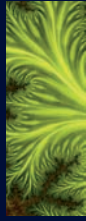


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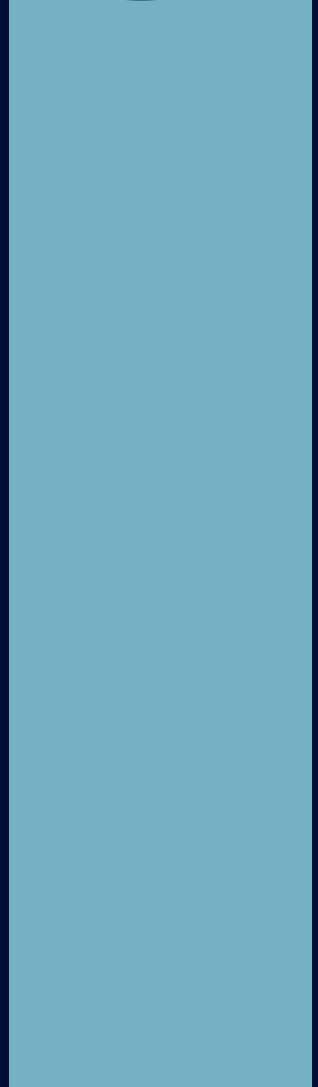
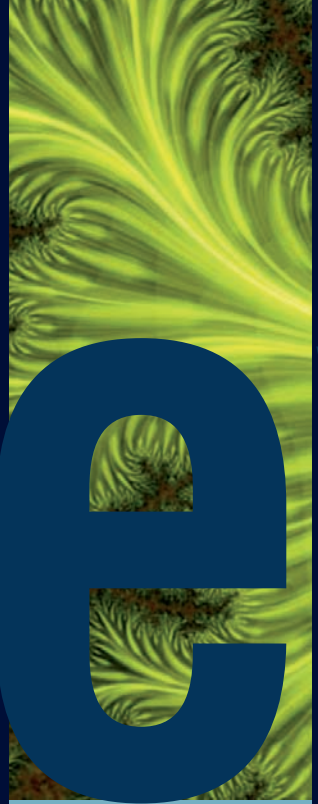
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annual report  
**2010**

# foreword



**Manuela Juárez**  
Director IMDEA Food Institute  
Madrid, May 2011



The Madrid Institute for Advanced Studies in Food (IMDEA Food Institute) is a research center focused on food, nutrition and health. IMDEA Food Institute was created by the Madrid Regional Government in coordination with universities, and other local research institutes and business. It was constituted as a non-profit organization in November 2006 within the framework of the IV Regional Plan for Scientific Research and Technological Innovation (IV PRICIT). Its scientific and legal mandates are to bring the benefits of nutrition-related research to the society.

The Academic and Scientific trajectory of the Madrid Region in relation to classical food and nutrition research has been excellent. However, some of the cutting edge areas remain underrepresented in the Madrid's regional Science & Technology System's portfolio. Moreover, there is a noticeable lack of transfer of R&D results to the society. The main objective of IMDEA Food Institute is initiate and coordinate research of excellence in this area of knowledge, using a multidisciplinary and collaborative approach with academia and industry and focusing on approaches that can lead to the benefit of the society.

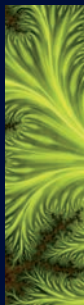
This report describes the activities of IMDEA Food Institute during 2010, in which a critical mass of senior researchers was achieved, specific and coordinated lines of research were established and the Institute began to create scientific alliances and to seek public funds.

IMDEA Food Institute research laboratories are now established in the CLAID Building of the Scientific Park of Madrid at the Campus of Cantoblanco. That is where it currently carries out its research, awarding priority to projects bearing on food & health in view of the scientific, economic and social importance of that relationship.

The Institute, physically located within the Cantoblanco Campus of the Universidad Autónoma de Madrid, houses sixteen researchers: six senior researchers, two senior assistant researchers, four postdoctoral researchers, two predoctoral researchers, one senior technician and one nutricionist, with additional input from an associate senior researcher of recognized international prestige in the field of nutritional genomics. Our continuing recruitment aims to bring additional multidisciplinary expertise from researchers of recognized international prestige in order to catalyze the scientific and societal goals of IMDEA Food Institute.

In 2010, IMDEA Food Institute secured almost 400.000 euros for R&D activities and has also obtained a loan for the construction of the new headquarters of 7 million euros, and in the "Marie Curie" Amarout Europe Programme with approximately 600.000 euros in funding.

# Words



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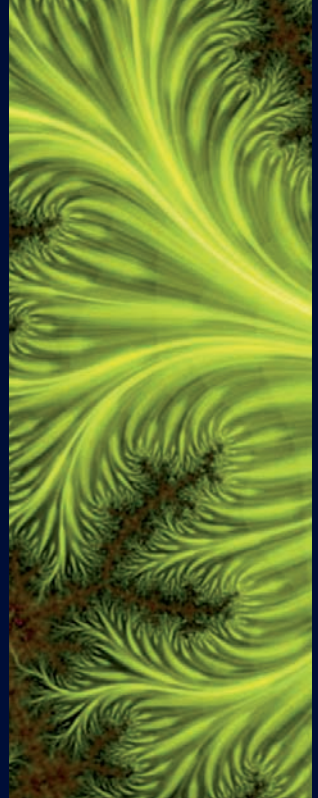
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general  
presentation

1





The IMDEA Food Institute is a non-profit independent research institution created in November 2006 by the Madrid Regional Government in Spain, with the purpose of promoting and building innovative translational research and technology in the field of Food Science.

The overall goals of IMDEA Food Institute can be summarized as follows:

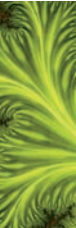
1. To plan and execute research of international excellence addressing and driven by the real needs of society, with special emphasis on improving the know-how and the competitiveness of food, nutrition and health related businesses based in the region of Madrid.
2. To create a physical and intellectual environment that will facilitate the recruitment of researchers of international prestige, to carry out cutting edge food and nutrition-related research for the medium and long-term benefit of the society.
3. To contribute to the training of researchers and technical personnel emphasizing interaction within multidisciplinary teams.
4. To promote public education related to nutrition and health.

Originally conceived with the broad goal of conducting applied research in various food-related areas—food&health, food quality and food safety—The IMDEA Food Institute's Scientific Council decided to focus its initial activities on Nutritional Genomics, a thriving area of research that was identified to be underrepresented in the Madrid Scientific community. Following the guidelines laid down by the Scientific Council, the Institute has been recruiting researchers specializing or able to provide multidisciplinary support to this research, and several projects are now underway.

Food&health is an area of crucial interest to the international scientific community. Moreover, it represents a major focus for today's food industry and one of the major concerns of the society at large. However, most of the current research in food and health is conducted using classical approaches, paying little attention to new “omics” based approaches, including genomics. Therefore, IMDEA Food Institute is developing the expertise, technology and experimental approaches (i.e., human cohorts) needed to bring nutrition research into the “Omics” Era.

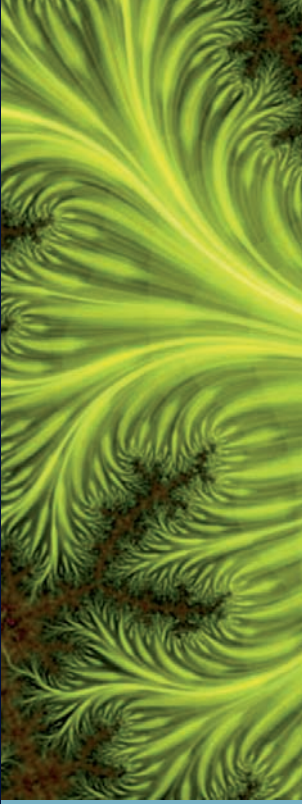
The following lines of research were pursued in 2010:

- Genomic bases of the health effects of food (Nutritional Genomics)
- Design and development of Functional Foods
- Program. Prevention of chronic and age-related diseases.



One of the priorities of the Institute has been the launching of the Cantoblanco Platform of Nutritional Genomics and Food “GENYAL”. This effort will vastly enhance the ability to conduct genetically-based dietary intervention studies aimed to both, scientific discovery and commercial applications. The availability of a large biobank will facilitate and speed up food and health-related biomedical research, including biomarker discovery and validation, and will contribute to gain better understanding the effects of food and food components on human health (nutrigenomics) and variability in response (nutrigenetics).





# 2

## Governing bodies and functional structure

- 2.1. Board of Trustees [11]
- 2.2. Scientific Council [12]
- 2.3. Delegated Commission [13]
- 2.4. Executive Board [13]
- 2.5. Research Units [14]

The organizational and functional structure of the IMDEA Food Institute is summarized in the diagram below with indication of its main bodies and units.

The main governing body of the Institute is its Board of Trustees constituted by representatives of the Madrid Regional Government (4), Madrid public universities (3), the Spanish National Research Council (CSIC), internationally renowned food and nutrition scientists (5) industrial partners (4) and independent experts (2).

The Institute carries out its scientific research activity directed by its own management team and advised by a scientific committee composed of members of recognized international prestige, the Scientific Council.

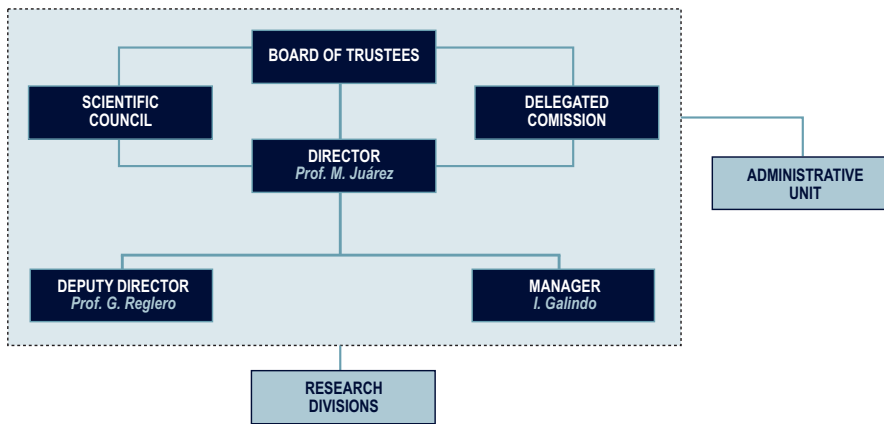


Figure 1. Management structure of IMDEA Food Institute



## 2.1. Board of Trustees

The Board of Trustees of the IMDEA Food Institute is its highest governing, representative and administrative body. The Board is responsible for fulfillment of the Foundation's objectives, for administering the property and rights that constitute its assets, and maintaining their yield and utility. Since its creation, the meetings of the Board of Trustees are held twice a year.

### PRESIDENT OF THE FOUNDATION

---

**Prof. José M<sup>o</sup> Ordovas**

*Director of Nutrition and Genomics Laboratory*

*JM-USDA-HNRCA Tufts University  
Boston, USA*

### VICE-CHAIRMAN OF THE FOUNDATION

---

**Excma. Sra. D<sup>a</sup>. Lucía Figar de Lacalle**

*Regional Minister of Education,  
Comunidad de Madrid, Spain*

### REGIONAL ADMINISTRATION REPRESENTATIVES

---

**Excma. Sra. D<sup>a</sup>. Lucía Figar de Lacalle**

*Regional Minister of Education,  
Comunidad de Madrid, Spain*

**Ilmo. Sr. D. Jon Juaristi Linacero**

*General Director of Universities and Research, Comunidad de Madrid, Spain*

**Ilmo. Sr. D. Manuel Molina Muñoz**

*General Director of Planning and Inspection, Comunidad de Madrid, Spain*

**Ilmo. Sr. D. Federico Ramos de Armas**

*General Director of the Environment, Comunidad de Madrid, Spain*

### INSTITUTIONAL TRUSTEES

---

**Prof. Federico Mayor Menéndez**

*Professor, Universidad Autónoma de Madrid, Spain*

**Prof. Mercedes Careche Recacoechea**

*Coordinator of the Food Science and Technology Area, IF-CSIC, Spain*

**Prof. Lucas Domínguez Rodríguez**

*Professor, Universidad Complutense de Madrid, Spain*

**Prof. Jesús Vázquez Minguela**

*Professor, Universidad Politécnica de Madrid, Spain*

### SCIENTIFIC TRUSTEES

---

**Prof. Michael Heinrich**

*Head of Centre for Pharmacognosy and Phytotherapy, The School of Pharmacy, University of London, UK*

**Prof. Jean Louis Sebedio**

*UMR- INRA. Université d'Auvergne, Institute de Nutrition Humaine, Clermont-Ferrand, France*

**Dr. Fabrizio Arigoni**

*Head of Nestlé Research Tokyo, Graduate School of Agricultural and Life Sciences, The University of Tokyo, Japan*

**Dr. Vincent Steinmetz**

*Director of the Agence pour la Recherche et l'Innovation en Champagne-Ardenne (CARINNA), Reims, France*

### EXPERT TRUSTEES

---

**Mr. Daniel de la Sota Rius**

*Director of the Innovation and New Technologies Department, CEIM, Madrid Business Confederation-CEOE, Madrid, Spain*

**Dr. Jorge Jordana Buttica de Pozas**

*General Secretary FIAB-Spanish Federation of Food and Beverages Industry, Madrid, Spain*

### COMPANY TRUSTEES

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**DANONE, S.A.**

**Dr. Agustí Monsterrat**

*Director of Research and Development, Barcelona, Spain*

**EMBUTIDOS FRIAL, S.A.**

**Ms. Paloma Frial**

*President  
Tres Cantos, Madrid, Spain*

**BIOSEARCH LIFE, S.A.**

**Ms. Mónica Olivares**

*Responsible of Research and Development, Madrid, Spain*

**GRUPO LECHE PASCUAL, S.A.**

**Dr. Marco Antonio Delgado**

*Director of Research and Development, Madrid, Spain*

### SECRETARY

---

**Mr. Alejandro Blázquez**



## 2.2. Scientific Council

The Scientific Council is a consolidated body within the Foundation with the task of advising on and analyzing research programs that the Institute may take on, and evaluating candidates for recruiting of researchers of different levels to carry on the research lines.

The IMDEA Food Institute Scientific Council is composed of researchers of recognized international prestige in areas relevant to the Institute.

### Scientific Council

**Prof. José M<sup>a</sup> Ordovas**

*Director of Nutrition and Genomics Laboratory, JM-USDA-HNRCA Tufts University  
Boston, USA*

**Prof. Michael Heinrich**

*Head of Centre for Pharmacognosy and Phytotherapy, The School of Pharmacy,  
University of London, UK*

**Prof. Jean Louis Sebedio**

*UMR- INRA. Université d'Auvergne, Institute de Nutrition Humaine, Clermont-  
Ferrand, France*

**Dr. Fabrizio Arigoni**

*Head of Nestlé Research Tokyo, Graduate School of Agricultural and Life Sciences,  
The University of Tokyo, Japan*

**Dr. Vincent Steinmetz**

*Director of the Agence pour la Recherche et l'Innovation en Champagne-Ardenne  
(CARINNA), Reims, France*

**Prof. Andreu Palou**

*Professor, Universitat de les Illes Balears (UIB), Palma de Mallorca, Spain*

**Prof. M<sup>a</sup> Carmen Dobarganes**

*Research Professor  
Institute of Fat-IG-CSIC, Sevilla, Spain*

**Prof. Vicente Sanchís**

*Professor, Universidad de Lérida, Lérida, Spain*

**Prof. Francisco Tomás-Barberán**

*Research Professor  
Centre for Soil Science and Applied Biology of the Segura (CEBAS-CSIC), Murcia, Spain*

**Dr. Gloria López-Gálvez**

*Scientific Officer, European Food Safety Authority (EFSA), Parma, Italy*



### 2.3. Delegate Commission

All the powers of the Board of Trustees are delegated to the Foundation's Delegate Commission, with the exception of approval of the action plan, budgets, annual accounts amendment of statutes, mergers, liquidation, extinction and any acts requiring the authorization of the Protectorate. Also, they may not elect or dismiss any trustee or appoint officers of the Board, elect or dismiss the Director, or take any decision having to do with the Scientific Council, or grant powers of attorney or general delegations. They may appoint and dismiss the Foundation's Manager and Deputy Director at the proposal of the Director.

#### **President**

*Ilmo. Sr. D. Jon Juaristi Linacero*

#### **Member**

*Ilmo. Sr. D. Federico Ramos de Armas*

#### **Member**

*Mr. Daniel de la Sota*

#### **Secretary**

*Mr. Julián García Pareja*

### 2.4 Executive Board

The executive board is composed of the Director, the Deputy Director and the General Manager. The Executive Board is responsible for managing and dealing with the main business administration and scientific activities of the whole Institute, except those decisions taken by or shared with the Board of Trustees.

#### **Director**

*Prof. Manuela Juárez Iglesias*

She represents the institute in dealings with third parties. Proposes and carries out initiatives to promote and manage research, negotiates agreements and alliances with third parties. The Director of the IMDEA Food Institute also optimizes and allocates economic and human resources and infrastructures.

#### **Deputy Director**

*Prof. Guillermo Reglero Rada*

He assists the Director in her duties and reports directly to her. The Deputy Director is chosen at the proposal of the Director from among persons of recognized prestige in the field of interest to the Institute. If the Director is absent, the Deputy Director acts on her behalf.





### Manager

*Ms. Inmaculada Galindo Fernández*

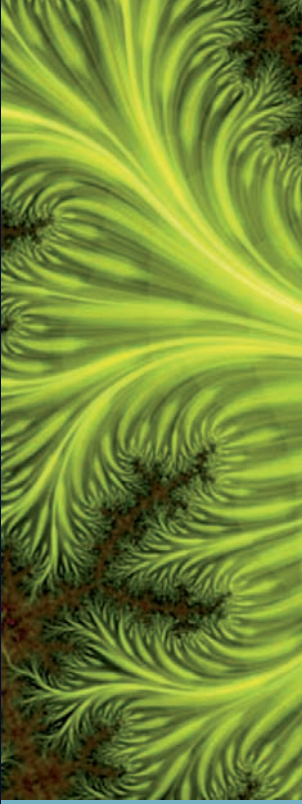
Responsible for the management and coordination of all those units and departments that are not directly involved with scientific and research affairs, including human resources, financial & accounting, legal issues and general services.

## 2.5. Research Units

The researchers and scientists are structured in Research Units defined according to their expertise and specialization.







# 3

## research lines

- 3.1. **RESEARCH LINE 1. Genomic basis of food related health (Nutritional Genomics) [16]**
- 3.2. **RESEARCH LINE 2. Design and development of Functional Foods [19]**
- 3.3. **RESEARCH UNIT. Cantoblanco Platform of Nutritional Genomics and Food "GENYAL" [23]**

IMDEA Food Institute carries out its work in a context of transferable multidisciplinary research of excellence. During, the activity has been focused on the strategic research area of Food & Health being related to “effects on chronic diseases and related metabolic disorders”:

- Research Line 1: Genomic bases of the health effects of food (Nutritional Genomics).
- Research Line 2: Design and development of Functional Foods.
- Horizontal Research Unit: Cantoblanco Platform of Nutritional Genomics and Food “GENYAL”.

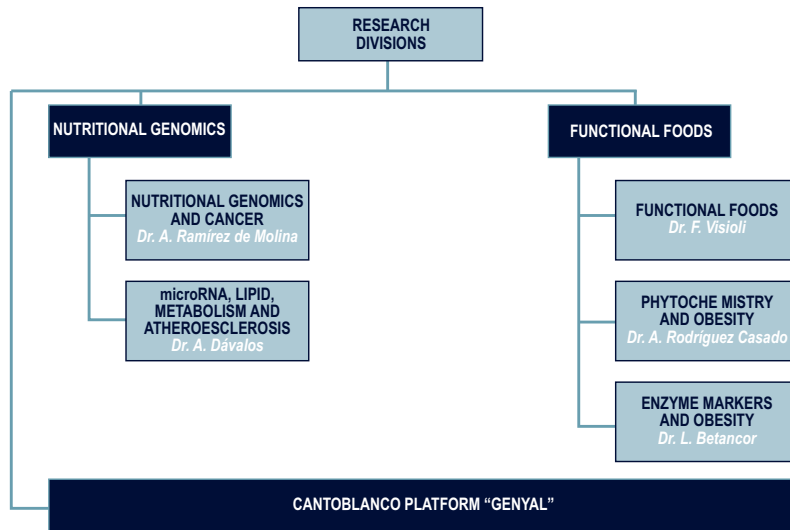


Figure 2. Researchers and research lines of IMDEA Food Institute.

### 3.1. RESEARCH LINE 1

#### Genomic bases of the health effects of food (Nutritional Genomics)

Dietary prevention or mitigation of major chronic diseases such as obesity, diabetes, cardiovascular disorders or cancer may benefit strongly from knowledge of the human genome and the consequent emergence and application of genomics. The new techniques that are being developed and the knowledge emerging from genome studies are revolutionizing the process of identifying genes and genomic regulation processes involved in different prevalent diseases.

The objective of the Nutritional Genomics line of research at IMDEA Food Institute is to study the interface between the nutritional environment and cellular and genetic processes, with the goal of arriving at a genetic understanding of how certain nutrients and bioactive components of foods affect the balance between health and disease by

altering the expression of an individual's genetic profile. From a nutrigenetic point of view we examine whether genetic variants can predict individual response to dietary components that alter cancer, CVD or obesity processes and modify individual susceptibility to their development. On the other hand, a nutrigenomic approach is used to analyze how certain nutrients and components of foods affect the human genome, altering gene expression or structure, with a beneficial effect on human health. Several bioactive food components can modify transcription, expression, and regulation of genetic targets that are known to influence different disease-related signaling pathways that determine the development or the aggressiveness of the disease. Several projects are in progress in this area, mainly focusing on the activity and action mechanism of different natural antioxidants and phytochemicals. Various experimental approaches are being pursued, including genomic studies, in vitro assays with different human cell systems, and in vivo experiments using animal models. Finally, both approaches converge in the conduct of pilot dietary intervention studies based on the knowledge of specific genotypes and phenotypes and nutritional status and requirements, focusing on the prevention, mitigation, cure or improvement of the response to treatments of patients with chronic diseases.

### Scientific team of Research Line 1. Genomic bases of the health effects of food

#### Nutritional Genomics and Cancer Unit

Head of the Unit: Dr. Ana Ramírez de Molina

Members: Dr. Teodoro Vargas Alonso

Postdoctoral Research

Margarita González-Vallinas

Predoctoral researcher

Dr. Susana Molina

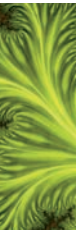
Postdoctoral Researcher Senior

Laboratory Technician



This group is specialized on the analysis of bioactive compounds (ie rosemary extracts, polyphenols, etc..) as potential nutritional supplements, nutraceuticals or functional food ingredients with beneficial effect on prevention, development, progression or treatment of gastric tumors. The effect of these compounds will be studied not only in cell lines, but will be validated in animal models for further studies in humans. We will study the mechanism by which this effect occurs through different gene expression studies both in cells and in different animal models.

In addition, clinical samples of patients with cancer are studied to identify new genetic biomarkers associated with cancer development, progression or response to treatment that can be easily modulated by diet. This genomic study is performed at both gene variants (SNPs) that predict susceptibility to the disease, and at the level of mRNA or



microRNAs with prognostic or predictive value as new biomarkers with a key role in the onset, incidence, progression, severity and / or treatment of patients with cancer. The molecular relationship between obesity and cancer is also being analyzed. The final aim of this research group is to identify new genetic biomarkers and molecular targets that could be modulated by diet or nutritional supplements exerting a beneficial effect in patients with cancer and related diseases.

### microRNAs, Lipid Metabolism and Atherosclerosis Unit

Head of the Unit: Dr. Alberto Dávalos

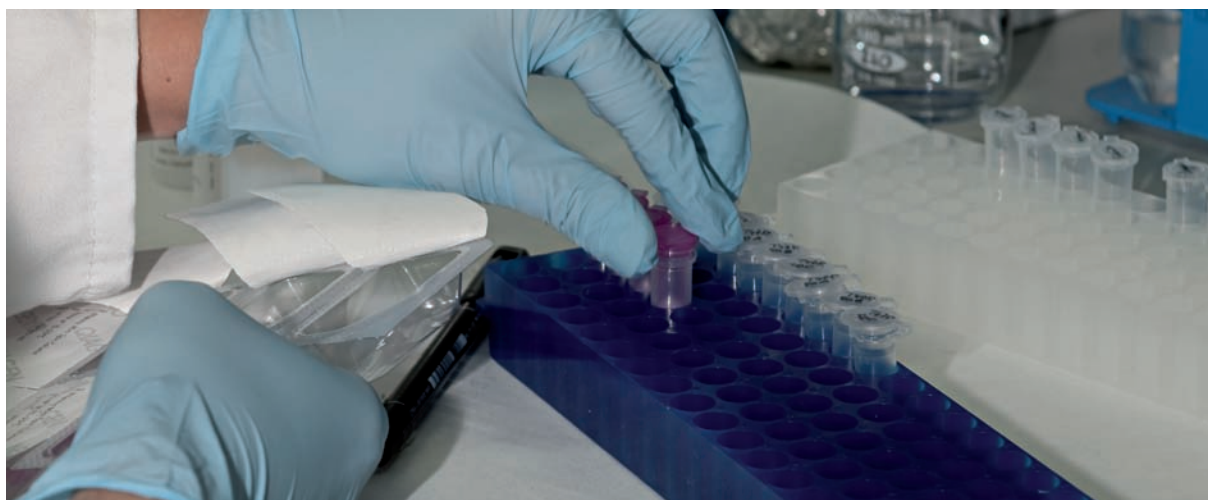
Members: Dr. Lidia Daimiel

Postdoctoral researcher



This group's research program focuses on identifying new cellular mechanisms that governs cholesterol and lipoprotein metabolism, particularly through non-coding RNAs. Diseases from dietary excess related to dyslipidemia is the major cause of mortality worldwide. Thus, our research focus on the identification of new non-coding RNAs, particularly microRNAs that regulate the metabolism of cholesterol and lipoproteins and the effect that minor dietary components (micronutrients) such as polyphenols and other bioactive peptides exert on the expression of these microRNAs. This, in order to understand and modify the expression of microRNAs through the diet and prevent cardiovascular diseases related to metabolism of cholesterol and lipoproteins. We will give special emphasis on the study of microRNAs that regulate HDL metabolism and reverse cholesterol transport in order to alter the progression of atherosclerosis and its regression.

microRNAs have been recognized as critical modulators of cardiovascular system in health and disease. This research group hopes to identify new therapeutic strategies through modulating microRNAs levels by the diet, to treat dyslipidemia and to prevent atherosclerosis and cardiovascular diseases.



## 3.2 RESEARCH LINE 2

### Design and development of Functional Foods

The objective of this line of research is to develop and apply advanced techniques and methodologies to produce novel effective functional foods, taking into account the genetic aspect, i.e. the way that variations in each individual's genome may be related to differential response to the various bioactive food ingredients.

The goal is to work toward the wellbeing of the population by ameliorating their health through the development of effective, safe functional foods as a nutritional tool to help achieve healthy diets. This line of research is also meant to contribute to the economic development of the Madrid region, by developing high added-value products for the food industry and help them become more competitive and profitable.

The idea of improve health and even prevent degenerative disorders through diet is a very attractive one. Over 20 years ago, the governments of developed countries such as Japan began to see functional foods as means to reduce public health costs. The FOSHU regulation is now fully operational there. The European Union began to take official notice of functional foods in the mid-1990s with the FUFLOSE Strategic Action, part of the Fourth FP, which established a definition and laid down the bases for such products. Since then, scientific programs and work on standardization and legislation are ongoing.

Functional foods appeared in the Spanish food market in 2000, lagging a little behind the international trend. The first products to appear were vitamin- and mineral-enriched beverages; later, Spain saw the addition of fiber, calcium and active lactic bacteria strains. More recently, dairy and meat products added with polyunsaturates, phytosterols, peptides, etc. have been introduced to the market.

There is no question about the utility of ameliorating degenerative disorders through diet; however, claims must have solid and proven scientific bases. That is a requirement that the European Union Regulation on Nutrition and Health Claims wants for Foods, which came into force not long ago and is still at the stage of drafting and implementing legislation and definition of assessment methods and tools. This bill regulates the design, production, and marketing of functional foods. This regulation offers the food industry an opportunity to market products with a proven ability to prevent or ameliorate disorders and subject to validation by the European Food Safety Agency (EFSA).

Heart and circulatory disorders cause 1.9 million deaths a year in the European Union, i.e. approximately half of all deaths occurring in the European countries. In addition to causing death and morbidity, cardiovascular disorders are also a heavy burden on the European economy, given the high cost and long duration of patients' care.



The causes of cardio- and cerebrovascular disorders are manifold, but the most important risk factors are the cardiovascular (CVRF). Some of these factors, such as sex and age, are non-modifiable, but others like diet and its effects on blood pressure, cholesterol, or incidence of diabetes, can be modulated.

The development of new foods and new food ingredients with cardiac healthful effects requires a multi-disciplinary approach within an integrated project that takes into account the latest advances in human genome research and new research tools, for instance nutrigenomics, transcriptomics, proteomics, and metabolomics.

This program proposes the study of new bioactive ingredients; optimization of production procedures; determination of their chemical composition and evaluation of their bioavailability; their potential biological activity in vitro and in cell cultures; their toxicological safety; and their health effects in experimental animals and in nutrigenetic dietary intervention assays in humans. The potential lines of research are multiple: as an example, considerable attention continues to be paid to the addition of probiotics to foods and examples of products that could fall within this line of research include fats and oils endowed with better nutritional properties, alteration of lipids through enzymatic reactions, enrichment of dairy products with bioactive lipids using natural processes, prebiotic carbohydrates, proteins that exert physiological effects on the organism, whether directly or via in vivo enzymatic hydrolysis, i.e. during gastrointestinal digestion, or antioxidant and anti-inflammatory molecules with various physiological effects.

This line of research will be pursued by developing the following activities:

1. Development of procedures to produce bioactive ingredients to be incorporated into functional foods, using advanced chemical, enzymatic, extraction, fractionation, and purification technologies with which to produce safe, highly active products.

The following biological activities are being investigated: antihypertensive, antioxidant, reduction of lipid peroxidation in vivo and neutralization of free radicals, modulation of inflammation mediators, immunostimulation, cholesterol reduction and balancing of the plasma lipid profile.

2. Evaluation of the benefit/risk ratio of functional ingredients using in vitro procedures, with cell cultures and assays on experimental animals.
3. Performance of studies aimed at producing evidence-based data on the effects of functional products in humans, also taking into account the variations in the genome of each individual.



## Scientific team of Research Line 2. Design and development of Functional Foods

### Functional Foods: From cells to humans Unit

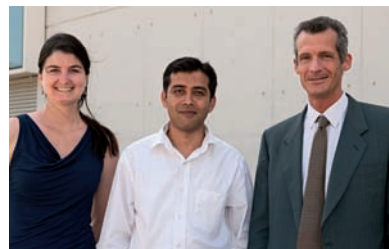
Head of the Unit: Dr. Francesco Visioli

Members: Dr. Nathalie Nicod

Post-doctoral researcher

Dr. Nasiruddin Khan

Post-doctoral researcher



Francesco Visioli's group studies cardiovascular disease and its prevention from two different angles. The first one concerns basic research of the mechanisms that lead to the development of atherosclerosis. In particular, this group studies the contribution of improper folding of proteins (endoplasmic reticulum stress, ER stress) in the development of atherosclerosis and arterial stiffness (increasingly important with the aging of the population).

In addition, the group studies the preventive activity of nutritional components, especially polyphenols, essential fatty acids, and thiols, with the aim of generating evidence to support the development of functional foods.

Of note is the extensive experience of the group in these studies, having developed these research projects at both the cellular and human levels. Finally, this group is fostering collaborations between IMDEA Food Institute and private companies, to jointly develop functional foods and nutraceuticals with evidence-based activities.

### Phytochemistry and obesity Unit

Head of the Unit: Dr. Arantxa Rodríguez Casado

Members: Marta González

Predoctoral researcher



The main focus of this research group is to study various aspects of dietary phytochemicals, with special interest in their effectiveness in reducing obesity and obesity-related diseases. The group works with different bioactive plant extracts containing flavonoids, terpenoids, phytosterols, carotenoids, phenolic acids, and other groups of phytochemicals with relevant effects on adipose tissue. Such effects include induction of apoptosis, inhibition of adipocyte differentiation and lipid accumulation, and induction of lipolysis.

The specific research goal is to find potential agents that inhibit the differentiation of preadipocytes, to stimulate the lipolysis, and to induce apoptosis of existing mature adipocytes, in turn reducing the total volume of adipose tissue.



Relevant changes on markers of obesity - especially triglycerides, cholesterol, phospholipids, and glucose in metabolic disorders associated during obesity process - are monitored in the presence of specific phytochemicals. In addition, the effects of these minor components on the expression of obesity-related genes are investigated in vitro and in vivo studies.

Finally, this group is establishing partnerships with private laboratories to obtain extracts with a defined phytochemical composition, to optimize their effectiveness in the treatment and prevention of obesity and associated diseases and to incorporate them in food ingredients, dietary supplements, or drug components.

### Enzyme markers and obesity Unit

Head of the Unit: Dr. Lorena Betancor

Members: Postdoctoral researcher

[In selection process](#)

This group's research program is focused on the production of polyunsaturated fatty acids (PUFAs) from fish oil by active and stable lipase catalyzed enzymatic hydrolysis. This intensive application of enzymatic processes could significantly improve the already excellent functional properties p.e. soya milk and its derivatives.

They also work on the early detection of enzymatic biomarkers associated with obesity, by developing a «reporter» method to detect minimal changes in enzymatic activity in blood that allow to determine whether a nutrient or set of them may influence the risk of obesity of the population according to their individual characteristics. This enzymatic method consists in the use of magnetic particles functionalized with antibodies (AC) anti aminotransferasa aspartate (AST) and alanine aminotransferase (ALT), two liver enzymes commonly linked to obesity. This highly sensitive, simple and low cost model would detect changes in the transcriptome of individuals by microarray methods and Nutrigenomics could be used for comparative studies with hypersensitive people using the developed model system.





### 3.3. RESEARCH UNIT

#### Cantoblanco Platform of Nutritional Genomics and Food “GENYAL” Platform for Genetics-based Dietary Intervention Studies



In promoting health by food, an understanding of the human genome and variations in its key candidate genes may be of very great help in deciphering the molecular mechanisms that determine the inter-individual response to diet and thus generating a series of biomarkers through which to determine precisely the effects of foods on the human organism. At IMDEA Food Institute we therefore believe that at this time the scientific community must acquire the necessary tools to undertake the requisite R&D with this new approach. The final aim of this project is to improve the quality of life of the population with the proper use of food. In addition, this project might constitute also a technological jump for the improvement of the competitive and economical status of the alimentary industry supported on the area of food for health.

The Cantoblanco Platform of Nutritional Genomics and Food constitutes a major, high-level scientific tool to assist in examining how the genomes of individuals interact with the foods in their diets and these interact in turn with the genome, in order to determine the benefits or risks of given nutrients and food ingredients for individual health. It is intended for use in basic or applied research on gene-diet interactions, in the fields of nutrigenetics or nutrigenomics alike. At this moment there is no tool for food/health research like this Platform which once fully operational will be able to serve Spanish and foreign research groups working in the field of nutritional genomics. The platform can also serve enterprises in the food sector that wish to carry out the dietary intervention studies necessary to develop products or to obtain approval of nutrition or health claims for food products from the European Food Safety Authority, US authorities or other countries like Japan which specifically regulate this issue. The Cantoblanco Platform of Nutritional Genomics and Food is promoted and administered by IMDEA Food Institute and count on the collaboration of the Universidad Autónoma de Madrid.

The Cantoblanco Platform of Nutritional Genomics and Food is a stable platform based on volunteer cohorts from the general population. Each cohort is composed of a large number of individuals with characterized phenotypic and genetic features for the analysis of the association between variants in candidate genes associated with chronic non-transmissible diseases and the possible response to diet. It is constituted by the following elements:

- A DNA Biobank constituted and administered following the Spanish Law in Biomedical Research.
- A Clinical Database constituted and administered following the Data Protection Act.



The platform is supported on the human and technological resources of IMDEA Food Institute in three different aspects:

1. The ability to carry out the phenotypic characterization of the population mainly based on anthropometrical determinations, data regarding life style such as diet and physical activity, clinical history or socioeconomic information.
2. The ability to develop the genotypic stratification of the population mainly based on the determination of genetic variants involved in nutrients metabolism and the most prevalent nutritional-related diseases in our society.
3. Economical and administrative capacity of the Platform.

The Cantoblanco Platform of Nutritional Genomics and Food follows **two steps of action:**

1. **Constitution of specific cohorts of population based on their phenotypic and genotypic characteristics.** This project has the authorization of the Ethics Committee of the Universidad Autónoma de Madrid.

A university campus like the one at Cantoblanco is a particularly suitable setting for population recruitment since every day there are over thirty thousand people aged from 17 to 70 who are particularly willing to comprehend and become involved in activities related to scientific development. All volunteers will undergo phenotypic and genotypic stratification. The genomic DNA of each participant is being isolated by standard procedures from peripheral venous blood; DNA quality and concentration will be checked and stored, and polymorphisms of interest will be analyzed by high-performance genotyping. Individuals are also being carefully characterized in terms of ambient factors (food, tobacco and alcohol consumption, exercise, stress, dietary habits, socio-economic status etc.), and also subjected to phenotyping for the principal anthropometric variables, arterial blood pressure and other clinical parameters. Observational phenotype-genotype association studies will be performed as a last part of this first step.

2. **Interventional studies in specific cohorts of population.** Once cohorts are built with known phenotypic and genotypic characteristics, the platform will be run in such a way as to provide a service to the local, national and international scientific community in the field of food and health, and also to other interested parties in the private sector in need to demonstrate health benefits of functional foods, nutritional supplements or drugs as well as to demonstrate benefits based on personalized approaches.

In addition to the population recruited by GENYAL, The Platform also works with external population of specific intervention studies for the analysis of gene-diet interactions.

According to the Law in Biomedical Research, The Cantoblanco Platform of Nutritional Genomics and Food display the following **organizational structure:**



**General Director:**

Prof. Guillermo Reglero Rada. Full Professor of Food Science and Technology, Universidad Autónoma de Madrid. Deputy Director IMDEA Food Institute.

**Scientific Director:**

Dr. Ana Ramirez de Molina. Senior Researcher IMDEA Food Institute.

**Procedures Director:**

Dr. Francisco Marín. Professor of Food Science and Technology, Universidad Autónoma de Madrid.

**Business Development Director:**

D<sup>a</sup> Inmaculada Galindo. Manager IMDEA Food Institute.

**Technical Responsible (Genotypic Characterization):**

Dr. Susana Molina. Senior Laboratory Technician IMDEA Food Institute.

**File Responsible ( Phenotypic Characterization):**

D<sup>a</sup> Isabel Espinosa. Nutritionist IMDEA Food Institute.

According to the law, two external committees evaluate all projects regarding The Cantoblanco Platform of Nutritional Genomics and Food:

**GENYAL Scientific Committee:**

This committee will go through all planned actions of the Platform and will give scientific and technological advice.

**President:**

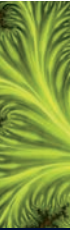
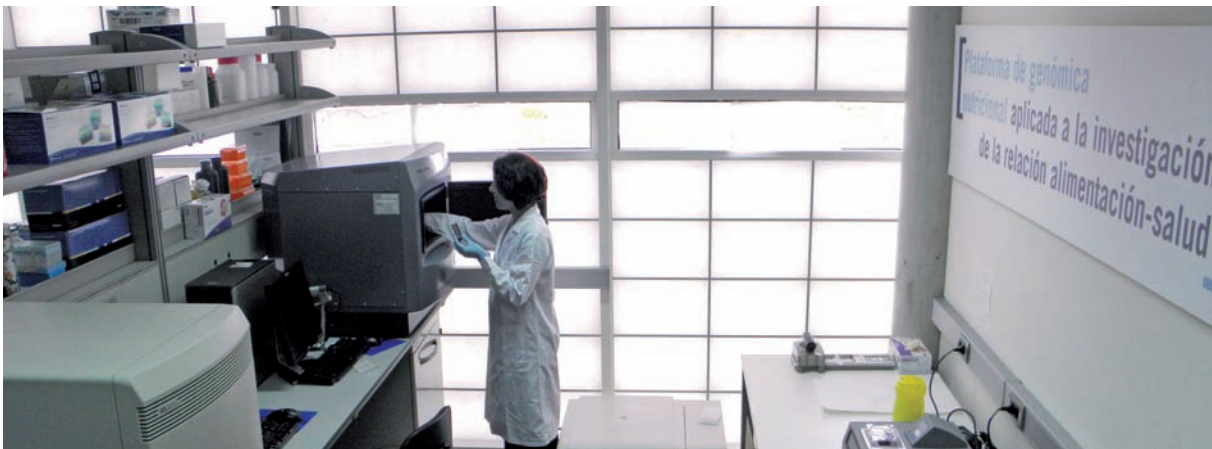
Prof. D. José María Ordovás Muñoz. Full Professor Tufts University (Boston, MS).

**Vocals:**

D. Daniel Ramón Vidal. Chief Executive Biopolis S.L. Full Professor Universidad de Valencia.

D. Francisco Tomás Barberán. Professor of Research, CSIC. CEBAS Director.

D. Ricardo Ramos Ruiz. Technical Director of Genomics Unit, Scientific Park of Madrid.



## GENYAL Ethical Committee:

This committee will evaluate all planned actions and procedures of the Platform before the required additional ethical committees of each project:

### President:

Prof. D<sup>a</sup> Manuela Juárez Iglesias. Professor of Research, CSIC.

### Vocales:

D. José Fernández Piqueras. Full Professor of Genetics, Universidad Autónoma de Madrid.

D. Augusto Silva. Scientific Researcher and member of the ethical committee, CSIC.

D. Gregorio Varela. Full Professor San Pablo CEU University. SEN President.

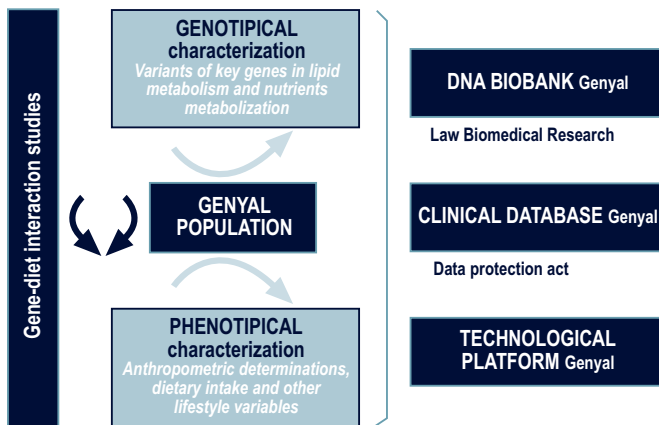
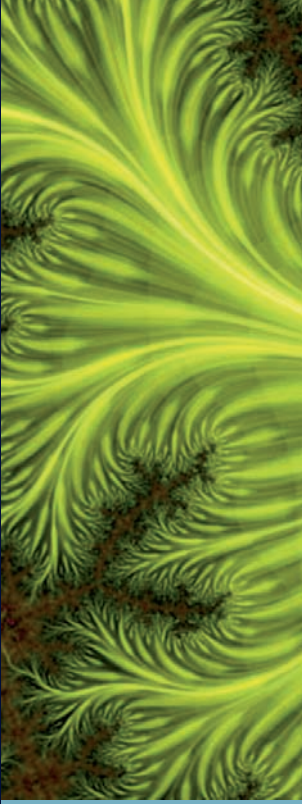


Figure 3. Structure of Cantoblanco Platform of Nutritional Genomics and Food





# 4

## scientists

- 4.1. **Scientist [28]**
- 4.2. **Senior Researchers [29]**
- 4.3. **Assistant Senior Researcher [31]**
- 4.4. **Postdoctoral and Predoctoral Researcher [32]**
- 4.5. **Senior Technician [34]**

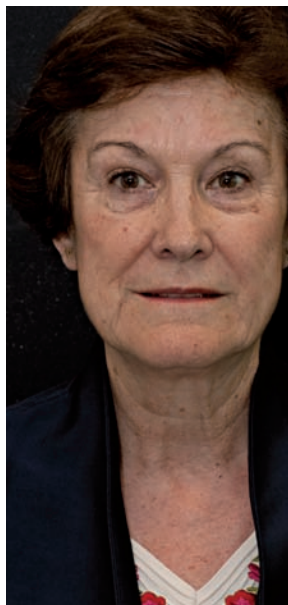
# scientists

## Prof. Manuela Juárez

Director  
Research Professor

Manuela Juárez Iglesias is PhD Chemistry. She is Research Professor in the Consejo Superior de Investigaciones Científicas (CSIC). Since 2007 she is Director of IMDEA Food Institute.

Her Scientific Contributions includes more than two hundred papers in scientific journals, monographic or chapter of books and the participation in patents in Food Science and Technology Area. She has succeeded Award of research in Food Science and Technology of the Foundation CEOE, 1996, Honour Medal to the Invention from the Foundation García Cabrerizo, 2006, Award from Dairy Industrial Federation on diffusion of the healthful properties of dairy products and International Prize Hipócrates of Medical Research on Human Nutrition in 2009 and the International Dairy Federation (IDF) Award 2010. She has occupied the charge of Director of the Instituto del Frío, Manager of the Area of Science and Food technology of the National Plan of R&DT, the coordination of the Food Technology Area of the National Agency of Evaluation and Prospective, General Assistant director de Programación, Seguimiento y Documentación Científica of CSIC and Vice-President of Scientific and Technological Research of CSIC. She is Director of IMDEA Food Institute, Vice-President of the Singular Science



and Technology Infrastructures Scientific Committee (MICINN) and Member of the Spanish Scientific Committee Food Safety Authority.

## Prof. Guillermo Reglero

Deputy Director  
Professor

Guillermo J. Reglero-Rada is PhD in Chemical Sciences. From 1999 he is Full Professor of Food Technology of the Universidad Autónoma de Madrid. Before he was Senior Researcher of the Consejo Superior de Investigaciones Científicas (CSIC). Since 2007 he is Deputy Director of IMDEA Food Institute. He is author of several publications of international impact and of several transferred patents.

In 2001 he received the Prize «Archer Daniels» granted by the American Oil Chemists Society. Between 2002 and 2006 he has been Manager of the Area of Science and Food technology of the National Plan of R&DT.

He directs a research team in Food Science and Technology that is employed on obtaining food functional ingredients with projects of funding both public and private. This line of investigation includes the development of extraction processes, fractionation and purification by means of the technology of supercritical fluids and the chemical and functional characterization of natural products with biological activities of food interest.

He is the coordinator of the Program «Design and validation of active ingredients for the development of functional foods» (ALIBIRD), which belongs to the Activities for



Research Group of the Community of Madrid made up of 14 groups of 7 public research organizations.

He participate in the project CONSOLIDER FUN-C-FOOD for Food and Health, composed of researchers from different Spanish research centers. He also participate in the CENIT project HIGEA and NOCHEMFOOD Project from the Sixth Framework Programme of the EU and in various projects of the National Plan of I+D.

# senior researchers

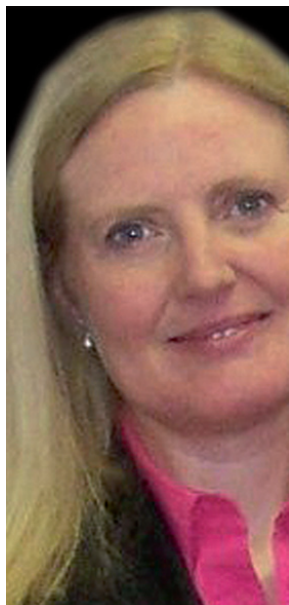
## Prof. Dolores Corella

Associate Senior Researcher

Dolores Corella Piquer, PhD in Pharmacy and Bsc in Food Science and Technology, is a Full Professor of Preventive Medicine and Public Health at the University of Valencia. Since 1998 she has been Director of the Genetic and Molecular Epidemiology Research Unit. She focuses on the study of genetic determinants of disease and has developed research methodology for analyzing gene-environment interactions, both for monogenic and complex multigenic diseases.

Within the gene-environment interaction study, gene-diet interactions have constituted an important research line giving rise to the development of Nutritional Genomics.

Since 2003, Dr. Corella has participated in the PREDIMED Study (PREvención con DIEta MEDiterránea) and from 2006, in the CIBER on Physiopathology of Obesity and Nutrition, taking part in various studies centered on the analysis of obesity risk factors, both genetic and environmental, as well as the impact of gene-diet interactions. She has directed more than 30 research projects related to cardiovascular genomics and various Doctoral Theses in this area. She has more than 160 articles published in prestigious international journals in the fields of genomics, nutritional genomics, obesity and cardiovascular diseases, and has been quoted many times. Her research group also took part in



the INBIOMED network. Currently she is collaborating with the COMBIOMED network. Dr. Corella is one of the pioneers in the development of nutritional genomics in Spain, and together with Dr Ordovás, Director of the Nutrition and Genomics Laboratory, Human Nutrition Research Center, Boston, USA, published the first works on gene-diet interactions, which have already become classics in this new discipline.

## Prof. Francesco Visioli

Senior Researcher

Francesco Visioli earned a degree in Pharmacy and Pharmaceutical Chemistry from the University of Milan and a PhD in Biotechnology from the University of Brescia. After being Full Professor of physiopathology at the UR4 of the Université Paris 6 "Pierre et Marie Curie", where he directed the "Micronutrients and cardiovascular disease" unit, he is now Senior Investigator at the Madrid Institute for Advanced Studies (IMDEA)-Food. He is also Assistant Professor at the College of Pharmacy, Oregon State University. After being involved in neurochemistry, Dr. Visioli's research currently concerns essential fatty acids, namely those of the omega 3, and series natural antioxidants, as related to atherosclerosis and cardiovascular disease. In particular, Dr. Visioli's group discovered the biological and pharmacological properties of olive oil phenolics, including hydroxytyrosol. In addition, Dr. Visioli is being studying bioactive components of plant foods, including lycopene from tomato and biophenols from wild greens. His research ranges from in vitro studies of bioactivity (test tubes, cell cultures) to in vivo tests, performed on laboratory animals and/or humans. Dr Visioli has a publication record of over 170 papers and book chapters, which have been cited over 4000 times. He gave invited lectures in over 60 meetings. As related to human health, Dr. Visioli created a method to evaluate the nutritional profile of foods (foodprofile.org), which was



published in 2007 and field-tested in 2009.

Dr. Visioli is member of the Board of Directors of the International Society for the Study of Fatty Acids and Lipids (ISSFAL), member of EFSA's expert database, and member of several learned societies, including the British Nutrition Society. Currently, Dr. Visioli is the Editor-in-Chief of Pharmacological Research, Associate Editor of Lipids and of Prostaglandins, Leukotrienes and Essential Fatty Acids, and First Editor of the British Journal of Nutrition, in addition to being a member of the Editorial Board of several other journals.



**Dr. Ana Ramírez de Molina**  
Senior Researcher

Ana Ramírez de Molina, PhD in Biochemistry and Molecular Biology, and Bsc in Chemistry (Biochemistry), has developed her scientific career in the field of lipid metabolism and its relationship with the molecular and cellular biology of cancer. She was awarded as outstanding PhD Thesis by the Autonomía University in 2002 for her work on the alterations of the lipid metabolism performed at the "Instituto de Investigaciones Biomédicas (CSIC)" under the supervision of Prof. Juan Carlos Lacal. She performed a postdoctoral stay with Professor Paul Workman, Head of the Cancer Research UK Centre for Therapeutics, and worked as a postdoctoral researcher in the Translational Oncology Division of CSIC-UAM-Hospital La Paz for three years. In 2005 and 2006 she worked as an associated researcher at the Molecular Pathology Division of the Sloan Kettering Cancer Center (New York) under the supervision of Prof. Carlos Cordón-Cardó, and afterwards she worked as the Deputy Scientific Director of TCD Pharma, a spin-off company from CSIC focused on the development of new tumoral markers and therapies in Cancer. On 2007 she became the Director of Research and Innovation of TCD Pharma focused on the development of a diagnostic platform based on tumoral genomics and the coordination of the preclinical development of new inhibitors of the lipid metabolism as antitumoral drugs, where she had been working till she joined IMDEA Food Institute as a "Ramón y Cajal" researcher in 2009. As a result of this work, in the last years she has supervised two PhD Thesis, published more than 25 articles in prestigious international journals of the field, and is co-inventor of 8 patents in different phases of exploitation by a biotechnology company.



**Dr. Alberto Dávalos**  
Senior Researcher

Alberto Dávalos, PhD in Pharmacy (Universidad Complutense de Madrid) and Bsc in Pharmacy and Biochemistry at the Universidad San Marcos (Lima), has studied the role of cholesterol and lipoprotein metabolism in the progression of cardiovascular disorders related to dyslipidemia. Particularly, he evaluated the effects of dietary polyphenols and their effects on lipid metabolism. During his PhD with Begoña Bartolomé at the CSIC (Madrid), he studied the bioavailability and the antioxidant effects of dietary polyphenols. He developed different methodologies to evaluate their antioxidant effects. He worked in the laboratory of Prof. Miguel A. Lasunción as postdoc at the Hospital Ramón y Cajal (Madrid). There, he studied the effects of grape juice ingestion and cardiovascular risk factors related to lipid metabolism. He also studied the stringency of cholesterol for normal cell function and lipoprotein metabolism. In 2008, he joined Prof. William C. Sessa lab at Yale University School of Medicine (New Haven), where he studied the role of caveolae proteins in endothelial cell function and atherosclerosis. He also joined Prof. Carlos Fernández lab at New York University School of Medicine (New York) where his studies focused on the role of microRNAs in cholesterol metabolism. In professor Fernández lab, he contributed to decipher the role of miR-33a/b as regulator of HDL-cholesterol levels and reverse cholesterol transport, fatty acid metabolism and insulin signaling. He joined IMDEA Food Institute in September 2010 where he leads a research group. His research program focuses in identifying and characterizing new microRNAs that regulate lipid metabolism and the effects of minor dietary components (micronutrients) on their expression. He hopes to



identify new therapeutic strategies through modulating microRNAs levels by the diet to treat dyslipidemia and to prevent atherosclerosis and cardiovascular diseases.



# assistant senior researcher



**Dr. Arantxa Rodríguez Casado**

Senior Assistant Researcher

Arantxa Rodríguez Casado, PhD in chemistry (Universidad Complutense de Madrid, 1998) has pursued research in the field of Biophysics, studying different aspects of molecular biological systems. She has focused on the connection between the structure of biomolecules - proteins, nucleic acids, lipids - and their functionality, with the ultimate goal of understanding the complex mechanisms of interaction between them. In the Food field, she has worked on two applied research lines: Conservation and

Quality, and Restructured Foods in collaboration with Professor Mercedes Careche (Instituto del Frio - CSIC), developing new methodologies for identification of defects in food, and studying the correlation between rheological properties and structural aspects of new functional foods. She worked as a research associate for more than three years in the Department of Cell Biology and Biophysics, School of Biological Sciences at the University of Missouri- Kansas City (MO, USA) under the supervision of Professor George Thomas, on the study of structural proteins. Then she worked for almost two years at the Birkbeck College, University of London, in the group of Professor Helen Seibill deal-

ing with the 3D reconstruction of proteins by electron microscopy (TEM and SEM) and digital image processing, with particular focus on the morphology of biomolecules. She also has worked in the Biomedicine field at the Institute of Structure of Matter - CSIC collaborating with Professors Pedro Carmona and Adolfo Toledano (Instituto Cajal -CSIC); in early diagnosis of neurodegenerative diseases by vibrational microspectroscopy, and also in characterizing specific structures in nucleic acid triple helices, with the focus on gene therapy. All these years dedicated to this work are reflected in 30 publications with a high impact factor in her research field.

**Dr. Lorena Betancor**

Senior Assistant Researcher

Dr. Lorena Betancor graduated as a Bsc in Biochemistry at the Universidad de la Republica (Montevideo, Uruguay). She obtained a PhD in Molecular Biology at the Autonomia University in Madrid working under the guidance of Prof. JM Guisan at the Institute of Catalysis and Petrochemistry (CSIC). There she specialized in enzyme technology particularly in developing strategies for the immobilization and stabilization of enzymes of biotechnological interest (e.g food industry, fine chemistry, pharmaceuticals). Upon completion of her PhD, she worked as a post doc at Georgia Institute of Technology where she explored the enzymology and molecular biology of nitroreductases and mutases. She deepened her knowl-

edge in enzyme immobilization using novel nano structured materials as supports and applying them in the design of in vitro biocatalytic reactions for cofactor regeneration and microfluidics. Between 2006 and 2009 she

joined Prof. Peter Leadlay's group at the University of Cambridge as a post doctoral fellow from the Spanish Ministry of Science and Education. There Dr. Betancor developed new strategies for the expression and purification of multienzymatic systems and explored the use of polyketide synthases in vitro applying her expertise in enzyme immobilization. She joined IMDEA Food Institute in February 2009 as a "Ramón y Cajal" researcher to work in functional foods and nutrigenomics. She is co author of more than 40 papers in international peer-reviewed journals,

6 book chapters and 4 patents and has been invited to review areas of enzyme immobilization and biocatalysis by relevant biotechnological review journals (Trends in Biotechnology, Biotechnology and Genetic Engineering Reviews).

#### Research Interests

During her pre and post doctoral research Dr. Betancor has explored almost all the fields related to enzyme technology: expression, purification, immobilization-stabilization of enzymes and application of immobilized preparation to biocatalytic processes and biosensors. Now, a new challenge will be taken by working towards the production of new functional ingredients for the food industry and the design of improved ways of obtaining additives of known value for the human health.



# predoctoral&postdoctoral researcher

## Dr. Nathalie Nicod

Postdoctoral Researcher

Nathalie Nicod obtained her Chemistry Diploma (BSc) at the University of Lausanne (CH) in 2000. Her diploma thesis was on biphenyl stereochemistry with Prof. Schlosser. However her interest lied in nutritional biochemistry and in order to gain a more human vision of nutrition she spent a year and a half as research assistant in the Physiology Institute of Lausanne with Dr. Luc Tappy (2000-2002). She supervised a in a clinical trial on the effects of dexamethasone-induced insulin resistance. Thereafter she wanted to tie her to backgrounds together (Chemistry and Physiology), thus she obtained her PhD in Molecular Nutrition (Nutritional Biochemistry) at Cornell University (NY) in (2002-2008) under the supervision of Dr. Robert Parker, where she investigated the role of ATP-binding cassette lipid transporters in vitamin E secretion and status. She was a Marie-Curie postdoctoral fellow in frame of the IAPP-ADIBET project (The role of adipose tissue in obesity: beta cell crosstalk) at IDIBAPS (Barcelona) with Dr. Ramon Gomis. She investigated the effect of the single nucleotide polymorphism rs7903146 on alternative splicing of TCF7L2. She is now a postdoctoral fellow at IMDEA Food Institute in Dr. Francesco Visioli's group looking at the effects of dietary lipids on reverse cholesterol transport.



## Dr. Nasiruddin Khan

Postdoctoral Researcher

Dr. Nasiruddin Khan has done his B.Sc in Chemistry (with Honors) in Aligarh Muslim University, India. Afterwards he completed his Ph.D in Nutrition and Food Science at the University of Barcelona (2006-2010) under the direction of Dr. Cristina Andres Lacueva, Professor of the Pharmacy School, Department of Nutrition and Food Science. He did his master in Nutrition and Metabolism at the University of Barcelona (2008). During his doctorate he emphasized mainly on Cocoa studies and its effect in human subjects by analysing adhesion molecules on the surface of leukocytes, soluble adhesion molecules and cytokines and other inflammatory markers (ICAM-1, VCAM -1, E-selectin, P-selectin, MCP-1 and IL-6) mainly in cardiovascular diseases like atherosclerosis.

In the year 2007 he made a stay at Department of Internal Medicine, University of Ulm, Stuttgart, Germany to study in-vitro migration assay of monocytes and lymphocytes under the noble direction of Prof. Nikolaus Marx, MD. In (2009) he studied the effect of cocoa metabolites on the production of reactive oxygen species (ROS) and gene expression (HO-1, Nrf2) performed under the direction of Dr. Richard Siow, Professor of Physiology in Cardiovascular Division , King's College London.

The main lines of investigation that he carries are biomarkers of inflam-



mation, cardiovascular diseases such as atherosclerosis and the initial process involved in inflammation, polyphenols from fruit and vegetables, flavanol and its metabolites . He has attended several international conferences and Seminars. He has several publications in journals of high impact factor and has also participated as author in several book chapters regarding the effects of cocoa phenolic s in immunology and cardiovascular diseases.



**Dr. Lidia Daimiel Ruiz**  
Postdoctoral Researcher

Dra Lidia Ángeles Daimiel Ruiz obtained her degree in Biological Sciences at Universidad Autónoma de Madrid (2003). Then, she worked as a Third Cycle student in the Laboratory of Human Genetics in the Department of Biology at Universidad Autónoma de Madrid, under the supervision of Prof. Juan José González Aguilera, and Prof M<sup>a</sup> Antonia Fernández Peralta (2003-2006). This work was focused on the study of genetic alterations of colorectal tumours and its relationship with the diagnosis and prognosis of the cancer. She specifically studied the methylation status of some tumour suppressor genes and the presence of SNPs associated to high risk of colorectal cancer development. Afterwards, she started working on her PhD as graduate student of CIBER Physiopathology of the Obesity and Nutrition in the Department of Biochemistry-Research at Hospital Ramón y Cajal in Madrid under the supervision of Dr. Javier Martínez-Botas and Dr. Diego Gómez-Coronado. The aim of her PhD was to study the effect of cholesterol availability alterations on gene expression and to identify new lipid-regulated genes. For this study, she used wide-genome expression analyses techniques such as microarrays and she participated in the design and development of the Cholestchip<sup>TM</sup>, a focused microarray for the study of genes involved in lipid metabolism and cell cycle, which is currently commercialized by BlackBio S.L. She obtained her PhD in Genetics and Cell Biology at Universidad Autónoma de Madrid in 2010 and has recently joined to IMDEA Food Institute for the study of the effects of bioactive components of food on the microRNA-mediated lipid metabolism regulation.



**Dr. Teodoro Vargas Alonso**  
Postdoctoral Researcher

Dr. Teodoro Vargas Alonso, has recently joined IMDEA Food Institute (January 2011) in the research project "Identification of new biomarkers and bioactive compounds in human cancer", has developed his scientific career at the Research Center of the "12 de Octubre" Hospital (Madrid). He has worked in the field of human genetics, particularly, in molecular analysis and genetic screening of mutations and polymorphisms, and its relationship with different diseases. His PhD was done at the Neurosciences Department, and during this period, he published 8 articles (5 as first author) in international journals, dealing with several aspects of the neurodegenerative process in the Alzheimer Disease (AD). His thesis focused on the identification of different genetic polymorphisms associated with an increased risk for AD, identification of biomarkers in AD patients, and he successfully developed a lentivirus-mediated gene therapy focused on restore alterations that occur at neurological level in a murine model of amyloidosis.



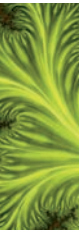
**Marta González**  
Predoctoral Researcher

Marta González Castejón graduated in Biology at the Universidad Autónoma de Madrid in 2007. During her final year she did her Graduating Dissertation at the Department of Biology of UAM, working on the construction and analysis of mutant bacteria strains. Thanks to this project and her course subjects she is familiar with techniques of molecular biology and genomics. In March 2009 she joined IMDEA Food Institute, having obtained a Madrid Region Research Staff Support Contract for completion of her doctoral thesis on the topic "New functional ingredients that affect the expression of genes involved in development of obesity and metabolic syndrome", directed by Dr. Arantxa Rodríguez Casado, and has a Master's degree course in Nutrition and Health at the Universidad Complutense de Madrid.



**Margarita González-Vallinas**  
Predoctoral Researcher

Margarita González-Vallinas Garrachón graduated in Pharmacy (year 2008) and Biochemistry (year 2010) at the Universidad de Salamanca and received the Third National Award to Excellence in Academic Achievement of the Pharmacy degree. During Summer 2007, she did an internship in the CNB granted by the CSIC. During the academic year 2007-2008, she got a Collaboration fellowship to work in the Nutrition and Bromatology Department at the University of Salamanca. Next academic year, 2008-2009, she was awarded an Erasmus grant in Belgium where she performed a research project at the Laboratory of Food Technology at the Catholic University of Leuven (Belgium). In April 2010 she joined IMDEA Food Institute for the completion of the doctoral thesis on the topic Gene-nutrient interactions: analysis of the beneficial effect of natural compounds in cancer development, thesis directed by Dr. Ana Ramírez de Molina. From September 2010, she is studying the Master in Genetic and Cell Biology at the Universidad Autónoma de Madrid.



### Dr. Susana Molina

Postdoctoral Researcher,  
Senior Laboratory Technician

Susana Molina Arranz, PhD in Molecular Biology Autonomía University of Madrid (2005), pursued her PhD studies in the group of Prof. Luis Carrasco at the "Centro de Biología Molecular Severo Ochoa" (CSIC-UAM). During these years she worked on viral RNA translation, specializing in techniques such as viral infections, radioactive labellings, western blotting, cloning and protein purifications. In the same group she worked as a postdoctoral researcher on analysis of the ethiology of several human diseases, studying the implication of a fungal. In this work she participated in the development of methods to determine the presence of yeasts in human samples, including antibodies recognizing different yeast antigens or detection of fungal DNA by RT-PCR. In 2007 she joined Dr. Juan M. Torres' group at "Centro de Investigación en Sanidad Animal" (INIA), where she collaborated in different projects on prion diseases and their strain barriers. Between 2008 and 2009 she was in the group of Fernando Valdivieso at the "Centro de Biología Molecular Severo Ochoa" (CSIC-UAM), where she started working as a technician generating biological tools for therapeutic investigation of Alzheimer Disease.



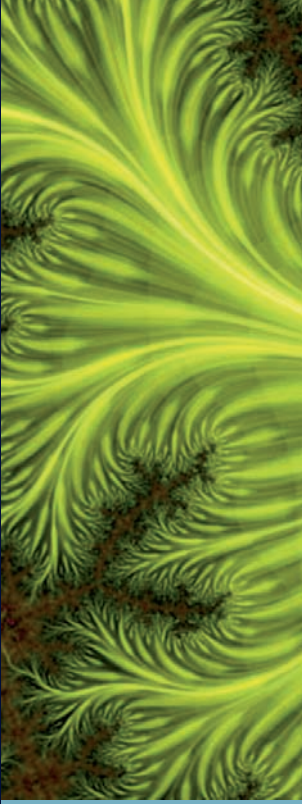
## senior technician

### M<sup>a</sup> Isabel Espinosa

Senior Technician,  
Nutritionist/Dietician

M<sup>a</sup> Isabel Espinosa, BSc in Food Science and Technology (UAM) and with a Degree in Human Nutrition and Dietetics (UAM), has worked in the Endocrinology and Nutrition department at La Paz and Puerta de Hierro Hospitals in the Comunidad de Madrid. In 2008 she collaborated in developing a nutrition and health programme for the Mahou-San Miguel group in Madrid, Barcelona, Lerida, Tenerife, Málaga, Burgos and Guadalajara. She has experience in anthropometric assessment, in nutritional control and development of catering menus, and in dietary consultation and monitoring. During the last two years she has been imparting specialized seminars and conferences in nutrition and food technology. She has published several articles in the field for the general public, and she has also experience in updating quality control systems (ISO9001/00, ISO 14001/04 and EMAS regulation 7617/2001).





# 5 scientific infrastructures

- 5.1. Definitive Headquarters [36]
- 5.2. Temporary Facilities [38]
- 5.3. Scientific Infrastructures [38]

## 5.1. Definitive headquarters

The Institute will be located on the Cantoblanco Campus on land donated by the Universidad Autónoma de Madrid near the UAM-CSIC Institute for Food Science Research “CIAL”, the “Severo Ochoa” Molecular Biology Centre and the CLAID Building in the Madrid Science Park.

There, the Institute will be able to take advantage of synergies with the research and scientific services centers on the Cantoblanco University Campus an essential consideration for a centre devoted to targeted basic research, applied research and transfer of research results.

The end result is a high-level food R&D environment, especially appropriate for the transfer of the results of IMDEA Food’s Institute research in association with the Madrid Science Park, which can support the numerous food research groups in the Region, serve as an international scientific benchmark and attract new innovative enterprises that require its services.

The land covers an area of 4200 m<sup>2</sup>, with room for 7000 m<sup>2</sup> of floor space and a plan area of 2000 m<sup>2</sup>, a maximum of 6 levels and 70 parking spaces.

The Institute’s strategic plan conceives of a modular development in phases.

### Phase I

This phase of the project covers all the requirements and contingencies for IMDEA Food Institute to initiate and maintain operations for a period of five years. In this first phase the building will include complete architectural preparation of the entire habitable area of the building, including the basement, which will house the general facilities, function hall and covered car park. The building will have two separate but linked areas for laboratories and for common areas and offices.

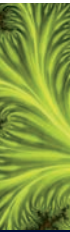


The laboratory area will occupy two floors totaling 530 m<sup>2</sup>, with five 50m<sup>2</sup> laboratories each. There will also be auxiliary laboratories and a service area on each floor for cold rooms, freezer cabinets, scales, etc., thus constituting a working area that meets all space and functionality requirements.

The office area will occupy five floors, for Management and Administration and meeting rooms and another three for offices. The spatial distribution is designed with personal development in mind, open-plan to give a sense of space, visibility and communicability between research groups, facilitating teamwork, interpersonal communication and a measure of privacy without loss of the visual contact, all essential to proper performance of the various activities that will be going on in the building—research, administration / management and institutional activities.

## Phase II

In this phase it is planned to complete the building, making up a total floor area of 6517 m<sup>2</sup>.



## 5.2. Temporary facilities

The newly opened building CLAIID the Madrid Science Park, co-financed by the Autonomous University of Madrid and located at in the University Campus Cantoblanco welcomes new headquarters IMDEA Food Institute since July 2010. It has joined the administrative and research headquarters of the Food-Health Area. These spaces accommodate the instruments most technologically advanced research in the field of nutrigenomics, in an environment characterized by excellence in research, equipped with common services and infrastructure shared with other research centers.



## 5.3. Scientific infrastructures

IMDEA Food Institute has been fitted out for research in Line 1 Food & Health, with the following advanced scientific and technical equipment:

### 5.3.1. TECHNOLOGICAL PLATFORM OF NUTRITIONAL GENOMICS AND FOOD-BIOBANK

#### Current strength:

- Equipment for real-time PCR Applied Biosystems ® 7900HT Fast Real Time System
- SNP analysis platform for high performance by RT-PCR Applied Biosystems ® Open Array
- 1 thermal cycler Applied Biosystems ® 2720 Thermal Cycler
- 1 DNA Quantifier Nanodrop ND-2000
- 1 Megafuge 40R Heraeus centrifuge
- Stadiometer
- Bioelectrical impedance scale that calculates weight, body fat percentage, body muscle percentage, visceral fat percentage, basal metabolism and body fat index
- Tape measure to measure waist and hip sizes
- Tensiometer for measuring blood pressure and heart rate



Available in Building CLAUD:

- Frozen -80 ° C New Brunswick U570
- 1 crushed ice machine
- 1 System Millipore Milli-Q Advantage A10

### 5.3.2. CELL CULTURES UNIT

Building envelope CLAUD:

- -80 ° C Freezers New Brunswick U570
- Liquid Nitrogen Tank
- 1 System Millipore Milli-Q Advantage A10
- 1 CO2 Incubator HERACell 150i model
- 1 refrigerated centrifuge ScanSpeed 416
- Gel documentation system LIAS ChemLite 400F
- Digital Camera attached to the microscope SC30
- Horizontal flow cabinet Telstar Bio-IIA biosafety
- CO2 Incubator MMM-CO2CELL
- Olympus Microscope CKX41

### 5.3.3. MOLECULAR BIOLOGY AND GENOMICS UNIT

- 1 thermal cycler for PCR Applied Biosystems 2720 Thermal Cycler ®
- 1 Megafuge 40R Centrifuge Heraeus
- Spectrophotometer ND-2000 (Nanodrop)
- Basic equipment for electrophoresis of nucleic acids
- Cabin filter for vapor extraction
- 1 tabletop centrifuge HERMLE Z216MK
- 1 Microcentrifuge SPECTRAFUGE MINI
- 1 Thermoblock PHMT 20x1, 5ml tubes
- 1 Subaqua Grant Bath
- 2 magnetic stirrers Magstar Genie
- 1 vortex Genie 2
- Gel documentation system LIAS ChemLite 400F



Available in Building CLAID:

- Centrifuge Beckman Coulter Avanti J foot-26 XP
- Frozen -80 ° C New Brunswick U570
- 1 crushed ice machine
- 1 System Millipore Milli-Q Advantage A10
- Microcentrifuge Hettich 320R
- Incubator 29 ° C NÜVE FN500
- Ultrasonic bath NÜVE nb20

#### 5.3.4. CELL BIOLOGY AND PROTEOMICS UNIT

- Plate reader ASYS UVM340
- Spectrophotometer ND-2000 (Nanodrop)
- Telstar Freeze LyoQuest
- Basic equipment for protein electrophoresis and Western blotting

Available in FPCM (headquarters located in Tres Cantos)

- FACS flow cytometer Scalibur
- Fluorescence microscope equipped with mercury lamp NIKON C-SHG
- Gel documentation system for chemiluminescence LIAS ChemLite 400F

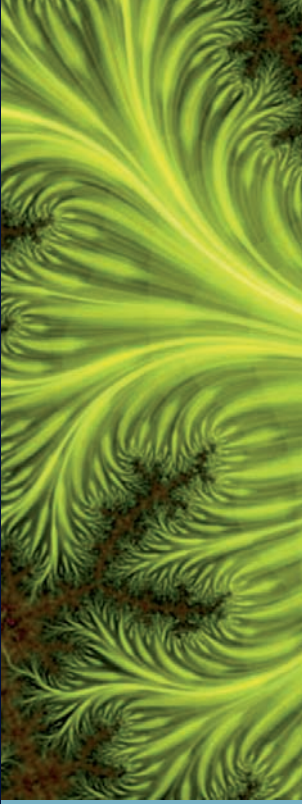
#### 5.3.5. ANALYTICAL UNIT

- System high performance liquid chromatography (HPLC Agilent 1200)
- UV-visible spectrophotometer cary50 Variant
- 4000 Laborota Rotavapor efficient Heidolph
- cold-hot bath Julabo F12

Available in Building CLAID:

- Ouhau Pioneer Precision Balance
- Phenomenal VWR pH meter





# 6

## research projects

- 6.1. Competitive research projects [42]
- 6.2. Contracts with Companies [47]
- 6.3. Research Grants [47]

## 6.1. Competitive research projects

### DIETCAN

#### Investigational Nutrigenetic Studies for Cancer Prevention

#### Alterations in lipid metabolism in cancer: influence of diet ingredients on development, onset and/or progress of the disease

IP: Dr. Ana Ramírez de Molina

Funding: Fundación Mapfre

Duration: 2009-2011

This research line is focused on using information on individual genetic variations to stimulate pilot dietary intervention studies. The main goal is to examine whether genetic variants can predict individual responses to dietary components that alter cancer processes and modify individual susceptibility to cancer. These studies will allow for personalization of cancer preventive dietary strategies to reduce cancer risk or to improve responses to anticancer treatment in genetically susceptible individuals.

Bioactive food components and genes that determine human cancer risk. Several bioactive food components can modify transcription, expression, and regulation of genetic targets that are known to influence different cancer-related signaling pathways that determine the aggressiveness of the disease or the detoxification of carcinogens. On the other hand, individual genetic variants may influence carcinogenesis at multiple levels. Furthermore, individuals carrying some genetic variants also appear responsive to the effects of some bioactive food components.

This research line focuses on the development of individualized, targeted nutrition with the aim of establishing prevention strategies that can reduce cancer risk in genetically susceptible humans, or improving the management of patients with this disease based on individual genetics. Bioactive food components in dietary interventions may include essential nutrients and non-nutrients found in foods. This approach includes the identification of new biological markers in cancer developed by different gene expression analysis, as well as dietary intervention studies using cell culture and animal models. The information generated from such investigations might serve as the basis for exploratory pilot clinical studies in humans.



## DIETGEN

### Gene-nutrient interactions: Study of the potential beneficial effect of dietary incorporation of rosemary extracts on the development of colon cancer

**Funding:** Spanish Ministry of Science and Innovation

**IP:** Dr. Ana Ramírez de Molina

**Duration:** 2009-2013

Carnosic acid extracted from rosemary is a powerful natural antioxidant, recognized as safe by the EFSA. Its capacity to alleviate cell damage caused by oxidative stress and additional evidence such as its regulatory action on lipid metabolism, or detoxifying enzymes like GST, suggests that this component of rosemary has a beneficial effect on human carcinogenesis. Promising results have recently been reported in leukemia cells, indicating that as a dietary component this ingredient could have beneficial effects on cancer. However, additional studies are needed to confirm and analyse the clinical importance of these preliminary findings and look more closely into the mechanics of this effect.

This project proposes separation and isolation of carnosic acid by supercritical chromatography as a potential functional ingredient of rosemary for future foods if the EFSA regulations are further developed, or as nutraceuticals and/or nutritional supplements affecting the development, course and treatment of colon cancer. It is proposed to elucidate the mechanics of this effect by means of various gene expression studies in human tumor cells treated with this ingredient, and also in samples from patients with colon cancer, in whom it is proposed to study the expression of carnosic acid-target genes, as well as other related genes bearing on the response to nutritional components. This study should lead to the identification of new genes associated with the development of colon cancer which could be readily modulated by diet and which might play a fundamental role in the onset, incidence, progress, severity and/or treatment of this disease.

## FITOGEN

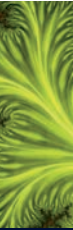
### Functional Ingredients derived from phytochemicals that influence genetic mechanisms implicated in the development of multigenic disorders (obesity and metabolic syndrome)

**IP:** Dr. Arantxa Rodríguez Casado

**Funding:** Madrid Region. Grant for Recruitment of Research Support Personnel (CPI/0631/2008)

**Duration:** 2009-2012

This research project seeks to establish connections between certain aspects of genomics in the control of multigenic disorders and the health effects of certain phytochemicals when



included in the diet. The research line considers certain phytochemicals found in dandelion (*Taraxacum officinale*) with properties that suggest they are a potential source of functional ingredients for the treatment and prevention of metabolic disorders in that they positively and simultaneously regulate several genetic/molecular mechanisms implicated in the development of obesity and metabolic complications deriving from it (diabetes, high blood pressure and high cholesterol). Dandelion is highly antioxidant thanks to high concentrations of carotenoids, flavonoids coumarin derivatives, and it is also strongly anti-inflammatory, reducing the levels of pro-inflammatory markers associated with the development of obesity (IL-6 and TNF- $\alpha$ ), as well as being effective in the regulation of NO and COX-2 production. As an effective regulator of insulin secretion it is anti-hyperglucemic and hence a good option for prevention of complications in diabetes. The triterpenes and phytosterols that it contains reduce the risk of thromboembolism. Its vitamin A catalyses hepatic metabolism and activates the expression of uncoupling proteins (UCP) and hepatic genes implicated in the development of obesity. Lactones from the sesquiterpene in the leaf extracts reduce total cholesterol and triglyceride levels in serum and hepatic tissues and raise the HDL-cholesterol level.

## REDUCOL

**New bioactive food ingredients derived from mushrooms. Effectiveness according to genetic profiles (AGL2010-21537)**

IP: Dr. Arantxa Rodríguez Casado

Funding: Spanish Ministry of Science and Innovation

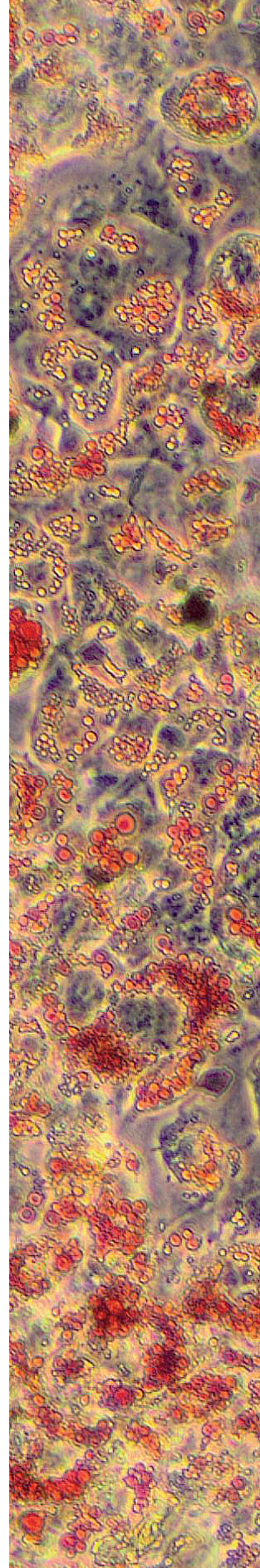
Duration: 2010-2013

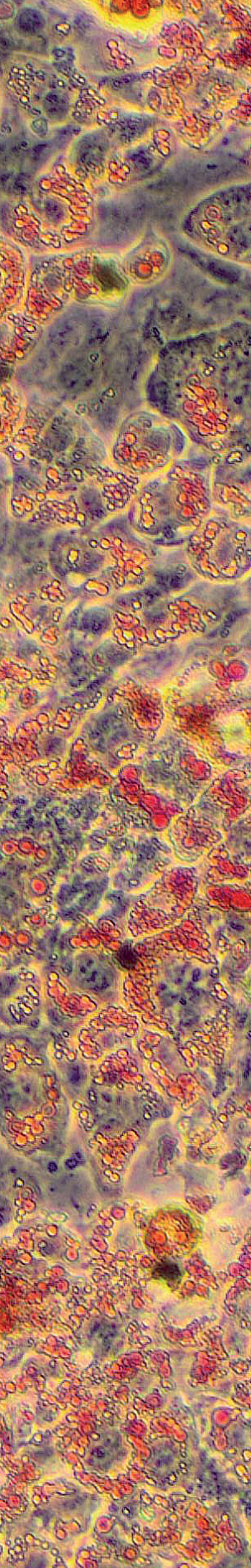
This project is oriented towards the development of functional foods capable of effectively reducing serum cholesterol levels by acting simultaneously on two levels:

1. Acting on endogenous cholesterol synthesis and on its haemo-entero-hepatic cycle. It is proposed at once to use active products found in foods that can inhibit the cholesterol biosynthesis pathway and to modify hepatic circulating cholesterol by means of receptor modulation.
2. Hindering cholesterol absorption by displacement of mixed micelles, sequestration of biliary acids during intestinal digestion to prevent re-absorption, inhibition of pancreatic lipase and modulation of the enterocyte proteins responsible for cholesterol absorption.

The experimental approaches that are required to implement this line include:

- a) In vitro digestion model systems to determine bioaccessibility.
- b) Model systems of cellular absorption via Caco2, to determine bioavailability.





- c) Advanced LC/CG-MS analytical techniques to identify the behaviour of the active principles and the derived metabolites.
- d) Expression of genes implicated in cholesterol homeostasis to determine the effect of different foods and active molecules.
- e) Genotyping of populations to adjust the design of foods to different genetic profiles.

## NUTRIGEN

### Design and Validation of Active Ingredients for the Development of Functional Foods (ALIBIRD S2009/AGR1469)

Madrid Region consortium comprising 14 R&D groups. IMDEA Food Institute is responsible for “analysis of the effects of bioactive ingredients, with special emphasis on benefits for cardiovascular health and the behaviour and effects of those bioactive compounds”.

IP: Dr. Ana Ramírez de Molina

Funding: Madrid Region. (S2009/AGR-1469)

Duration: 2009-2013

The role of IMDEA Food Institute is to study the heart-healthy effect of target functional foods (antioxidants, microbial enzymes, structured and functional lipids, bioactive peptides, prebiotics and probiotics) in humans, taking into account the variations in individual genomes. This activity will consist fundamentally in studies of cohorts with particular genetic traits. According to the strategy laid down in the Consortium’s Work Plan, coordinated by Prof. Guillermo Reglero Rada, the groups will study procedures for producing one or two products of each type—i.e. ten in all. These will be evaluated in terms of industrial feasibility and will be subjected chemical and biological characterization. Following this process it is hoped that at least three of the ingredients will be sufficiently viable for getting into the next step of the project, in which they will be assessed for safety and put through pre-clinical (toxicology and efficacy) and nutrigenetic clinical studies.

## OBESIKIT

### Detection of enzymatic markers by oriented antibody immobilization

IP: Dr. Lorena Betancor (in collaboration with the University of the Republic, Uruguay)

Funding: IMDEA Food Institute

Duration: 2009-2014

The aim is to develop a novel methodology for detection in blood of tiny variations in the activity of reporter enzymes as means of determining whether a nutrient or set of nutri-



ents could affect the risk of obesity in a particular person. To that end it is proposed to develop functionalized magnetic particles with antibodies against aspartate aminotransferase and alanine aminotransferase, two hepatic enzymes commonly associated with obesity. Thus, using an economical, simple but highly sensitive enzymatic method, it should be possible to achieve early detection of individuals in whom it would be easier to observe changes in their transcriptome by means of microarrays and to conduct comparative nutrigenomic studies with hyposensitive individuals.

## FUN-C-FOOD

### New ingredients and functional foods to improve health

Coordinating centre: CSIC- Center of Soil Science and Applied Biology

Programme INGENIO-CONSOLIDER

Funding: Spanish Ministry of Science and Innovation

Duration: 2007-2011

Research programme aimed at producing and characterizing new bioactive food ingredients and applying them to the development of new functional foods, backed up by studies of bioavailability, biological activity and food safety. This research programme explores the relationship between foods and health, in particular with regard to functional foods and bioactive food ingredients. The programme also proposes to include new food ingredient production technologies for the formulation of functional foods, for advanced bioanalysis (including both comprehensive chemical and functional characterization), evaluation of biological activity, bioavailability and metabolism, and a study of possible benefits and risks for human health. New functional foods will be developed with one or more added functional ingredients, which will be assayed for efficacy and possible toxicological risks. The programme also includes research activities that take advantage of the latest scientific tools in the field of genomics, transcriptomics, proteomics, metabolomics, metabonomics and nutrigenomics. This will be the first initiative to integrate food science and omic methods in Spain.





## 6.2. Contracts with Companies

### CENIT-PRONAOS

#### Nutrition intervention studies for the analysis of diet-gene interactions

within the framework of the CENIT Project for “the development of a new generation of functional foods with special emphasis on obesity prevention”

IP: Dr. Ana Ramírez de Molina

Funding: BIOSEARCH LIFE, S.A. /Spanish Ministry of Science and Innovation – CDTI

Duration: 2009-2012

## 6.3. Research Grants

#### Programme: Ramón y Cajal (2007-01920)

Dr. Arantxa Rodríguez Casado

Title: Infrared and Raman spectroscopies of biological substances (proteins, lipids, nucleic acids, polysaccharides)

Funding: Spanish Ministry of Science and Innovation

Duration: 2008-2012

#### Programme: Ramón y Cajal (RYC2008-03734)

Dr. Ana Ramírez de Molina

Title: Alterations of lipid metabolism in cancer: towards a personalized diagnosis and therapy

Funding: Spanish Ministry of Science and Innovation

Duration: 2009-2014

#### Programme: Ramón y Cajal (RYC2008-03732)

Dr. Lorena Betancor Dutrenit

Title: Preparation of functional food ingredients using immobilized enzymes

Funding: Spanish Ministry of Science and Innovation

Duration: 2009-2014

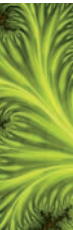
#### CPI/0631/2008

#### Contract for the support of research staff

Marta González Castejón

Funding: Comunidad de Madrid

Duration: 2009-2012



## Grant Agreement n° 229599

### “Marie Curie” AMAROUT Europe

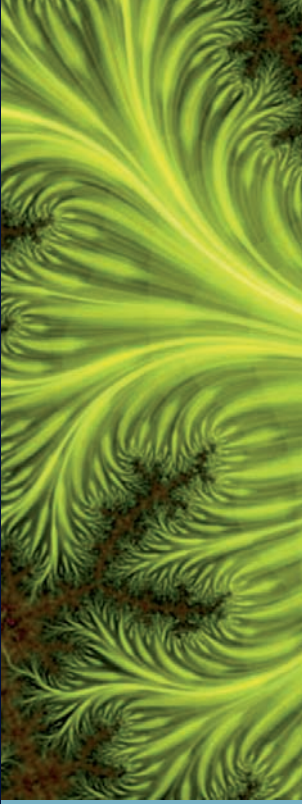
Funding: European Commission. VII R&TD Framework Program

Duration: 2009-2012

Call 2010

- **Prof. Francesco Visioli**  
Type: Incoming Fellow  
Category: Very experienced researcher
- **Dr. Alberto Dávalos**  
Type: Incoming Fellow  
Category: Experienced researcher





# 7

## scientific results

- 7.1. Publications [50]
- 7.2. Books and chapters of books [52]
- 7.3. Thesis directed or in progress [53]
- 7.4. Awards [53]

## 7.1. Publications

Listed below are the scientific contributions published in international media by IMDEA Food Institute researchers. The Institute became operational in 2010 and therefore many of these contributions began as collaborations and projects with other institutions.

### 2010

1. Al-Saffar NM, Jackson LE, Raynaud FI, Clarke PA, **Ramírez de Molina A**, Lacal JC, Workman P, Leach MO. The Phosphoinositide 3-Kinase Inhibitor PI-103 Downregulates Choline Kinase  $\{\alpha\}$  Leading to Phosphocholine and Total Choline Decrease Detected by Magnetic Resonance Spectroscopy. *Cancer Research* 2010; 70(13): 5507-17.
2. **Visioli F.**, Poli A., and Paoletti R. Nutritional intervention helps pharmacology in the management of the metabolic syndrome. *Mediterranean Journal of Nutrition and Metabolism* (2010) 3: 203-207.
3. **Dávalos A.** and Fernández-Hernando, C. microRNAs, Plasma Lipids, and Cardiovascular Disease. *2010 Curr Cardiovasc Risk Rep*, DOI 10.1007/s12170-010-0145-1.
4. Tosin M, **Betancor L**, Stephens E, Spencer JB, Leadlay P.F. (2010) Synthetic chain terminators off-load intermediates from a type I Polyketide Synthase. *ChemBiochem.* 11, 539-46.
5. **Betancor L** and Luckarift HR (2010) "Co-immobilized coupled enzyme systems in biotechnology." *Biotech. Gen. Eng. Reviews.* 27, 1-20.
6. **Rodríguez-Casado A, Espinosa-Salinas I, Molina S, Ramírez de Molina A.** Genomic bases of the effect of bioactive phospholipids. *2010 Current Nutrition and Food Science* (In press).
7. Lamaziere A., Richard D., Barbe U., Kefi K., Bausero P., Wolf C., and **Visioli F.** Differential distribution of DHA-phospholipids in rat brain after feeding: a lipidomic approach. *PLEFA*. In press.
8. **Visioli F.**, Alarcon de la Lastra C., Andres-Lacueva C., Aviram M., Calhau C., Cassano A., D'Archivio M., Faria A., Favé G., Fogliano V., Llorach R., Vitaglione P., Zoratti M., and Edeas M. Polyphenols and human health: a prospectus. *Critical Reviews in Food Science and Nutrition*. In press.
9. Couriel JA, **Betancor L**, De Las Rivas B, Munoz R, Guisan JM, Fernandez-Lorente G. "Hydrolysis of Tannic Acid Catalyzed by Immobilized/Stabilized Derivatives of Tannase from *Lactobacillus plantarum*" *J. Agric. Food Chem.* Accepted.
10. Fernandez-Lorente, G, Felice, M, Lopez-Vela, D, Pizarro, C, Wilson, L, **Betancor, L**, Avila, Y, Guisan JM Crosslinking of lipases adsorbed on hydrophobic supports: highly selective hydrolysis of fish oil catalyzed by RML. *J. Mol. Cat: B Enzymatic.* Accepted.
11. **Ramírez de Molina A**, de la Cueva A, Machado-Pinilla R, Moncho-Amor v, Gómez del Pulgar T, Cerbrían A, Perona R, Lacal JC. Acid ceramidase is a key factor for resistance to the antitumoral effect of ChoK inhibitors in NSCLC tumors. Submitted 2010.
12. **Ramírez de Molina A**, de la Cueva A, Sarmentero-Estrada J, García-Oroz L, Lacal JC. Combination of cisplatin with ChoK inhibitors as a new alternative of treatment for NSCLC patients. Submitted 2010.
13. De la Cueva A, **Ramírez de Molina A**, Sarmentero-Estrada J, Lacal JC. Combination of 5-FU with Chokls as a new alternative therapy in colorectal cancer. Submitted 2010.
14. Álvarez-Miranda MA, Becerra M, Tébar LA, **Ramírez de Molina A**, Gómez del Pulgar T, Andera L, Lacal JC. Combinatorial efficacy of TRAIL and MN58b against colon cancer to overcome TRAIL resistance. Submitted 2010.

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**15. Rodríguez-Casado A, González-Castejón M, González-Vallinas M, Ramírez de Molina A.** Beneficial effect of phytochemical compounds in cancer development and progression. Under preparation.

**16. Visioli F.,** Poli A., and Paoletti R Nutritional intervention helps pharmacology in the management of the metabolic syndrome. *Mediterranean Journal of Nutrition and Metabolism* (2010) 3: 203-207.

**17. Anadón, A.,** Martínez-Larrañaga, M.R., Martínez, M.A., Ares, I., Ramos, E., Gómez-Cortés, **Juárez, M.**, and De La Fuente, M.A. Acute oral safety study of dairy fat rich in trans-10 C18:1 versus vaccenic plus conjugated linoleic acid in rats. *Food and Chemical Toxicology*, 48, 591-598 (2010).

**18. Alonso, L.;** Fontecha, J.; Cuesta, P.; **Juarez, M.** and Gilliland, S. E. Industrial application of  $\gamma$ -cyclodextrin for manufacturing low cholesterol butter *Milchwissenschaft* 65, 36-37 (2010).

**19. Toral, P.G.;** Frutos, P.; Hervás, G.; Gómez-Cortés, P.; **Juárez, M.**; De la Fuente, M.A. Changes in milk fatty acid profile and animal performance in response to fish oil supplementation, alone or in combination with sunflower oil, in dairy ewes. *Journal of Dairy Science* 93, 1604–1615 (2010).

**20. Pressurized liquid extraction as an alternative process to obtain antiviral agents from the edible microalga *Chlorella vulgaris*.** Santoyo S, Plaza M, Jaime L, Ibañez E, **Reglero G**, Señorans FJ. *J Agric Food Chem.* 2010 Aug 1;58(15):8522-7.

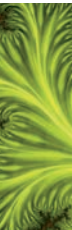
**21. Ocaña A, Gómez-Asensio C, Arranz-Gutiérrez E, Torres C, Señoráns FJ, Reglero G.** In vitro study of the effect of diesterified alkoxyglycerols with conjugated linoleic acid on adipocyte inflammatory mediators. *Lipids Health Dis.* 2010 Apr 6;9:36.

**22. Ocaña-Fuentes A, Arranz-Gutiérrez E, Señorans FJ, Reglero G.** Supercritical fluid extraction of oregano (*Origanum vulgare*) essentials oils: anti-inflammatory properties based on cytokine response on THP-1 macrophages. *Food Chem Toxicol.* 2010 Jun;48(6):1568-75. Epub 2010 Mar 21.

**23. Soler-Rivas C, Marín FR, Santoyo S, García-Risco MR, Señoráns FJ, Reglero G** Testing and enhancing the in vitro bioaccessibility and bioavailability of *Rosmarinus officinalis* extracts with a high level of antioxidant abietanes. *J Agric Food Chem.* 2010 Jan 27;58(2):1144-52.

**24. Mendiola JA, Martín-Alvarez PJ, Señoráns FJ, Reglero G, Capodicasa A, Nazzaro F, Sada A, Cifuentes A, Ibañez E** Design of natural food antioxidant ingredients through a chemometric approach. *J Agric Food Chem.* 2010 Jan 27;58(2):787-92.

**25. Anadón A, Martínez MA, Ares I, Ramos E, Señoráns FJ, Reglero G, Torres C** Acute and repeated dose (28 days) oral safety studies of an alkoxyglycerol extract from shark liver oil in rats. *J Agric Food Chem.* 2010 Feb 10;58(3):2040-6.



26. Ruiz-Rodríguez A, **Reglero G**, Ibañez E. Recent trends in the advanced analysis of bioactive fatty acids. *J Pharm Biomed Anal.* 2010 Jan 20;51(2):305-26. Epub 2009 May 22. Review.

27. Toral, P.G.; Hervás , G.; Gómez-Cortés , P.; Frutos ,P.; **Juárez , M.**; De la Fuente, M.A. Milk fatty acid profile and dairy sheep performance in response to diet supplementation with sunflower oil plus incremental levels of marine algae. *Journal of Dairy Science.* 2010. 93, 1655–1667.

28. Bodas, R., Manso, T., Mantecón, A.R., **Juárez M.**, De la Fuente, M.A., Gómez- Cortés, P. Comparison of the fatty acid profile in cheeses from ewes fed diets supplemented with different plant oils. *Journal of Agricultural and Food Chemistry.* 2010. 58,10493–10502.

## 7.2. Books and chapters of books

1. Gil, A.; **Juárez, M.**; Fontecha, J. Tomo 2. Capítulo 20 “Influencia de los tratamientos tecnológicos sobre el valor nutritivo de los alimentos”. En: “Tratado de Nutrición 2ª Edición”.

ENCICLOPEDIA: Director: Ángel Gil Hernández. Ed. Médica Panamericana. (2010) ISBN 978-84-9835-347-1.

# books and chapters of books



# thesis directed or in progress

## 7.3. Thesis directed or in progress

**Title:** Combinatory 5-Fluoracyl and cis-platinum treatment with choline kinase alpha inhibitors as a new alternative for cancer therapy.

**PhD student:** Ana de la Cueva Herrera

**Directors:** Ana Ramírez de Molina (IMDEA Alimentación) and Juan Carlos Lacal (CSIC)

**Start date:** December 2007

**Title:** Influence of new functional ingredients in the expression of genes related to obesity and metabolic syndrome.

**PhD student:** Marta González Castejón

**Director:** M<sup>o</sup> Arantxa Rodríguez Casado

**Start date:** March 2009

**Title:** Beneficial effect of phytochemicals agents in the prevention, development and treatment of tumors related to food.

**Doctorand:** Margarita González-Vallinas

**Director:** Ana Ramírez de Molina

**Start date:** April 2010

**Title:** Development of Nutritional Genomics platform for studying gene-nutrient interaction.

**Doctorand:** Isabel Espinosa Salinas

**Director:** Ana Ramírez de Molina

**Start date:** February 2010

## 7.4. Awards

M. Juárez. International Dairy Federation (IDF) Award. 2010.

# awards

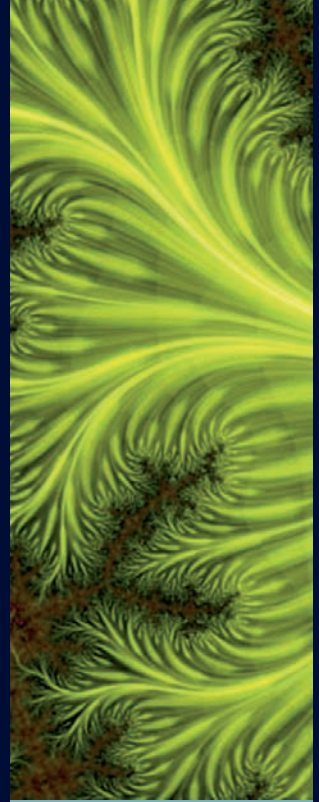
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# dissemination activities

# 8

- 8.1. Organization of conferences and seminars [55]
- 8.2. Invited conferences, courses and seminars [55]





IMDEA Food Institute has taken part in national and international science fairs and dissemination events, including the following:

## 8.1. Organization of conferences and seminars

**Workshop:** Nutritional genomics for the study of food and health relationship.

**Venue and date:** Pavilion C- University Campus of Cantoblanco, Madrid (Spain), 11 November 2010

In the framework of X Madrid Science Week 2009, IMDEA Food Institute organized a Seminar focused on the interface between the nutritional environment and cellular and genetic process, with the goal of arriving at a genetic understanding of how certain nutrients and bioactive components of foods affects the balance between health and diseases by altering the expression of an individual's genetic profile.

## 8.2. Invited conferences, courses and seminars

The list includes invited lectures and conferences in courses, masters, technical seminars and workshops given by researchers of the IMDEA Food Institute.

### 1. 7th Cancer Drugs Research & Development Conference

**Conference:** Preclinical development of TCD-717, a second generation of ChoK inhibitors as a new anticancer agent.

**Speaker:** Ramírez de Molina A

**Venue and date:** San Diego, California, USA. 2010 (Spain), January 2008

**Organizer:** GTCbio

### 2. Nutrition and Metabolism International Meeting

**Lecture:** Nutritional genomics for the determination of lipid metabolism alterations on nutritional-related diseases.

**Authors:** Espinosa-Salinas I, González-Vallinas M, Rodríguez-Casado A, Molina S, González-Castejón M, Marin F, Reglero G, Ramírez de Molina A.

**Venue and date:** Hotel Abades Nevada Palace. 16-19 de Junio 2010

**Organizer:** Associazione Italiana di Dietetica e Nutrizione Clinica (ADI)



**3.** Frontiers in tumour progression Nature-CNIO Conferences

**Lecture:** Effect of bioactive natural extracts in tumor progression.

**Authors:** Molina S, González-Vallinas M, García-Risco MR, Fornari T, Santoyo S, Reglero G, Ramírez de Molina A.

**Venue and date:** Palacete de los duques de Pas-trana. 24th-27th October 2010

**Organizer:** Centro Nacional de Investigaciones oncológicas, Nature, nature cell Biology and nature reviews.

**4.** IV Congress of the International Society of Nutrigenetics and Nutrigenomics ISNN

**Lecture:** Identification of a metabolic gene expression profile for the analysis of lipid metabolism alterations on nutritional-related diseases.

**Authors:** Espinosa-Salinas I, González-Vallinas M, Rodríguez-Casado A, Ramos R, Molina S, Ramírez de Molina A.

**Venue and date:** Baluarte. Palacio de Congre-sos y Auditorio de Navarra. 18th-20th Novem-ber 2010.

**Organizer:** ISNN

**5.** IV Congress of the International Society of Nutrigenetics and Nutrigenomics ISNN

**Lecture:** Nutritional Genomics for the determi-nation of the mechanism of action of the bene-ficial effect of bioactive extracts in tumor pro-gression.

**Authors:** Molina S, González-Vallinas M, Gar-cía-Risco MR, Fornari T, Santoyo S, Reglero G, Ramírez de Molina A.

**Venue and date:** Baluarte. Palacio de Congre-sos y Auditorio de Navarra. 18th-20th Novem-ber 2010.

**Organizer:** ISNN

**6.** IV Congress of the International Society of Nutrigenetics and Nutrigenomics ISNN

**Lecture:** Nutritional Genomics: SNPs selection for disease-causing genes considering protein biophysical properties.

**Authors:** González-Castejón M, Marín F, Soler C, Espinosa-Salinas I, Ramírez de Molina A, Regle-ro G, Rodríguez-Casado A.

**Venue and date:** Baluarte. Palacio de Congre-sos y Auditorio de Navarra. 18th-20th Novem-ber 2010.

**Organizer:** ISNN

**7.** Oncobio 2010

**Conference:** *Effect of bioactive natural extracts in tumor progression.*

**Authors:** González-Vallinas M, Molina S, Gar-cía-Risco MR, Fornari T, Santoyo S, Reglero G, Ramírez de Molina A.

**Venue and date:** Hospedería del Colegio Fonse-ca. 26<sup>th</sup>-27<sup>th</sup> November 2010

**Organizer:** CNIO, Universidad de Salamanca

**8.** Alimentos Funcionales en la Industria Agro-alimentaria.

**Lecture:** Pasado, presente y futuro del binomio alimentacion-salud.

**Speaker:** F. Visioli

**Venue and date:** 10<sup>th</sup>-11<sup>th</sup> November 2010.

**Organizer:** IMAP. Comunidad de Madrid.

**9.** X Congresso: Problematiche Emergenti in Car-diologia

**Lecture:** Il ruolo terapeutico dell'alimentazio-ne: che novità?

**Speaker:** F. Visioli

**Venue and date:** Colorno, Italy. 10<sup>th</sup>-11<sup>th</sup> Novem-ber 2010.

**Organizer:** Associaioni Regionali Cardiologi Ambu-latoriali.

**10.** **Lecture** Non-coding RNAs activity in dise-ase of dietary excess

**Speaker:** A. Davalos

**Venue and date:** CNIC. Madrid. 10<sup>th</sup>-11<sup>th</sup> Novem-ber 2010.

**Organizer:** Centro Nacional de Enfermedades Car-diovasculares CNIC

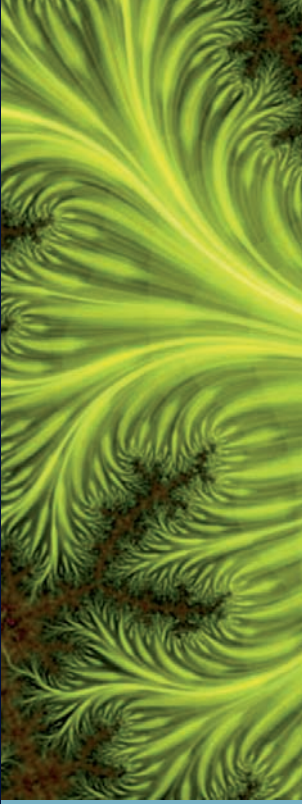
**11.** **Lecture:** Non-coding RNAs activity in dise-ase of dietary excess

**Speaker:** A. Davalos

**Venue and date:** Universidad de Leeds (UK). 22<sup>th</sup> November 2010.

**Organizer:** School of Food Science and Nutrition, Universidad de Leeds (UK)





# 9

**strategic  
alliances**

IMDEA Food Institute is strongly committed with and actively participating in national and international forums, networking, panel discussions in science and innovation, through the establishing of strategic alliances with public and private entities.

#### **Cooperation Agreement with Universidad Complutense de Madrid**

On July 2007 a Framework Cooperation Agreement was concluded between the Universidad Complutense de Madrid and IMDEA Food Institute with the aim of facilitating cooperation in research and technology development activities (R&D&I activities), participation in projects, participation in graduate programs (2007-2011).

#### **Cooperation Agreement with Universidad Politécnica de Madrid**

On November 2007 a Framework Cooperation Agreement was concluded between the Universidad Complutense de Madrid and IMDEA Food Institute with the aim of facilitating cooperation in research and technology development activities (R&D&I activities), participation in projects, participation in graduate programs (2007-2011).

#### **Cooperation Agreement with Universidad Autónoma de Madrid**

On 18 February 2008 a Framework Cooperation Agreement was concluded between the Universidad Autónoma de Madrid and IMDEA Food Institute with the aim of facilitating cooperation in research and technology development activities (R&D&I activities) and training of researchers, to regulating the use of shared spaces and equipment and cooperation between personnel of both institutions (2008-2012).

#### **Association Agreement with Madrid Science Park**

On 9 June 2008 a General Association Agreement was concluded with Madrid Science Park for cooperation between the Park and IMDEA Food Institute, with the aim of making the most of the advantages that such an association offers in terms of R&D&I activities, and more specifically in the activities and services that characterize it as a site and agent of innovation, in addition to providing

cooperative access to the network of parks in Madrid and Spain and allied agents.

#### **Cooperation Agreement with Tufts University. Boston (USA)**

On 1<sup>st</sup> Feb, 2010 was concluded a Cooperation Agreement between Tufts University, Boston (USA) and IMDEA Food Institute to promote areas of interest in teaching and research at both institutions, and to promote greater understanding in either institution of the related economic, cultural and social issues (2010-2012).

#### **International Campus of Excellence UAM+CSIC**

IMDEA Food Institute has joined the International Campus of Excellence UAM+CSIC, which was awarded International Campus of Excellence status by the Spanish Ministries of Education and Science and Innovation on 26 November 2009.

#### **Collaboration with the Consejo Superior de Investigaciones Científicas (Madrid)**

IMDEA Food collaborates with the Consejo Superior de Investigaciones Científicas for the participation of a research group at the CSIC in the development of IMDEA research activities.

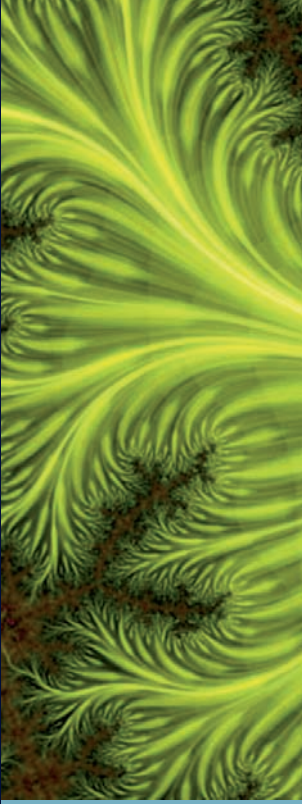
#### **Collaboration with the Hospital Universitario "Ramón y Cajal"**

IMDEA Food Institute collaborates with the Department of Biochemistry and Research of the Hospital «Ramón y Cajal» (Madrid), in the field of lipid metabolism.

#### **Collaboration with the Hospital Universitario "La Paz"**

IMDEA Food Institute collaborates with the Department of Nutrition and Dietetics, Department of Clinical Oncology and Research Unit of the Institute IdiPaz University Hospital «La Paz»(Madrid), in the field nutritional genomics.





# 10

## scientific highlights

- 10.1. **Nutritional Genomics: a new approach for understanding and improving human health [60]**
- 10.2. **Genomic research in cardiovascular diseases [62]**
- 10.3. **Novel risk factors for nutritional-related diseases and their dietary modulation [66]**
  - 10.3.1. MIRNAS [66]
  - 10.3.2. ER ST [68]

# nutritional

## Nutritional Genomics: a new approach for understanding and improving human health

Gene-environment interactions are major drivers of cardiovascular diseases, cancer, obesity, diabetes and other chronic Diseases. Among the environmental factors, diet is one the most important contributors. Thanks to recent advances in the investigation of the whole human genome, a new field has emerged that connects the human genome and its variability with the biological effects of food intake and the different responsiveness found in humans: Nutritional Genomics.

Nutritional Genomics focuses on the analysis of how bioactive substances or nutrients affect the balance between health and disease, following interactions with individual genomes. This approach allows the identification of active nutrients and of the mechanics of their beneficial effect through modulation of the human genome, making it possible to identify new genes (biomarkers) regulated by substances in diet with important roles in the onset, incidence, progression or treatment of the disease. In addition, Nutritional Genomics provides a means of understanding the modulation of the response to diet by an individual's genetic profile, followed by nutritional intervention studies focused on the development of an individualized nutrition for the prevention, mitigation or improvement of the quality of life of patients with chronic diseases. In synthesis, the ultimate goal of Nutritional Genomics is to find an optimum dietary regimen for a given individual, taking into account not only his/her nutritional needs, but also his/her genetic profile, in order to prevent the onset of different diseases or to manage them more effectively in clinical settings.

Nutritional Genomics multi-disciplinarily applies genomics, transcriptomics, proteomics, and metabolomics to human nutrition, in order to better understand the relationship between nutrition and health. Nutritional Genomics uses high-throughput genomic tools in nutrition research. Therefore, one of the essential tools of Nutritional Genomics is gene expression profiling (transcriptome level), along with similar approaches to the

# genomics

analysis of protein expression (proteome level) and to the determination of metabolites (metabolome level), in the end integrating their analyses.

At IMDEA Food Institute, we are using this multidisciplinary approach to investigate the influence of diet and individual genetic variations as risk factors for health disparities in populations. Indeed, certain genotypes are more severely affected than others by specific types of dietary factors. We are using genomics (with the latest technologies in the field such as the ABI PRISM 7900HT sequence detection system and the taqman OpenArray genotyping platform), which will be further integrated with proteomic and metabolomic analysis, in order to identify and characterize genes regulated by different bioactive constituents in foods and gene-subsets that influence the balance between health and disease, in a concerted effort to identify causative genes and new biomarkers. The ultimate aim is to palliate and/or prevent chronic diseases.

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# genomic

## Genomic research in cardiovascular diseases

Cardiovascular diseases are a heterogeneous group of disorders to which major genetic and environmental contributors have been identified. The relative weight of each of these factors has yet to be exactly assessed: there are manifold interactions among them which are still largely unknown. Moreover, little is known of the role of classic environmental factors (diet, exercise, stress, etc), and the principal genetic factors have not been identified as yet. Therefore, it will be necessary - in the coming years - to look more closely at the principal genes associated with cardiovascular diseases and at how they are modulated by the environment.

In order to investigate the genes chiefly implicated in cardiovascular diseases, a proper classification by phenotype is necessary with respect to both final (ischaemic cardiopathy, ischaemic cerebrovascular diseases, haemorrhagic cerebrovascular disease, venous thrombosis, etc) and intermediate phenotypes. Intermediate phenotypes are, in principle, easier to investigate as they are simpler to assess than the more complex final phenotype. The main intermediate phenotypes that have been investigated thus far are plasmatic concentrations of lipids and lipoproteins, arterial blood pressure, and glycaemia. In addition, other new phenotypes are being incorporated into the diagnostic array, with major emphasis on markers of oxidative stress, endothelial damage and the new characterization of metabolites in different biological samples through new advances in proteomics and metabolomics. The goals of IMDEA Food Institute include the study of these new markers in different biological samples and the investigation of the principal genes implicated in inter-individual variation and, possible, diet-driven modulation.

Exploiting the advances achieved in phenotypic characterization of various intermediate and final phenotypes of cardiovascular disease - combined with novel tools of genotyping techniques such as high-performance genotyping chips to conduct complete genome studies of varying density (100K, 500K, 1000K, etc) - it is now possible to use a novel approach to the discovery of new genes implicated in cardiovascular diseases. The last

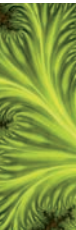
in cardiovascular diseases



# research

few years have seen a progression from the search for candidate genes based on protein functionality to “genome-wide association studies” (GWAs), which has made it possible - through statistical tests - to identify new loci associated with the different phenotypes of interest. IMDEA researchers have taken part in some of these GWAs, cooperating in the discovery of new loci associated with lipid metabolism, including two loci associated with LDL-cholesterol concentrations (1p13 near CELSR2, PSRC1 and SORT1; and 19p13 near CILP2 and PBX4), a locus with HDL-cholesterol (1q42 at GALNT2) and 5 loci with triglycerides (7q11 near TBL2 and MLXIPL, 8q24 near TRIB1, 1q42 at GALNT2, 19p13 near CILP2 and PBX4 and 1p31 near ANGPTL3). These recently-discovered loci require more detailed studies of the genes potentially implicated, of their functional variants and, lastly, of the main gene-environment interactions. This line of functional characterization is also considered as very important at IMDEA Food Institute, in addition to its participation in future GWAs and specific direct sequencings of selected samples.

Research into new genetic variants associated with different intermediate and final cardiovascular disease phenotypes requires a simultaneous study of the principal gene-environment interactions. One of the most important environmental factors is diet. However, because of its extreme complexity, diet has been the least effectively investigated factor, also owing to the difficulty of finding validated instruments with which to measure diet - with sufficient validity and precision - in large groups of individuals. IMDEA



Food Institute is specializing in the most rigorous study of diet, for which it is developing a line of research for the design and validation of dietary questionnaires. At the same time, we are working on the use of computer tools to improve management and quantification of actual diets. In parallel to dietary studies, IMDEA Food Institute is also working to develop valid instruments to standardize measurements of other environmental factors such as exercise, stress, etc. This approach copes with the recommendations made by the PhenX project in the USA, which stressed the need for standardization in the measurement of environmental exposures and phenotypes, an approach which is crucial to integrate the results of the different studies.

Once the instruments for measuring environmental exposures have been characterized and a rigorous methodology for genetic analyses has been established using different genotyping platforms on which IMDEA Food Institute researchers are working, our studies will concentrate on population surveys. To that end, sampling protocols, recruiting techniques, measurement standards, data management, integrated storage platforms, various kinds of data analysis, etc. are being optimized. All this will make it possible to undertake studies of gene-environment interactions in the principal phenotypes of interest.

The tools that have been designed for phenotypic characterizations and for genetic and environmental determinations - notably concerning diet - will enable IMDEA Food Institute's researchers to conduct nutrigenomic studies with a maximum of methodological rigor and to investigate the influence of both dietary patterns and specific components of diet on intermediate and final phenotypes of cardiovascular disease, in large-scale studies of population cohorts. One area of particular current interest is the effect of the Mediterranean diet and its components, particularly olive oil, nuts, pulses, fruits, and vegetables, on lipid phenotypes and inflammation markers. Also, the latest discoveries on the putative protective roles of coffee and cacao against diabetes and cardiovascular diseases in the American population warrants research among the Spanish Mediterranean population, in studies that include the principal regulating genes.

In addition to the observational studies on large cohorts, it is crucial to conduct nutritional intervention studies in humans with the main components of the diet whose effects are to be investigated. These compounds may include functional foods that can be developed for the food industry, to help improve cardiovascular health. Within this innovative, leading-edge line, IMDEA Food Institute is also making a special effort to include the element of genetic variability so as to better approximate inter-individual variability as a means to optimizing personalized diets.



# novel risks

## Novel risk factors for nutritional-related diseases and their dietary modulation

### 10.3.1. microRNAs

IMDEA researchers, in collaboration with international colleagues, observed that a genetic variant on the perilipin 4 (PLIN4) locus was associated with an increased risk of obesity yet, carriers with higher omega-3 fatty acid intakes tended to weigh less than carriers who consumed little or no omega-3 fatty acids. Furthermore, the researchers identified a microRNA (miRNA) which may help to elucidate the mechanism behind the gene-diet interaction.

#### microRNAs May Explain Gene-Diet Interaction

*Omega-3 fatty acid intake and body weight appear to be related in carriers of a genetic variant on the perilipin 4 (PLIN 4) gene locus.*

BOSTON/MADRID: Eating more n-3 polyunsaturated fatty acids, commonly known as omega-3 fatty acids, may help carriers of a genetic variant on the perilipin 4 (PLIN4) gene locus lose weight more efficiently. Based on this observation, researchers at the Jean Mayer Human Nutrition Research Center on Aging (USDA HNRCA) at Tufts University and at IMDEA Alimentación, identified a miRNA which may elucidate the underlying biological mechanism.

Led by Prof. Jose M. Ordovas, Director of the Nutrition and Genomics Laboratory at the USDA HNRCA and President of the Board of Trustees and Scientific Council of IMDEA Food Institute, researchers genotyped seven single nucleotide polymorphisms (SNPs), also known as gene variants, from men and women of mostly white European ancestry enrolled in the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) study and

for nutritional-related diseases  
and their dietary modulation

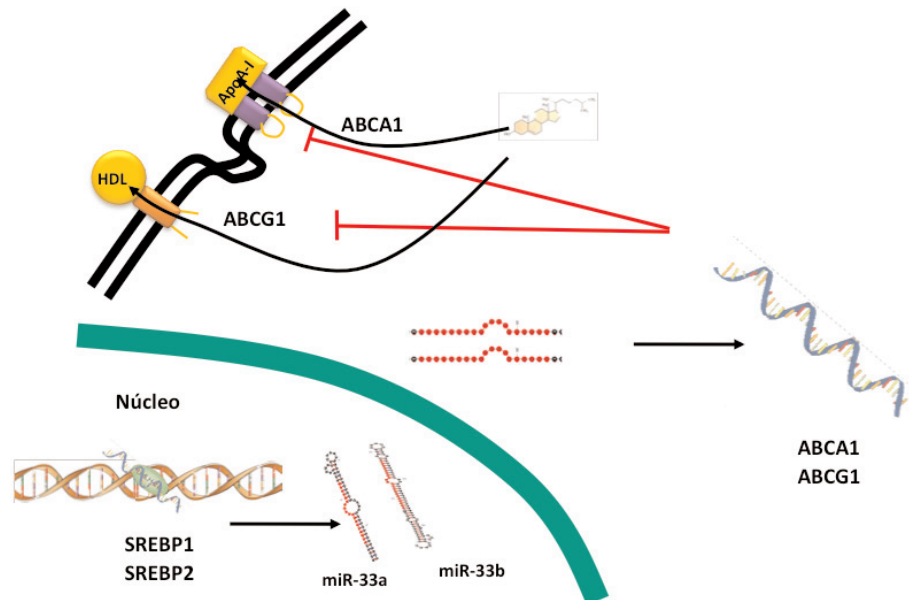
# k factors

the Framingham Offspring Study. Carriers of the gene variant tended to weigh more and exhibit higher body mass index (BMI), which would increase their risk of becoming obese. Yet, carriers with higher omega-3 fatty acid intakes tended to weigh less than carriers who consumed little or no omega-3 fatty acids.

Ordovas believes this to be the first example of a genetic variant that creates a miRNA binding site that influences obesity-related traits through a gene-diet interaction. Although further research is necessary, the findings suggest that miRNA activity is a possible target for dietary-based weight-loss therapies for obesity. The results were published online April 6 by the journal PLoS ONE.

“We tested for miRNA activity after seeing significant interactions between the gene variant, characteristics of obesity, and omega-3 fatty acid intake in our meta-analysis in two large populations,” says Ordovas, “When a gene variant is that informative, you get a strong sense that it may be functional.”

Figura. Regulation of lipid homeostasis by the bifunctional SREBPs-miR-33a/b locus



The family of perilipin genes controls the release of perilipin proteins which dictate how fat is stored and broken down in the body. The current study adds to a body of research of the perilipin gene family and its role in obesity risk, yet most of the work focuses on perilipin 1 (PLIN1). “In the past, studies have shown gene variants in the PLIN1 gene locus are associated with obesity risk and appear to be regulated by polyunsaturated fats. It is encouraging that we saw both loci expressed in similar ways,” Ordovas adds.

Ordovas and colleagues say future studies could explore the role of miRNA in both the PLIN1 and PLIN4 genes. “Variants that may create or destroy miRNA binding sites have tremendous potential for functional consequence, and we would want to investigate if this is occurring in the other perilipin genes”. “Also, replication of our results in larger populations which record the dietary information of its participants would help clarify the role of perilipin genes interacting with dietary fats such as omega-3 fatty acids and impacting weight.”

Omega-3 fatty acids are polyunsaturated fats mostly found in fatty fish such as tuna, salmon and sardines. In the recently issued 2010 Dietary Guidelines for Americans, the USDA recommends replacing saturated fatty acids with polyunsaturated and monounsaturated fats whenever possible.

### 10.3.2. ER stress

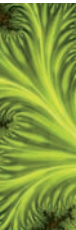
The endoplasmic reticulum (ER) is a membranous network of branching tubules and flattened sacs that is present in all eukaryotic cells. It extends throughout the cytoplasm of the cell and is contiguous with the nuclear envelope. The ER is mainly recognized as a protein-folding factory, responsible for the biosynthesis, folding, assembly and modification of numerous soluble proteins and membrane proteins. The ER seems to be a key site where intracellular signals are sensed, integrated and transmitted, allowing the coordination of downstream responses. Physiological states that increase the demand for protein folding, or stimuli that disrupt the reactions by which proteins fold, create an imbalance between the protein-folding load and the capacity of the ER, causing unfolded or misfolded proteins to accumulate in the ER lumen — a condition referred to as ER stress. Recently, a set of intracellular pathways that signal the presence of cellular stress was identified. These pathways are collectively known as the unfolded-protein response (UPR), and studies of the UPR have broadened the understanding of the mechanisms by which inflammation can be initiated. Until now, oxidatively-modified and electronegative LDL [LDL(-)] has been the only modified lipoprotein detected and characterized in plasma. Its increased concentration in hypercholesterolemia, type 2 diabetes, uremia, exhausting physical exercise, and postprandial lipemia suggested a valid correlation with increased cardiovascular disease risk. Possibly linked to increased electronegativity, the major difference between native LDL and LDL(-) is the misfolding of its apopro-





tein in LDL(-), with a marked increase in beta-sheet structure and a significant conformational shift. In brief, apoprotein misfolding and LDL aggregation can well represent the modification able to transform a cholesterol carrier into a particle that elicits atherogenic responses in the artery wall. In synthesis, the roles played by the ER and associated stress in cardiometabolism are likely to be relevant and manifold; mounting evidence indicates the ER as an important target of dietary or pharmacological intervention.

At IMDEA Food Institute, ER stress and its sequelae (as related to atherosclerosis and cardiometabolism) will be studied from at least two –somewhat specular - viewpoints. What is the contribution of ER stress in liver cells to newly-formed lipoproteins? This might bear particular importance in atherosclerosis, as the misfolding of apoB, its aggregation, resistance to proteolysis, and cytotoxicity are common motifs shared by modified LDL and amyloidogenic proteins. Based on these analogies, it has been proposed that atherogenesis could be considered as a disease produced by the accumulation of cytotoxic and pro-inflammatory misfolded lipoproteins. ER stress is exacerbated by, e.g. age and, possibly, general or localized inflammation and oxidative stress. These conditions would lead to the formation of misfolded apoproteins and, consequently, atherogenic lipoproteins. ER stress can be induced, *in vitro*, by several agents, including tunicamycin (which inhibits *N*-linked glycosylation), 2-deoxyglucose (a non-metabolically active form of glucose that results in glucose deprivation), or thapsigargin, an inhibitor of  $\text{Ca}^{2+}$  reuptake into the ER. Apoprotein misfolding can be evaluated by appropriate methods already in use, such as circular dichroism, and under further development, such as mass spectrometry, all available in our Department. What are the effects of lipopro-



teins modified by eg glycation or oxidation, on endothelial activation? What are the effects of aging and associated misfolded apoB on endothelial activation? Relevant to this issue, we have preliminary findings that link NOX4 activity to overproduction of reactive oxygen species. Notably, NOX4 is attached to the ER. We have found pharmacological means to modulate such activity and, in turn, decrease endothelial activation.

After studying the basic mechanisms, pharmacological/nutritional agents can be searched for. Suitable candidates are essential fatty acids and plants' secondary metabolites. The former act – intracellularly – as antioxidants by lowering NAD(P)H activity, while the latter stimulate cellular antioxidant response.

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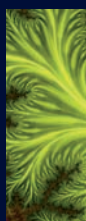
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