratory (Heidelberg, Germany) and showed that the evolution of a new protein fold from an existing one is unlikely to occur through a series of intermediate folded sequences.

In 1997 he moved to R Tycko's Lab at the National Institutes of Health (Bethesda, USA) and obtained solid state NMR evidence for a helix-loop-helix structure in the HIV-Rev protein in fibrillar state.

In 2000 he returned to Madrid to work with M. Rico´s group at the CSIC on the NMR structure of a protein with a novel fold. He was awarded a Ramón y Cajal contract in 2002 and joined the Centro Nacional de Investigaciones Oncológicas to establish and lead the NMR group. He characterized native and engineered homing endonucleases as tools for gene repair, and the solution structure of the Proliferating Cellular Nuclear Antigen (PCNA) ring.

Late in 2007 he joined the Structural Biology Unit at the CIC bioGUNE as an Ikerbasque Research Professor to work on the structure-function of protein complexes involved in chromatin remodelling and DNA repair.

STRUCTURAL BIOLOGY OF CANCER LAB



The Structural Biology and Cancer Lab primarily uses NMR for biomolecular structural characterization and incorporates complementary structural and functional studies through collaborations. This integrative structural and functional approach is indispensable to understand protein complexes relevant in chromatin remodeling and DNA replication and repair. We study the INhibitor of Growth (ING1-5) family of tumor suppressors, which restrict cell growth and induce apoptosis through transcription regulation. They form interaction networks, binding histone H3 tails and recruiting Histone Acetyl Transferase (HAT) and Histone Deacetylase (HDAC) complexes to the chromatin. The lab has characterized the structure of ING4 as a dimeric protein that recognizes histone H3 trimethylated at lysine 4 through its PlantHomeoDomain (PHD). Structure-sequence alignments suggest that homodimerization of other ING proteins, and even heterodimerization, may occur, especially between the highly homologous ING4 and ING5. The team is characterizing the structure of ING5 and its N-terminal domain, and the possible formation of heterodimers and also is studing the structural and functional implications of ING5 mutants detected in cancer.

PCNA is a DNA sliding clamp, an essential factor for DNA replication and repair. It has a ring-shape structure and interacts with many proteins, including ING1. The group found by NMR that some interactions are extremely weak in solution, likely mediated by other factors in the cell. The PCNA associated factor p15 is overexpressed in cancer, with high levels correlating with poor prognosis, and becomes ubiquitylated upon DNA damage and also found that p15 is an intrinsically disordered protein that binds and threads through the PCNA channel with its N- and C-terminal tails remaining disordered at both sides of the ring. P15 binds simultaneously and independently to DNA, suggesting a regulation of PCNA sliding velocity on the DNA. This might facilitate the switch from replicative to translesion synthesis polymerase binding at stalled replication forks. The lab is investigating the structure and binding properties of ubiquitylated p15.

Principal Investigator
Ikerbasque Research Professor

Paola Fucini

Paola Fucini obtained her PhD degree in 1998, from the Ludwig-Maximilians-Universität in München, for a thesis conducted at the Max-Planck-Institute for Biochemistry, in Martinsried (Germany), under the supervision of Prof. Angelika Noegel and Tad Holak. With this first study she started her career in structural biology becoming interested in tackling the fascinating process of protein folding. During her postdoctoral studies, as a Research Associate in the group of Prof. Chris Dobson and Carol Robinson, first at the Oxford Center for Molecular Science (University of Oxford) in the period 1998-2001 and later in 2002, at the Chemical Laboratory at Cambridge University, UK, she developed an in vitro transcription/translation system for the preparation of nascent chain ribosomal complexes, suitable for Mass Spectrometry, NMR and Cryo-EM analysis. The system allowed pioneering studies on co-translational protein folding which she later pursued as an independent Group Leader at the Max-Planck-Institute for Molecular Genetics, AG Ribosomen, in Dahlem, Berlin (2002-2007). There, after acquiring further expertise in ribosome X-ray crystallography, she started to developed three main research lines, namely (i) the mode of action of antibiotics and translational factors, (ii) the process of co-translational protein folding and sorting, (iii) ribosome biogenesis. These studies, consolidated as Professor in X-ray Crystallography for RNA and Protein complexes at the Cluster of Excellence for Macromolecular Complexes at the University of Frankfurt (2007-2012), are currently continued since 2013 as Research Professor in the ideal environment offered by the Centro de Investigación Cooperativa en Biociencias, CIC bioGUNE, en Derio, Bizkaia.

Principal Investigator
Ikerbasque Research Fellow

Sean Connell

Dr. Connell graduated from the University of Alberta (Canada) in 1997 with a B.Sc.. While supported by an Alberta Heritage Foundation for Medical Research Studentship he earned his Ph.D. in Medical Microbiology in 2003 from the University of Alberta (Canada) and was awarded the Cangene Gold Award from the Canadian Society for Microbiologists for his thesis on the tetracycline resistance protein Tet(O). From 2003-2006, and with the support of an Alexander von Humboldt Research Fellowship, he completed his first post-doc at the Universitätsklinikum Charite (Berlin, Germany) where under the supervision of Prof. Spahn he began using cryo-electron microscopy to characterize complexes of the translational machinery. From 2007-2012 he worked as an independent researcher at the Goethe-Universität (Frankfurt, Germany) and studied macromolecular machines like the ribosome and fatty acid sythetase using cryo-electron microscopy. Currently as a Principle Investigator in the CIC bioGUNE (2013-present) he is studying the regulation of ribosome assembly, anti-infectives that target the initiation phase of protein synthesis and the structure of the polyketide synthase.

Sean Connell is a Ikerbasque Research Fellow and has been working in the Structural Biology Unit of the CIC bioGUNE since January 2013. His research interests focus on understanding, at a biochemical and structural level, the molecular details of processes involved in regulating gene expression. In particular, he aims to understand how the cell regulates protein synthesis and how disruption of this regulation can contribute to pathogenesis during bacterial and/or viral infection. He has expertise in the preparation of macromolecular complexes for structural studies, functional characterization of complexes by biophysical means and the structural investigation of macromolecular complexes by cryo-EM.

RIBOSOME STRUCTURAL BIOLOGY LAB

Amino acids are assembled into proteins following the genetic instructions encoded in the mRNA in a process called translation. This is primarily governed by a large macromolecular machine called the ribosome. Research in the Fucini and Connell labs focuses on understanding, at a biochemical and structural level, the molecular details of processes that regulate the ribosome at several levels including:

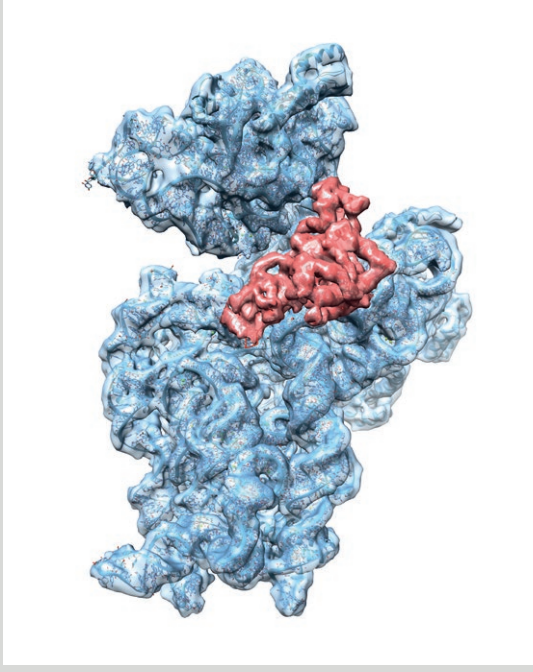
1. Inhibition of core ribosomal activities by antibiotics.
Medically relevant antibiotics target the ribosome and inhibit its core functions to exert their anti-microbial activities. The lab aims to understand how these antibiotics interact with and inhibit the ribosome to improve existing drugs or develop novel antibiotics.

2. Regulation of core activities like initiation, elongation and termination by native protein factors.
During protein synthesis the ribosome has several functional activates which are coordinated by specific protein factors. The lab aims to understand how these factors work together with the ribosome.

3. Ribosome Biosynthesis.
Assembling a ribosome requires orchestrating the structural integration of more than 55 ribosomal proteins and three nucleic acid strands in Escherichia coli. This assembly process is facilitated by ribosome assembly factors and the lab aims to understand how these factors guide the maturation of the ribosome.

4. Co-translational folding and protein sorting.
The nascent protein is synthesized in the core of the ribosome and passes through a 100Å long conduit to emerge outside the ribosome. This passage is a highly dynamic and 'personalized' event, where the ribosome and the protein chain communicate to regulate the translation and compartmentalization of the nascent protein. The lab aims to understand the details of this communication.

Accordingly, the groups have expertise in the preparation and structural characterization of ribosomal complexes. To provide a complete structural understanding of ribosomal functions we employ complementary structural biology methods like X-ray crystallography, NMR (Fucini Lab) and cryo-EM (Connell Lab).



Aitor Hierro

Principal Investigator
Ikerbasque Research Professor

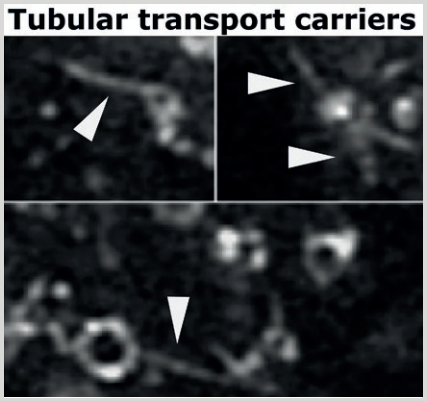
Aitor Hierro obtained his Bachelor and Doctorate degrees in Biochemistry at the University of the Basque Country (UPV/EHU). As a PhD student, he examined the regulatory effects of phosphorylation of a nuclear chaperone and its interaction with histones. Between 2002 and 2007, he conducted his postdoctoral research at the National Institutes of Health (Bethesda, USA) under the supervision of Prof. James H. Hurley. During this period, his research was focused on the multivesicular-body sorting pathway.
In 2008, Dr. Hierro joined CIC bioGUNE and began his independent research work on structural aspects of endosomal trafficking regulation and its role in physiological malfunction and disease. His research focuses on protein interactions regulating the higher levels of functionality. This research concentrates on the subtle interactions that regulate the transport of components between cell compartments and the role of miss-deliveries in the genesis of various diseases.
One of the most important challenges in the trafficking field is deciphering the fidelity code by which cargo proteins are selectively recognized and delivered.
Dr. Hierro's laboratory has been focusing on the mechanisms and specific interactions during selective recruitment of cargo molecules from endosomes;
He also investigates how the trafficking routes in this compartment are exploited by toxins and pathogens.

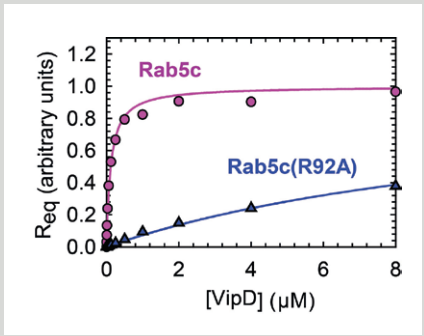
Dr. Hierro's lab uses a multidisciplinary approach including X-ray crystallography, electron microscopy, small angle X-ray scattering, biochemical reconstitution, ITC and SPR to uncover these higher order mechanisms in intracellular trafficking. The group fosters trans-disciplinary collaboration among world-class experts in computational simulations and cell biology for testing the mechanisms of the proposed structural models.

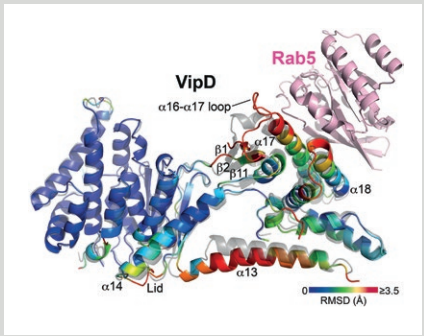
MEMBRANE TRAFFICKING LAB

Living cells constantly recycle receptors, proteins and lipids with a direct impact on nutrient uptake, re-sensitisation to environmental signals, immune surveillance and waste management. Failure to recycle results in reduced signalling, oxidative stress, protein mislocalisation and aggregation, which are pathological hallmarks of many cardiovascular, cancer, and neurodegenerative diseases. Endosomes are key recycling compartments where the biosynthetic and endocytic pathways intersect. Here, the fate of sorting receptors is directly linked to their selective recruitment into tubulo-vesicular carriers. Our understanding of receptor recycling in a motif-dependent manner, the formation of such tubulo-vesicles and the functional components defining their architecture remains very limited. Retromer is a novel protein coat complex with a central role in multiple receptor-sorting events in the endosomes. Retromer combines receptor recruitment with membrane tubulation properties, but unlike other classical coats, it does so through a single-layer or "cage-free" organization.

This laboratory is interested in understanding how retromer components form a coat around tubulo-vesicles, how transmembrane receptors are selectively recruited to control essential cell processes, and how certain pathogens subvert and co-opt these interactions.







Nicola G A Abrescia

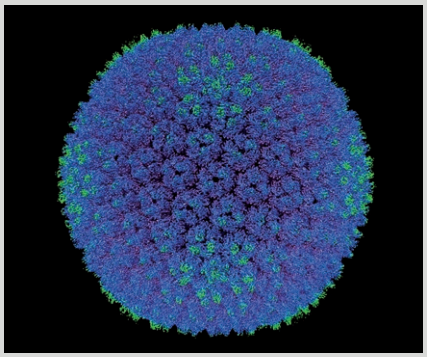
Principal Investigator
Ikerbasque Research Professor

Dr. Abrescia received his undergraduate degree from the Università degli Studi di Milano (Milan, Italy) in Physics after defending his Minor Thesis in 1996 on crystallogenesis and X-ray crystallography of DNA fragments. Following his graduation he joined the Subirana lab at the Universitat Politecnica de Catalunya (Barcelona-Spain). He completed his graduate studies at the beginning of 2001; the work was supported by a pre-doctoral Training Mobility Research Marie Curie fellowship. During his graduate studies he also worked as a visiting student, at the Institute of Cancer Research-UK, at Yale and Harvard (USA). In spring 2001 he began his appointment as a postdoctoral research scientist at the Division of Structural Biology at The Wellcome Trust Centre for Human Genetics at University of Oxford with MRC Prof. DI Stuart.

Since October 2008 he has held a tenured Ikerbasque Research Professorship from the Basque Foundation for Science and he is Group Leader at the Structural Biology Unit at the CIC bioGUNE. Major contributions during his academic training, among others, have been a PNAS article in 2002, two Nature articles in 2004, a NSMB and Mol Cell in 2008.

Since becoming Group Leader, Dr. Abrescia authored several articles, mainly as corresponding author, in relevant journals such as PLoS Biolog, Nuclic Acids Research, Ann. Rev. Biochem., Nature Methods. He has presented his scientific activities in more than 40 congresses, 14 of which as an invited speaker.

STRUCTURAL VIROLOGY LAB



The Abrescia Lab's field of expertise is in Structural Biology and Virology. The research group is focused on the understanding of viral pathogenesis, the virus-cell recognition mechanisms and the assembly principles of viruses.

Major targets of the investigation are viruses with an internal membrane and biomedical relevant human and animal enveloped viruses (members of the Flaviviridae and Bunyaviridae families).
The Abrescia Lab integrates state-of-the-art X-ray crystallography, electron microscopy, electron tomography structural techniques and biophysical methods such as Circular Dichroism and Multi-laser light scattering (MALLS) with expertise in recombinant protein production in bacterial and mammalian cell systems.

Specifically, access to high-end crystallographic and electron microscopy infrastructure is routinely available which allows the group to resolve the viral structures to atomic detail. New lines of research directed to the development of DNA vaccines and to the study of the mechanical properties of viruses are been established with success.

Finally, the group combines the generated structural knowledge with functional studies thanks to a network of worldwide recognized collaborators in the academic and private sectors.

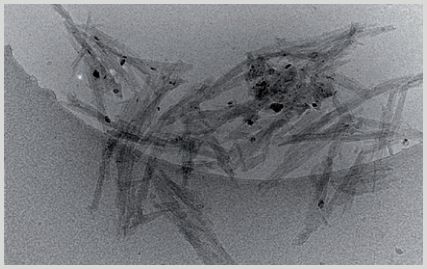
Joaquín Castilla

Principal Investigator
Ikerbasque Research Professor

Dr. Joaquín Castilla is a Ikerbasque Research Professor incorporated at CIC bioGUNE in 2009. He has a long experience working in prions since 1998 at Center for Animal Health (CISA -INIA). In 2003, he moved to Switzerland to work as Research Scientist at Serono Research Institute. He became Assistant Professor this year, first at the University of Texas, Medical Branch and later at Scripps (Florida) from 2006 leading an independent group.
His expertise is based on in vitro and in vivo replication of prions. Particularly, his group is studying the strain and species barrier phenomena in a cell-free system, trying to dissect the molecular mechanisms by which prions propagate and focusing on new anti-prion therapeutic approaches.
The most important achievements of his group are: i) development of the most sensitive method for prion detection, ii) generation of prion infectivity in a test tube contributing to validate the "protein-only" hypothesis, iii) prion detection in blood for the first time in pre-symptomatic and symptomatic animals and, iv) confirmation that the in vitro prion propagation faithfully mimicked the three major phenomena governing transmissible spongiform diseases: infectivity, strain concept and transmission barrier.

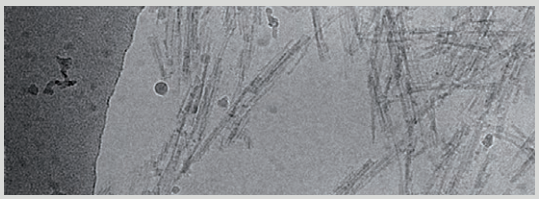
Dr. Castilla has published more than 75 peer reviewed articles (H index: 32 – Times cited: 3162 – Cumulative Impact Factor: ~595) which many of them have been instrumental for understanding the molecular mechanisms for prion propagation.

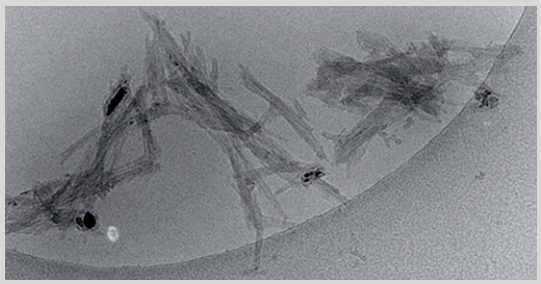
PRION RESEARCH LAB



Transmissible spongiform encephalopathies (TSEs) are fatal neurodegenerative disorders affecting both humans and animals. TSEs can be of genetic, sporadic or infectious origin. The infectious agent associated with TSEs, termed prion, appears to consist of a single protein, an abnormal conformer (PrPSc) of a natural host protein (PrPC), which propagates by converting host PrPC into a replica of itself. One of the characteristics of prions is their ability to infect some species and not others. This phenomenon is known as transmission barrier. Interestingly, prions occur in the form of different strains that show distinct biological and physicochemical properties, even though they are encoded by PrP with the same amino acid sequence, albeit in presumably different conformations. In general, the transmission barrier is expressed by an incomplete attack rate and long incubation times (time from the animal inoculation until the onset of the clinical signs) which become shorter after serial inoculation passages. Compelling evidence indicates that the transmission barriers are closely related to differences in PrP amino acid sequences between the donor and recipients of infection, as well as the prion strain conformation. Unfortunately, the molecular basis of the transmission barrier phenomenon and its relationship to prion strain conformations is currently unknown and we cannot predict the degree of a species barrier simply by comparing the prion proteins from two species.

The Prion Research Lab has conducted a series of experiments using the Protein Misfolding Cyclic Amplification (PMCA) technique that mimics in vitro some of the fundamental steps involved in prion replication in vivo, albeit with accelerated kinetics. The in vitro generated prions possess key prion features, i.e., they are infectious in vivo and maintain their strain specificity. The group has used PMCA to efficiently replicate a variety of prion strains from, among others, mice, hamsters, bank voles, deer, cattle, sheep, and humans. The correlation between in vivo data and our in vitro results suggest that PMCA is a valuable tool for assessing the strength of the transmission barriers between diverse species and for different prion strains; the group is using the method to determine which amino acids in the PrPC sequence contribute to the strength of the transmission barrier. These studies are proving very useful in evaluating the potential risks to humans and animals, of not only established prion strains, but also new (atypical) strains.
For example, while classical sheep scrapie is unable to cross the human transmission barrier in vitro, bovine spongiform encephalopathy (BSE) propagated in sheep does so efficiently. In addition, the group has also generated prions that are infectious to species hitherto considered to be resistant to prion disease.





Marcelo Guerin

Principal Investigator
Ikerbasque Research Professor

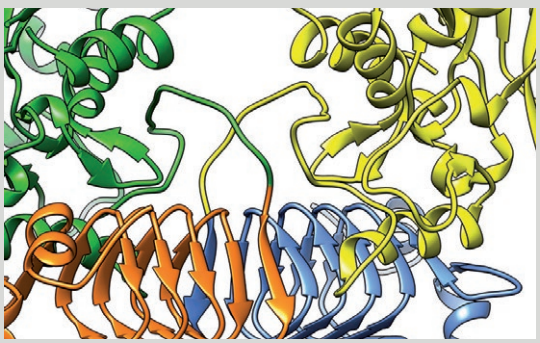
His interest in glycobiology began as an undergraduate student, while working with glycosyl hydrolases in the Leloir Institute at Buenos Aires, Argentina (1991-1996). This research center was named in honor to Luis F. Leloir, who discovered the first sugar nucleotide and was awarded the Nobel Prize in Chemistry in 1970.
He then completed his doctoral studies in biochemistry and molecular biology studying mechanistic aspects of glycosyltransferases in the Leloir Institute (1997-2002). To further advance toward the understanding of the molecular mechanism that governs glycosyl transfer reactions, he moved to the Structural Biochemistry Unit at the Institut Pasteur in Paris, France, where he was first introduced to macromolecular crystallography (2003-2007). After this postdoctoral training, he continued his work on the mycobacterial cell envelope when he transferred as a postdoctoral fellow to the Mycobacteria Research Laboratories in the Department of Microbiology, at Colorado State University in the United States (2008-2009). In 2009, he was awarded an Ikerbasque Research Professor position as the Head of the Structural Glycobiology Group (SGP).
He started his work at the Unit of Biophysics (CSIC-UPV), the Basque Country, Spain. More recently, he moved to the Structural Biology Unit, CIC bioGUNE, at the Technological Park of Bizkaia, the Basque Country, Spain, as the Head of the Structural Glycobiology Lab. He is particularly interested in investigating the structural and mechanistic properties of carbohydrate modifying enzymes. To this end, the group is using a multidisciplinary approach including protein biochemistry, protein biophysics and structural biology.

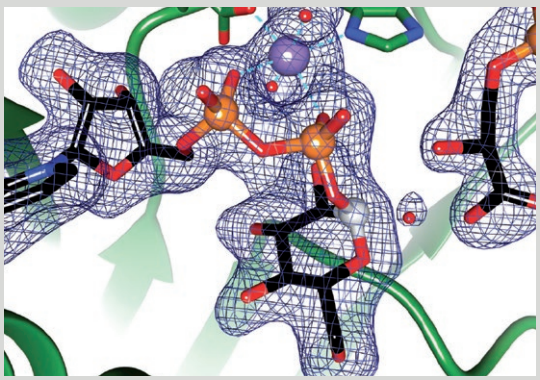
STRUCTURAL GLYCOBIOLOGY LAB

The Structural Glycobiology Lab investigates the structural determinants and the modulation of substrate specificity of proteins involved in the biosynthesis and modification of glycans. They use a multidisciplinary approach including X-ray Crystallography, Small Angle X-ray Scattering, Electron Microscopy, Protein Biophysics, Protein Biochemistry and Molecular Biology, to elucidate mechanistic aspects of these processes at the molecular level. Research is concentrated - but not limited – on two main lines:

1. Carbohydrate-Modifying Enzymes.
Most of the enzymes encoded in eukaryotic/prokaryotic/archaeans genomes that are responsible for the biosynthesis, degradation and modification of glycan structures are Carbohydrate-Modifying Enzymes, including: glycoside hydrolases (GHs), glycosyltransferases (GTs), polysaccharide lyases (PLs), carbohydrate esterases (CEs) and other auxiliary proteins (e.g. redox enzymes, carbohydrate binding modules). They are highly selective in nature, allowing the recognition of subtle structural differences in the sequences and stereochemistry of their carbohydrate substrates. In this context, the long-term goal of the Lab is to investigate the structural determinants and the modulation of substrate specificity of Carbohydrate-Modifying Enzymes at the molecular level.

2. The cell envelope of Mycobacterium tuberculosis.
The cell envelope of M. tuberculosis contains glycans and lipids of exceptional structure that play prominent roles in the biology and pathogenesis of tuberculosis (TB). Consequently, the chemical structure and biosynthesis of the cell envelope is currently intensively studied in order to identify novel drug targets. The long-term goal of the lab is (i) to investigate the mechanistic aspects of proteins involved in the biosynthesis of this particularly complex structure, and (ii) to understand in molecular detail the fundamental question of how the cell envelope is organized in space and time, within the context of its interaction with the host.





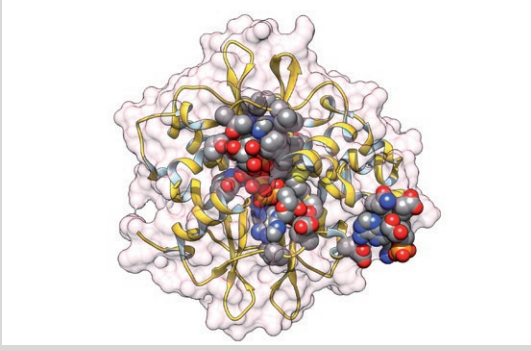
Alfonso Martínez de la Cruz

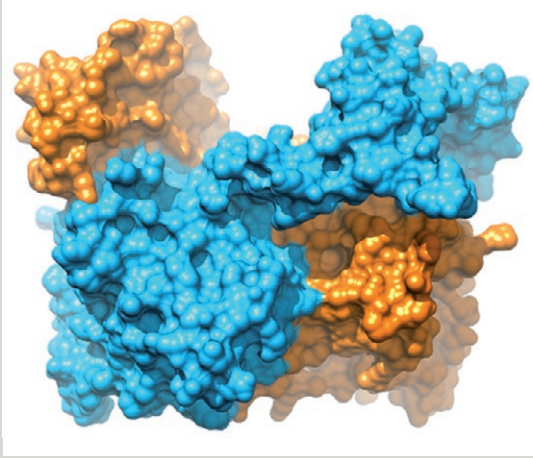
Principal Investigator

Alfonso Martínez de la Cruz got his undergraduate degree in Chemistry from the Universidad Autónoma de Madrid, Spain (1992). He finished his PhD work at the Department of Crystallography of Institute Rocasolano in Madrid (1997). Afterwards, he held three post doctoral positions, first at the Max Planck Institute Für Medizinische Forschung in Heidelberg, in the lab of Professors Ken Holmes and Wolfgang Kabsch, where he carried out structural studies of proteins involved in Chagas disease (March-October, 1997). In October 1997 he moved to Sung-Hou Kim´s lab at Univ. of California, Berkeley. His work at Berkeley focused on the nascent Structural Genomics Initiative, aimed to perform high-throughput structure determination of proteins to setup the limits of the protein fold universe. In September 2000, he returned to Spain and joined the lab of Prof. José María Mato at the Univ. of Navarra, first as postdoctoral fellow and later as a Scientist at the Center for Applied Medical Research (CIMA). During his stay in Pamplona he performed structural studies on enzymes regulated by S-adenosylmethionine, a hub molecule of the methionine cycle, that regulates the activity of important metabolic enzymes linked to the development of human liver diseases, including liver cancer and rare pathologies. The relevance and complex regulation of one of this enzymes, cystathionine beta-synthase (CBS), focused his attention for future studies. In January 2005, he joined CIC bioGUNE, in Bilbao, as Principal Investigator.

METABOLIC AND RARE DISEASES LAB

At the present the Metabolic and Rare Disease Lab is devoted to understand the molecular mechanisms by which structural motifs known as "CBS domains" regulate the activity of proteins with biomedical interest, including cystathionine beta-synthase, the enzyme from which these motifs were baptized. His group has wide expertise in Macromolecular X-ray crystallography and in Biophysical techniques applied to elucidate the regulation of two families of proteins: (i) human cystathionine b-synthase, and (ii) the Cyclin M (CNNM) family of magnesium transporters. Mutations within the amino acid sequence of these proteins are linked to different rare diseases, like Homocystinuria or Familial Hypomagnesemia, but also to more prevalent pathologies, that include cancer and cognitive disorders like Alzheimer disease or Down Syndrome. Among his most sound results is the long-sought crystal structure of full-length human cystathionine b-synthase in its "basal" and its "activated" state, as well as the three-dimensional structure of the intracellular region of the human CNNM2 transporter.





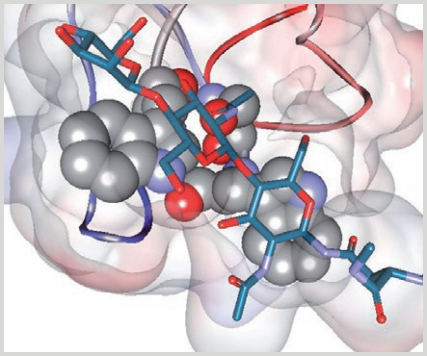
Jesús Jiménez-Barbero

Scientific Director
CIC bioGUNE

Principal Investigator
Ikerbasque Research Professor

Earlier in his career, JJB worked at CERMAV-CNRS, Grenoble, 1986 (Predoc); Univ. Zurich (Switzerland), 1987 (Postdoc); National Institute for Medical Research (UK) 1988 (Postdoc; and Carnegie Mellon Univ., USA; 1990-92 (Postdoc and visiting). After working at IQOG-CSIC (1992-2002) as tenured and senior research scientist (1996), he held a CSIC Research Professor position at CIB-CSIC since 2002. He has also held Visiting Professorships at École Normale Supérieure, Paris (2004), Univ. Pierre et Marie Curie, Paris VI, (2009), and Univ. Milano-Bicocca (2010-12). From the management perspective, he is current President of the Royal Society of Chemistry of Spain (since 2012), and was Secretary General of the same Institution (2004-11). He is the Head of the Chemistry Panel of the National Plan for Research of the Ministry of Economy and Competitiveness since 2009, and has been the representative of Spain in the CMST committee of EU-COST (2012-14). Besides managing his research group, with already 20 PhD students supervised as well as more than 25 postdocs, he was serving as Head of Department of Chem & Phys Biol Dept. at CIB-CSIC from 2009-2014.
He was appointed Ikerbasque Research Professor in 2013 and therefore, he moved to the Basque Country to become Scientific Director of CIC bioGUNE (Nov 2014).

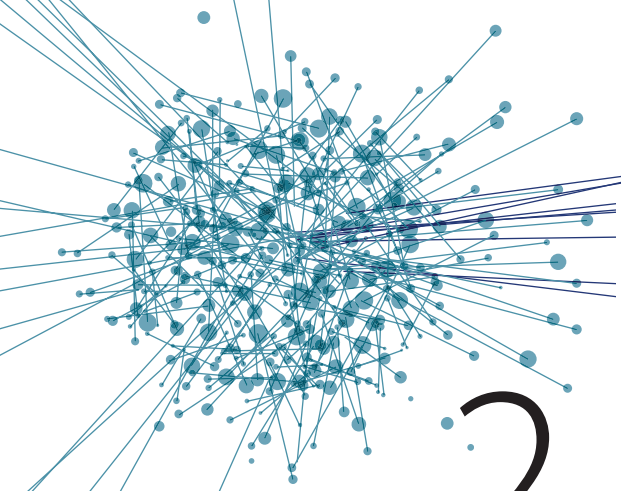
CHEMICAL GLYCOBIOLOGY LAB



From the scientific perspective, the research group is focused in exploring molecular recognition events from the chemical perspective, mostly in unravelling the molecular basis of the recognition of glycans by receptors in solution. The group employs a multidisciplinary approach, using the synergic combination of organic synthesis, protein biochemistry and molecular biology, biophysics, molecular modeling, and NMR, using a wide network of collaborations with specialists worldwide. Major contributions in the field include our systematic studies on the interactions of glycans with specific lectins (the 1st reported NMR structure of a glycan/lectin complex was achieved in his lab in 1995). Such detailed investigations have contributed significantly to our global understanding of glycan-mediated interactions in health and disease, including infectious and inflammatory processes. These studies conducted to the 2010 International Whistler Award in Carbohydrate Chemistry, following the Bruker award of the NMR division of RSEQ (2008) and the Janssen-Cilag award of RSEQ (2003).

The group does not only apply, but also develop, NMR methods for studying the structural and dynamic properties of ligands and their interaction with relevant proteins. Particularly, the fine chemical details of the interactions between sugars and proteins have been explored, with special emphasis on the relative role of sugar-aromatic stacking forces in the recognition process. The origin and relative importance of the forces that mediate these interactions are still under study and are a key part of the research in the group. Recent advances in the research are focused on disentangling how receptors recognise a given epitope in complex N-glycans, which present multiple epitopes. This has lead to the use of a precise NMR methodology, even using living cells, assisted by molecular dynamics and biophysical and structural biology methods, including X-ray crystallography. Recent methodology developments have permitted to use paramagnetic metals (lanthanides) to unravel hidden conformational features of N-glycans and to detect their molecular recognition events. The use of lanthanides is complementary to the employment and generation of other chemical novel NMR-sensitive tags, especially those based on 19F nuclei. The expansion, exploitation, and generalization of these novel concepts is generating a breakthrough in the field, with huge possibilities in the molecular recognition arena, permitting the access to the detailed study of the interactions of large and complex glycans, which were previously inaccessible to the study by NMR or other means, due to their intrinsic flexibility.

METABOLISM AND CELL SIGNALING IN DISEASE



2

We investigate metabolic pathways and disorders, as metabolic syndrome, liver disease and several rare diseases. We also focus on non-invasive biomarker discovery and the interplay between metabolism and signalling mechanisms in cancer.

01.
Cancer Cell Signaling and Metabolism Lab
Arkaitz Carracedo's Lab

02.
Exosomes Lab
Juan M Falcón's Lab

03.
Biology of Schwann Cell Disorders Lab
Ashwin Woodhoo's Lab

04.
Ubiquitin-likes and Development Lab
Rosa Barrio's Lab

05.
Wnt Signaling Pathway Lab
Robert Kypta's Lab

06.
Breast Cancer Stem Cells Lab
María Vivanco's Lab

07.
Physiopathology of the Hypoxia-signalling Pathway Lab
Edurne Berra's Lab

08.
Liver Disease Lab
Malu Martínez-Chantar's Lab

09.
Liver Metabolism Lab
José M Mato's Lab

Arkaitz Carracedo

Principal Investigator
Ikerbasque Research Professor

Dr. Carracedo´s scientific career started and has always been related to a single question: "What are the differences between normal and cancer cells that can allow us to develop more selective and effective therapies?"
During his undergraduate studies and later in his PhD thesis under the supervision of Dr. Velasco (Complutense University, Spain), he approached this question by studying a family of compounds, cannabinoids, which show a high selectivity between normal and cancer cells. As a postdoctoral fellow he joined Pier Paolo Pandolfi´s laboratory (MSKCC and BIDMC/Harvard, USA), with one idea in mind: to elucidate the interface between cell signaling and metabolism and apply it to the concept of precision medicine. This perspective of cancer research has become his independent line of research in his new position in the CIC bioGUNE institute in Bilbao, Spain, which he holds from September 2010.

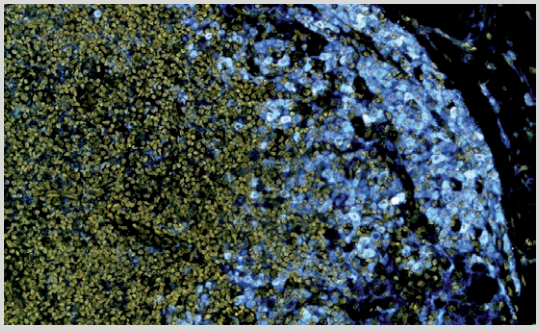
CANCER CELL SIGNALING AND METABOLISM LAB

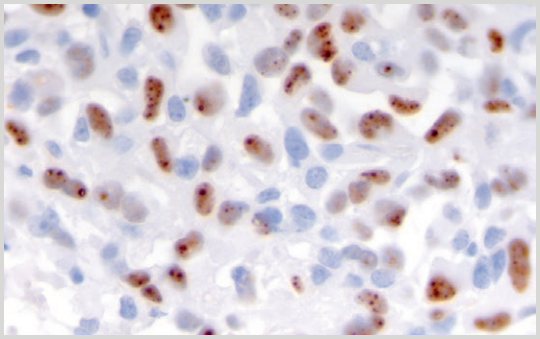
The research in the Carracedo lab is aimed at deconstructing the essential requirements of cancer cells with special emphasis on the translation of the acquired knowledge from bench to bedside. In order to define the genuine features of cancer cells, we focus on the signalling and metabolic alterations in prostate and breast cancer. Through the use of a hierarchical approach with increasing complexity, we work on cell lines and primary cultures (using cell and molecular biology technologies), mouse models of prostate cancer that are faithful to the human disease and the analysis of human specimens through the development of prospective and retrospective studies. Our work stems from the hypothesis that cancer is driven by signalling and metabolic alterations that, once identified, can be targeted for therapy. The center and our collaborator institutions offer state-of-the-art technologies (from OMICS to in vivo imaging), which allow us to build and answer our hypotheses with high level of confidence. To address our scientific questions in cancer, the Carracedo lab has developed a series of research lines:

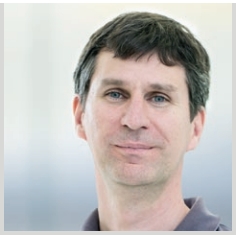
1. Bioinformatics-based discovery.
The lab takes full advantage on publicly available human prostate and breast cancer datasets in order to identify candidate genes to contribute to cancer pathogenesis, progression and response to therapy. Best hits are then validated employing genetic mouse models, xenograft surrogate assays and the latest advances in cellular and molecular biology combined with OMICs technologies.

2. Genetic mouse models as a source for the identification of novel cancer players.
Genetically engineered mouse models (GEMMs) can faithfully recapitulate many aspects of human cancer. Dr. Carracedo envisions the molecular analysis of GEMMs with high throughput technologies as a mean to identify novel cancer-related genes. These hits are then validated through the analysis of human cancer specimens and cellular and molecular biology approaches.

3. Multi-OMICs analysis for non-invasive biomarker identification.
Biofluids are the perfect source for cancer biomarkers that can inform about the presence or features of cancer. The lab has undertaken a biomarker discovery approach by applying the latest OMICs technologies to biofluid specimens from well-annotated prostate cancer patients, in order to define better molecules that inform about this disease.





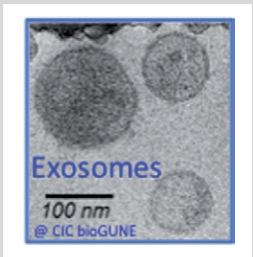


Juan Manuel Falcón

Principal Investigator
Ikerbasque Research Professor

Biochemist and cellular biologist with wide experience in performing high-content omics-based analyses. During his Ph.D at the Biomedical Research Institute "Alberto Sols" in Madrid, Dr. Falcon used yeast genetics as tool for studying Cystic Fibrosis. As postdoctoral fellow generate a knockout mouse for the POMT1 gene codifying an essential enzyme in development, and with implications in muscular dystrophies.
As postdoctoral researcher in the Human Genetics Department of University of California, Los Angeles (USA) he focused on the biochemical and functional characterization of proteins associated with the Hermansky-Pudlak syndrome (HPS) which is caused by defects in the formation of lysosome-related organelles using mouse and flies as model organisms.
In CIC bioGUNE started his research in the study on Exosomes —extracellular vesicles of endocytic origin- as a source for biomarker discovery and a tool for therapeutic applications, and Metabolomics as a platform for unraveling markers and metabolic pathways altered in diseases.
Thanks to a number of national and international collaborations Dr. Falcon´s group has characterized Exosomes secreted by many in vivo and in vitro experimental models of several diseases, as well as from different body fluids. In addition, he is also involved in the identification of Molecular Chaperones that increase in vivo stability of proteins implicated in Metabolic Rare Diseases-caused by protein miss-folding (e.g. Cystic fibrosis, Porphyries).
Currently he is focused on identification of minimally invasive markers for hepatic, infectious and neurological disorders by applying high-content "-omics" technologies on different biological sources including body fluids and Exosomes.

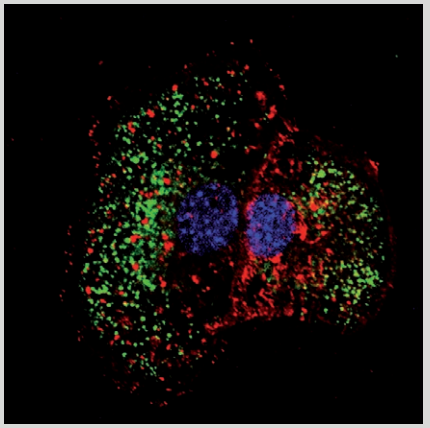
EXOSOMES LAB



The discovery of cell-secreted extracellular vesicles (EVs) including Exosomes has provided a new cellular component with the ability to influence different biological and pathological processes. In the last years these vesicles has attracted the interest in clinical, pharmaceutical and manufacturing areas. All cellular systems in culture or forming part of a tissue in the body secrete EVs containing proteins, nucleic acids, lipids and metabolites into the environment. They have been shown to act as important mediators of intercellular communication and regulators of cellular niches, and their altered characteristics in many diseases suggest them to be helpful for the diagnostic purposes. The group has been working in Exosomes since 2006 and acquired wide experience in isolate and characterize these vesicles from different biofluids and cell lines, in normal and pathological conditions.
The lab's current scientific interests are:

1) To elucidate the functional role of exosomes in metabolism.
The goal is to identify genes, proteins and metabolites that form part of the Exosomes in normal and pathological conditions. The improvement in the knowledge of the cargo of these vesicles will provide also clues about the functional role and implications of them in biology. Technological advances in the past 20 years have permitted large-scale measurements of biochemical and cellular constituents for study as a unified whole, creating all the '-omics' technologies including proteomics, genomics and more recently metabolomics. The group has already showed the presence in hepatic Exosomes of an elevated number of metabolic enzymes involved in endogenous and xenobiotics compounds, and we are currently studying the implications of these vesicles in the metabolism of those compounds.

2) To develop diagnosis and therapeutics tools based on Exosomes.
Exosomes constitutes a platform to identify low-invasive disease biomarkers. The group is currently comparing the composition of Exosomes in different scenarios in order to generate a repertoire of differentially expressed molecules that could be candidate biomarker of disease. In addition, behind the idea to obtain a "magic bullet" —a desired activity encapsulated in a vehicle with a known specific target- the group is trying to define the cellular preferences displayed by Exosomes. In this aspect the group is focused in identifying the molecular determinants that define the cellular specificity, and also the molecular machinery involved in the biogenesis of Exosomes. A better knowledge of the biology and the mechanisms of action of Exosomes will help to manipulate these vesicles with therapeutics purposes.



Ashwin Woodhoo

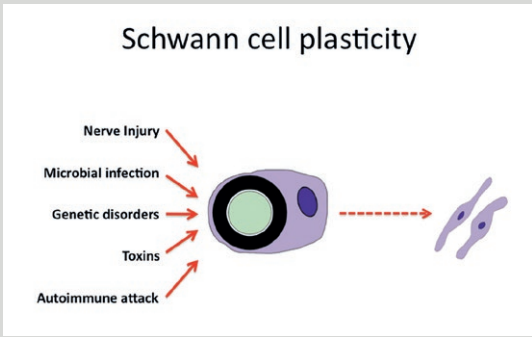
Principal Investigator
Ikerbasque Research Fellow

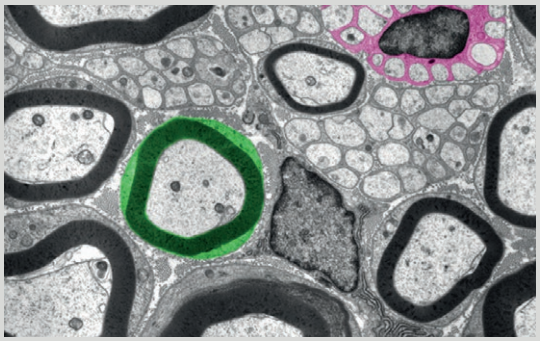
Dr. Ashwin Woodhoo started his research career in the group of his mentors Profs. Kristján R. Jessen and Rhona Mirsky at Univeristy College London, first as a PhD student (Dec 2001- Dec 2006), followed by a short post-doctoral period (Jan 2007- Dec 2008).
There, he learnt and developed several projects related to Schwann cell biology. He then joined the group of Dr Malu Martínez-Chantar and Prof. José M. Mato at the CIC bioGUNE to start his independent research lines on the control of gene expression changes during Schwann cell development and in pathological conditions by epigenetic and post-transcriptional mechanisms. Since 2015, he is directing his own laboratory at the CIC bioGUNE.

He has received different fellowships, including the Juan de la Cierva (2009), AECC fellowship (2010), Ramón y Cajal (2010 - 2015) and Ikerbasque Research Fellowship (2014 - 2019), and his work has received funding from the Instituto Carlos III, Fundación Científica AECC, Spanish Ministry of Economy (Plan Nacional i+D+i and Europa Excelencia), Basque Department of Education, Fundación BBVA and the Royal Society.

BIOLOGY OF SCHWANN CELL DISORDERS LAB

Axon myelination is essential for rapid saltatory conduction of nerve impulses in the vertebrate nervous system. A central feature of several of these pathological conditions in the peripheral nervous system (PNS) is the destruction of myelin and the reprogramming of myelinating Schwann cells to a 'progenitor-like' state, a highly unusual feature in mammals. This rests on the surprising plasticity of Schwann cells that allows them to switch between differentiation states. The work of the laboratory addresses a set of interlocking issues in Schwann cell biology that deal with Schwann cell myelination, and the response of Schwann cells to pathological conditions. More specifically, the lab is focused on identifying the key mechanisms that drive Schwann cell reprogramming in different pathological conditions, including nerve injury, genetic disorders, immune cell attack and microbial infections.
For these, the group has been examining the role of autophagy, and the role of DNA methylation, histone modifications and non-coding RNAs in this process using high-throughput techniques.
Another related ongoing project in the lab on is focused on the identification of therapeutical targets for neurofibromatosis type 1 and malignant peripheral nerve sheath tumours (MPNST).



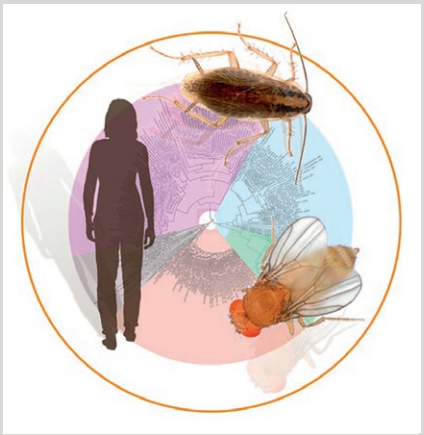


Rosa Barrio

Principal Investigator

Rosa Barrio started her work on ubiquitin-like genes during her PhD at the Center of Molecular Biology Severo Ochoa (Madrid, Spain), where she characterized the ubiquitin genes in Drosophila. During her postdoctoral stay in the laboratory of Prof FC Kafatos (Harvard University-USA, IMBB-Greece, EMBL-Germany) she initiated her work on SALL transcription factors, which she continued at the laboratory of Dr JF de Celis and Prof García-Bellido at the CBMSO (Madrid, Spain). Mutations in the genes encoding those factors cause hereditary human diseases, such as the Townes-Brocks and the Okihiro syndromes (TBS and OS).
She obtained a Ramón y Cajal contract in 2003. Since December 2004 she is in charge of the Laboratory 1 at the Functional Genomics Unit of CIC bioGUNE. The laboratory is currently investigating different aspects of the role of SALL and SUMO during development. In addition, the laboratory developed new technology for the isolation of proteins modified by SUMO and other Ubiquitin-likes, both in vivo and in cultured cells, either in Drosophila or in mammalian systems, which will have wide applications in the field. Rosa Barrio coordinated two European projects, one of them dedicated to the training of early stage researchers (ITN program, UPStream); the other grant being a large consortium of European groups interested in the field of the ubiquitin-likes (COST, PROTEOSTASIS).

UBIQUITIN-LIKES AND DEVELOPMENT LAB



Post-translational modifications by ubiquitin-like modifiers (proteins similar to ubiquitin) can influence many aspects of protein homeostasis, such are stability, localization or activity. SUMOylation is a reversible process by which SUMO, the Small Ubiquitin-like Modifier, is attached to target proteins and modify their properties. We discovered that SUMO has an important role in cholesterol intake, contributing to steroid hormone synthesis through the regulation of the Scavenger Receptors SR-B1 and the nuclear receptor Ftz-f1, homologous to the human Steroidogenic Factor 1, SF-1. The regulation of hormonal synthesis is a crucial step that determines animal viability and size. This novel function of SUMOylation is conserved in several tissues in different organisms.

To investigate more in detail the function of the ubiquitin-likes, we are developing new molecular tools to isolate and identify proteins modified by SUMO and other Ubiquitin-like modifiers in human cells and in model systems, such is Drosophila. We generated a versatile, highly specific, easy-to-use toolbox composed of vectors useful to analyze the modification of a protein of interest or to identify modified sub-proteomes.

Among the transcription factors regulated by SUMOylation, we are interested on the SPALT-Like (SALL) family of proteins, necessary for numerous biological processes. Mutations in SALL1 and SALL4 cause the rare diseases Townes-Brocks and Okihiro (Duane-Radial Ray) Syndromes, respectively, being also involved in the susceptibility to tumors. Patients might present dysplastic kidneys, supernumerary thumbs, malformed ears, sensorineural hearing loss and severe growth retardation. We are investigating the mechanism by which a truncated form of SALL1 causes the Townes-Brocks symptoms. We hypothesized that these are caused by the malfunctioning of primary cilia and we are currently performing the experiments necessary to prove this hypothesis.

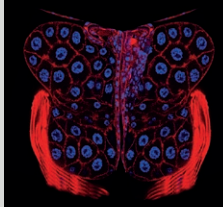
Primary fibroblasts derived from a Townes-Brocks patient, which exhibit mutation in the gene SALL1. The fibroblasts were kindly provided by Dr. Wilkie, Oxford, UK. Markers: Acetylated tubulin (red), F-actin (green), DNA (blue).

Representation of SUMO evolution across species, with associated functional consequences in human, Blattella and Drosophila.

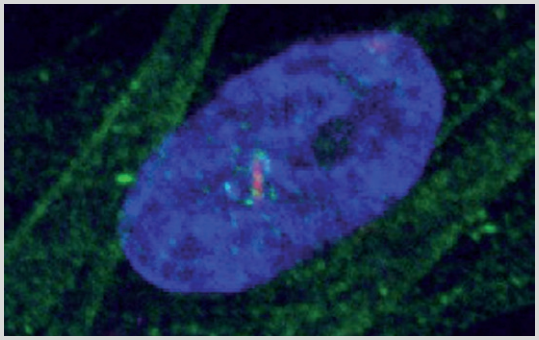
COVER

Steroid synthesis regulation: SUMO, Ftz-f1, Scavenger Receptors, and lipids meet in the ring gland

Image Credit: Ana Talamillo and Rosa Barrio, CIC bioGUNE



This confocal image shows a wild type *Drosophila melanogaster* ring gland. This gland is responsible for the synthesis of the steroid hormone ecdysone, which controls animal growth and development. In this issue, Talamillo and coworkers report that the capture of lipids by the ring gland, which are necessary for the synthesis of the hormone, depends on the ubiquitin-like SUMO protein, the nuclear hormone receptor Ftz-f1, and the Scavenger Receptor Snmp1. The nuclei of the gland are *marked* with DAPI (blue) and the cell contours are marked by phalloidin (red). The image has been mirror-duplicated.

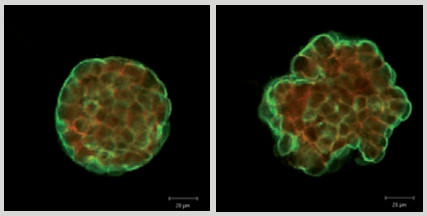


Robert Kypta

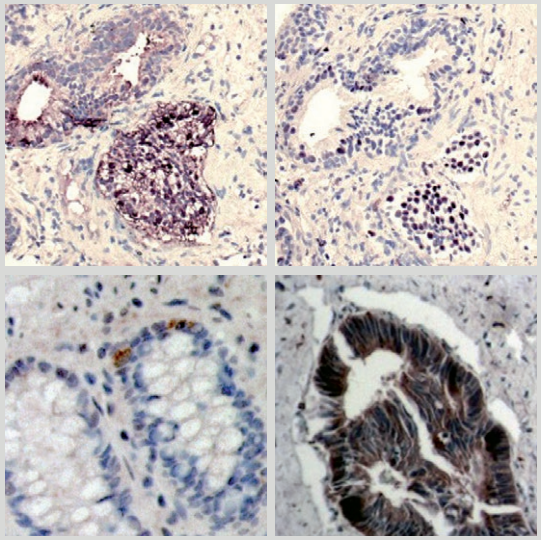
Principal Investigator

Robert Kypta was an undergraduate at Oxford University and carried out his PhD at EMBL in Heidelberg, where he studied the roles of Src family tyrosine kinases in the cellular response to PDGF. He did his postdoctoral training in Louis Reichardt's lab at the University of California San Francisco on cell adhesion in neurons, finding an association between the cadherin-catenin complex and receptor tyrosine phosphatases. He returned to the UK to start his own lab as a Wellcome Trust Career Development Fellow at the MRC Laboratory for Molecular Cell Biology, focusing on catenin function in cell models of neuroblastoma and colorectal cancer. He then took up a Lectureship at Imperial College London, where his group identified new links between components of the Wnt signalling network and the androgen receptor, a key driver of prostate cancer progression and a major therapeutic target. He set up his lab at CIC bioGUNE in 2005 with the goal of developing new therapies based on studies of signalling pathways that determine tumour and stem cell fate. His research has resulted in several awards, including an ARTP Prize and an Androgens Meeting Prize.

WNT SIGNALING PATHWAY LAB



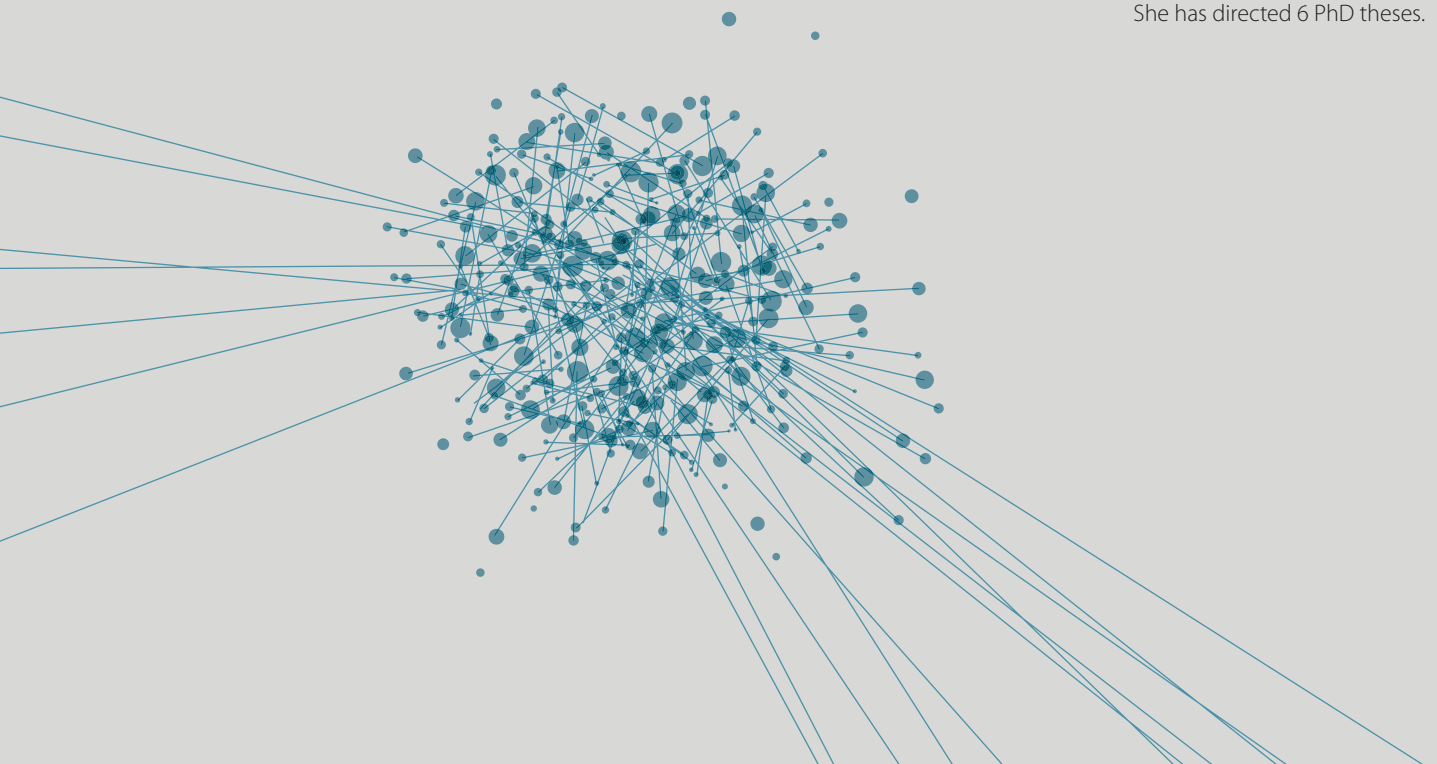
The Wnt Signalling Pathway Lab is interested in understanding how extracellular signals determine cell fate and function. Studies are focused on cell signalling in two areas: cancer, particularly metastatic and treatment-resistant disease, and neural stem cell differentiation, which is relevant to the development of therapies for stroke and neurodegenerative diseases. A general goal is to identify and characterise Wnt receptors and effectors in both contexts and use the information to develop new treatments. A major interest is Wnt-11, which is highly expressed highly in metastatic prostate and other cancers - the picture shows examples of Wnt-11 immunostaining (brown) in prostate cancer (top left, ERG oncoprotein right), normal colon (bottom left) and a tumour metastasis (right). Antibodies have been developed that block Wnt-11 function and receptors have been identified that transduce the Wnt-11 signal. The lab also studies other Wnts and their receptors in neural stem cells and breast cancer and the protein kinase GSK-3, a key component of Wnt and other signalling pathways. Finally, in collaboration with colleagues at Imperial College London, the lab is investigating the tumour suppressor Dkk-3, a secreted protein that inhibits tumour cell invasion by modulating TGF-beta/Smad/MMP signalling. The picture opposite shows the effect of loss of Dkk-3 on prostate epithelial acinar morphogenesis.



María del Mar Vivanco

Principal Investigator

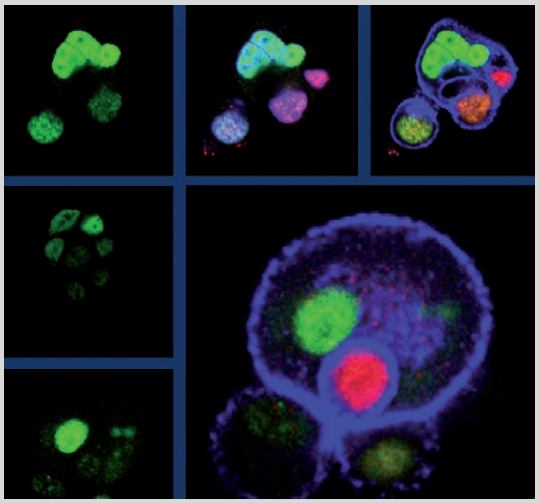
María Vivanco graduated from the University of the Basque Country, worked at Sandoz (Basel) and carried out her PhD thesis at EMBL (Heidelberg).
After her post-doctoral studies at UCSF (San Francisco), Maria started her own lab at the Institute of Cancer Research in London, where she identified mammary stem/progenitor cells in the human mammary gland.
She has directed her group at CIC bioGUNE since 2005, characterising mammary stem cells and examining their role in resistance to therapy. She is currently studying cancer stem cells as new therapeutic targets.
She is on the EMBL Alumni board and the committee of the European Network for Breast Development and Cancer and has worked with breast cancer charities, including Breakthrough and Acambi.
She has directed 6 PhD theses.

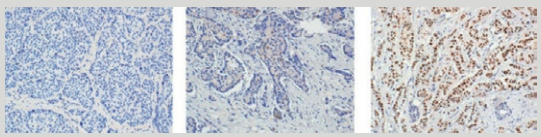


BREAST CANCER STEM CELLS LAB

Breast cancer is a very heterogeneous disease. The identification and characterisation of cells with stem-like properties (cancer stem/progenitor cells, CSCs) in breast cancer has opened new possibilities for anti-cancer therapies. Furthermore, CSCs have been implicated in tumour initiation and resistance to current treatments, including to hormone therapy. In addition, characterisation of the regulation of normal epithelial cell differentiation is fundamental to understanding breast cancer heterogeneity.

The main objective of the laboratory is to gain further insight into the roles of steroid hormone receptors in normal breast tissue and during breast cancer development. Thus, the influences of hormones, other signalling factors and the microenvironment in breast stem cells and in their transformation into cancer initiating cells are being explored, particularly focusing on their effects during development of resistance to hormone therapy. Recent work from the lab has revealed the role of CSCs in resistance to tamoxifen and has highlighted the molecular heterogeneity observed in response to the cell environment. Presently, studies are in progress to improve further our knowledge of the molecular mechanisms regulating stem and cancer stem cells with the final aims of (i) identifying biomarkers of resistance to therapy and (ii) progressing our understanding of breast cancer biology.





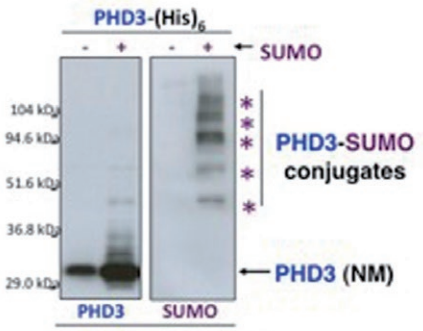
Edurne Berra

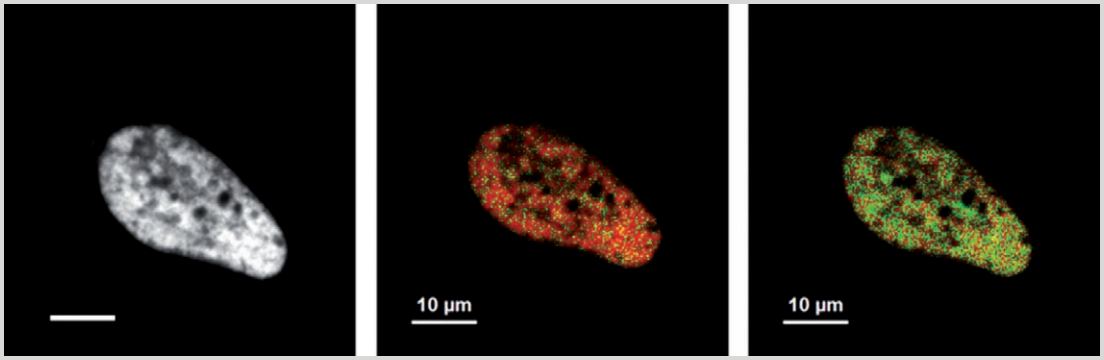
Principal Investigator

Edurne Berra got her Degree in Pharmacy at the University of Navarra (Pamplona, Spain) and a Licence Spéciale at the ULB (Brussels, Belgium). She started her research career, supervised by Dr J. Moscat at the CBM "Severo Ochoa" (Madrid, Spain), studying the signalling pathways triggered by the atypical PKC isotypes (PKCζ and λ). After a first postdoctoral at the Glaxo-Wellcome-CSIC laboratory of Molecular and Cell Biology (Madrid, Spain), Edurne moved to Dr J. Pouysségur's lab (Nice, France) who was starting a new research line on angiogenesis and hypoxia. She was appointed *Chargé de Recherche* (CNRS-CR1) at the same lab and she got her HDR *(Habilitation à la Direction de Recherche)*.
In November 2007, Edurne joined CIC bioGUNE to lead her independent group (HypoxiPATH), which is devoted to establish new players of the hypoxia signalling pathway, and to further translate this research in hypoxia related pathologies such as cancer.
Edurne has authored more than 50 scientific publications in highly prestigious journals (Cell, EMBO Journal, PNAS...) that received more than 7000 citations.
Edurne has been awarded the *Fundación Renal "Iñigo Alvarez de Toledo"* Prize (2007), the "Dr Joseph Amalrich" Prize for Excellence in Cancer Research (2002) and the HFSP (1999) and EMBO (1998) Fellowships. She is Associate Editor of FEBS Open BIO. Edurne is member of the Spanish Society for Biochemistry and Molecular Biology (SEBBM), the Spanish Society for Cancer Research (ASEICA) and the European Association for Cancer Research (EACR), and she is on the committee of the Spanish and the European Hypoxia Network.

PHYSIOPATHOLOGY OF THE HYPOXIA-SIGNALLING PATHWAY LAB

Oxygen homeostasis is vital for most organisms and hypoxia, even transient, can provoke irreversible damage. To deal with hypoxia the so-called hypoxia-signalling pathway has evolved. This pathway is essential during embryonic development and in adulthood but it is also associated with a wide range of pathological states, including, but not limited, to ischemic and neurodegenerative diseases, inflammatory and metabolic disorders, and cancer. HypoxiPATH is aimed at deciphering the molecular basis of the hypoxia cascade and its crosstalk with other signalling pathways. The group is investigating the role of post-translational modifications (PTMs) by using state-of-the-art in cellulo and in vivo approaches. We have reported the physiological relevance of PHD3-SUMO conjugates as HIF transcriptional repressors. We try to understand the role of DUBs acting as new regulators of the hypoxia cascade that we have identified through a RNAi based genetic screen. In addition, HypoxiPATH is interested in understanding the relationship between these signalling networks and pathologies in which hypoxia is involved. The team's work has shown the efficient revascularisation triggered by the silencing of PHDs, opening new possibilities for therapy in ischemia. We have also provided new insights into the design of smart systems for cancer therapeutics.
We believe that a detailed understanding of the signalling pathway triggered by hypoxia is a major step towards establishing its implications in health and disease and could open future therapeutic applications.





Malu Martínez Chantar

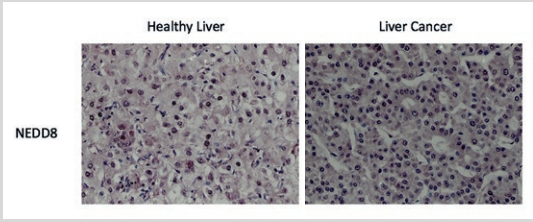
Principal Investigator

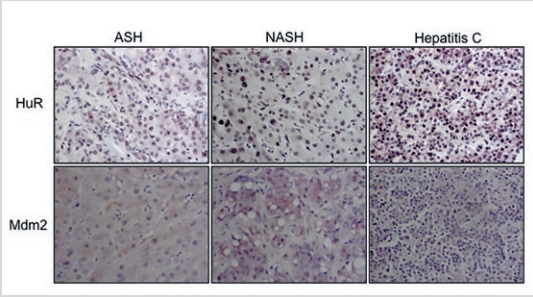
Malu Martínez Chantar is an independent Group Leader at CIC bioGUNE, has published more than 80 publications in prestigious journals, and has established a high number of collaborations with important research groups in the field of liver health and injury all over the world. Moreover, she has been co-PI of four NIH with Dr. Lu (USC, Keck School of Medicine USC, Los Angeles, USA) in the field of liver disease. She was one of the partners in an ambitious European project so called HEPADIP Consortium, which was created in response to the topic of the 3rd call for proposals in the EU FP6 Programme. Actually, she is the coordinator of the Traslational Area of the National Institute for the study of Liver and Gastrointestinal Diseases (CIBEREHD) and the group is part of the Cholestasis and Metabolic Disorders Program. In this respect, she is member of the Scientific Advisory Board of the C3M Inserm Nice and the biopharmaceutical company Mitotherapeutix, Connecticut, USA.

LIVER DISEASE LAB

Non-alcoholic fatty liver disease (NAFLD) is a clinicalpathological term that includes a spectrum of alterations ranging from the simple accumulation of triglycerides in the hepatocytes (steatosis) to steatosis with hepatic inflammation (steatohepatitis or NASH). NASH, in turn, also progresses to cirrhosis and HCC. The mechanisms that lead to the expression of NASH are not clear, but it is a condition associated with obesity, insulin resistance, and diabetes. Since the incidence of these diseases is increasing, the prevalence of NASH is also expected to increase in coming years (today it varies between 13 to 15 % of the population). NASH is now considered to be an emerging disease in USA and occidental countries. Nowadays, lacking accurate, sensitive diagnostic test, distinguishing steatosis from steatohepatitis requires the use of invasive techniques like liver biopsy.
To summarize, the lack of information about the factors implicated in the NASH pathogenesis, as well as in the prognostics characteristics and the treatment of this pathology, highlights the need of new approach in order to understand the mechanisms involved in the development of NASH and the progression to cirrhosis and liver cancer. Over the last few years, the lab has elucidated new molecular mechanisms implicated in the proliferation, regeneration and apoptosis and identified targets that contributing to the abnormal hepatic lipid metabolism and proliferation ended in the development of cirrhosis and liver cancer. The most important projects ongoing in the laboratory are focused on the role of posttranslational modifications throughout different stages of liver disease and ranges from effects on whole organ, such as NEDD8 inhibition on development of fibrosis, to more molecular approaches such as autophagy in hepatic steatosis and the role of LKB1 in hepatocellular carcinoma.

In this respect, metabolism has been one of the most important goals as well as the mitochondria function in liver disease. Finally, the lab mantains a closed collaboration with the company *OWL Metabolomics* in the development of OWLiver® Care and OWLiver®, two non-invasive assays for fatty liver screening and for NASH diagnosis and *Millennium Pharmaceuticals* and *Mitotherapeutix* for the discovery of new drugs for the treatment of cirrhosis-NAFLD dependent and Liver Cancer.



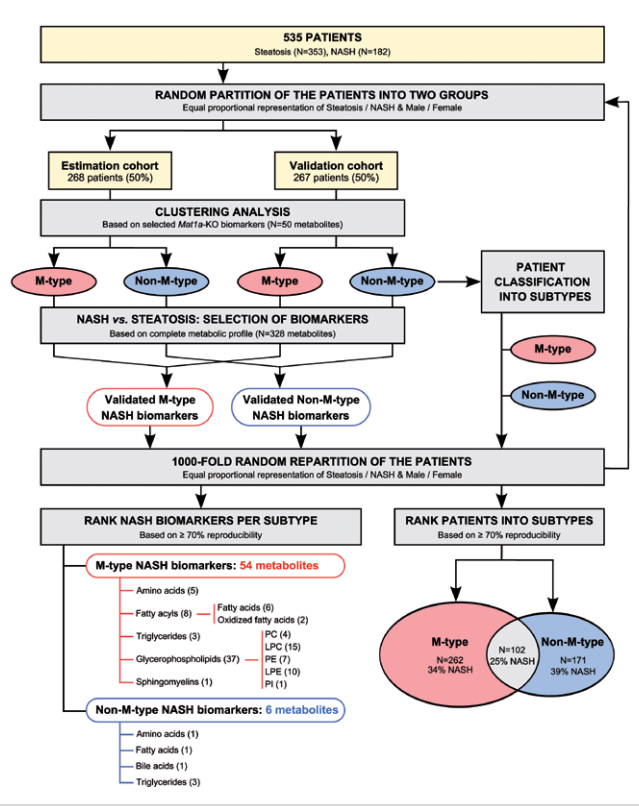


José M Mato

General Director
CIC bioGUNE and CIC biomaGUNE
Principal Investigator

José M Mato is founder and General Director of the Centers bioGUNE (Bilbao) and biomaGUNE (San Sebastián), and Research Professor of the Spanish National Research Council (CSIC), Spain.
A graduate in Biochemistry at the Complutense University of Madrid, Professor Mato received a PhD degree from Leiden University and was awarded the CJ Kok prize for his thesis. He was a postdoctoral fellow at the Biozentrum of the University of Basel and the National Institutes of Health, and a faculty member at the Jiménez Díaz Foundation in Madrid before been named Research Professor at the CSIC. He has been Professor of the Faculty of Medicine of the University of Navarra and Visiting Professor at the University of Pennsylvania and Thomas Jefferson University. From 1992 to 1996 Professor Mato was President of the CSIC and in 2004 was awarded the Spanish National Research Prize in Medicine.

LIVER METABOLISM LAB



Professor Mato has been working in the field of methionine adenosyltransferases (MAT) genes and proteins for over 30 years. MAT catalyzes the synthesis of S-adenosylmethionine (SAMe, the principal biological methyl donor) from methionine, an essential amino acid, and ATP. This is the only reaction that metabolizes methionine in mammals. Two genes encode for MAT: *MAT1A*, which is expressed in normal differentiated liver, and *MAT2A*, which is expressed in all extrahepatic tissues as well as in fetal liver. A third gene, *MAT2B*, encodes a MAT2β subunit that regulates *MAT2A*-encoded enzyme. In the middle 80s his laboratory discovered that hepatic MAT activity was markedly reduced in patients with chronic liver disease independently of its etiology. Subsequently, the laboratory of Mato cloned *MAT1A* gene and promoter and discovered the differential expression of *MAT1A* and *MAT2A* genes in developing rat liver. In collaboration with the laboratory of Shelly Lu, at the Cedars-Sinai Medical Center in Los Angeles (US), described their transcriptional and post-transcriptional regulation and how changes in MAT expression affect liver health, growth, death, and malignant degeneration. Together, they developed the *Mat1a* knockout (KO) mouse model, which exhibits hypermethioninemia, chronic SAMe deficiency, increased oxidative stress, spontaneously develop steatohepatitis, fibrosis and hepatocellular carcinoma (HCC). Patients with liver injury often show reduced expression of *MAT1A*, indicating that the *Mat1a* KO mouse model is relevant to study human NASH. The laboratory of Mato also developed the *Gnmt* KO mouse model, where hepatic SAMe accumulates to supraphysiological level and the mice also develop steatohepatitis and HCC but by different mechanisms than *Mat1a* KO mice. The *Gnmt* KO model is relevant to human disease as children with *GNMT* mutations were identified to have liver injury. These models have been instrumental in teaching us about the various functions of SAMe and pathways that it regulates.

This work stimulated pharmaceutical companies to study the effect of SAMe therapy on liver disease and in 1999 the laboratory of Mato demonstrated that SAMe treatment increased survival in human alcoholic liver cirrhosis. Recent studies from this laboratory have revealed that SAMe, through regulation of mitochondrial function, red-ox processes, and CYP450, causes major changes in cellular metabolism that are vital for maintaining lipid homeostasis. Ongoing studies, merging epigenetics, transcriptomics, proteomics and metabolomics, are defining how changes in SAMe concentration alter the flux of metabolites such as fatty acids and bile acids and how these changes lead to fat accumulation and liver injury. Another major focus of this laboratory is to develop non-invasive tests to diagnose liver diseases. Using mass spectrometry metabolomics, in collaboration with the biotech company OWL (co-founded by Dr. Mato) the laboratory of Mato developed the first non-invasive serum test to diagnose nonalcoholic steatohepatitis. Dr. Mato is considered one of the world's leading authorities on SAMe and MAT.

The Plan Nacional of R&D of the Spanish Ministry of Economy and Competitiveness (MINECO) has uninterruptedly funded his laboratory since the early 1980s, been his laboratory also funded uninterruptedly by the NIH during the last 15-years.

TECHNOLOGY PLATFORMS AND RESEARCH SUPPORT FACILITIES

Our scientists have engaged in their research collaborations with colleages, engineers and technology experts at the universities, other research and technology centers and biotech companies, as well as with medical doctors in hospitals.

01.
Animal Facility

02.
Electron Microscopy

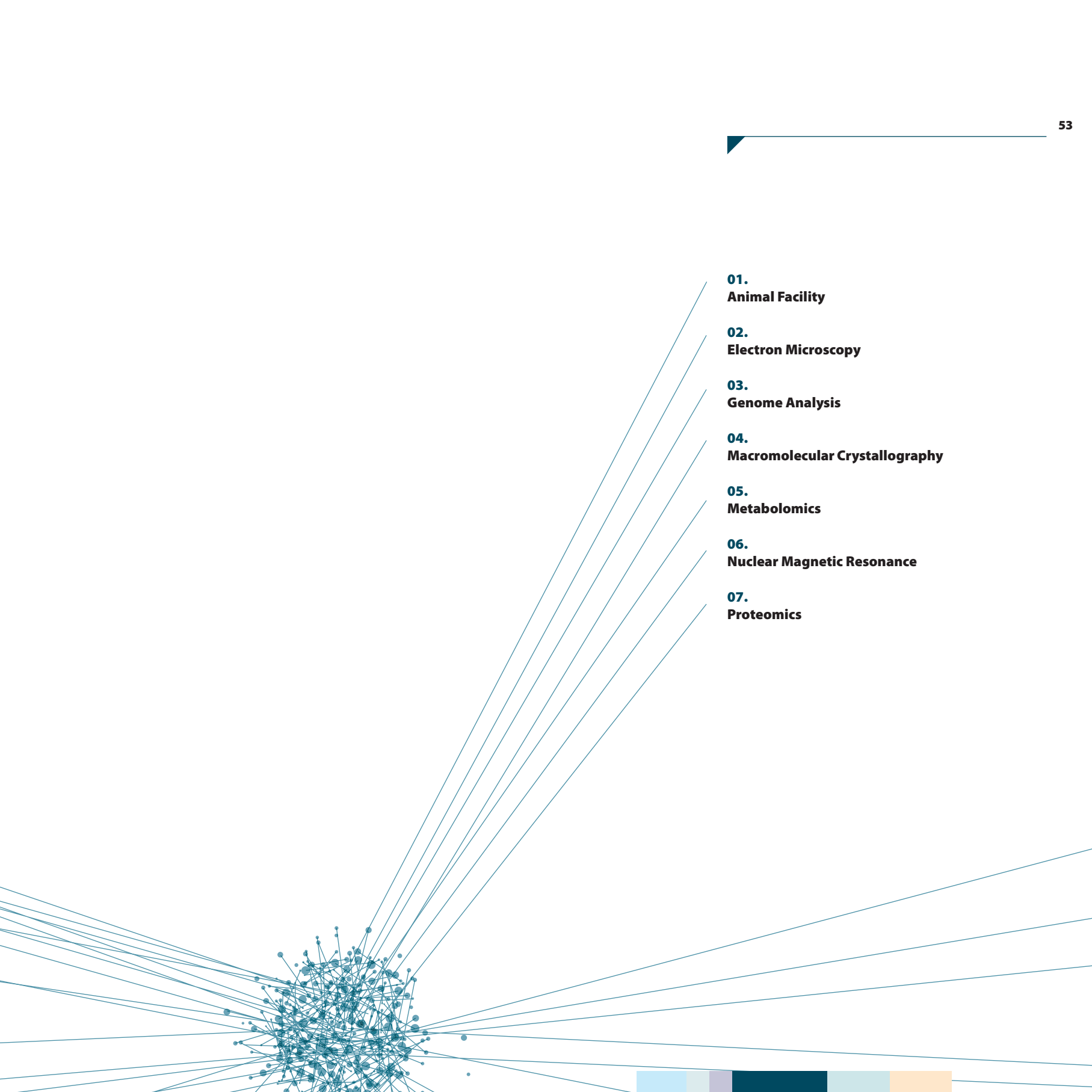
03.
Genome Analysis

04.
Macromolecular Crystallography

05.
Metabolomics

06.
Nuclear Magnetic Resonance

07.
Proteomics



01.

Animal Facility

Prevention and cure through models of human disease

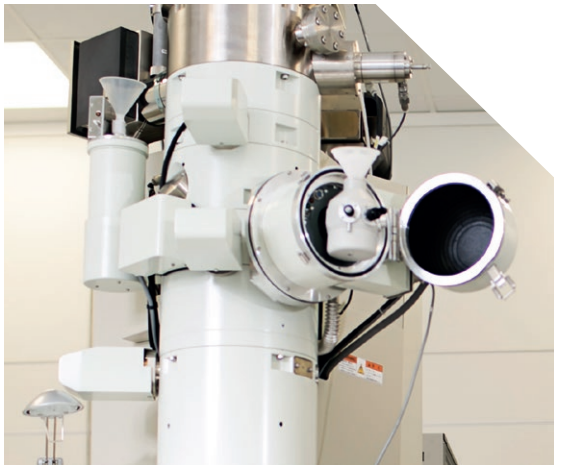
The CIC bioGUNE´s Animal Unit (AU) is an AAALAC accredited facility which includes a Specific Pathogen Free (SPF) area to house rodents from commercial sources and to produce and keep strains of genetically engineered mice (GEM). The AU works for the continuing improvement in their services and also engages in the development of new services through the collaboration with researchers from different areas of interest. The AU provides users with assessment and the necessary equipment to carry out research on laboratory animals, procures care and ensures the welfare of the animals, ensuring strict abiding to all legal and ethical standards concerning the use of animas for research. The Animal Care and Use Program (ACUP) of the CIC bioGUNE´s AU was initially accredited by AAALAC in June, 2008. Accreditation was renewed in 2011 and most recently, in 2014.

02.

Electron Microscopy

The Electron Microscopy Platform is an open access facility at the CIC bioGUNE. The mission of this platform is to offer high tech instrumentation, competitive service, specialized training and support in projects requiring transmission electron microscopy (TEM) to determinate the sub-nanometric structure of different types of samples.

This platform is mainly focused on structural biology for life science research. Nevertheless we also provide TEM analysis for material science users. Our platform offers research institutes and companies access to two cryo-transmission electron microscopes and sample preparation instrumentation. The sample preparation and data collection service is provided by the cryo-electron microscopy (cryo-EM) expert staff at the EM Platform.



03.

Genome Analysis

Defining roles of genomic variants related to cell disorders

The main objective of this platform is the set-up of high-throughput technologies in order to provide support for the characterization of genomes from different points of view. In particular, this laboratory handles molecular biology techniques and bioinformatics analyses applied to the investigation of DNA variants at the whole genome level, the expression of coding and non-coding RNAs and the characterization of DNA methylation profiles, mainly for projects within the Biomedical field, but applicable to any other biological question.

04.

Macromolecular Crystallography

X- Ray Crystallography is the most powerful technique existing today to elucidate the structure of a biological macromolecule at atomic detail. It can be applied to study the crystal structure of proteins, nucleic acids, macromolecular complexes or viruses.
The Macromolecular Crystallography is an efficient tool to infer molecular mechanisms as well as to understand the relationship existing between the structure of a macromolecule and its biological function.
The platform offers crystallization as a service and collaborative research to internal and external researchers. We have the infrastructure and the know how to tackle ambitious projects.

Currently the Macromolecular Crystallography Platform offers:

> Advice in crystallization procedures and quality sample preparation.

> High-throughput screening with more than 1800 commercial conditions or customized crystallization solutions for specific user requirements.

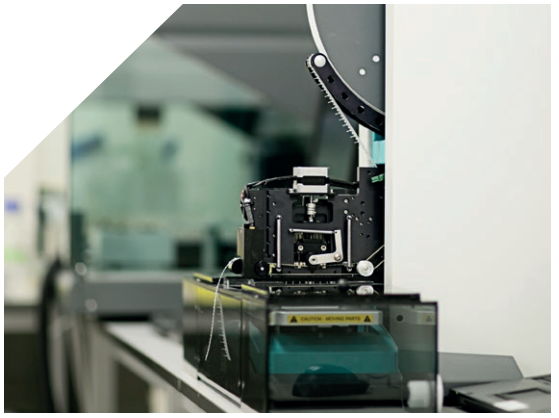
> Crystallization plates stored and imaged at 21ºC in a Crystal farm.

> Crystallization plates stored at 4ºC, 18ºC, 25ºC.

> Personal training for data collection using the X-Ray home system.

> Support and training in quick cryosoaking technique for in-house derivatization.

> Individual and group training from data collection to structure determination.



05.

Metabolomics

Metabolomics constitutes one of the most powerful technologies to understand how a living organism interacts with its environment. Metabolomics can be defined as the quantitative and qualitative analysis of all metabolites (small molecules with a molecular weight of less than 1,500 Da) in a given organism. This results in the construction of a metabolome or metabolic fingerprint, analogous to the genome or the proteome

Active since early 2011, the CIC bioGUNE metabolomics platform has already established a name in the field of methionine metabolism. The platform´s team uses their expertise in targeted, (semi-) quantitative analysis the platform assisted in the publication of a variety of research papers concerning the methionine pathway [1-5]. Moreover, this capacity has drawn the attention of the pharmaceutical industry and established fruitful collaborations.

Small molecules define living processes

The analytical methods and extraction protocols allow for the simultaneous quantification of methionine, S-adenosylmethionine (SAMe), decarboxylated SAMe, methylthioadenosine (MTA), S-adenosylhomocycteine (SAH), homocycteine and various polyamines. Recently we have expanded the scope of this assay by including oxidative stress indicators, namely the oxidized and reduced forms of glutathione. The group has optimized extraction methods for most biological matrices including plasma, serum, tissue, cultured hepatocytes and other cell types. In addition to the metabolites from the methionine cycle the group has set up assays for the quantitation of ecdysones and retinoids that are important in development and differentiation processes.

Besides the targeted assays the group has been investing in the setup and execution of untargeted, LC-MS-based metabolomics experiments [6]. In untargeted metabolomics the metabolic response of any biological system towards e.g. a pathophysiological stimulus or a genetic modification can be monitored by comparing it to proper controls [7]. Since it is an untargeted approach, the analysis should cover a vast chemical space in order to detect and identify as many differentiating metabolites (biomarkers) as possible.

This is accomplished by applying multiple extraction techniques and using different column chemistries. An important aspect in the search for potential biomarkers is their statistical validation. To this end we have developed robust statistical methods and quality control measures. These untargeted metabolomics studies have proven to be of high value in the search for non-invasive disease biomarkers and phenotyping studies.

06.

Nuclear Magnetic Resonance

The NMR paltform at CIC bioGUNE features three modern BRUKER AVANCE III spectrometers that are highly complementary and ideally suited for a double-track strategy:

The 800 MHz high-field spectrometer with TCI cryoprobe is set up for protein NMR experiments (using 1H, 2H, 13C and 15N nuclei) at highest sensitivity.

The 600 MHz medium-field spectrometer with flexible configuration and ample accessory (including 7 probeheads, dedicated 19F and HR-MAS equipment, automatic sample changer) enables the largest range of NMR experiments beyond standard biomolecular applications

A second 600 MHz IVDr spectrometer equipped with a SampleJet is devoted to metabolomic studies of biofluids (i. e. urine and serum) and/or tissue samples. It has an operational capacity of up to 30000 samples year.

07.

Proteomics

Experts in Mass Spectrometry based Proteomics

The aim in the Proteomics Platform at CIC bioGUNE is to achieve high quality standards on mass spectrometry based proteomic analysis. Proteomics is much more than just protein identification, and the platform fosters the development and settling of new proteomic technologies and methodologies. Lately we have been focusing our efforts on improving and expanding the portfolio of analytical techniques offered so we can add our little contribution to the ambitious endeavor of understanding the complexity of the proteome.

Among others the platform offers analyses such as Label Free quantification of complex proteomes and post-translational modification analysis on high-end nLC MS/MS systems, tissue MALDI-TOF Imaging and natural peptidome analysis by so called middle-down analysis. We count with nano scale Acquity chromatographers coupled on line to Orbitrap XL-ETD & Synapt G2S, and Autoflex III Smartbeam MALDI-TOF mass spectrometers; micro scale chromatography systems for orthogonal peptide separation etc.

In that way the platform offers their services to any company or technological agent; and the knowledge for collaborative research projects to any interested researcher.

SCIENTIFIC ADVISORY BOARD

The Scientific Advisory Board (SAB) is composed by internationally distinguished scientists with different perspectives and expertise. They cover from basic to applied research in different topics, from chemistry to biomedicine, including technology transfer activities. It is currently formed by the following scientists:

Adriano Aguzzi
Institute of Neuropathology, University Hospital of Zurich, Switzerland

Tom Blundell
Department of Biochemistry, University of Cambridge, UK

Avelino Corma
Instituto de Tecnología Química, CSIC-UPV, Valencia, Spain

Christian Griesinger
Max Planck Institute for Biophysical Chemistry, Göttingen, Germany

Richard Henderson
MRC Laboratory of Molecular Biology, Cambridge, UK

Nancy E. Hynes
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Shelly Lu
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