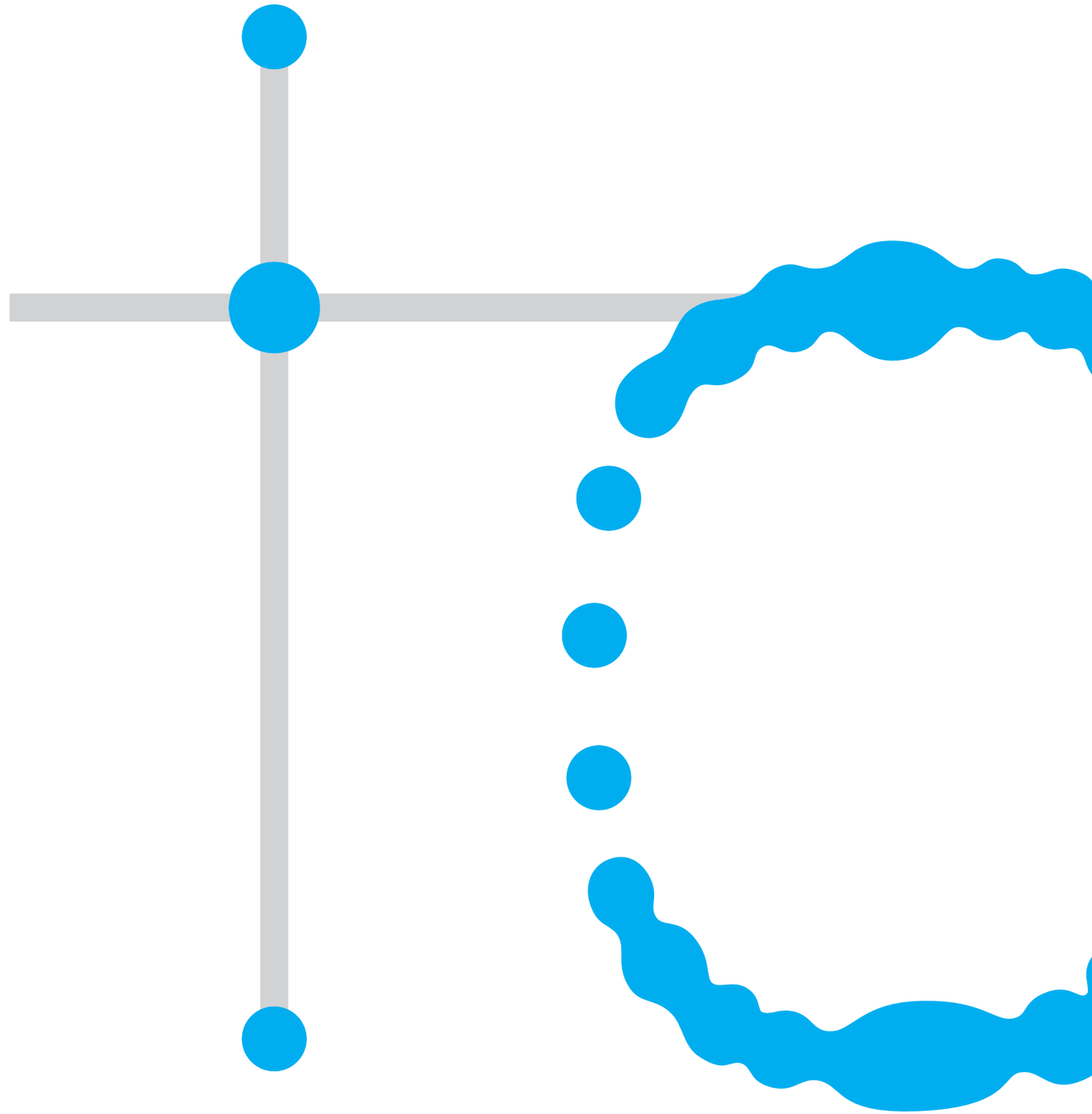
INSTITUTE FOR INTEGRATIVE SYSTEMS BIOLOGY

MEMOIR 2017-2020

Index



The Institute for Integrative Systems Biology (I²SysBio) journey started in the connected minds of several life science researchers at that time working in different fields, in different institutions and in different professional settings, but all of them convinced of the strength of research collaboration and, particularly, in the field of Systems Biology. From the beginning, effort was focused on bringing together, under the same physical and intellectual space, diverse researchers working in different disciplines, with the common trait of being collaboration pursuers and sharing the interest in building a true multidisciplinar institute where Integrative Systems Biology would happily grow.

Universitat de València (UV) and Agencia Estatal del Consejo Superior de Investigaciones Científicas (CSIC) signed the foundational agreement of I2SysBio in 2016, this is five years after the first seed of the institute was sown. One year later, in 2017, the I2SysBio began its journey. In these four years period (2017-2020) under the direction of Prof. José Luis García and Juli Peretó the institute has completed the incorporation of research groups, moving from both institutions, and, also, from its ally biotech company ADM Biopolis, which signed a permanent collaboration agreement even before the institute foundation. More important, during these years I²SysBio has steadily and quickly increased its scientific staff. It is a great pleasure to observe the ability of our staff researchers to recruit young scientists interested in acquiring training with us, and also to note the attractiveness and interest of our institute for established researchers outside our borders who are committed to strengthening our potential with their brilliant careers. Not with less efforts, today our technical and administrative support staff has also increased, which is gradually providing us with a more efficient management of our resources and our research capacity.

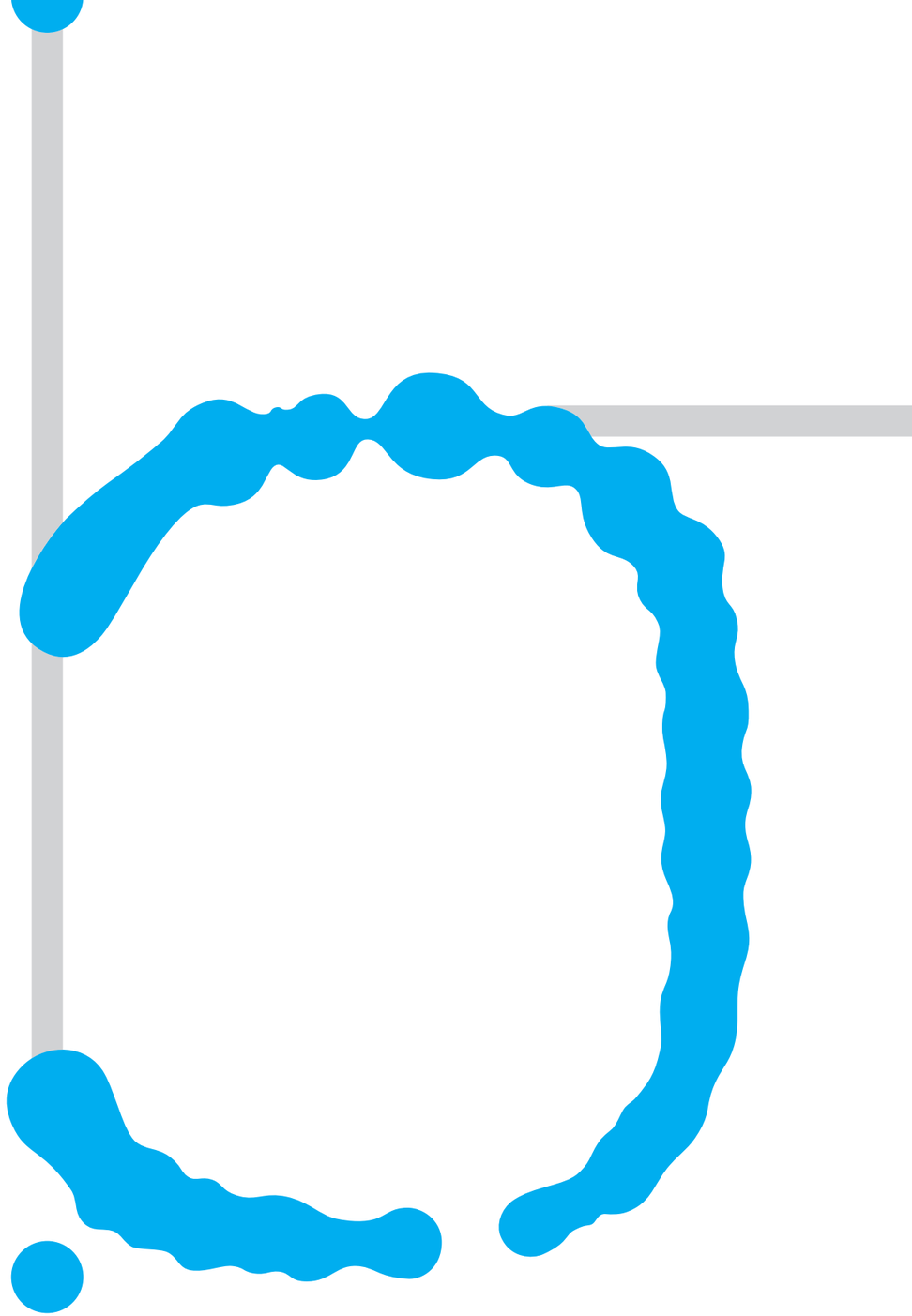
Although our infrastructures are not yet complete, we have also seen significant improvements in our scientific equipment and services so that our research groups can use new methodologies and approaches, allowing us to face new challenges. This is also reflected in the diversification of national and international funding sources and new projects, as well as in many strategic collaborations inside and outside our walls, and in a growing number of contracts with companies based on knowledge transfer projects.

I2SysBio has a vocation for internationalization, self-demanding and real progress in the horizons towards which it is moving. For this reason, we set up an external scientific advisory board to monitor our activity, which we hosted at our institute for the first time in December 2019. The ability of the new direction team to react to its advice has been limited, like many other things, by the restrictions and limitations of the health crisis, but we know that we have important pending tasks to maintain our course and pace towards a reference institute in Integrative Systems Biology, inside and outside Spain. However, and making true the saying that “every crisis brings new opportunities”, I²SysBio has matured and strengthened throughout the year 2020, despite the significant setbacks we have suffered. The great potential of our institute to provide new and tangible solutions from Systems Biology to the needs of society has become clearly evident, and we have been happy and proud to be part of this contribution by belonging to I²SysBio.

The new direction team of this still short adventure feel very honored to write these introductory words to our first scientific report, and also very excited about the harvest that we are beginning to reap from the efforts of all our personnel that give life to this institute.

From left to right: Vicent Soler (Minister of Finance and Economic Model), Rosa Menéndez (President of the CSIC), Carmen Vela (Secretary of State for Research, Development, and Innovation), Esteban Morcillo (Rector of the University or Valencia), José Luis García (I2SysBio Co-director 2016-2020), Juli Peretó (I2SysBio Co-director 2016-2020), José Pío Beltrán (Institutional delegate of the CSIC in the Valencia Community). Official inauguration of the building, 6 February 2018.

From left to right: Emilia Matallana and Santiago F. Elena codirectors from 2020.



GENERAL INFORMATION

2011 2011 Memorandum of understanding UV-CSIC. 11 November.

2012 2012-2014 Development of the scientific project and building design.

2013

2014 2014 Beginning of building works. February.

2015 2015 Signature of UV-CSIC-ADM-BIOPOLIS agreement. 2 October.

2016 2016 First I²SysBio publication. 5 February.
2016 Signature of UV-CSIC agreement. March 8.
2016 Co-directors appointment. June 1.

2017 2017 First research groups move to the new building. March 21.
2017 First Expociencia participation. May 28.
2017 GVA decree as University Institute. September 1.

2018 2018 Official inauguration of the building. February 6.
2018 Board of Trustees first meeting. October 29.

2019 I²SysBio-CRM Associated Unit. May 6.
2019 I²SysBio SAB first meeting. December 5.

2020 2020 New Co-Directors appointment. August 10.

Introduction

The I²SysBio is a joint research institute involving Universitat de València (UV) and Agencia Estatal Consejo Superior de Investigaciones Científicas (CSIC), open to strategic alliances with biotech companies. The institute is located in a building that was completed at the end of 2015 in the Scientific Park (Parc Científic, Campus Burjassot-Paterna) of the UV. The foundational agreement of I²SysBio was signed by CSIC and UV in March 2016. The first research groups moved into the new building in March 2017, and the centre was officially inaugurated in February 2018.

The I²SysBio Scientific Programs focus on research into structure, function, dynamics, evolution, and manipulation of complex biological systems. The mission of I²SysBio can be defined within five areas of action:

CREATE a multi- and inter-disciplinary work environment where scientists from different backgrounds work together dynamically and continuously to solve common problems.

DEVELOP high-quality research and achieve excellence in the field of integrative systems biology.

PRODUCE high value-added knowledge with potential transfer to industry.

TRAIN researchers in a multidisciplinary field with broad future projection.

BOOST the development of integrative systems biology in Spain.

The I²SysBio's aim is to become an international reference center in the development of integrative systems biology and, in particular, from an evolutionary perspective. At the same time, the I²SysBio seeks to provide solutions to problems that may arise in the pharmaceutical, biotechnological, biomedical and agribusiness sectors that are open to a systems approach (e.g., through metabolic engineering and synthetic biology).
The I²SysBio is backed by a Scientifc Advisory Board (SAB) composed of recognized researchers in the area of Integrative Biology of Systems.

Structural information

Scientific Committees

Scientific Committee

Tomás Matus
Transcriptional Orchestration of Metabolism

Rafael Sanjuán
Virus Experimental Evolution

Carlos García Ferris
Evolutionary Genetics

Javier Buceta
Theoretical and In Silico Modeling of Biological Systems

Juli Peretó (chair)
Biotechnology and Synthetic Biology

Scientific Advisory Board (SAB)

Susanna Manrubia, Chair
Group of Evolutionary Systems and Interdisciplinary Group of Complex Systems,
National Biotechnology Centre, CSIC, Madrid.

Sebastian Bonhoeffer
Department of Environmental Systems Science, Institut für Integrative Biologie, ETH, Zürich

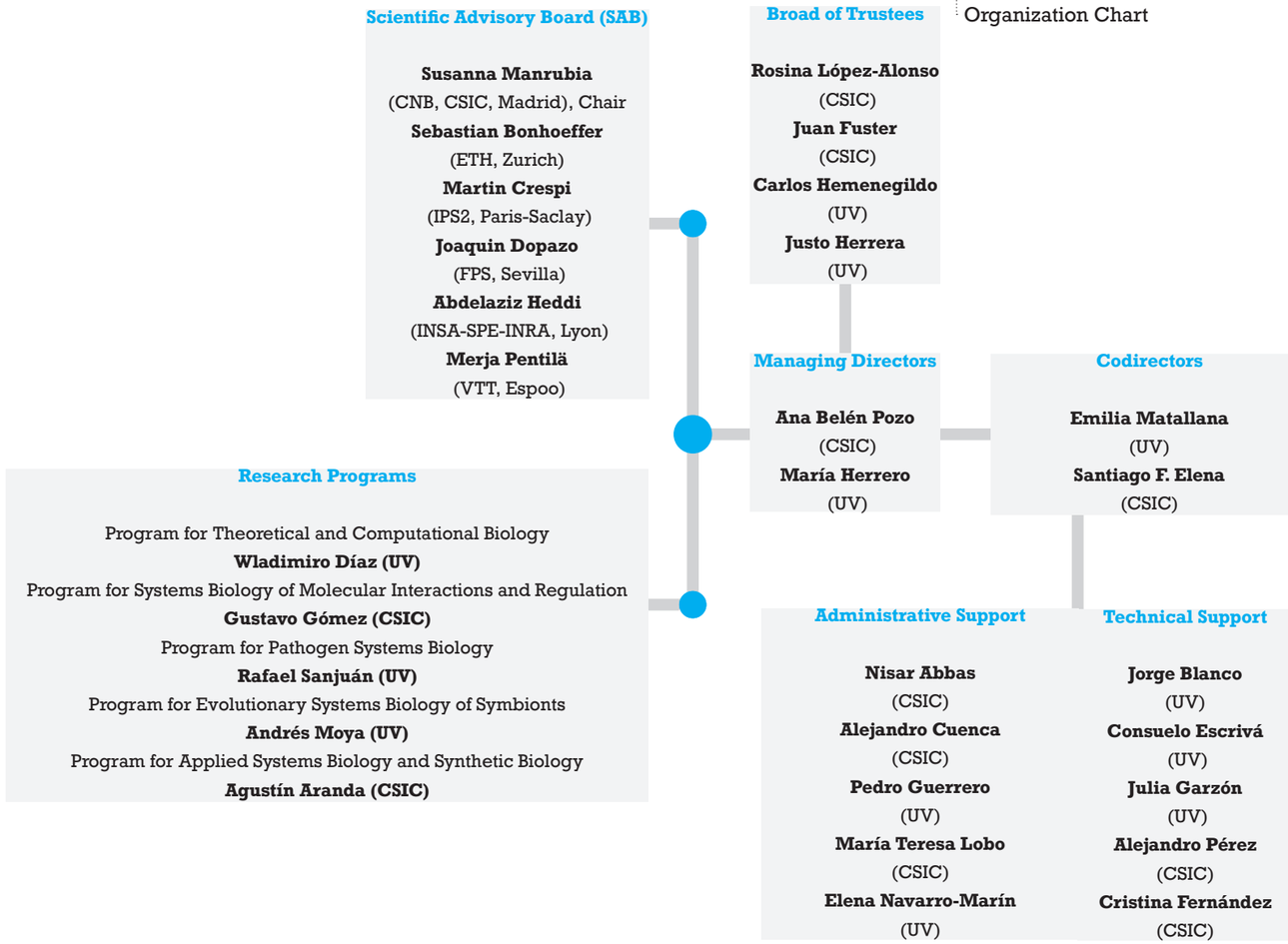
Martin Crespi
Department of Developmental Genomics and Genetics, Institute of Plant Sciences Paris Saclay,
Gif-sur-Yvette

Joaquin Dopazo
Clinical Bioinformatics Area, Progress and Health Foundation, Virgen del Rocío Hospital, Sevilla

Abdelaziz Heddi
Biologie Fonctionelle, Insectes et Interactions, UMR INSA-SPE-INRA, Lyon

Merja Penttilä
Industrial Biotechnology and Food Solutions, VTT Technical Research Centre of Finland, Espoo

Organization Chart

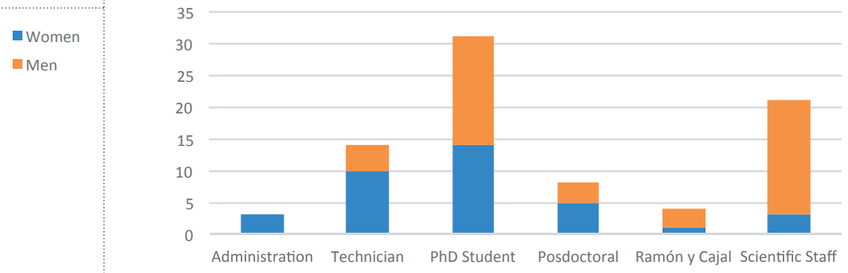


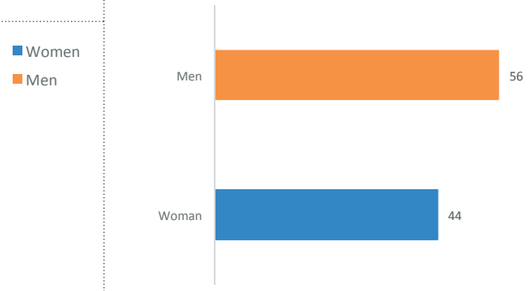
The diagram represents the organization of I²SysBio in 2020. From 2015 to 2019 José L. García (Director) and J. Peretó (Vice-director) were on duty.

Statistics

I²SysBio Staff

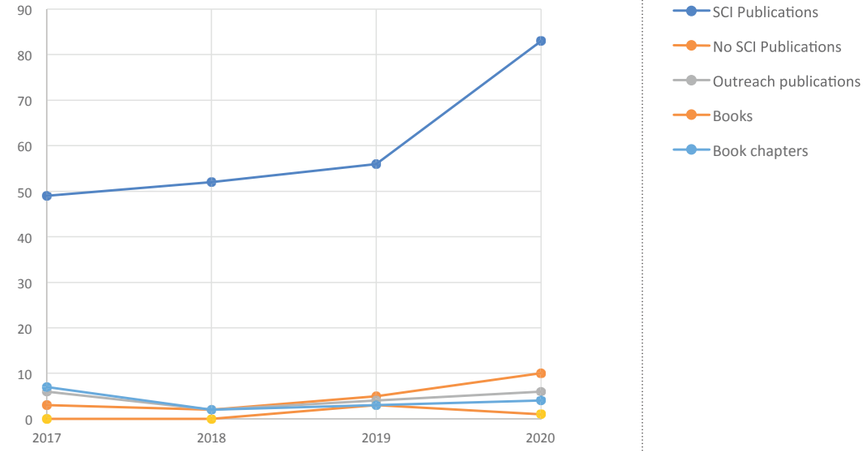
	Woman	Men
Administration	3	0
Technician	10	4
PhD Student	14	17
Posdoctoral	5	3
Ramón y Cajal	1	3
Scientific Staff	3	18
Total	44	56

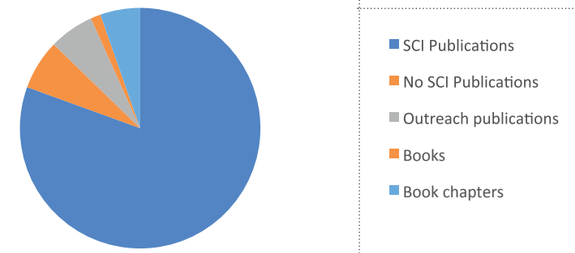




Scientific Production

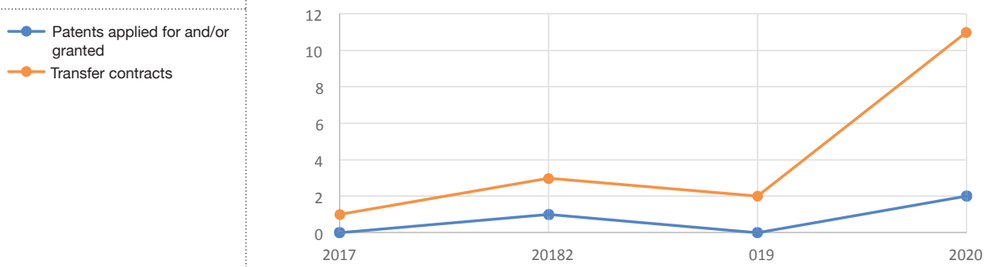
	2017	2018	2019	2020	Totals
SCI Publications	49	52	56	83	240
No SCI Publications	3	2	5	10	20
Ourtreach publications	6	2	4	6	18
Books	0	0	3	1	4
Book chapters	7	2	3	4	16

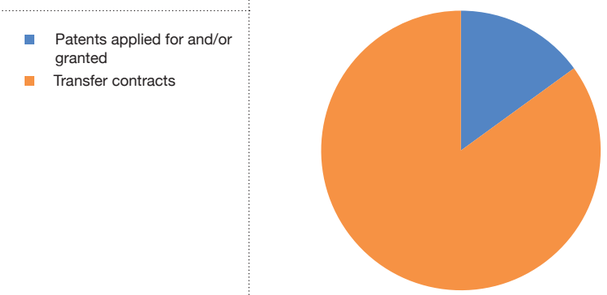




Technological transfer

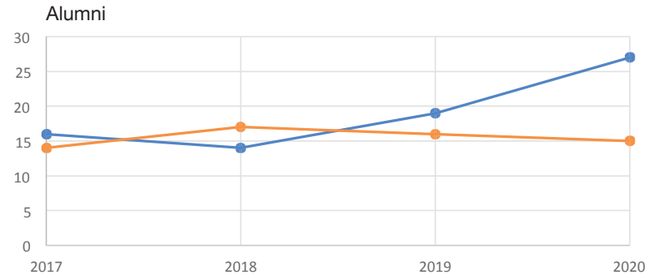
	2017	2018	2019	2020	Totals
Patents applied for and/or granted	0	1	0	2	3
Transfer contracts	1	3	2	11	17

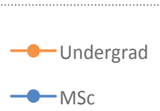


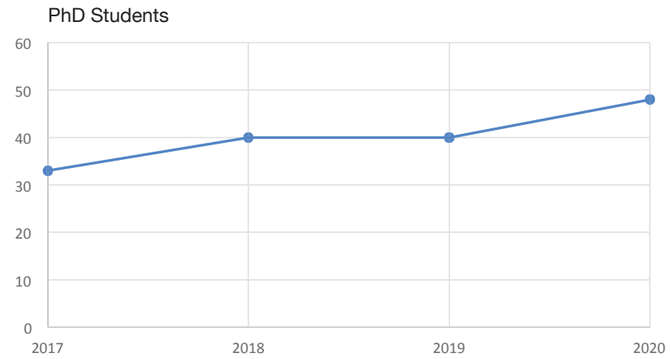


Human resources

	2017	2018	2019	2020
PhD Students	33	40	40	48
PhD	9	3	8	6
MSc	16	14	19	27
Undergrad	14	17	16	15

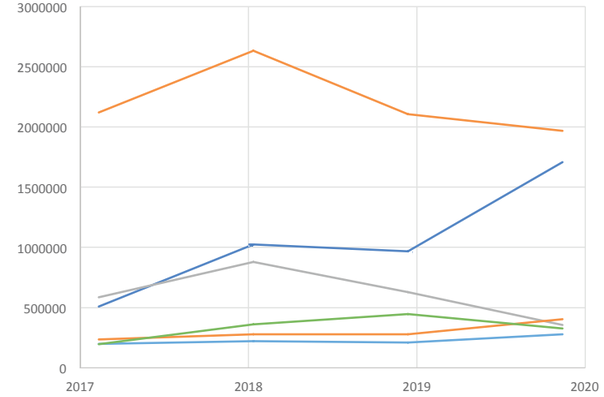


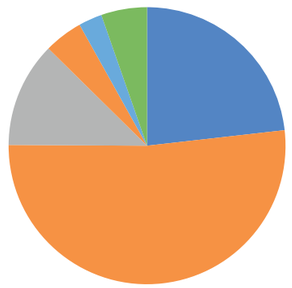




Budget

	2017	2018	2019	2020	Totals
National grants (€)	426480,63	989910,63	925972,97	1734086,41	4076450,64
International grants (€)	2184821,00	2742258,40	2167197,40	2017483,40	9111760,20
Regional grants (€)	511816,50	829710,35	557731,25	260233,25	2159491,35
Private grants (€)	128487,64	174416,78	177132,98	312849,93	792887,33
Private contracts (€)	88487,64	114454,78	102170,98	177187,93	482301,33
Others (€)	86333,33	266562,87	360033,00	227992,00	940921,20





Mural by artist Paula Bonet in the lobby of the I²SysBio, created in October 2016.

Contact information

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Parc Cientific
C/ Catedrático José Beltrán, 2
46980 Paterna Valencia

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Social Network
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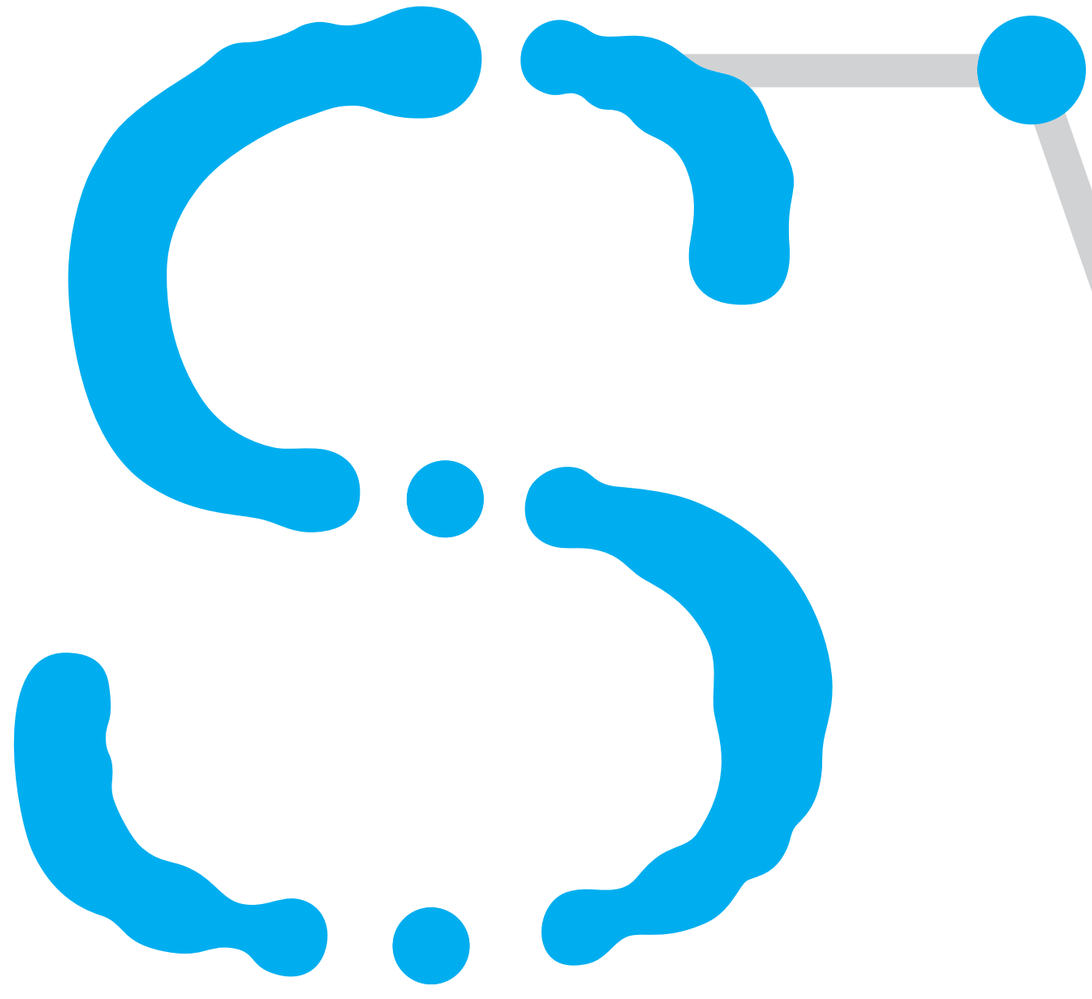
Facebook: https://www.facebook.com/i2sysbio/
Instagram: https://www.instagram.com/i2sysbio/



ACTIVITIES OF THE CENTER

Research programs and research groups

Program for Theoretical and Computational Biology

Program for Systems Biology of Molecular Interactions and Regulation

Program for Pathogen Systems Biology

Program for Evolutionary Systems Biology of Symbionts

Program for Applied Systems Biology and Synthetic Biology

New incorporations

Program for Theoretical and Computational Biology

The Theory, Bioinformatics and Computing group (TBC) is a starting integrated activity of I²SysBio members sharing a diverse research experience based on a strong mathematical and computational background. Our mission is to be the reference group at I²SysBio in management, analysis and modelling of large biological datasets. In this sense, part of our research is expected to be integrated within experimental lines of other Scientific Programs run at I²SysBio. Current work is based on new mathematical methods and big data high performance computing applied to genomic and metagenomic data. In recent years, the group has carried out relevant research in the fields of metagenomics, health genomics and the development of tools for the analysis and visualisation of bioinformatic data.

Head of the group

Vicente Arnau
Associated Professor, UV

Wladimiro Díaz
Associated Professor, UV

Carlos Peña-Garay
Tenured Scientist, CSIC

Other members

María José Olmo
Predoctoral contract, FPI Program

José Manuel Martí
Predoctoral contract, FPI Program

José Miguel Juanes
Predoctoral contract, project UV

Samuel Pique
Postdoctoral contract

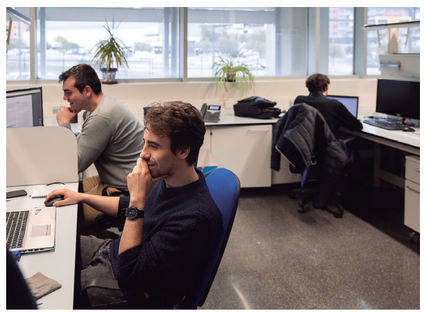
Elena Cristina Rusu
Predoctoral contract, FDEGENT Program

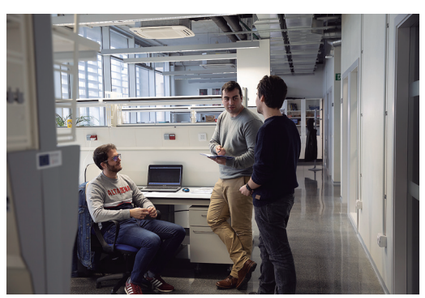
Antonio Fabregat
Technician contract

Theory, Bioinformatics and Computing group (TBC)

Metagenomics and high performance computing.

The Theory, Bioinformatics and Computing group (TBC) is a starting integrated activity of I²SysBio members sharing a diverse research experience based on a strong mathematical and computational background. Our mission is to be the reference group at I²SysBio in management, analysis and modelling of large biological datasets. TBC main research area is time evolution of biological systems. Current work is based on new mathematical methods and big data high performance computing applied to longitudinal metagenomic data. Other research areas include the development of tools for the detection of virus insertion in the human genome, the definition of methodologies for the search of new viruses in plasma and the characterisation of metabolic pathways from proteomic data. Members of the group have joined other I²SysBio groups in the request for funds to the National Research Program with projects focused on identifying early-warning markers of phase transitions between health and disease states during viral infections or the modelling of the human microbiome spatial and time evolution. The group, with the collaboration of I²SysBio, is proposing to establish a centre of reference in extremophiles and astrobiology studies in low radioactivity based at the Canfranc Underground Laboratory (LSC).
We have participated in the development of Reactome software, an intuitive bioinformatics tool for the visualization, interpretation and analysis of knowledge of metabolic pathways. We develop new methodologies for the study of the complexity of genomes, proposing new metrics for the evolutionary characterization of genomes. We make extensive use of the extraordinary I²SysBio computing system.





Relevant publications

Antonio Fabregat, *et al.* (2017).
Reactome pathway analysis: a highperformance in-memory approach.
BMC Bioinformatics.

José M. Juanes, *et al.* (2017).
VISMapper: ultra-fast exhaustive cartography of viral insertion sites for gene therapy.
BMC Bioinformatics 18:421.

Moreno-Picot, S, *et al.* (2018).
Efficient Analysis and Synthesis Using a New Factorization of the Gabor Frame Matrix.
IEEE Transactions on Signal Processing, 66 - 17, pp. 4564 – 4573.

Ener C. Dinleyici, *et al.* (2018).
Time series analysis of the microbiota of children suffering from acute infectious diarrhea and their recovery after treatment.
Frontiers in Microbiology, (2018) 9, 1230.

Jose Manuel Martí (2018).
Robust analysis of time series in Virome Metagenomics. The Human Virome.
Methods in Molecular Biology (2018) vol 1838 Humana Press. N. Y.

Jose Manuel Martí (2019).
Recentrifuge: robust comparative analysis and contamination removal for metagenomics.
PLOS Computational Biology (2018) 15:6.

Jose Manuel Martí, *et al.* (2020).
Metatranscriptomic dynamics after Verticillium dahliae infection and root damage in Olea europaea.
BMC Plant Biology 20:79.

Carlos Llorens, et al. (2020).
Reverse-transcribing viruses of the families Belpaoviridae, Metaviridae and Pseudoviridae (order Ortervirales).
Reference Module in Life Sciences.

Almudena Devesa-Peiro, et al. (2020).
Uterine disorders affecting female fertility: what are the molecular functions altered in endometrium?. Fertility and Sterility.
Volume 113, Issue 6, June 2020, Pages 1261-1274.

Andrés Moya, et al. (2020).
Driven progressive evolution of genome sequence complexity in Cyanobacteria.
Scientific Reports volume 10, Article number: 19073 (2020).

Projects

MECANISMOS MOLECULARES Y RUTAS PARTICIPANTES EN LA INTERCONEXIÓN ENTRE TRANSCRIPCIÓN Y DEGRADACIÓN DE MRNAS DURANTE LAS RESPUESTAS AL ESTRÉS EN LEVADURAS.
Financial entity: Conselleria d'Educació i Ciència.; GEVA - Generalitat Valenciana. PRGV - Programa Prometeo (GV).
Duration: from 01/01/2015 until 31/12/2018.
Total amount to the group: 216.400,00 €.

HOMEOSTASIS MOLECULAR EN EL DOGMA CENTRAL. RECAMBIO DE MRNAS Y PROTEÍNAS Y LOS MECANISMOS DE COMUNICACIÓN CRUZADA ENTRE ELLOS. PROYECTO MINECO.
Financial entity: Ministerio de Economía y Competitividad.
Duration: from 01/01/2016 until 31/12/2020.
Total amount to the group: 181.500,00 €.

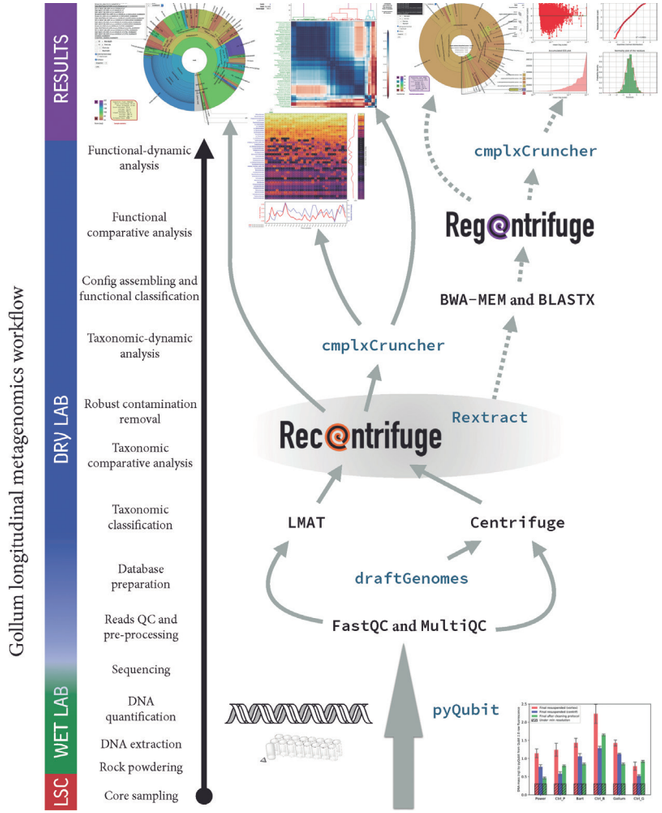
ASESORAMIENTO PARA LA EJECUCIÓN DEL PROYECTO DE DESARROLLO DE UNA APLICACIÓN DE AUTORÍA DE LISTADOS DE SECUENCIAS DE NUCLEÓTIDOS Y AMINOÁCIDOS EN FORMATO ST26.
Financial entity: EVERIS SPAIN, S.L.
Duration: from 31/07/2018 until 30/1/2019.
Total amount to the group: 10.176,40 €.

APLICACIÓN DE TECNOLOGÍAS Y DATOS ÓMICOS Y BIOCOMPUTACIÓN AL ÁMBITO AGROALIMENTARIO.
Financial entity: AINIA.
Duration: from 01/08/2019 until 31/12/2019.
Total amount to the group: 2720€.

FUSIÓN MULTIMODAL DE GRANDES DATOS PARA PROPORCIONAR UN SOPORTE AFECTIVO Y COGNITIVO DE BAJO COSTE EN CONTEXTOS DE APRENDIZAJE. PROYECTO MINECO.
Financial entity: Ministerio de Economía y Competitividad.
Duration: from 01/01/2015 until 31/12/2019.
Total amount to the group: 77.319€.

PAPEL DEL CÓDIGO EPIGENÓMICO DEL HUÉSPED EN LA EVOLUCIÓN DE LAS POBLACIONES VIRALES.
PID2019-103998GB-I00.
Financial entity: Ministerio de Ciencia, Innovación y Universidades.
Duration: from 01/01/2020 until 31/12/2022.
Total amount to the group: 290.400,00 €.

APPLICATION OF EXTREME RESOLUTION NEXT-GENERATION SEQUENCING FOR ILLUMINATING FUNDAMENTAL ASPECTS OF VIRAL EVOLUTION AND PATHOGENESIS.
Financial entity: Conselleria de Innovación, Universidades, Ciencia y Sociedad Digital.
Duration: from 01/01/2020 until 31/12/2021.
Total amount to the group: 40.000€



Recentrifuge plots of the evolution of fungal MTS classified reads at species level during the V. dahliae infection.

CAMBIOS CON LA EDAD DE LAS INTERACCIONES DEL MICROBIOMA CON SU HOSPEDADOR HUMANO Y DETERMINACIÓN DE UN NUCLEO PERMANENTE DE SIMBIONTES MUTUALISTAS.
PID2019-105969GB-I00.
Financial entity: Ministerio de Ciencia, Innovación y Universidades.
Duration: from 01/01/2020 until 31/12/20203.
Total amount to the group: 290.400€.

Head of the group

Javier Buceta Fernández
Teanured Scientist, CSIC

Other members

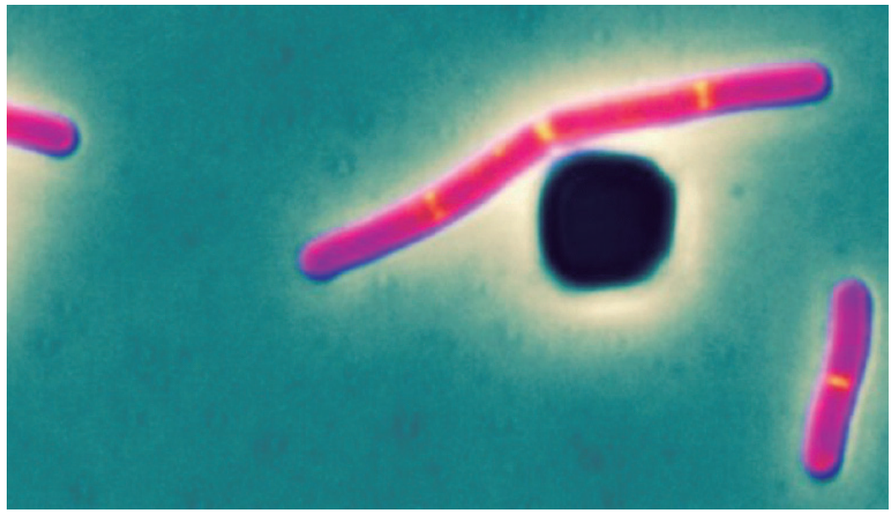
Yanyan Chen
Postdoc at Dr. Frank Zhang
(Lehigh University, Bethlehem, USA)

Samira Anbari
Teaching Assistant at the Chemical and Biomolecular Engineering Dept.
(Lehigh University, Bethlehem, USA)

Theoretical and In Silico Modeling of Biological Systems

We are interested in understanding the problem of growth and size/shape homeostasis in biology.

This topic includes the regulation of size at the cellular level and the interplay between mechanical cues and gene regulation to trigger division. At the collective level we are trying to elucidate, and formalize, the mechanisms shaping tissues. Questions of interest include, are the mechanisms to reliably achieve the elongation of tissues and their 3D packing. Finally, we are interested in combining approaches from big data and modeling to understand how viral zoonoses propagate and lead to outbreaks.



Recentrifuge plots of the evolution of fungal MTS classified reads at species level during the *V. dahliae* infection.

Relevant publications

Anbari S, Buceta J (2020). Self-sustained Planar Intercalations Due to Mechanosignaling Feedbacks Lead to Robust Axis Extension During Morphogenesis. *Scientific Reports (Nature)* 10:10973

Mageeney C, et al. (2020). Mycobacterium Phage Butters-Encoded Proteins Contribute to Host Defense against Viral Attack. *MSystems* 5:e00534-20

Canela-Xandri O, et al. (2020). TiFoSi: an Efficient Tool for Mechanobiology Simulations of Epithelia. *Bioinformatics* 36:4525

Deter HS, et al. (2020). A Cell Segmentation/Tracking Tool Based on Machine Learning. *Methods in Molecular Biology* 2040:399

Chen Y, Buceta J. (2019). A Non-Linear Analysis of Turing Pattern Formation. *PLoS ONE* 14:e0220994

Gómez-Gálvez P, et al. (2018). Scutoids are a Geometrical Solution to 3D Packing of Epithelia. *Nature Communications* 9:2960

Chen Y, Buceta J. (2018). A Markovian Approach Towards Bacterial Cell Size and Homeostasis in Anomalous Growth Processes. *Scientific Reports (Nature)* 8:9612

Fiorillo G, et al. (2018). A Predictive Spatial Distribution Framework for Filovirus-Infected Fruit Bats. *Scientific Reports (Nature)* 8:7970

Li H, et al. (2018). Differentiation of Live and Heat-killed E. coli by Microwave Impedance Spectroscopy. *Sensors and Actuators C: Chemical* 255:1614

Buceta J. (2017). Finite Cell-Size Effects on Protein Variability in Turing Patterned Tissues. *J. Royal Society Interface* 14:20170316

Projects

MECHANOBIOLOGY OF E. COLI FILAMENTATION AND EPITHELIAL REMODELING (FILEMON)
Funding Agency: Ministerio Ciencia e Innovacion (Plan Nacional) PID2019-105566GB-I00
Institutions: CSIC
From: 2020, until: 2023
Principal Investigator(s): J. Buceta
Amount: 205,700EUR

CATASTROPHE MODELING FOR NATURAL DISASTERS AND HEALTH RELATED THREATS
Funding Agency: Research FUTUREs (Lehigh Intramural Competitive Funds)
Institutions: Lehigh University
From: 2020, until: 2022
Principal Investigator(s): J. Buceta/P. Bocchini/D. Conus/B. Davison
Amount: $249,775

USING A QUEUEING FRAMEWORK TO EXPLORE THE DESIGN PRINCIPLES OF SYNTHETIC CIRCUITS IN MICROORGANISMS
Funding Agency: National Science Foundation (NSF), Systems and Synthetic Biology Program, #1922542
Institutions: South Dakota University/ Lehigh University
From: 2019, until: 2023
Principal Investigator(s): J. Buceta/N. Butzin/M. Nepal
Amount: $1,138,000

SCUTOIDS AS A NEW PARADIGM OF CELLULAR ORGANIZATION IN TISSUES: BIOMECHANICS AND TOPOLOGY
Funding Agency: FIG Grant (Lehigh University Intramural Competitive Funds)
Institutions: Lehigh University
From: 2019, until: 2020
Principal Investigator(s): J. Buceta
Amount: $30,000

RISK ASSESSMENT OF EBOLA OUTBREAKS THROUGH PROBABILISTIC MODELING OF CHIROPTERA ZOONOTIC DYNAMICS AND SOCIOECONOMIC FACTORS
Funding Agency: NIH 1R15GM123422-01A1
Institutions: CSIC/Lehigh University
From: 2018, until: 2020
Principal Investigator(s): J. Buceta/P. Bocchini
Amount: $441,605

Other achievements

Sigma Xi (Scientific Research Honor Society) Fellow, 2020

ISA Award (International Projection), 2020

Excellence in Research Scholarship and Leadership Award (P.C. Rossin Engineering College, Lehigh University), 2019

Program for Systems Biology of Molecular Interactions and Regulation

The main objective of this program is to study molecular interactions in a broad sense. These range from the identification and analysis of regulatory networks, the study of physical interactions between proteins or between transcription factors and promoters, to the covariation in expression and accumulation of mRNAs and metabolites.

In addition to processes like transcriptional and translational regulation, this Program will also address non-coding RNA-mediated regulation and the effect of stochasticity on these processes. Finally, we also aim to analyze these interactions within an evolutionary context.

The Program combines experimental approaches using omics-based techniques and high-throughput analytical techniques interactions with mathematical and statistical methods of interaction inference and analysis.

Biosystems Design

Head of the group

Guillermo Rodrigo
Tenured Scientist, CSIC

Other members

Rafael Ballesteros-Garrido
Postdoctoral contract

María-Carmen Marqués
Postdoctoral contract

Raúl Ruiz.
Postdoctoral contract. Roswitha Dolcemascolo (Predoctoral contract)

Rosa Márquez Costa
Predoctoral contract

María Heras-Hernández
Predoctoral contract

Lucas Goiriz
Predoctoral contract

Roser Montagud Martínez
Technician contract

Arantxa Rosado
Technician contract

Biosystem Design: Our research combines systems biology with synthetic biology.

Relevant publications

Montagud-Martinez R, *et al.* (2020) Probing the operability regime of an engineered ribocomputing unit in terms of dynamic range maintenance with extracellular changes and time. J. Biol. Eng. 14: 12.

Rodrigo G (2019) Ab initio noise-mean scaling laws in gene expression. Phys. Rev. E 100: 032415.

Ballesteros-Garrido R, *et al.* (2019) Bacterial population control with macroscopic HKUST crystals. ACS Appl. Mater. Interfaces 11: 19878-19883.

Rodrigo G, Stocks NG (2018) Suprathreshold stochastic resonance behind cancer. Trends Biochem. Sci. 43: 483-485.

Cordero T, *et al.* (2018) Boolean computation in plants using post-translational genetic control and a visual output signal. ACS Synth. Biol. 7: 2322-2330.

Rosado A, *et al.* (2018) Binary addition in a living cell based on riboregulation. PLoS Genet. 14: e1007548.

Cervera H, *et al.* (2018) Viral fitness correlates with the magnitude and direction of the perturbation induced in the host's transcriptome: the tobacco etch potyvirus - tobacco case study. Mol. Biol. Evol. 35: 1599-1615.

Rodrigo G (2018) Post-transcriptional bursting in genes regulated by small RNA molecules. Phys. Rev. E 97: 032401.

Rodrigo G, and Farés MA (2018) Intrinsic adaptive value and early fate of gene duplication revealed by a bottom-up approach. eLife 7: e29739.

Projects

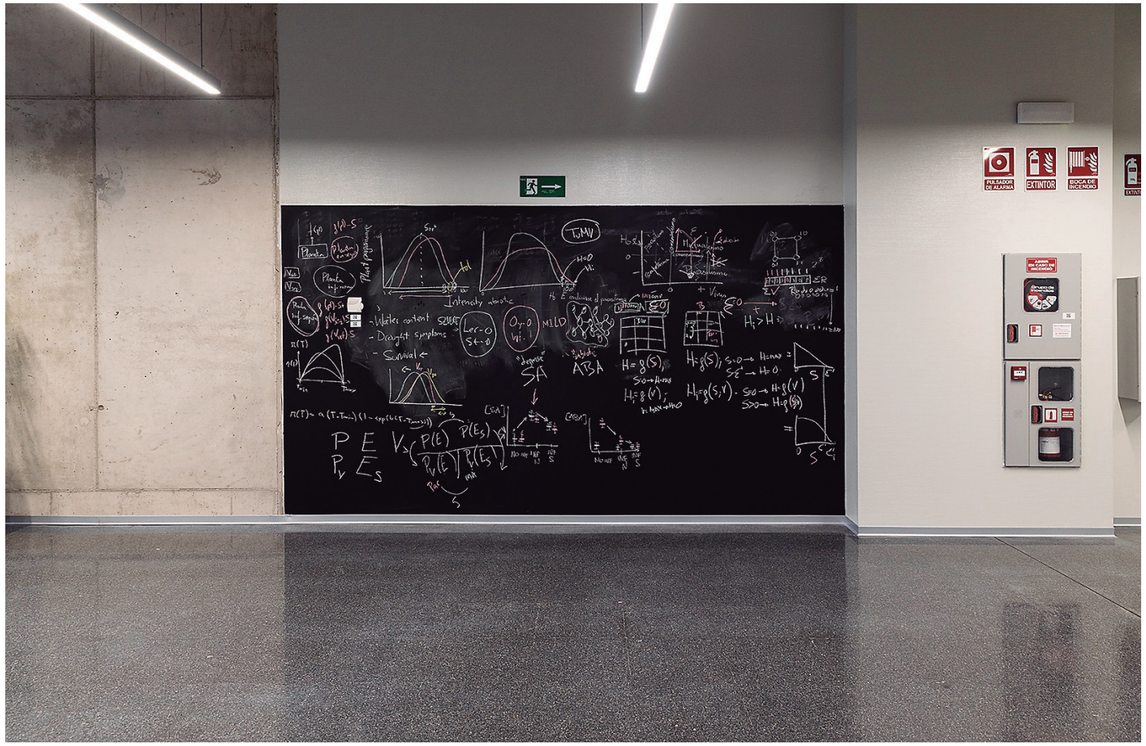
IMPORTANCIA Y RESULTADOS PRÁCTICOS DE SISTEMAS DE DIAGNÓSTICO PERSONALIZADO Y AUTO-DIAGNÓSTICO EN LA PANDEMIA DE COVID-19.
Financial entity: Fundación General CSIC (FGCCLC-2021-0005).
Duration: from 2020 to 2021.
Total amount to the group: 3.000 €.

RAPID, ULTRASPECIFIC, AND PORTABLE SARS-COV-2 DIAGNOSTICS BASED ON CRISPR-CAS TECHNOLOGIES AND COMMERCIAL IMMUNOCHROMATOGRAPHIC ASSAY STRIPS (COV-CRISPIS).
Financial entity: CRUE – Banco Santander (Fondo Supera Covid-19).
Duration: from 2020 to 2021.
Total amount to the group: 150.000 € .

PROGRAMMABLE RIBONUCLEOPROTEINS THAT REGULATE TRANSLATION FOR CIRCUIT SEQUENCE-TO-FUNCTION DESIGN IN BIOTECHNOLOGY (RNAPLUSPLUS).
Financial entity: Geralitat Valenciana (SEJI/2020/011).
Duration: from 2020 to 2022.
Total amount to the group: 199.035 €.

SYSTEMS BIOLOGY OF SYNTHETIC RIBOREGULATION: THERMODYNAMICS, NOISE, AND OPERABILITY (SYSY-RNA).
Financial entity: Ministerio de Ciencia, Innovación y Universidades, Gobierno de España (PGC2018-101410-B-I00).
Duration: from 2019 to 2021.
Total amount to the group: 175.000 € .

ENABLING PROTEINS WITH RNA RECOGNITION MOTIFS FOR SYNTHETIC BIOLOGY AND BIO-ANALYTICS (RNACT).
Financial entity: European Commission (H2020-MSCA-ITN-2018 #813239).



Duration: from 2020 to 2022.
Total amount to the group: 250.900 €

THEORETICAL AND EXPERIMENTAL ANALYSIS OF THE STIMULUS-RESPONSE DYNAMICS OF GENETIC SYSTEMS WITH INTERLINKED POSITIVE AND NEGATIVE FEEDBACKS.
Financial entity: Geralitat Valenciana (GV/2016/079).
Duration: from 2016 to 2017.
Total amount to the group:16.000 €.

Head of the group

Gustavo Gómez
Senior Scientist, CSIC

Other members

María Carmen Márques
Postdoctoral contract

Joan Márquez Molins
Predoctoral contract, Generalitat Valenciana

Pascual Villalba Bermell
Predoctoral contract

Andrea Gabriela Hernández
Predoctoral contract

Alejandro Sanz Carbonell
Predoctoral contract

Antonio Bustamante.
Predoctoral contract, SENECYT

Luis Cervera Seco
Student, JAE-INTRO

Non-coding RNA-mediated regulatory networks

Regulatory networks of response to stress miRNAs modulate the recovery of plant-cell homeostasis under adverse environmental conditions, however, there are fundamental questions that remain unanswered. Our scientific objective is contribute to elucidate how the miRNA-mediated regulatory pathways ultimately control gene expression and functionally connects plant responses with stress conditions. This knowledge is pivotal for a better understanding of the molecular mechanisms that enable plants to respond and eventually adapt to the environmental changes.

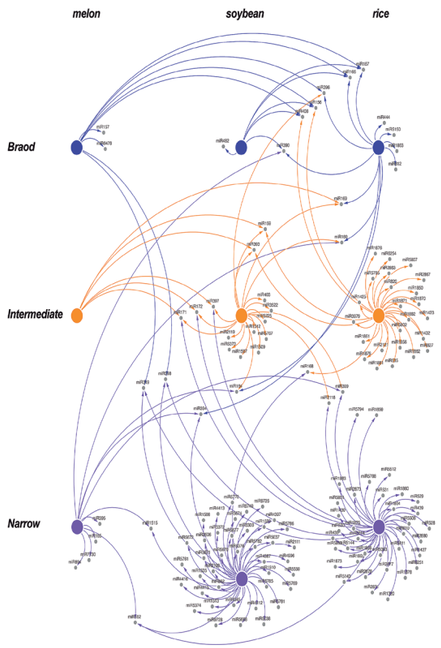
VIROIDS-HOST INTERACTIONS

Viroids are a class of sub-viral long noncoding RNAs (240-400 nt) composed of a circular single-stranded molecule. Viroid infection comprises a series of coordinated steps involving: a) intracellular compartmentalization and replication; b) export to neighboring cells; and c) entry to vascular tissue for long-distance trafficking. Since they lack protein-coding activity, viroids are compelled to subvert endogenous lncRNA-directed regulatory routes to complete their life cycle in the infected cell. We employ host-viroid interactions as experimental system to study cellular biology aspects related to the elucidation of the lncRNA-directed regulatory pathways.

NCRNAS AS BIOMARKERS FOR SARS-COV2 INFECTION

Small RNAs (sRNAs) are a widespread class of RNAs (20-25 nt in length). They can be endogenous (miRNAs) or exogenous (e.g., those derived from viruses). Our objective is to generate a comprehensive map of the sRNAs generated during SARS-CoV-2 infection. This is aimed at providing novel biomarkers for the development of ultrasensitive sensory systems. In addition, we also are focused in study how different endogenous miRNAs are perturbed as a consequence of infection in order to complement the previous picture and to boost multiplexed diagnostics.

We are interested in decipher the regulatory pathways mediated by non coding RNAs for a better understanding of the molecular mechanisms that allow organisms to respond and eventually adapt to stress conditions.



The general architecture of the miRNA-mediated response to stress is conserved in other crops. Graphic representation of the connectivity between stress responsive miRNAs identified in melon, soybean and rice according it categorized range of response to stress. Interactions between stress responsive miRNAs support that the functional categorization of the stress responsive miRNA families is comparable in the three analyzed crops. Nodes represent functional groups (Broad - blue, Intermediate - orange and Narrow – magenta) of stress responsive miRNAs in melon, soybean and rice. Edges represent weighted associations between miRNAs based on response-range in each analyzed crop.

Relevant publications

Marquez-Molins, *et al*. (2020)
Hop stunt viroid: a polyphagous pathogenic RNA that has shed light on viroid-host interactions.
Mol. Plant. Pathology DOI: 10.1111/mpp.13022

Corrêa, R., *et al*. (2020)
Viral Fitness Determines the Magnitude of Transcriptomic and Epigenomic Reprograming of Defense Responses in Plants.
Mol. Biol. Evo. 37: 1866-81.

Sanz-Carbonell, A., *et al*. (2020)
Dynamic architecture and regulatory implications of the miRNA network underlying the response to stress in melon.
RNA Biology 2: 292-308.

Marquez-Molins, J., *et al*. (2019)
Highly efficient construction of infectious viroid-derived clones.
Plant Methods 15: 87.

Cervera, L., *et al*. (2019).
Identification and characterization of a stress-responsive TAS3-derived tasiRNAs in melon. *Plant & Cell Physiology* 60: 2382-2393

Sanz-Carbonell, *et al.* (2019)
Inferring the miRNA-mediated regulatory network of response to stress in melon.
BMC Plant Biology 19: 78.

Bustamante, A., *et al*. (2018)
Alternative processing of its precursor is related to miR319 decreasing in plants exposed to cold.
Scientific Reports 8: 15538.

Pallas, V., Gomez, G. (2017)
Viroid Movement, Chapter 8 in Viroids & Satellites.
Hadidi, A., Flores, R., Randles, J. & Palukaitis, P. Editors. Academic Press.
Pages: 83-91.

Owens, R., *et al*. (2017)
Changes in the Host Proteome and Transcriptome Induced by Viroid Infection. Chapter 10 in Viroids & Satellites. Hadidi, A., Flores, R., Randles, J. & Palukaitis, P. Editors. Academic Press. Pages: 105-114.

Castellano M., *et al*. (2017)
Changes in the DNA methylation of the host male gametophyte of viroid-infected cucumber. J. Experimental Botany 67: 5857-5868.

Projects

VALIDACIÓN FUNCIONAL DE LAS REDES DE SNCRNAS QUE REGULAN LA REPUESTA A ESTRÉS EN MELÓN. ANÁLISIS DE SU POTENCIAL COMO FUENTE DE TOLERANCIA.
Financial entity: MINECO PROYECTOS DE I+D+I, Programa Estatal Investigación, Desarrollo e Innovación Orientada a retos de la Sociedad (PID2019-104126RB-I00).
Duration: From 01/06/2020 to 30/05/2023.
Total amount to the group: 214.170€.

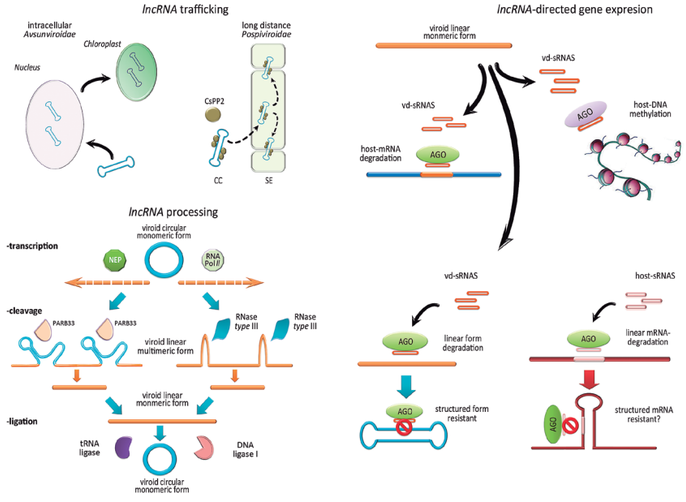
RAPID, ULTRASPECIFIC, AND PORTABLE SARS-COV-2 DIAGNOSTICS BASED ON CRISPR-CAS TECHNOLOGIES AND COMMERCIAL IMMUNOCHROMATOGRAPHIC ASSAY STRIPS.
Financial entity: Fondo supera COVID19. financiado crue–banco Santander.
Duration: From 01/06/2020 to 30/05/2021.
Total amount to the group: 150.000 €.

VALIDACIÓN FUNCIONAL DE LAS REDE DE SNCRNAS QUE REGULAN LA REPUESTA A ESTRÉS EN MELÓN. ANÁLISIS DE SU POTENCIAL COMO FUENTE DE TOLERANCIA.
Financial entity: MINECO PROYECTOS DE I+D+I, Programa Estatal Investigación, Desarrollo e Innovación Orientada a Retos de la Sociedad (AGL2016-79825-R).
Duration: From 30/12/2016 to 30/07/2020.
Total amount to the group: 157.300 €.

CHARACTERIZATION OF THE PLANT-STRES RESPONSE MEDIATED BY NCRNAS IN CUCURBITS.
Financial entity: MINECO PROYECTOS DE I+D+I, Programa Estatal Investigación, Desarrollo e Innovacion Orientada a retos de la Sociedad (AGL2013-47886-R).
Duration: From 01/01/2014 to 30/06/2017.
Total amount to the group: 205.700€

IDENTIFICACIÓN Y CARACTERIZACIÓN DE MIRNAS ESPECÍFICAMENTE EXPRESADOS EN PLANTAS DE MELÓN EXPUESTAS A ESTRÉS BIÓTICO Y ABIÓTICO.
Financial entity: CSIC (201540I003).
Duration: From 1/10/2015 to 30/09/2017.
Total amount to the group: 7.500€.

OPTIMIZACIÓN PARA USO A ESCALA INDUSTRIAL DE UN SISTEMA PARA LA EXPRESIÓN SELECTIVA DE COMPUESTOS HETEROLOGOS EN CLOROPLASTOS MEDIADO POR NCRNAS.
Financial entity: MINECO PROYECTOS DE I+D+I, Programa Explora (BIO2014-61826-EXP).
Duration: From 1/09/2015 to 30/12/2017.
Total amount to the group: 78.650€.



Simplified representation of the lncRNA-directed mechanisms in plants studied using the viroid-host interaction model.
The different aspects regarding lncRNA trafficking, lncRNA processing and lncRNA-directed gene expression are explained in the text.
vd-sRNAs: viroid-derived sRNAs, CC: companion cells, SE: sieve elements.

Other achievements

Promotion to CSIC Senior Scientist (2020).

Head of the group

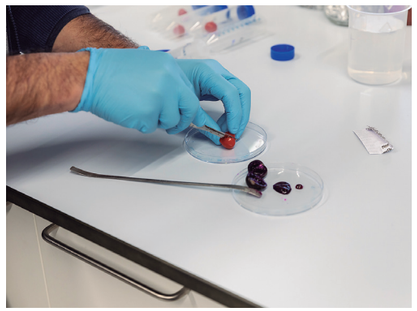
José Tomás Matus
Researcher, Ramón y Cajal Program, UV

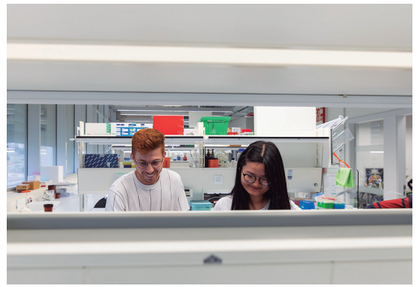
Other members

Pablo Romero
Tecnician contract

Chen Zhang
Predoctoral contract, Chinese Government CSC

Luis Orduña
Predoctoral contract, FPI Program





Transcriptional Orchestration of Metabolism

Understanding how plant secondary metabolites are produced has enormous potential for the agro-industrial and pharmaceutical sector by favoring the design of healthier foods and plant-based drugs. Our research group uses systems biology tools and multi-omics approaches to identify enzymatic and regulatory components of plant metabolism in order to increase their production in metabolic engineering processes. In turn, we seek to optimize the production of these metabolites in *in vitro* cultures. In particular, we are interested in the transcriptional regulation of secondary metabolism through the action of transcription factors (proteins that bind to DNA and activate or repress structural genes of metabolite synthesis pathways). We study various plant species such as tomato, grapevine, Chinese wormwood, blackberries, and cannabis. Our main lines of research are: 1) Genomic characterization of families of plant transcription factors through the use of public transcriptomics (RNA-seq) data and combination with functional characterizations *in planta*, 2) Integration of multi-omics data with temporal dynamics to identify new regulators and unknown enzymatic steps of plant secondary metabolism, using *in vitro* cultures and cell suspensions hormonally stimulated in the production of metabolites and 3) Genomic analyses of plants responses to environmental stresses associated with climate change, addressing different bioinformatic methods coupled with experimental data and using the grapevine as a model of a non-climacteric fleshy fruit.

Discovering enzymes of plant secondary metabolism and understanding their regulation by identifying and characterizing transcription factors, with the view of using plants as factories for functional and therapeutic metabolites.

Relevant publications

De Ollas C, *et al*. (2021).
Identification of ABA-mediated genetic and metabolic responses to soil flooding in tomato (*Solanum lycopersicum* Mill).
Front. Plant Sci. doi: 10.3389/fpls.2021.613059

Orduña L, Li M, *et al*. (2020).
Orchestration of the stilbene synthase gene family and their regulators by subgroup 2 MYB genes.
bioRxiv 2020.12.31.424746;

Llorente B, *et al*. (2020).
Synthetic conversion of leaf chloroplasts into carotenoid-rich plastids reveals mechanistic basis of natural chromoplast development. Proceedings of the National Academy of Sciences (PNAS).

Leiva-Ampuero A, *et al*. (2020).
Salinity impairs photosynthetic capacity and enhances carotenoid-related gene expression and biosynthesis in tomato (*Solanum lycopersicum* L. cv. Micro-Tom).
PeerJ 8:e9742.

Romero P, *et al*. (2020).
Comprehending and Improving Cannabis Specialized Metabolism in the Systems Biology Era. Plant Science Vol 298.
Special Issue: Specialized Metabolism.

Ferreira V, *et al*. (2019).
Genetic analysis of a white-to-red berry skin color reversion and its transcriptomic and metabolic consequences in grapevine (*Vitis vinifera* cv. 'Moscatel Galego'). BMC Genomics. 20, 952 .

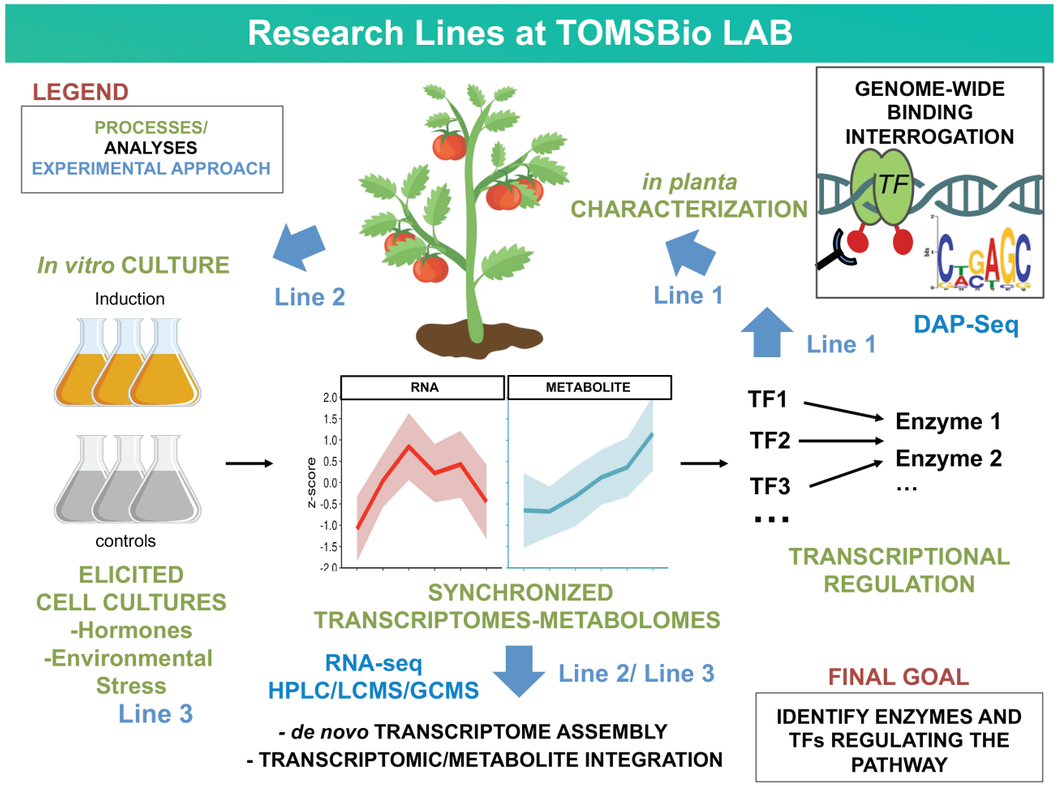
Santibáñez C, *et al*. (2019).
Differences in berry primary and secondary metabolisms identified by transcriptomic and metabolic profiling of two table grape color somatic variants.
bioRxiv 861120.

Matus, J. T., *et al*. (2019).
Ome-wide Studies of Grapevine Fruit Composition and Responses to Agro-environmental Factors in the Era of Systems Biology.
Lausanne: Frontiers Media SA

Matus JT, *et al*. (2019). Status and Prospects of Systems Biology in Grapevine Research. In: The Grape Genome (Compendium of Plant Genomes).
Cantu, Walker, eds.

Projects

NETFRUIT. SYSTEMS BIOLOGY APPROACHES TO UNDERSTAND THE ROLE OF MYB TRANSCRIPTION FACTORS IN THE REGULATORY NETWORKS OF SECONDARY METABOLISM OF FLESHY FRUITS (PGC2018-099449-A-I00).
Financial entity: Agencia Estatal de Investigación, Ministerio de Ciencia e Innovación.
Duration: from 2019 until 2021.
Total amount to the group: 127.050 € + FPI Contract



Graphical abstract of the Research lines at TOMSBio Lab (Transcriptional Orchestration of Metabolism).

Panomics and Evolutionary Systems Microbiology

Head of the group

Christina Toft

Other members

Jesús Navarro Huertas
Technician contract

The group seeks to understand the evolution and molecular mechanisms underlying functional innovation, which is the driving force of biological complexity and ecological diversification. We use theoretical and experimental evolution in our quest to answer our questions and hypotheses.

Biological complexity and ecological diversification are both driven by the evolution of novel functions. The Panomics and Evolutionary Systems Microbiology group's main research interest lies in understanding the molecular mechanisms underlying functional innovation at different levels and contexts. Many mechanisms have been proposed to generate innovations, most of which confer proteins robustness to mutations -- that is allowing proteins to perform their functions, despite the presence of destabilizing mutations, hence mutations drifting to fixation. Gene duplications, molecular chaperones and co-adaptive mutations are three such mechanisms, which are all investigated by the group. Understanding how these mechanisms generate innovations and in which contexts, is not only interesting from a basic science point of view but potentially extremely valuable in relation to health (e.g. the evolution of antibiotic resistance), biotechnology (e.g. generating new products) and agriculture (e.g. pest control by targeting their endosymbionts and infection factors of plant pests). Currently, our main focus is on one of the major mechanisms of innovation, gene duplication. Here we use the baker's yeast *Saccharomyces cerevisiae* as a model, as it contains anciently duplicated genes originating from both whole-genome and small-scale duplication, furthermore, it is easy to manipulate in the laboratory and has a short generation time. With these properties, we are able to look for adaptive signatures left in the genome over millions of years but also observe evolution in it act by performing experimental evolution and re-evaluate the changes at the genomic and transcriptomic level. This approach of using both theoretical and experimental evolution is very powerful as it allows us to set hypotheses based on the theoretical work and later test it in the laboratory.

Relevant publications

Macías LG et al (2019) Comparative genomics between *Saccharomyces kudriavzeviiand S. cerevisiae*applied to identify mechanisms involved in adaptation. Frontiers in Genetics 10:187. doi: 10.3389/fgene.2019.00187

Morard M et al (2019). Aneuploidy and ethanol tolerance in Saccharomyces cerevisiae. Frontiers in Genetics 10:82. doi: 10.3389/fgene.2019.00082

Morard M et al (2020) Genome structure reveals the diversity of mating mechanisms in Saccharomyces cerevisiae x Saccharomyces kudriavzevii hybrids, and the genomic instability that promotes phenotypic diversity. Microb Genom. 6(3):e000333. doi: 10.1099/mgen.0.000333.

Sabater-Muñoz B et al (2020) Transcriptional Rewiring, Adaptation, and the Role of Gene Duplication in the Metabolism of Ethanol of Saccharomyces cerevisiae. mSystems. 5(4):e00416-20. doi: 10.1128/mSystems.00416-20.

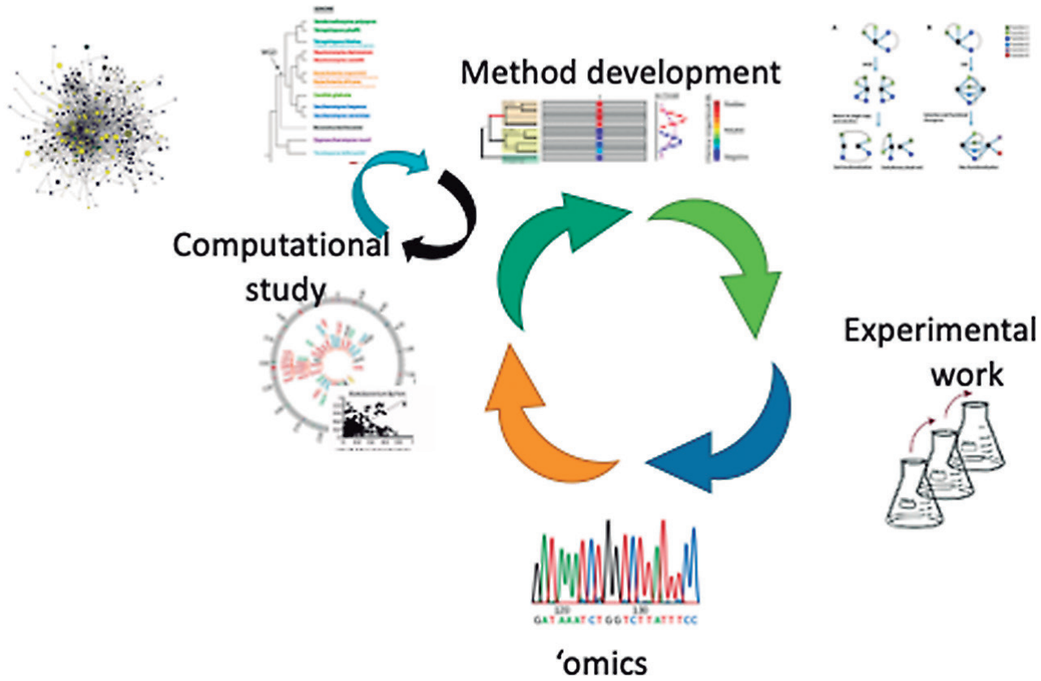
Morard M et al (2020) Genomic instability in an interspecific hybrid of the genus Saccharomyces: a matter of adaptability. Microb Genom. 6(10). doi: 10.1099/mgen.0.000448.

Macías LG et al (2020) GWideCodeML: A Python Package for Testing Evolutionary Hypotheses at the Genome-Wide Level. G3 (Bethesda). g3.401874.2020. doi: 10.1534/g3.120.401874.

Sabater-Muñoz B, Toft C. (2020) Evolution from Free-Living Bacteria to Endosymbionts of Insects: Genomic Changes and the Importance of the Chaperonin GroEL. Results Probl Cell Differ. 69:77-103. doi: 10.1007/978-3-030-51849-3_3. PMID: 33263869.

Projects

SEJI/2018/046,
DESENTRAÑANDO LA INNOVACIÓN FUNCIONAL: LA DUPLICACIÓN GENÓMICA COMO FUENTE DE PROCESOS INNOVADORES.
Financial entity: Generalitat valenciana, programa a la excelencia científica de investigadores juniors (SEJI).
Duration: 2018-2020.
Total amount to the group: 199.078,7 €.
CT Principal Investigator.



We combine theoretical and experimental research in a multidiscipline way. In the theoretical part we look for adaptive signatures left in the genomes over millions of years and create software where necessary. In the experimental part of our research, we evolve microorganisms to observe evolution in the act.

Program for Pathogen Systems Biology

The main objective of the Pathogen Systems Biology Scientific Program is to carry out an integrative exploration of host-pathogen and pathogen-pathogen interactions from an evolutionary perspective, focusing mainly on viruses and bacteria. For this, we use theoretical, computational, and experimental approaches. We are interested in different topics including viral discovery, gene and protein regulatory networks, host range determinants, the genetic basis of adaptation to novel hosts, and the implications of pathogen systems biology and evolution for the development of new therapeutic strategies. We also aim at establishing links between different levels of biological organization, from molecular details to population and community level processes.

The program includes the following research lines:

- Detection of new or unexpected viruses in human, environmental, and wildlife samples.
- Understanding cellular pathways utilized by infecting viruses.
- Evolution of cell tropism in viruses and implications for viral emergence.
- Investigating virus-resistance mechanisms from an evolutionary perspective.
- Characterizing host determinants of immune responses and their effects on viral evolution.
- Systems biology approaches to understanding viral protein evolution and how viruses accommodate mutations.
- Understanding virus-virus interactions using a social evolution approach.
- Computational systems biology of virus-host interactions.
- Mathematical and computational modelling of virus population dynamics.
- Role of pathogen genetic variation in different aspects of infectious diseases such as diagnostics, transmission, disease presentation, host specificity, drug resistance, and immune escape.
- Molecular epidemiology and epidemiological surveillance of viral and bacterial pathogens.
- Identification of novel antivirals and therapeutics against viral and bacterial pathogens.
- Isolation of novel bacteriophages against multidrug-resistant bacteria as biomedical and agronomic tools.
- Nanotechnology-based bacteriophage delivery and bacterial sensing.
- Directed evolution of therapeutic viruses, including bacteriophages and oncolytic viruses.

Heads of the group

Rafael Sanjuán Verdeguer

Associate professor, UV

José Manuel Cuevas Torrijos

Researcher, Ramón y Cajal Program, UV

Other members

Juan Vicente Bou Prados. Technician contract

Layla Panach Gonzalez. Technician contract

Rubén Corral San Miguel. Technician contract

Alejandra Larrieux Lima. Predoctoral contract, FPI program

Lucas Mora Quilis. Predoctoral contract, FPU program

Ernesto Alejandro Segredo Otero. Predoctoral contract, FPU program

Iván Andreu Moreno. Predoctoral contract, FPU program

Verónica Salomé Pazmiño Ibarra. Predoctoral contract

María Concepción Cebria Mendoza. Predoctoral contract

Yasmine Baktash. Postdoctoral contract

Robby Sungani Concha Eloko. Predoctoral contract, Santiago Grisolia program

María Dolores Arocas Castillo. Technician contract

Jorge Moreno García. Student

Viral Experimental Evolution

In our research group we study different aspects of the evolution of viruses from an experimental approach to find out how viruses change over time and how these changes allow them to adapt to different environments.

We have experience working with a wide range of viruses: with and without envelope, RNA or DNA, human viruses, other animal viruses, bacterial viruses... etc. Our main research topics include viral transmission, social evolution, emergence of new viruses, viral metagenomics (human virome), the use of viruses as oncological treatment and the discovery of new phages with therapeutic potential. To do this we use the usual techniques of cell culture and molecular biology, as well as flow cytometry, automated fluorescence microscopy, next-generation sequencing, mathematical modeling, and electron microscopy.

Relevant publications

Andreu-Moreno I, *et al.* (2020). Cooperative nature of viral replication. Science Advances.

Bou JV, Sanjuán R (2020). Experimental evolution reveals a genetic basis for membrane-associated virus release. Molecular Biology and Evolution.

Domingo-Calap P, *et al.* (2020) Social Bacteriophages. Microorganisms.

Segredo-Otero E, Sanjuán R. (2020) The role of spatial structure in the evolution of viral innate immunity evasion: A diffusion-reaction cellular automaton model. PLoS Computational Biology.

Domingo-Calap P, *et al.* (2019). Social evolution of innate immunity evasion in a virus. Nature Microbiology.

Bou JV, *et al.* (2019). Membrane-associated enteroviruses undergo intercellular transmission as pools of sibling viral genomes. Cell Reports.

Moreno-Andreu I, Sanjuán R (2018). Collective infection of cells by viral aggregates promotes early viral proliferation and reveals a cellular-level Allee effect. Current Biology.

Sanjuán R. (2018). Collective properties of viral infectivity. Current Opinion in Virology.

Sanjuán R (2017). Collective infectious units in viruses. Trends in Microbiology.

Cuevas JM, *et al.* (2017). Multi-virion infectious units arise from free viral particles in an enveloped virus. Nature Microbiology.

Contracts and technology transfer

Phage therapy applications:

Contract with HIPRA SA for phage discovery and testing to treat bovine diseases. 2020: 21.000 €.

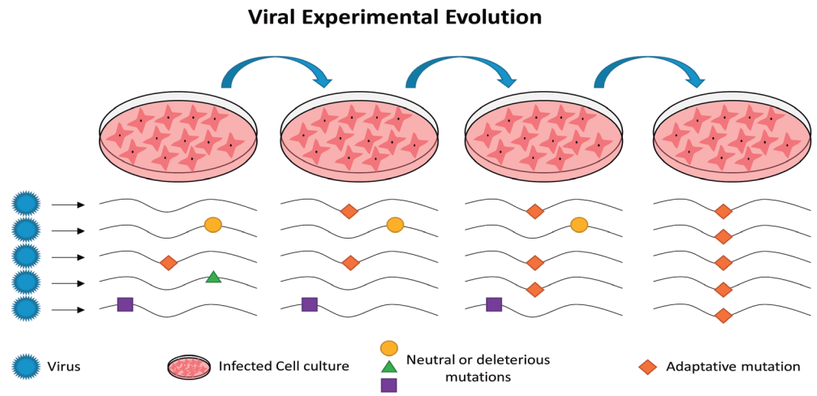
COVID-19 applied research:

Coinventor of a VSV vector encoding the SARS-CoV-2 surface protein S (deposited in European Virus Archive for public distribution). 2020.

Contracts with the Asociación de la Industria Navarra (AIN, 3100 €), Colchones Delax SL (5000 €), Global Termobiomasa SL (9000 €), Hidro-Water SL (5000 €),

Instituto Tecnológico del Embalaje, Transporte y Logística (ITENE, 15.000 €), and NUREL-SAMCA SA (8.500 €) for testing the anti-coronavirus activity of several surface treatments. 2020.

Contract with JECMA Consultoría y Medio Ambiente (4300 €) and SELENTA Hospitality Group SL (13.000 €) for COVID-19 surveillance in surfaces, waters, and air. 2020.



Due, among other things, to their high mutation rates, viruses evolve very quickly. This makes them an ideal system to study the theory of evolution from different perspectives. In the figure we see the example of how a viral population can adapt to its environment by favoring, by natural selection, a variant that has an adaptive mutation and discarding the rest.

Projects

VIGILANCIA EPIDEMIOLÓGICA DEL COVID-19 EN AGUAS RESIDUALES. GENERALITAT VALENCIANA
Duration: 2020
Total amount to the group: 40.000 €.

EVOLUCIÓN DIRIGIDA DE VIRUS ONCOLÍTICOS. BFU2017-84762.
Financial entity: Ministerio de Ciencia y Universidades
Duration: 2018 – 2020
Total amount to the group: 330.330 €.

CARACTERIZACIÓN DEL VIROMA DE SANGRE MEDIANTE ULTRA-SECUENCIACIÓN EN POBLACIÓN ESPAÑOLA: UNA ESTRATEGIA DE VIGILANCIA FRENTE A POTENCIALES VIRUS EMERGENTES.
SAF2017-82287-R.
Financial entity: Ministerio de Economía, Industria y Competitividad.
Duration: 2018-2020.
Total amount to the group: 133.100 €.

COLLECTIVE INFECTIOUS UNITS AND THE SOCIAL EVOLUTION OF VIRUSES.
ERC-2016-COG-724519.
Financial entity: European Research Council.
Duration: 2017-2022.
Total amount to the group: 1.969.821 €.

EVOLUCIÓN EXPERIMENTAL Y RESISTENCIA A ANTIBIÓTICOS Y ANTIVIRALES.
Prometeo/2016/122.
Financial entity: Generalitat Valenciana.
Duration: 2016-2019.
Total amount to the group: 237.597 €.

Molecular Epidemiology

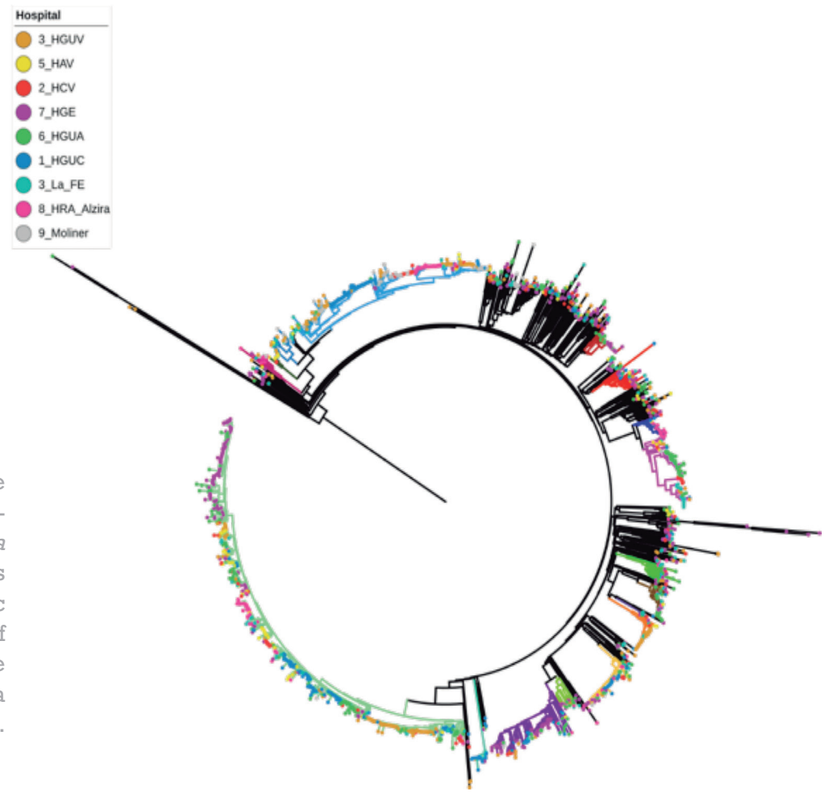
Head of the group

Fernando González-Candelas

Professor, UV and FISABIO researcher

Other members

María Alma Bracho. Senior Researcher
Leonor Sánchez Busó. Postdoc Researcher
Carlos Francés Cuesta. Predoctoral Student
Marta Plá Díaz. Predoctoral Student
Neris García González. Predoctoral Student
Beatriz Beamud Arangure. Predoctoral Student
Lorena Mejía Castañeda. Predoctoral Student
Sandra Carbó. Predoctoral Studen
Ivan Ansari Toledano. IT Thechnicia
Lidia Ruiz Roldán. Lab Thechnician
Carlos Valiente Mullor. Predoctoral Student
Paula Ruiz Hueso. Former Predoctoral Student
Alvaro Chiner Oms. Former Predoctoral Student
Juan Angel Patiño. Former Predoctoral Student



Phylogenetic tree of carbapenemase-producing *Klebsiella pneumoniae* isolates from the genomic surveillance study of this pathogen in the Comunitat Valenciana (Spain).

The Molecular Epidemiology (EpiMol) group is part of the Evolution and Health group of the Universitat de València and the FISABIO Salud Pública. The research group is integrated in the Joint Research Unit «Infección y Salud Pública» FISABIO-UV and the I2SysBio (CSIC-UV). We use evolutionary theory, bioinformatics and the latest sequencing technologies in the genomic surveillance of a wide range of bacteria and viruses, in close collaboration with Public Health and Clinical Microbiology laboratories.

Our research group has been working for years on the application of methods and concepts of evolution and genetics of molecular populations to the study of pathogenic microorganisms, in what is known as molecular epidemiology. In addition, we take problems and return relevant results to the health authorities, achieving an interesting application of a basic biological discipline. For instance, in this context, we are studying a wide prospective collection of isolates of a bacterium of great interest for public health, *Klebsiella pneumoniae*, to analyse the evolutionary processes that affect its dynamics in the population of the Valencian Community, with special interest in strains resistant to antibiotics. Due to its clinical and public health relevance, we focus the research on beta-lactamase producing strains with extended spectrum and/or carbapenemasas.Current research projects include genomic and molecular epidemiology of STIs (*Neisseria gonorrhoeae*, *Treponema pallidum*, *Chlamydia trachomatis*), antimicrobial resistance (ESBL-producing Enterobacteriaceae, *Pseudomonas aeruginosa*, *Staphylococus aureus*), opportunistic pathogens (*Legionella pneumophila*, *Vibrio*), nosocomial pathogens (*Klebsiella pneumoniae*, *Lactococcus garviae*), foodborne pathogens (*Listeria monocytogenes*, *Salmonella enterica*), and a wide range of virus (HCV, HAV, HBV, HIV, mumps, CMV, EVs, HPV, among others). We are frequently involved in the analysis of transmission and outbreaks, and we have a strong interest in the application of molecular epidemiology and evolution in forensic settings (Microbial Forensics). During the last year we have been also involved on the study of SARS-CoV-2 combining pathogen genomics and epidemiology to inform public health interventions.

Relevant publications

Majander, Kerttu *et al*. (2020). Ancient bacterial genomes reveal a formerly unknown diversity of *Treponema pallidum* strains in the early modern Europe. Current Biology 30: 1-16. https://doi.org/10.1016/j.cub.2020.07.058

Beale, Mathew A. *et al*. (2020). Yaws re-emergence and bacterial drug resistance selection after mass administration of azithromycin: a genomic epidemiology investigation. *Lancet Microbe* 1(6): e263-e271. https://doi.org/10.1016/S2666-5247(20)30113-0.

Sironi, Manuela *et al*. (2020). SARS-CoV-2 and COVID-19: A Genetic, Epidemiological, and Evolutionary Perspective. *Infection, Genetics and Evolution* 84:104384. https://doi.org/10.1016/j.meegid.2020.104384

Domingo-Calap, *et al*. (2020). Isolation of Four Lytic Phages Infecting *Klebsiella pneumoniae* K22 Clinical Isolates from Spain. Int J Mol Sci. 2020 Jan; 21(2): 425.

Francés-Cuesta, *et al.* (2019). Whole-genome sequencing of *Neisseria gonorrhoeae* in a forensic transmission case. *Forensic Science International: Genetics* 42: 141-146.

Chiner-Oms, *et al.* (2019). Genomic determinants of sympatric speciation of the *Mycobacterium tuberculosis* complex across evolutionary timescales. *Scientific Advances* 5(6):eaaw3307.

Chiner-Oms, *et al*. (2019). Genome-wide mutational biases fuel transcriptional diversity in the *Mycobacterium tuberculosis* complex. *Nature Communications* 10(1):3994.

Beamud, *et al.* (2019). Characterization of New Recombinant Forms of HIV-1 From the Comunitat Valenciana (Spain) by Phylogenetic Incongruence. Front Microbiol. 2019; 10: 1006.

Patiño-Galindo, *et al.* (2017). The molecular epidemiology of HIV-1 in the Comunidad Valenciana (Spain): analysis of transmission clusters. *Sci Rep*. 2017; 7: 11584.

Arora, *et al*. (2017). Origin of modern syphilis and emergence of a pandemic *Treponema pallidum* cluster. *Nature Microbiology* 2:16245.

Other achievements

Premio Top Rated Poster at the 28th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID, Madrid. 21-24 abril 2018) a: García González, N.; Sabater, S.; Gomila, B.; Moreno, R.; González Candelas, F. 2018. Comparison of phenotypic testing and next-generation sequence analysis for antimicrobial resistance genes in *Klebsiella pneumoniae* isolates.

Premio Top Rated Abstract at the ESCMID Conference on Coronavirus Disease (ECCVID) al trabajo “Genomic epidemiology of SARS-CoV-2 in Spain” presentado por Fernando González Candelas, Mireia Coscollá, Iñaki Comas y Consortium SeqCOVID-Spain. Septiembre 2020.

Premio en la XX Edición de los Premios Anuales de Onda Cero Valencia en su modalidad de Ciencia al Equipo investigación genoma Covid19 de la Fundación FISABIO, dirigido por el Prof. Fernando González Candelas. Noviembre 2020.

Miembro Experto del panel 3 (Biodiversidad y Ecología) de la Fonds Wetenschappelijk Onderzoek (Fundación de Investigación de Flandes), Bélgica. Desde 1 de enero de 2017 hasta 31 de diciembre de 2018.

Miembro del Comité Científico de la Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunidad Valenciana (FISABIO) desde el 25 de enero de 2017 hasta la fecha.

Scientific Chairperson del panel 3 (Biodiversidad y Ecología) de la Fonds Wetenschappelijk Onderzoek (Fundación de Investigación de Flandes), Bélgica. Desde 1 de enero de 2019 hasta 31 de diciembre de 2022.

Miembro del Comité Asesor 3, Biología Celular y Molecular, de la Comisión Nacional Evaluadora de la Actividad Investigadora. BOE-A-2297 de 20 de febrero de 2019. Desde 20 de febrero de 2019 hasta la fecha. Miembro del Comité Científico del Programa Valenciano de Investigación Vacunal COVID-19. Desde 1 de marzo de 2021 hasta la fecha.

Projects

SEQCOVID. ADDRESSING UNKNOWNS OF COVID-19 TRANSMISSION AND INFECTION COMBINING PATHOGEN GENOMICS AND EPIDEMIOLOGY TO INFORM PUBLIC HEALTH INTERVENTIONS.
Financial entity: Agencia del Consejo Superior de Investigaciones Científicas (CSIC) - PTI Salud Global, Instituto de Sanidad Carlos III.
Duration: from 01/01/2020 until 31/12/2021.
Total amount to the group: 700.000 €.

GENOMICS AND THE EVOLUTION OF BACTERIA RESISTANT TO ANTIBIOTICS: FROM MOLECULAR EPIDEMIOLOGY TO PHYLOGENOMICS.
Financial entity: Ministerio de Ciencia, Innovación y Universidades.
Duration: from 01/01/2018 until 31/12/2021.
Total amount to the group: 193.600 €.

EVOLUTION AND HEALTH: EXPERIMENTAL EVOLUTION OF ANTIVIRAL AND ANTIBIOTIC RESISTANCE. PROMETEO/2016/122.
Financial entity: Generalitat Valenciana.
Duration: from 01/01/2016 until 31/12/2019.
Total amount to the group: 237.600 €.

THEMATIC NETWORK ON THE GENOMICS OF ADAPTATION. CGL2015-71726-REDT.
Financial entity: Ministerio de Economía y Competividad.
Duration: from 01/01/2016 until 31/12/2017.
Total amount to the group: 13.000 €.

FAST BACTERIAL EVOLUTION: PROCESSES AND OPPORTUNITIES FOR THE DEVELOPMENT OF GENOMIC EPIDEMIOLOGY. BFU2014-58656R.
Financial entity: Ministerio de Economía y Competividad.
Duration: from 01/01/2015 until 31/12/2017.
TOTAL AMOUNT TO THE GROUP: 190.000 €.

Head of the group

Santiago F. Elena Fito
CSIC

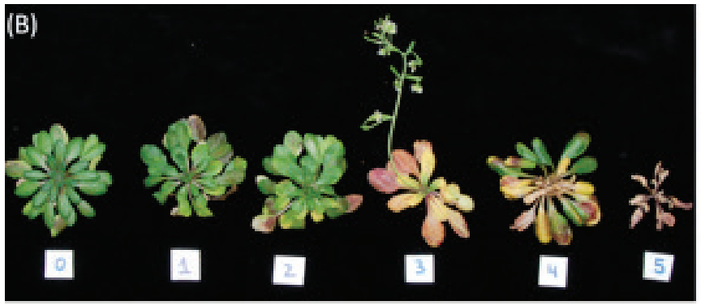
Other members

Paula Agudo Coma. Laboratory Technician
Francisca de la Iglesia Jordán. Laboratory Technician
Juan C. Muñoz Sánchez. Predoctoral Contract
Rebeca Navarro Canales. Predoctoral Contract
Mª José Olmo Uceda. Predoctoral Contract, FPU Program
Héctor Cervera Benet. Predoctoral Contract, FPI Program
Rubén González Miguélez. Predoctoral Contract, FPI Program
Anamarija Butković. Predoctoral Contract, Grisolía, Program
José L. Carrasco Jiménez. Postdoctoral Contract
Silvia Ambrós Palaguerri. Postdoctoral Contract
Denis Kutnjak. Postdoctoral Contract
Julia Hillung. Postdoctoral Contract
Fernando Martínez García. Postdoctoral Contract
Anel Nurtay, Research contract. (Fundació La Caixa)

Evolutionary Systems Virology

The group uses three different approaches. The first is based on the experimental analysis of viral evolutionary dynamics. The second is based on phylogeographic analysis and molecular epidemiology of viruses. The third is based on the development and analysis of mathematical and simulation models of complex adaptive systems.
As a guide, mention some topics in which we are currently being working on: (1) Effect of host heterogeneity in the response to infection on the composition of viral populations. (2) Evolutionary genetics of the adaptation process of emerging viruses to their new hosts as well as the role of fitness trade-offs in the evolution of the host range. (3) An evolutionary systems biology approach to the molecular interactions between the host cell and the virus. By combining omic techniques and complex network theory we are exploring how the few viral proteins disrupt the complex regulatory and biochemical networks of the host cell, resulting in disease. (4) Interaction between genetic robustness and evolvability. What are the short- and long-term advantages of genetic robustness for organisms as mutable as RNA viruses? (5) Interaction between the epigenetic regulation of resistance genes to infection and virus adaptation. (6) Role of defective genomes in the pathogenesis and evolvability of betacoronavirus. (7) Interaction between infection and characteristics of the host's life history, specifically, age and stages of development.

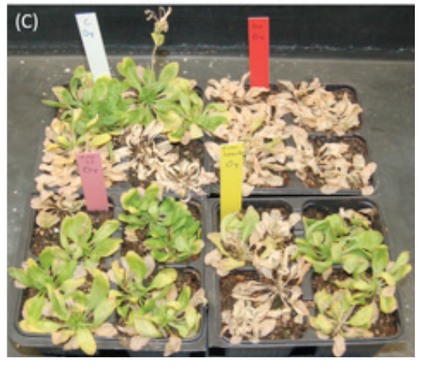
We are interested in the study of population genetic mechanisms that generate and maintain the diversity of RNA viruses.



(A) TuMV in its natural host turnip. (B) Scale of symptoms induced by TuMV in Arabidopsis. (C) The effect of drought varies between plants infected or not with TuMV. (D) The GWAS technique identifies genes associated with symptomatology. (E) Visualization of the Orsay virus in *Canorhabditis elegans*.

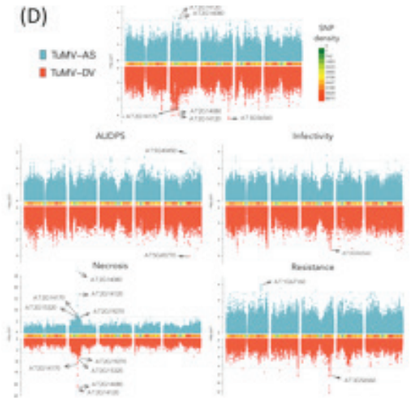
Contracts and technology transfer

Givert X, Sitjà, M, Fenech MM., Elena SF, García S. 2018. Porcine reproductive and respiratory syndrome virus cDNA clone and uses thereof. WO 2018/024677 A1.



Relevant publications

Butković A, *et al*. (2020). Adaptation of turnip mosaic potyvirus to a specific niche reduces its genetic and environmental robustness. *Virus Evol*. 6: veaa041.
Mushegian AR, Elena SF. (2020). RNAs that behave like prions. *mSphere* 5: e00520-20.
Corrêa RL, *et al*. (2020). Viral fitness determines the magnitude of transcriptomic and epigenomic reprogramming of defense responses in plants. *Mol. Biol. Evol.* 37: 1866-1881.
Da Silva W, *et al*. (2020). Transmission modes affect the population structure of *Potato virus Y* in potato. *PLoS Pathog*. 16: e1008608.
Zwart MP, Elena SF (2020) Modeling multipartite virus evolution: the genome formula facilitates rapid adaptation to heterogeneous environments. *Virus Evol*. 6: veaa022.
González R, *et al*. (2020) From foes to friends: viral infections expand the limits of host phenotypic plasticity. *Adv. Virus Res*. 106: 85-121.
Lefeuvre P, *et al*. (2019) Evolution and ecology of plant viruses. *Nat. Rev. Microbiol*. 17: 632-644.
Carrasco JL, *et al*. (2019). Exploring the role of cellular homologous of the 30K-superfamily of plant virus movement proteins. *Virus Res*. 262: 54-61.
Cervera H, *et al.* (2018). Viral fitness correlates with the magnitude and direction of the perturbation induced in the host's transcriptome: the tobacco etch potyvirus – tobacco case study. *Mol. Biol. Evol.* 35: 1599-1615.
Chao L, Elena SF (2017). Nonlinear trade-offs allow the cooperation game to evolve from prisoner's dilemma to snow drift. *Proc. R. Soc. B* 284: 20170228.



Projects

PAPEL DEL CÓDIGO EPIGENÓMICO DEL HUÉSPED EN LA EVOLUCIÓN DE LAS POBLACIONES VIRALES (EPICOVIR).
PID2019-103998GB-I00.
Ministerio de Ciencia e Innovación (2020-2023).
290.400,00 €.

COUNTERACTING COVID-19 PROGRESSION BY THE USE OF THERAPEUTIC INTERFERING PARTICLES (TIPS).
PIE202020E153. CSIC (2020-2021).
140,000.00 €

PUESTA A PUNTO DE CAENORHABDITIS ELEGANS COMO SISTEMA MODELO PARA ESTUDIAR LA INTERACCIÓN VIRUS-HUÉSPED.
PIE202020E094. CSIC (2020-2021).
11.942,74 €

PLANT-VIRUS DYNAMIC INTERACTORES: IDENTIFYING EARLY-WARNINGS OF CRITICAL TRANSITIONS TO DISEASE.
PROMETEU/2019/012.
Generalitat Valenciana (2019-2022).
249.901,00 €.

ROL:FELS INTEGRATING CRITICAL PHENOMENA AND MULTI-SCALE SELECTION IN VIRUS EVOLUTION.
DEB1830688.
USA National Science Foundation (2018-2019).
42.392,00 $.

EPIGENETIC COMPLEXES AS HOST ORGANIZERS OF PLANT VIRAL EVOLUTION.
GRISOLIAP/2018/005.
Generalitat Valenciana (2018-2021).
66.578,40 €.

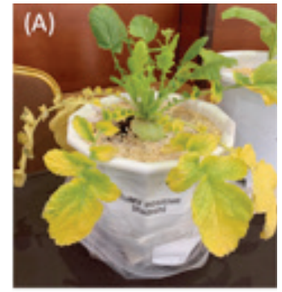
EVOLUCIÓN DE VIRUS EN HUÉSPEDES CON SUSCEPTIBILIDAD VARIABLE: CONSECUENCIAS EN EFICACIA Y VIRULENCIA Y CAMBIOS EN LAS REDES INTERACTÓMICAS DE PROTEÍNAS VIRUS-HUÉSPED.
BFU2015-65037-P.
Ministerio de Industria y Competitividad (2016-2020).
379.456,00 €.

COMPARATIVE SYSTEMS BIOLOGY OF HOST-VIRUS INTERACTIONS".
PROMETEOII/2014/021.
Generalitat Valenciana (2014-2017).
230.970,00 €.

ESTUDIO DE LA VARIABILIDAD GENÉTICA DEL VIRUS CAUSANTE DEL SÍNDROME RESPIRATORIO Y REPRODUCTIVO PORCINO (PRRSV).
HIPRA Scientific SLU (2011-2021).
925.950,01 €.

Other achievements

Elected member of the American Academy of Arts and Sciences in 2020.
Appointed a member of the Chinese Academy of Agricultural Sciences, Institute of Plant Protection in 2018.



Head of the group

Ron Geller
Researcher, Ramón y Cajal Program, UV

Other members

Florian Mattenberger
Predoctoral contract, FPI program

Beatriz Alvarez-Rodriguez
Technician contract

Clara Frances Gomez
Technician contract

Victor Latorre Rosello
Postdoc and technician 2017-2020,
Scientific Advisor and Medical Writer en MEDICAL STATISTICS CONSULTING SL

Marcelino Telechea
Technician contract

Cristina Vidal
2020-current

Luciana Ruso
Master student

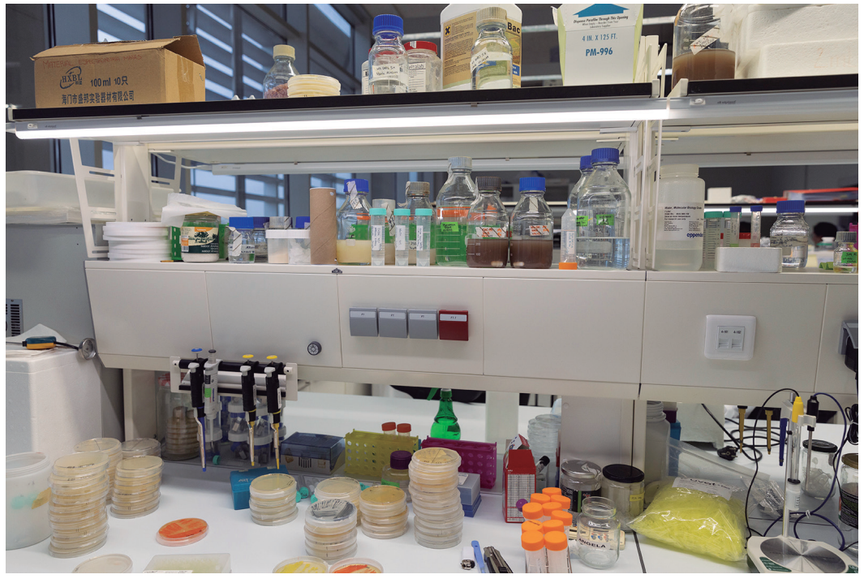
Marina Villa Nistal, 2018
Master student

Serafima Rys
Master student

Pierina Cetraro
Master student

Mateo Ilacqua
Student

Viral Biology



Our group studies the biology of RNA viruses and how they interact with the host.

We are studying the interaction of RNA viruses with the host. RNA viruses are responsible for many important infections, causing tremendous global morbidity and mortality, and include many emerging pathogens. By inve to better understand basic aspects of virus biology and identify new ways of controlling viral infections. In the group, we employ a wide range of experimental and computational tools, including bioinformatics, biochemistry and molecular biology, cell culture, experimental evolution, and in vivo pathogenesis models. Currently, we are focused on understanding the effects of mutations on viral proteins using deep mutational scanning approaches and experimental evolution. In addition, we are examining inhibitors of SARS-CoV-2 entry and replication, as well as the effect of mutations in the SARS-CoV-2 entry protein Spike on virus biology and immunity.ls.

Relevant publications

Siles-Lucas, M. *et al.* (2020) 'Potential Influence of Helminth Molecules on COVID-19 Pathology', *Trends in Parasitology*. Elsevier Ltd, xx(xx), pp. 1–3. doi: 10.1016/j.pt.2020.10.002.

Valdivia, A. *et al.* (2020) 'Suitability of Two Rapid Lateral Flow Immunochromatographic Assays for Predicting SARS-CoV-2 Neutralizing Activity of Sera', *Journal of Medical Virology*. doi: 10.1002/jmv.26697.

Gozalbo-Rovira, R. *et al.* (2020) 'SARS-CoV-2 antibodies, serum inflammatory biomarkers and clinical severity of hospitalized COVID-19 patients', *Journal of Clinical Virology*, 131(August), p. 104611. doi: 10.1016/j.jcv.2020.104611.

Bou, J. V., Geller, R. and Sanjuán, R. (2019) 'Membrane-Associated Enteroviruses Undergo Intercellular Transmission as Pools of Sibling Viral Genomes', *Cell Reports*, 29(3), pp. 714-723.e4. doi: 10.1016/j.celrep.2019.09.014.

Latorre, V., Mattenberger, F. and Geller, R. (2018) 'Chaperoning the Mononegavirales: Current Knowledge and Future Directions.', *Viruses*. Preprints, 10(12), p. 699. doi: 10.3390/v10120699.

Other achievements

Recommendation of article in Faculty Opinions https://facultyopinions.com/prime/733175160

Projects

INTERACTION OF RNA VIRUSES WITH THE HOST CELL, RAMON Y CAJAL
RYC-2015-17517
Financial entity: Ministerio De Economía Y Competitividad,
Duration: 2017 to 2021
Total amount to the group: €308,600

DEFINING THE ROLE OF HSP90 COCHAPERONES IN RSV REPLICATION, RESEARCH GRANT 2017, EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
Duration: 2017 to 2018
Total amount to the group: €20,000
Role: PI

REDES DE CHAPERONAS EN INFECCIONES VIRICAS RESPIRATORIAS
SEJI/2017/006
Financial entity: Generalitat Valenciana,
Duration: 2017 to 2019
Total amount to the group: €153,162
Role: PI

DETERMINACION DEL ESPACIO VIABLE DE SECUENCIA DE UNA CAPSIDE VIRAL
BFU2017-86094-R
Financial entity: Ministerio de Ciencia, Innovación y Universidades
Duration: 2018 to 2020
Total amount to the group: €96,800,
Role: PI

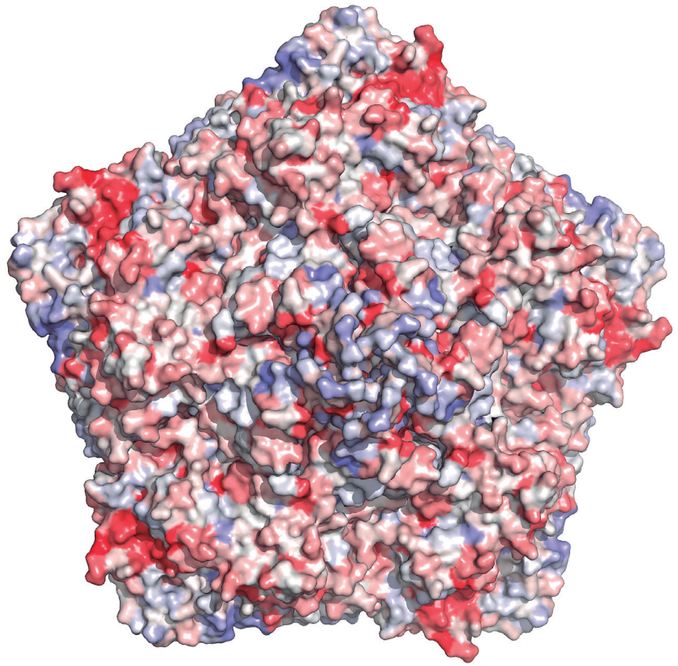
MULTIDISCIPLINARY APPROACH TO BLOCKING SARS-COV-2 ENTRY THROUGH ANTIVIRALS AND DECOY-ACE2 FRAGMENTS CSIC-COV19-082
Financial entity: Consejo Superior de Investigaciones Científicas
Duration: 2020 to 2021
Total amount to the group: €42000 (total €193200)
Role: Co-PI

ANTICOR. PLATAFORMA DE ALTO RENDIMIENTO PARA EL CRIBADO DE ANTIVIRALES Y ANTICUERPOS CONTRA SARS-COV-2 COVID_19-SCI
Financial entity: Conselleria de Innovación, Universidades, Ciencia y Sociedad digital de la Generalitat Valenciana
Duration: 2020 to 2020
Total amount to the group: €90,000
Role: PI

COVID-19: ANTI-INFECTIOUS AND ANTI-INFLAMMATORY ACTION OF IMMUNOMODULATORY PARASITE MOLECULES IN A SAFE-TO-USE SYNTHETIC FORMAT
Financial entity: CSIC-COVID19-104 Consejo Superior de Investigaciones Científicas
Duration: 2020 to 2021
Total amount to the group: €35,000 (Total €100,000)
Role: Co-PI

BLOCKACE: MULTIDISCIPLINARY APPROACH TO BLOCKING SARS-COV-2 ENTRY THROUGH ANTIVIRALS AND DECOY-ACE2 FRAGMENTS
Financial entity: Fondo Supera Covid19 Santander/CRUE/CSIC
Duration: 2020 to 2021
Total amount to the group: €26,000 (Total €150,000)
Role: Coordinating PI

One face of the CVB3 capsid high-resolution structure, colored according to the effect of mutations at each site on viral fitness.



APPLICATION OF EXTREME RESOLUTION NEXT-GENERATION SEQUENCING FOR ILLUMINATING FUNDAMENTAL ASPECTS OF VIRAL EVOLUTION AND PATHOGENESIS
AICO/2020/216
Financial entity: Conselleria de Innovación Universidades, Ciencia y Sociedad digital de la Generalitat Valenciana
Duration: 2020 to 2021
Total amount to the group: €40,00
Role: Coordinating PI

Head of the group

Mireia Coscollá Devís
Researcher, Ramón y Cajal Program, UV

Other members

Antoni Espert
Technician contract

Paula Ruíz Rodrigues
Technician contract

Chantal renau Minguez
Predoctoral contract

Carlos Gomis Olcina
Predoctoral contract

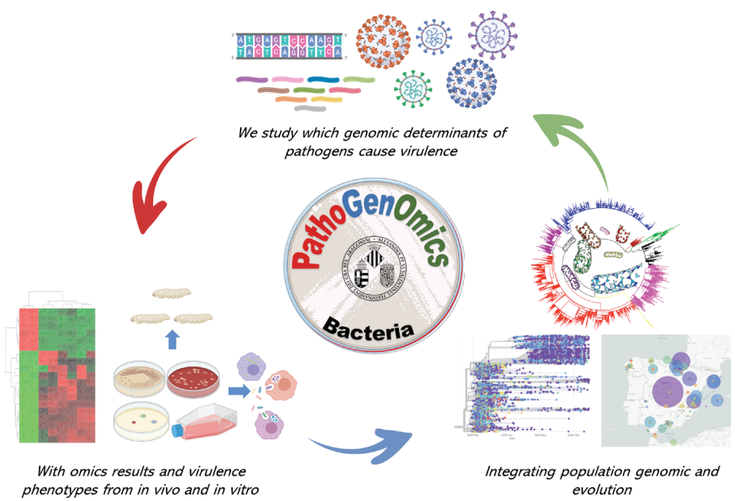
Guillem Santamaría
Predoctoral contract

Marta Gual
Master student

Bacterial Pathogenomics

The PathoGenOmics group at the I²SysBio aims to explain clinical and/or in vitro virulence phenotypes with pathogen biology by integrating infection biology, epidemiology and omics technologies.

Our scientific approach is to study microbial pathogens in the context of their host and disease. To do this, we focus, but not exclusively, on the study of obligate intracellular bacteria with a wide host range to address host specificity as a virulence marker. To do this, I will study two bacterial infections with a wide range of hosts, tuberculosis and brucellosis. We will try to understand the basis of virulence in a given host, for a better understanding of the virulence of the pathogen. Consequently, our goal is to uncover the role of compatibility between different groups of disease-causing bacteria and their respective hosts in predicting the transmission potential and virulence of certain associations. To approach this, we use a range of different omics where genomics is our main approach to study the evolution and molecular molecular epidemiology of the pathogen. But we also perform experimental infections to discover which genomic determinants are involved in different virulence read-outs, using among other approaches transcriptomic of host and pathogen. Additionally, we are studding viral relevant pathogens such as SARS-CoV-2 in multidisciplinary projects where we explore the evolution of SARS-CoV-2 to try to decipher the role of specific genomic determinants in virulence.



Pathogenomics reseach approch to show that we study which genomic determinants of pathogens cause virulence, using omics results and virulence phenotypes from in vivo and in vitro studies integrating population genomics and evolution.

Relevant publications

Alm E, Broberg EK, Connor T, et al. (2020) Geographical and temporal distribution of SARS-CoV-2 clades in the WHO European Region, January to June 2020. Euro Surveill. 2020 Aug;25(32):2001410. doi: 10.2807/1560-7917.

Borrell S, Trauner A, et al. (2019) Reference set of Mycobacterium tuberculosis clinical strains: A tool for research and product development. *PLoS One*;14(3):e0214088.

Otchere ID, van Tonder AJ, et al. (2019) Molecular epidemiology and whole genome sequencing analysis of clinical Mycobacterium bovis from Ghana. PLoS One. Mar 4;14(3):e0209395. doi: 10.1371/journal.pone.0209395.

Brites D, Loiseau C, et al. (2018) A New Phylogenetic Framework for the Animal-Adapted Mycobacterium tuberculosis Complex. *Front Microbiol*;9:2820.

Kuhnert D, Coscolla M, et al. (2018) Tuberculosis outbreak investigation using phylodynamic analysis. *Epidemics*;25:47-53.

Menardo F, Loiseau C, et al. (2018) Treemmer: a tool to reduce large phylogenetic datasets with minimal loss of diversity. *BMC Bioinformatics*;19(1):164.

Otchere ID, Coscolla M, et al. (2018) Comparative genomics of Mycobacterium africanum Lineage 5 and Lineage 6 from Ghana suggests distinct ecological niches. *Sci Rep* ;8(1):11269.

Sanoussi NDC, deJong BC, M et al. (2018)Low sensitivity of the MPT64 identification test to detect lineage 5 of the Mycobacterium tuberculosis complex. *Journal of medical microbiology*.

Blondiaux N, Moune M, et al. (2017) Reversion of antibiotic resistance in Mycobacterium tuberculosis by spiroisoxazoline SMARt-420. *Science*;355(6330):1206-1211.

Coscolla M. (2017). Biological and Epidemiological Consequences of MTBC Diversity. *Adv Exp Med Biol*;1019:95-116.

Ghielmetti G, Coscolla M, et al. (2017) Tuberculosis in Swiss captive Asian elephants: microevolution of Mycobacterium tuberculosis characterized by multilocus variable-number tandem-repeat analysis and whole-genome sequencing. *Sci Rep*;7(1):14647.

Ofori-Anyinam B, Dolganov G, et al. Significant under expression of the DosR regulon in M-tuberculosis complex lineage 6 in sputum. *Tuberculosis* 2017;104:58-64.

Coscolla M. (2017) Biological and Epidemiological Consequences of MTBC Diversity, Pages 95-116 in book Strain Variation in the Mycobacterium tuberculosis Complex: Its Role in Biology, Epidemiology and Control. Springer

Other achievements

2017. Swiss TB Award

Projects

Ramon y Cajal
Universitat de Valencia, Spain
Principal investigator
Start-End date: 01/09/2017 - 31/08/2022
208.600 €

GENETIC DETERMINANTS OF HOST SPECIFICITY IN THE MYCOBACTERIUM TUBERCULOSIS COMPLEX AND THEIR CONTRIBUTION TO VIRULENCE
Universitat de València
Mireia Coscolla
Principal investigator
Code according to the funding entity: RTI2018-094399-A-I00
Start-End date: 01/01/2019 - 31/12/2021
Duration: 3 years
157.300 €

GENÓMICA DE LA INTERACCIÓN ENTRE EL COMPLEJO MYCOBACTERIUM TUBERCULOSIS Y EL HUÉSPED.
Degree of contribution: Coordinator of total project, network or consortium
Universitat de València
Mireia Coscolla
91f8fcd09f0f9db9d0074e1076d1148a
SEJI
SEJI/2019/011
Principal investigator
Start-End date: 01/01/2019 - 31/12/2021
Duration: 3 years
193.123 €

ADDRESSING UNKNOWNS OF COVID-19 TRANSMISSION AND INFECTION COMBINING PATHOGEN GENOMICS AND EPIDEMIOLOGY TO INFORM PUBLIC HEALTH INTERVENTIONS
Entity where project took place: Instituto de Biomedicina de Valencia
Fernando González Candelas; Iñaki Comas Espadas
Instituto de Salud Carlos III
Type of entity: Public Research Body
202020E085
7/04/2020 - 16/04/2021
1.750.000 €

ADDRESSING UNKNOWNS OF COVID-19 TRANSMISSION AND INFECTION COMBINING PATHOGEN GENOMICS AND EPIDEMIOLOGY TO INFORM PUBLIC HEALTH INTERVENTIONS
Instituto de Biomedicina de Valencia
Fernando González Candelas; Iñaki Comas Espadas
Funding entity or bodies:
202020E085
Start-End date: 01/04/2020 - 31/03/2021
747.000 €

RED DE BIOLOGÍA DE SISTEMAS DE MICOBACTERIAS
Geographical area: National
Degree of contribution: Researcher
Entity where project took place:
Universitat de València
Mireia Coscolla
Nº of researchers: 12
Redes de Investigación de 2018
RED2018-102677-T
Start-End date: 2020 - 2021
Duration: 2 years
20.000 €

GENETIC BASIS OF HOST PATHOGEN INTERACTION OF TUBERCULOSIS IN WEST AFRICA
Type of project: Basic research (including archaeological digs, etc)
Type of entity: Associations and Groups
Nº of researchers: 1
Funding entity or bodies: ESCMID - The European Society of Clinical

MICROBIOLOGY AND INFECTIOUS DISEASES
Type of entity: Associations and Groups
Type of participation: Principal investigator
Start-End date: 01/07/2018 - 31/05/2019
Total amount: 20.000 €

Program for Evolutionary Systems Biology of Symbionts

Evolutionary Genetics 78-83

This Program aims to shed light on the mechanisms by which microorganisms reach a high degree of closely woven metabolic and genetic integration with their eukaryotic hosts during the process of mutualist symbiosis. Endosymbiotic bacteria (intracellular, either obligate or facultative) of insects and their intestinal microbiota represent the preferred experimental models.
Research approaches include genome sequencing and metagenomics, comparative and evolutionary as well as functional analyses (transcriptomics, proteomics and metabolomics). The functional study of complex regulatory and metabolic networks requires new bioinformatics and theoretical tools.

Evolutionary Genetics

Head of the group

Andrés Moya
Professor UV
and FISABIO researcher

Other members

Amparo Latorre
Professor of Genetics, UV
Francisco Silva
Professor of Genetics, UV
Rosario Gil
Associate Professor of Genetics, UV
David Martínez
Associate Professor of Genetics, UV
Carlos García Ferris
Associate Professor of Biochemistry and Molecular Biology, UV
Francisco Santonja Ruiz
Associate Professor of Statistics (UV)
Vincent Blay
Postdoctoral contract
Miquel Barberá
Postdoctoral contract
Rebeca Domínguez
Postdoctoral contract
Jorge Mariano Collantes
Predoctoral contract
Irene Creus Mart
Predoctoral contract
Paolo Cutti
Predoctoral contract
Mitchell Distin
Predoctoral contract
Emilio Garrote
Predoctoral contract
Jesús Marín
Predoctoral contract
María Muñoz Benavent
Predoctoral contract
Benjamì Pérez Roche
Predoctoral contract
Samuel Piquer
Predoctoral contract
Mariana Reyes
Predoctoral contract
Adrián Salazar
Predoctoral contract
Pascual Asensi
Technician contract

The Evolutionary Genetics group of I²SysBio (Symbiosis Joint Unit I²Sysbio/FISABIO) is devoted to the study of animal and human microbiome from an Evolutionary and Systems Biology perspective. We have four major research lines:

Human microbiota. The gut microbiota clearly influence the health of their hosts, humans included. By means of multi-omic-technologies, animal models and modelling the dynamics of microbial communities we study the human microbiome in health (how it changes by age, in time series…) and disease (colon cancer, intestinal infections…), with an interest to ascertaining the role played by key microbes in promoting human dysbiosis.
Mutualistic symbiosis insects-bacteria: Blattella germanica as a model. Prokaryotic-eukaryotic mutualistic symbioses are widely distributed and have a significant impact on animal evolution. Our current model, B. germanica has two symbiotic systems: the endosymbiont Blattabacterium and a complex hindgut microbiota. Using several omic and meta-omic approaches, we analyze their dialogue and variation throughout insect development, and the microbiota variations due to disturbances (dietary changes, antibiotics treatment...)
From endosymbionts to synthetic biology: Bartonella as an endosymbiotic chassis. The tree of life shows a variety of microorganisms with reduced genomes whose study can improve the understanding and engineering of minimal cells with applications. At present, we focus on the genome minimization of Bartonella quintana, a facultative endosymbiont of mammalian cells that can be grown in culture, to develop an endosymbiotic chassis useful in synthetic biology for therapeutic purposes.
Molecular and cellular control of aphid life cycles. Many insects cope with adverse seasons by entering into diapause. To elucidate the molecular and cellular bases of this process, we focus on the study of genes and pathways governing polyphenisms in aphids, paying particular attention to the involvement of the circadian clock machinery in seasonal switches between sexuality and parthenogenesis. We also investigate evolutionary and taxonomic issues in different aphid groups.

Symbiosis group studies the ecology and evolution of the symbiosis between prokaryotes and eukaryotes (with special emphasis on insects and humans), applying omic-technologies and the procedures of Integrative Systems Biology

Relevant publications

Arnoriaga-Rodríguez M, et al. (2020). Obesity impairs short-term and working memory through gut microbial metabolism of aromatic amino acids. *Cell Metabolism* 32:548-560.

Barberá M, et al. (2019). Insulin-like peptides involved in photoperiodism in the aphid *Acyrthosiphon pisum*. *Insect Biochemistry and Molecular Biology.*112:103185.

Domínguez-Santos R, et al. (2020). Unraveling assemblage, functions and stability of the gut microbiota of Blattella germanica by antibiotic treatment. *Frontiers in Microbiology* 11:487.

Ibarra-Juarez L, et al. (2020). Evidence for succession and putative metabolic roles of fungi and bacteria in the farming mutualism of the ambrosia beetle *Xyleborus affinis*. *mSystems* 5:e00541-20.

Julca I, et al. (2020). Phylogenomics identifies an ancestral burst of gene duplications predating the diversification of aphidomorpha. *Molecular Biology and Evolution* 37:730-756.

Moya A, et al. (2020). Driven progressive evolution of genome sequence complexity in Cyanobacteria. *Scientific Reports* 10:19073.

Rispe C, et al. (2020). The genome sequence of the grape phylloxera provides insights into the evolution, adaptation, and invasion routes of an iconic pest. *BMC Biology* 18:90.

Silva F, et al. (2020). *Blattella germanica* displays a large arsenal of antimicrobial peptide genes. *Scientific Reports* 10:21058.

Ruiz-Ruiz S, et al. (2019). Functional microbiome deficits associated with ageing: chronological age-threshold. *Aging Cell*. 19:13063.

Gil R, et al. (2018). *Tremblaya phenacola* PPER: An evolutionary beta-gammaproteobacterium collage. *The ISME Journal* 12:124-135.

Contracts and Patents

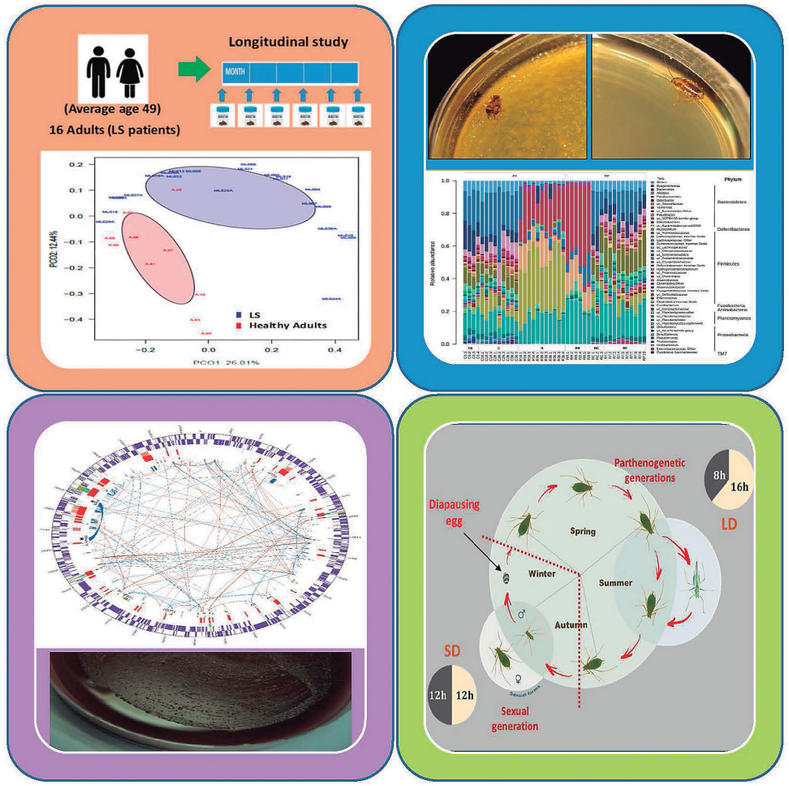
Contract: Bioprotective starters for cooked ham.
Financial entity: Christian Handen (Denmark).
Duration: 2016-2018.
Total amount to the group: 15,000 €

Patent's title: In vitro method for the diagnosis of a *Pneumocystis jirovecii* infection.
Application number: P202030563.
Reference number: P18784ES00.
Date: June 2020.

Patent's title: Gut microbiota composition and uses thereof.
Application number: 300371307.
Reference number: EP20382592.
Date: July 2020.

Other achievements

Andrés Moya. Member of the Gadea Foundation for Science (2017). Master Andrés Laguna Award (2019). Associate Editor-in-chief of *Biology* (Basel). 2019.



The Evolutionary Genetics group of I²SysBio (Symbiosis Joint Unit I²SysBio/ FISABIO) is devoted to the study of animal and human microbiome from an Evolutionary and Systems Biology perspective. We are also interested in the study of endosymbiosis and natural minimal cells as well as the molecular bases of circadian clocks.

Projects

REGULATION OF THE SYMBIOTIC INTERACTIONS IN INSECTS.
Prometeo/2014/065.
Financial entity: GV.
Duration: 2014-2017.
Total amount to the group: 267,830 €.

IDENTIFICATION OF NOVEL MODULATORS OF CHRONIC INFLAMMATION IN PREVALENT DISEASES: UNVEILING DIVERGENT MECHANISMS OF DISEASE.
PIE14/00045.
Financial entity: Instituto de Salud Carlos III.
Duration: 2015-2017.
Total amount to the group: 25,000 €

Projects

RECOGNITION OF THE PRIMARY INFECTION BY PNEUMOCYSTIS IN INFANTS: A SILENT THREAT TO PUBLIC HEALTH.
ELAC2014/HID0254.
Financial entity: EU ERAnet LAC.
Duration: 2016-2018.
Total amount to the group: 75,000 €

CHARACTERISATION, ORIGIN AND EVOLUTION OF AGGRESSIVE MIMICRY IN APHIDS.
CGL2015-68188-P.
Financial entity: Ministry of Economy and Competitiveness.
Duration: 2016-2018.
Total amount to the group: 157.663 €.

STABILITY, RESILIENCE AND FUNTIONAL REDUNDANCY OF THE HUMAN INTESTINAL MICROBIOTA DURING DEVELOPMENT AND IN RESPONSE TO ANTIBIOTIC STRESS AND *CLOSTRIDIUM DIFFICILE.*
SAF2015-65878-R.
Financial entity: Ministry of Economy and Competitiveness.
Duration: 2016-2019.
Total amount to the group: 435.600 €

ENDO AND EXOSYMBIONT SYSTEMS FOR INTERVENTION IN EUKARYOTIC HOSTS.
BFU2015-64322-C2-1-R.
Financial entity: Ministry of Economy and Competitiveness.
Duration: 2016-2019.
Total amount to the group: 187,550 €

A PHASE I/II RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED STUDY OF THE REPEATED LOW-DOSE FECAL MICROBIOTA RESTORATION IN HIV-INFECTED SUBJECTS.
Financial entity: GILEAD Fellowships program.
Duration: 2017-2018.
Total amount to the group: 16,000 €

CIBER IN EPIDEMIOLOGY AND PUBLIC HEALTH. FINANCIAL ENTITY: INSTITUTO DE SALUD CARLOS III.
Duration: 2017-2020.
Total amount to the group: 280,000 €.

MOBILE GENETIC ELEMENTS AND BIOLOGICAL SYSTESM.
APE/2018/A/017.
Financial entity: GV.
Duration: 2018.
Total amount to the group: 9,000 €

GENERATION OF SCIENTIFIC-TECHNOLOGICAL STRATEGIES WITH A MULTIDISCIPLINARY AND INTERINSTITUTIONAL APPROACH TO FACE THE THREAT POSED BY AMBROSIAL COMPLEXES IN THE AGRICULTURAL AND FORESTRY SECTORS OF MEXICO.
Financial entity: FORDECYT, CONACYT, Mexico.
Duration: 2018-2020.
Total amount to the group: Associated group. No funding.

COMMUNICATION ROLE ON PERCEPTION AND BELIEFS OF EU CITIZENS ABOUT SCIENCE (CONCISE).
Grant agreement: 824537.
Financial entity: EU.
Duration: 2018-2020.
Total amount to the group: Associated group. No funding.

MICROBIAL ENGINEERING, HEALTH AND QUALITY OF LIFE.
B2017/BMD3691.
Financial entity: Community of Madrid. R&D Programs in Biomedicine 2017.
Duration: 2018-2021.
Total amount to the group: associated group. No funding.

DEVELOPING AND VALIDATING A COMPUTATIONAL MODEL OF THE GUT MICROBIOTA-MUCOSA INTERACTIONS TO REPLACE AND REDUCE ANIMAL EXPERIMENTS.
Financial entity: National Centre for the Replacement, Refinement and Reduction of Animals in Research, UK.
Duration: 2018-2021.
Total amount to the group: 25,500 €

IMPACT OF THE MICROBIOTA ON COLORECTAL ONCOGENESIS IN PATIENTS WITH LYNCH SYNDROME.
Financial entity: AECC.
Duration: 2018-2021.
Total amount to the group: 299,848 €

DECIPHERING HOST IMMUNE GENE REGULATION AND FUNCTION TO TARGET SYMBIOSIS DISTURBANCE AND ENDOSYMBIONT CONTROL IN INSECT PESTS.
Financial entity: The French National Research Agency (ANR).
Duration: 2018-2021.
Total amount to the group: Associated group. No funding.

EVOLUTION, EXPERIMENTAL EPIDEMIOLOGY AND THERAPEUTIC ENGINEERING OF THE MICROBIOTA.
Prometeo/2018/A/133.
Financing entity: GV.
Duration: 2018-2021.
Total amount to the group: 280,933 €

COMPARATIVE INSECT CHRONOBIOLOGY.
Contract Number 765937.
Financial entity: EU, Marie Curie Training Network. H2020-EU.1.3.1.
Duration: 2018-2022.
Total amount to the group: 213,312 €.

SCIENCE AND TECHNOLOGY IN CHILDHOOD OBESITY POLICY.
Contract Number 774548.
Financial entity: EU H2020-EU.3.2.2.2.
Duration: 2018-2022.
Total amount to the group: 25,000 €

DESARROLLO DE HERRAMIENTAS PARA EL ESTUDIO DE FUNCIONES GÉNICAS IMPLICADAS EN LA REGULACIÓN DE POLIFENISMOS EN PULGONES.
PGC2018-100691-B-I00.
Financial entity: Ministry of Science and Innovation.
Duration: 2019-2021.
Total amount to the group: 86.600€.

DESIGN OF NEW ANTIBIOTICS RESISTANT TO CTX-M-15 SS-LACTAMASE BASED ON EVOLUTIONARY STUDIES.
Apostd/2020/120.
Financial entity: GV.
Duration: 2020-2022.
Total amount to the group: associated group. No funding.

CHANGES IN THE INTERACTIONS OF THE MICROBIOTA WITH ITS HUMAN HOST ACCORDING AGE AND DETERMINATION OF A PERMANENT NUCLEUS OF MUTUALISTIC SYMBIONTS.
PID2019-105969GB-I00.
Financial entity: Ministry of Science and Innovation.
Duration: 2020-2023.
Total amount to the group: 290,400 €

Program for Applied Systems Biology and Synthetic Biology

The main objective of this program is to This Program aims to carry out biotechnology research projects and develop products that are transferable to industry from an applied systems biology perspective (sometimes called industrial systems biology) and synthetic biology.

These approaches are seen as the natural extension of modern biotechnology and metabolic engineering in the post-genomic era, thanks to the development of computational tools that provide models of genome-scale metabolic networks, as well as to the ease of chemical synthesis of DNA and gene editing technologies, greatly facilitating experimental work.

Therefore, methodologies encompass both modelling and experimental approaches in model organisms that are of biotechnological interest, at both laboratory and pilot-plant scale. In fact, this program converges with the strategic objectives of Biopolis S.L., a leading biotech company in the sector already synergistically involved in scientific collaboration with some of the founder research groups and whose presence will boost new joint projects in the area of metabolic engineering.

Heads of the group

Manuel Porcar Miralles
Research, UV

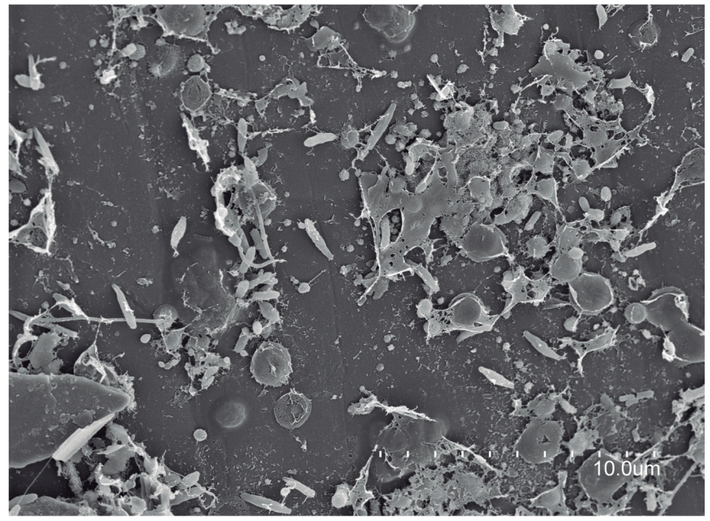
Juli Peretó Magraner
Professor, UV

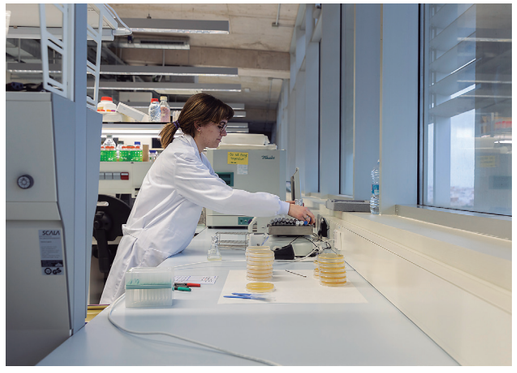
Other members

Mireia Llibertat Alonso-Monasterio Fernandez
Technician contract. EU H2020 Grant
María Jesús Clemente Peiró
Laboratory Technician
Adriel Latorre Pérez
Industrial Doctorate (Darwin Bioprospecting Excellence, S.L.)
Esther Molina Meno
Predoctoral contract, FPU program
Leila Satari Faghihi
Predoctoral contract, EU H2020 program
Kristie Tanner
Industrial Doctorate (Darwin Bioprospecting Excellence, S.L.)
Àngela Vidal Verdú
Predoctoral contract, FPU program
Alba Iglesias
Postdoctoral contract, EU H2020 program
Jara Suleña
Predoctoral contract
Alba Guillén
Predoctoral contract

Biotechnology and Synthetic Biology

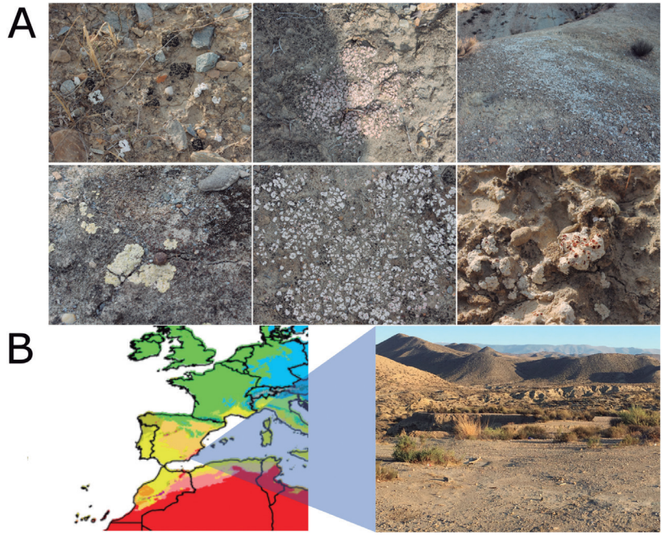
We do bioprospection of natural and artificial environments searching for new bacteria of potential biotechnological interest by combining improved culture methods with omic technologies. We also characterize microbial metabolisms by modeling and explore the frontiers of synthetic biology.





At the Biotechnology and Synthetic Biology lab of the Institute Integrative System Biology I²SysBio we work on different aspects of applied microbiology and in one of the newest scientific disciplines, Synthetic Biology. This can be defined as an approach to biotechnology with engineering principles. On that framework, we perform bioprospection in extreme natural or artificial environments, searching for bacteria, genes and enzymes with potential industrial developments. Those environments include solar photovoltaic panels, desert soils, insect guts, and reactors for biogas production. The group has experience in NGS techniques applied to determine the taxonomic profile of environmental samples as well as their metabolic and functional traits by metagenomics analysis. Other focus of our group is in studying, through computational modeling, how genome information translates into metabolic and ecological traits in microbial communities. We also contribute to the discussion on standards in Synthetic Biology, as well as to historical, philosophical, and sociological aspects of the field.

Electron scanning micrography of a biofilm on the Surface of PET bottle collected at Malva-Rosa beach.



A) Biocrust sampling sites in the Tabernas Desert. Six different biocrust are shown. B) Climate map zoom of Spain in the Köppen-Geiger climate classification map (1980-2016) from Beck et al (2018). The different climate areas are represented in colours. Warm-arid regions, corresponding to desert environments, are represented in red. Picture of the sampling area in the vicinity of the natural Park of the Tabernas desert (Almeria, south-eastern Spain). Figure 2. Microbial colonies obtained after culturing biocrust samples at 23 °C for two weeks. A) TSA 1X plate of sample 1.4.1. B) Microbial colonies under the binocular loupe.

Contracts and Patents

Technology transfer contract with ADM-Biopolis SL. Bases moleculares de la acción probiótica en Bifidobacterias (FDGENT grant, GVA). 2020.
34.000 €.

Relevant publications

Abendroth C, *et al*. (2017).
From grass to gas: microbiome dynamics of grass biomass acidification under mesophilic and thermophilic temperatures.
Biotechnol Biofuels 10:171.

Lazcano A, Peretó J. (2017).
On the origin of mitosing cells: a historical appraisal of Lynn Margulis endosymbiotic theory.
J Theor Biol 434:80-87.

Tanner K, *et al.* (2018).
Polar solar panels: Arctic and Antarctic microbiomes display similar taxonomic profiles.
Environ Microbiol Rep 10:75-79.

Porcar M, Peretó J. (2018).
Creating life and the media: translations and echoes.
Life Sci Soc Pol 14:19.

Porcar M, *et al*. (2019).
Words, images and gender: Lessons from a survey on the public perception of synthetic biology and related disciplines.
EMBO Rep 20: e48401.

Tanner K, *et al*. (2019).
Bioprospecting the solar panel microbiome: high-throughput screening for antioxidant bacteria in a *Caenorhabditis elegans* model.
Front Microbiol 10:986.

Molina-Menor E, *et al*. (2020).
Kineococcus vitellinus sp. nov., *Kineococcus indalonis* sp. nov. and *Kineococcus siccus* sp. nov., isolated nearby the Tabernas desert (Almería,Spain).
Microorganisms 8:E1547.

Tanner K, *et al.* (2020).
Extremophilic microbial communities on photovoltaic panel surfaces: a two-year study.
Microb Biotechnol 13(6):1819-1830.

Beal J, *et al*. (2020).
The long journey towards standards for engineering biosystems: Are the Molecular Biology and the Biotech communities ready to standardise?
EMBO Rep. 21(5):e50521.

Iglesias, A., *et al.* (2020).
Out of the abyss: genome and metagenome mining reveals unexpected environmental distribution of Abyssomicins.
Front Microbiol 11:645.

Projects

FOSTERING SYNTHETIC BIOLOGY: STANDARISATION THROUGH INTERNATIONAL COLLABORATION (BIOROBOOST)
Ref. 820699.
European Comission (H2020). 2018.
1.998.787,50 €.

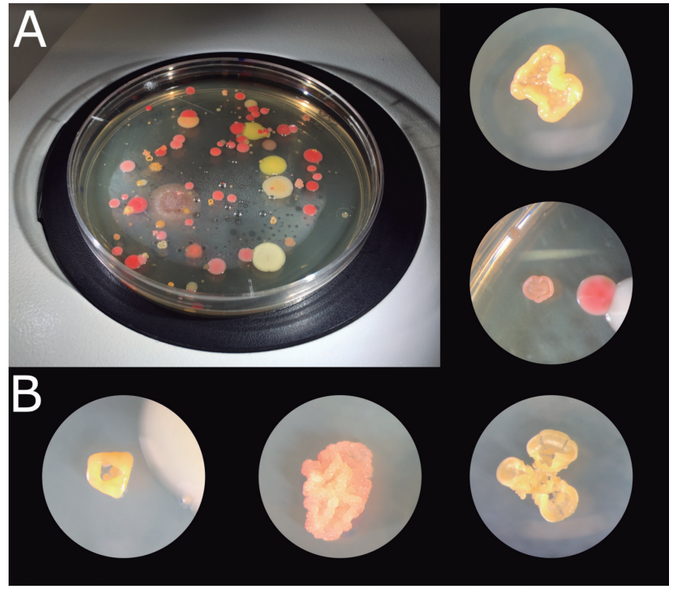
COMMUNICATION ROLE ON PERCEPTION AND BELIEFS OF EU CITIZENS ABOUT SCIENCE (CONCISE)
Ref. ID 824537.
European Comission (H2020).
Laboratorio de bioseguridad NCB2 para estudios de biología de sistemas y biología sintética en bacterias patógenas y de cuarentena (I²SysBio).
Ref. EQC2019-005585-P. MiCInn/AEI/FEDER. 2019.
168.658,05 €.

EXPLOITING LOW-WATER LIFESTYLES OF ENVIRONMENTAL BACTERIA FOR ENGINEERING SOLID-PHASE BIOPROCESSES (SETH).
Ref. RTI2018-095584-B-C41-42-43-44.
Ministerio de Ciencia e Innovación, AEI.
2019. 90.000 €.

RED IBEROAMERICANA PARA LA VIGILANCIA DE XYLELLA FASTIDIOSA (IBER-XYFAS).
Ref. 119RT0569. CYTED. 2019.
215.000 €.

GENOMIC-SCALE METABOLIC MODELS AND BACTERIAL REVERSE ECOLOGY: APPLICATION TO BACTERIA OF ECONOMIC INTEREST (BACTGEM).
Ref. PIE202020E120.
CSIC. 2020.
48.617,16 €.

MICROBIAL INTEGRATION OF PLASTICS IN THE CIRCULAR ECONOMY (MIPLACE)
Ref. PCI2019-111845-2.
European Comission (H2020). 2020.
1.442.000 €.



Industrial Yeasts Biotechnology

The Industrial Yeasts Biotechnology Group of I²SysBio analyzes the molecular mechanisms of adaptation to stress conditions in yeasts of industrial relevance, mainly wine yeast, both *Saccharomyces cerevisiae* as non-conventional yeasts.

Heads of the group

Emilia Matallana
Professor UV

Agustín Aranda
Tenured Scientist CSIC

Other members

Cecilia Picazo
Postdoctoral contract GVA
Helena Orozco
Postdoctoral contract GVA
Nubia Grijalva
Predoctoral contract SENESCHT
Beatriz Vallejo
Predoctoral contract FPU
Max Torrellas
Predoctoral contract FPI
Victor Garrigós
Predoctoral contract GVA
Marta Borrego
Laboratory Technician

The laboratory has studied yeasts response to adverse conditions in all the steps of the industrial use of yeasts. During biomass propagation and dehydration used to obtain starters as Active Dry Yeast, oxidative stress is of great importance, and the antioxidant systems, like thioredoxins, are targets to improve such processes. The use of natural antioxidants as argan oil is also a technological intervention useful to improve biotechnological performance of the mentioned biomass. Non- Saccharomyces yeasts are poorly adapted to the propagation and drying process, and their physiology and genetics are no as well characterized as *S. cerevisiae*, so their study is of great relevance to the enological industry, due to the contribution of such yeasts to the right organoleptic characteristics of wine. During grape juice fermentation the stress conditions evolve from one to another, from high osmolarity to high ethanol and starvation, and all that impacts yeast physiology and it is reflected in the metabolism of S. cerevisiae, influencing wine composition. Stress response is tightly linked with cellular metabolism and both are controlled in a coordinated fashion by the nutrient signaling pathways, that impact from cell proliferation to longevity. Manipulation of such pathways, or selection against chemical inhibitors of those are useful ways to improve wine yeast performance.

Relevant publications

Garrigós, V et al. Wine yeast peroxiredoxin TSA1 plays a role in growth, stress response and trehalose metabolism in biomass propagation. Microorganisms 2020, 8, 1537, doi:10.3390/microorganisms8101537.

Vallejo, B et al. Role of Saccharomyces cerevisiae Nutrient Signaling Pathways During Winemaking: A Phenomics Approach. Front. Bioeng. Biotechnol. 2020, doi:10.3389/fbioe.2020.00853.

Grijalva-Vallejos, N et al.. Evaluation of yeasts from Ecuadorian chicha by their performance as starters for alcoholic fermentations in the food industry. Int. J. Food Microbiol. 2020, doi:10.1016/j.ijfoodmicro.2019.108462.

Grijalva-Vallejos, N et al.. Potential application of yeasts from Ecuadorian chichas in controlled beer and chicha production. Food Microbiol. 2020, doi:10.1016/j.fm.2020.103644.

Torrellas, M. et al., E. Basal catalase activity and high glutathione levels influence the performance of non-Saccharomyces active dry wine yeasts. Food Microbiol. 2020, doi:10.1016/j.fm.2020.103589.

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Orozco, H et al.. Stress Response in Yeasts Used for Food Production. In Food Molecular Microbiology; 2019.

Aranda, A. et al. Yeast Life Span and its Impact on Food Fermentations. Fermentation 2019, 5, 37.

Picazo, C et al.. Saccharomyces cerevisiae Cytosolic Thioredoxins Control Glycolysis, Lipid Metabolism, and Protein Biosynthesis under Wine-Making Conditions. Appl Env. Microbiol 2019, 85, doi:10.1128/AEM.02953-18.

Gamero-Sandemetrio, E et al. Validation and biochemical characterisation of beneficial argan oil treatment in biomass propagation for industrial active dry yeast production. Innov. food Sci. Emerg. Technol. 2019, v. 51, 156-166–2019 v.51, doi:10.1016/j.ifset.2018.05.024.

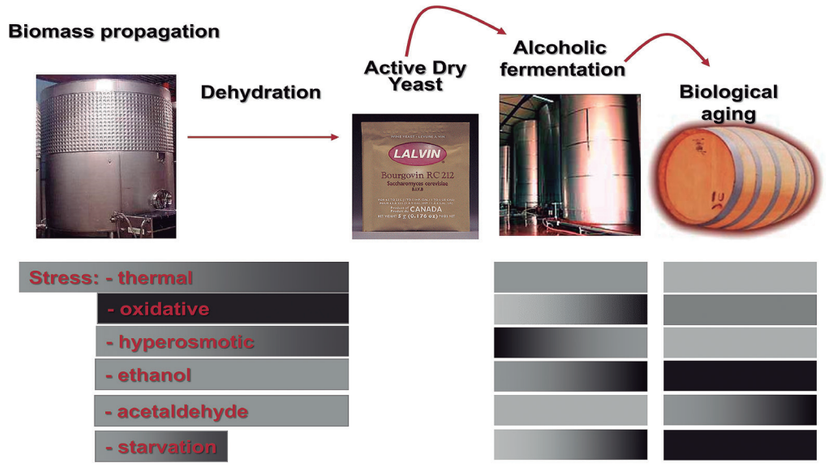
Gamero-Sandemetrio, E et al. Non-canonical regulation of glutathione and trehalose biosynthesis characterizes non-Saccharomyces wine yeasts with poor performance in active dry yeast production. Microb Cell 2018, 5, 184–197, doi:10.15698/mic2018.04.624.

Picazo, C et al.. Yeast thioredoxin reductase Trr1p controls TORC1-regulated processes. Sci Rep 2018, 8, 16500, doi:10.1038/s41598-018-34908-4.

Vallejo, B et al. Sch9p kinase and the Gcn4p transcription factor regulate glycerol production during winemaking. FEMS Yeast Res 2017, 17, doi:10.1093/femsyr/fow106.

Vallejo, B et al. Herbicide glufosinate inhibits yeast growth and extends longevity during wine fermentation. Sci Rep 2017, 7, 12414, doi:10.1038/s41598-017-12794-6.

Matallana, E.; Aranda, A. Biotechnological impact of stress response on wine yeast. Lett Appl Microbiol 2017, 64, 103–110, doi:10.1111/lam.12677.



Production and use of wine yeasts implies a set of adverse stress conditions. Overcoming such stresses is key for the technological efficiency of yeasts. Below each industrial process the most relevant stress conditions are depicted.

Gamero-Sandemetrio, E. et al. Zymography Methods to Simultaneously Analyze Superoxide Dismutase and Catalase Activities: Novel Application for Yeast Species Identification. Methods Mol Biol 2017, 1626, 189–198, doi:10.1007/978-1-4939-7111-4_17.

Projects

IMPACT OF THE METABOLIC REGULATION BY NUTRIENTS AND REDOX STATUS ON THE TECHNOLOGICAL PERFORMANCE OF WINE YEASTS
Co-IP: Emilia Matallana, Agustín Aranda Fernández
Funding agency: Ministerio de Ciencia e Innovación.
Code: AGL2017-8325 4-R
Dates: 01/01/2018 - 31/12/2020
Amount: 181.500 €

RESPONSES TO OXIDATIVE STRESS AND NUTRIENT AVAILABILITY INVOLVED IN WINE YEASTS METABOLISM AND TECNOLOGICAL PERFORMANCE
IP: EMILIA MATALLANA
Funding agency: Ministerio de Ciencia e Innovación.
Code: AGL2014-52984-R
Dates: 01/01/2015 - 31/12/2017
Amount: 190.000 €

Systems Metabolic Engineering

Heads of the group

José Luis García López (IP)
Scientist, CSIC

Marta Tortajada Serra (Co-IP)
R&D Director, Bioactives and Botanicals, Health & Wellness, ADM-Biopolis

Daniel Ramón Vidal (Co-IP)
R&D Director Bioactives Unit, ADM-Biopolis

Other members

Silvia Alfonso-Loeches
Postdoctoral contract
Araceli Lamelas Cabello
Postdoctoral contract
Patricia Álvarez Villanueva
Predoctoral contract
Paola Corbín Agustí
Predoctoral contract
Alba Arévalo Lalanne
Predoctoral contract, FDEGENT
Miguel Álvarez Herrera
Master Student

The group has been created by I²SysBio researchers and researchers from the ADM-Biopolis company with the aim of collaborating in the development of R&D projects by applying Systems Biology and Synthetic Biology to the optimization of industrial biotechnological processes.

The research lines of this group are focussed in different biotechnological fields such as the production of biopolymers (*e.g.*, polyhydroxyalkanoates), biofuels, enzymes, small molecules (drugs, dyes, antioxidants, monomers, etc.), probiotics, etc. The group develops omics and systems metabolic engineering techniques to optimize these processes. We work on the genetic and biochemical characterization of microbial metabolic pathways. In the pharmaceutical and food sectors we are developing projects that involve the use of metagenomics techniques for bacterial production of different compounds with the aim of defining a biotechnological process to ensure its supply to study their mechanisms of action and its future commercialization. In the field of environmental biotechnology, we are developing several European projects which aim to create platforms and biorefineries useful for biopolymer production through bacterial fermentation of synthesis gas (syngas) generated by pyrolysis of highly complex biological wastes (*e.g.*, municipal, commercial, sludge, agricultural) using different bacteria (*e.g.*, *Clostridium*, *Rhodospirillum*). The group also contribute to the Green and Sustainable Chemistry by developing clean industrial bioprocesses with several applications such as: i) production of biofuels by microbial fermentation; ii) production of chemical building blocks useful to generate bio-based polymers or chemical bulk compunds; iii) production of biocatalysts derived from genetically engineered enzymes with new catalytic properties; iv) development of bacterial polyextremophile chassis resistant to desiccation to use them for environmental applications.

Finally, this group is also particularly interested in the identification of the molecular mechanisms of action of probiotic microorganisms, based on the identification of metabolic pathways and molecular patterns relevant to their functional action. Metabolic models are developed at genomic scale (GEM) from the annotated sequences of bifidobacteria genomes to obtain the functional metabolic reconstructions and to analyze, among other aspects, growth capacities, carbon source utilization or essential factor requirements.

Relevant publications

Rivero-Buceta V, et al. (2020) Anti-staphylococcal hydrogels based on bacterial cellulose and the antimicrobial biopolyester poly(3-hydroxy-acetylthioalkanoate-co-3-hydroxyalkanoate). Int J Biol Macromol. 162:1869-1879.

Felpeto-Santero C, *et al.* (2019) Identification and expression of the 11β-steroid hydroxylase from *Cochliobolus lunatus* in *Corynebacterium glutamicum*. Microb Biotechnol. 12:856-868.

Ibero J, *et al.* (2019) High-quality whole-genome sequence of an estradiol-degrading strain, *Novosphingobium tardaugens* NBRC 16725. Microbiol Resour Announc. 8:e01715-18.

Uluşeker C, *et al.* (2019) Quantifying dynamic mechanisms of auto-regulation in *Escherichia coli* with synthetic promoter in response to varying external phosphate levels. Sci Rep. 9:2076.

Bustamante D, *et al*. (2019) In silico prospection of microorganisms to produce polyhydroxyalkanoate from whey: *Caulobacter segnis* DSM 29236 as a suitable industrial strain. Microb Biotechnol. 12:487-501.

Tanner K, *et al.* (2019) Bioprospecting the solar panel microbiome: High-throughput screening for antioxidant bacteria in a *Caenorhabditis elegans* model. Front Microbiol. 10:986.

García-Jiménez B, *et al.* (2018) FLYCOP: metabolic modeling-based analysis and engineering microbial communities. Bioinformatics 34:i954-i963.

Martínez I, *et al*. (2017) Metabolic and process engineering for biodesulfurization in Gram-negative bacteria. J Biotechnol. 262:47-55.

García JL, *et al.* (2017) Microalgae, old sustainable food and fashion nutraceuticals. Microb Biotechnol. 10:1017-1024.

Tortajada M. (2017) New waves underneath the purple strain. Microb Biotechnol. 10:1297-1299.

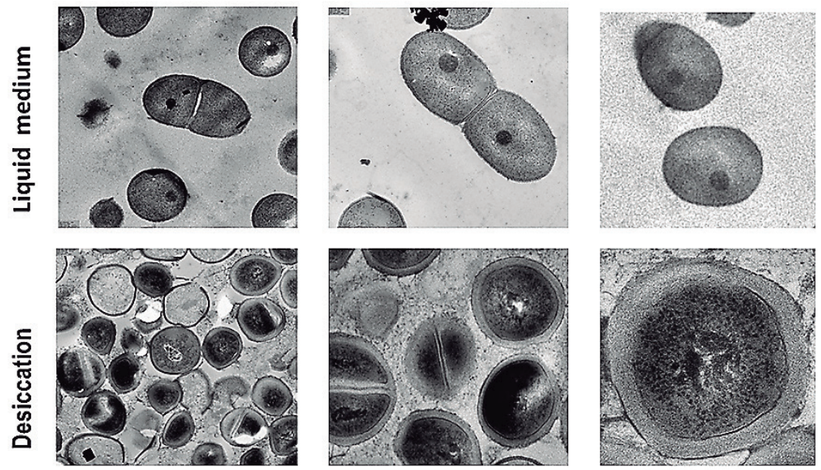
Contracts and Projects

SINNBIOSIS. INNOVATIVE SOLUTIONS IN SYSTEMS BIOLOGY.
Ref. INNTA1/2020/9.
Agencia Valenciana de Innovación (AVI). 2020.
75500 €

BATGEN. GENOMIC-SCALE METABOLIC MODELS AND BACTERIAL REVERSE ECOLOGY: APPLICATION TO BACTERIA OF ECONOMIC INTEREST.
Ref. PIE202020E120.
Intramural CSIC. 2020.
40000 €

SETH. EXPLOITING LOW-WATER LIFESTYLES OF ENVIRONMENTAL BACTERIA FOR ENGINEERING SOLID-PHASE BIOPROCESSES.
Ref. RTI2018-095584-B-C44.
Ministerio de Ciencia e Innovación. 2019.
169400 €.

IBER-XIFAS. Ibero-American network for the surveillance of *Xylella fastidiosa*. Ref. 119RT0569. CYTED. 2019.
115000 €



Electron microscopy of *Exigubacterium* sp. Helios cells before and after being subjected to a desiccation process. This xerotolerant strain was isolated from a solar panel in Paterna (Valencia). Bacteria tolerant to desiccation present a very thick envelop. (Seth project)

PROFERTILITY. MICROBIOME AND MOLECULAR BASES FOR IMPROVING ENDOMETRIAL HEALTH.
Ref. INNEST00/18/010. Agencia Valenciana de Innovación (AVI). 2018.
147500 €

IDENTIFYING A METABOLIC GENE CLUSTER.
Ref. 20186035. Biopolis-ADM. 2018.
44830 €

CONSTRUCTION, ANALYSIS AND EXPLOITATION OF GENOME-SCALE MICROBIAL METABOLIC MODELS FOR THE OVERPRODUCTION OF MICROBIAL METABOLITES.
Ref. 20171822.
Biopolis S.L. 2017.
58080 €

HELIOS. BIOTECHNOLOGICAL APPLICATIONS OF BACTERIA AND FUNGI RESISTANT TO DESICCATION. BIO2015-66960-C3-3-R.
Ministerio de Economía y Competitividad. 2016.
181500 €

Other achievements

Member XXXVI of the Spanish Royal Academy of Engineering. Daniel Ramón Vidal. 2020.

NutraChampion 2019 Award from NutraIngredients. Daniel Ramón Vidal. 2019.

Foundation of Darwin Bioprospecting Excellence S.L spin-off company. José Luis García. 2017.

New incorporations

Ana Conesa Cegarra
CSIC Full Professor

Genomics of Gene Expression

We are interested in understanding functional aspects of gene expression by combining a wide variety of high-throughput molecular techniques, including transcriptomics, epigenomics, proteomics, metabolomics, metagenomics and single-cell data, both for model and non-model species. Our lab develops statistical methods and user-friendly software tools to analyze these multi-omics data. Our most current interest is the application of long reads sequencing technologies for transcriptome analysis, the integration of multi-omics data to model chromatin-metabolome regulation, and the combination of environmental sequencing data to investigate the function of Microbial Dark Matter.

Alfonso Jaramillo Rosales
Senior Scientist, CSIC

De Novo Synthetic Biology

We are interested in the de novo design of biological macromolecules (RNA, proteins, gene circuits and viruses) that could be genetically-encoded in living cells. This includes only designing some of their molecular interactions from scratch. We approach these goals by a combination of experimental microbiology, theoretical physics, artificial intelligence and computational methods. We want to apply this fundamental research to the engineering of new organism-specific antimicrobials and to the engineering of new types of biological computations. In particular, we are interested in developing a phage therapy relying on synthetic phages and a new living matter able to learn complex algorithms. Check http://synth-bio.org

Irene Otero Muras
Tenured Scientist, CSIC

Computational Synthetic Biology

Our research is focused on the design, analysis and advanced control of biomolecular networks: nonlinear, complex systems -sometimes subject to significant molecular noise- with relevance in cell regulation, signaling and metabolic processes. In this context, our aim is to advance fundamental understanding and address innovative applications for systems and synthetic biology.

Pilar Domingo Calap
Research, Ramón y Cajal Program, UV

The Environmental and Biomedical Viruses Lab

Research at the Environmental and Biomedical Viruses lab is focused on the isolation and detection of viruses in nature with biomedical applications. Environmental virology, viral emergence, virus evolution, and phage discovery in the biomedical context, are the main research lines. Phages are ubiquitous in the environment and immensely diverse, making phage discovery a powerful source of new therapies against pathogenic bacteria, due to the emergence of multidrug-resistant strains. On the other hand, the lab is interested in environmental epidemiology, mainly in SARS-CoV-2 detection in wastewater and other natural environments, as a tool for monitoring populations and as early detection tool in surveillance. In addition, the group is interested in translational research, and has transfer contracts with national companies with biomedical and biotech purposes.

General Services

General Management

The I²SysBio Management, through Ana Belén Pozo Fernández-Freire (General Manager, CSIC) and María Herrero Soler (Institutes Support Unit Administrator, UV), oversees the public resources dedicated to the scientific and technical research. In the I²SysBio Centre the Management includes the next task:

- Finance & Administration
- Project Management
- Human Resources
- Procurement
- Assets Management
- Workplace Hazard Prevention Support

Technical Services

The Technical Services and Infrastructure Unit, consists of a multidisciplinary team whose functions are directed towards the development and satisfactory operation of the facilities and equipment. This Unit also offers specialized support to the different research groups and services of the I²SysBio in matters that are within its scope, also undertaking tasks related to the maintenance of some infrastructures.

The Unit has administrative responsibility and, in some cases, supervises equipment use, as well as giving support to end users of general equipment not assigned to other services. The services that integrate the Technical Services and Infrastructure Unit are the following:

- Technical management of projects related to Biosafety level II pathogens and GMOs.
- Advice on technical issues of Biosafety.
- Technical advice.
- Technical support for the Biosafety room level II.
- Adaptation of laboratories.
- Centralized autoclaving service.
- Centralized service for the preparation of culture media and solutions.
- Support to live collections of insects from I²SysBio.
- Technical service and maintenance support for the insect and phytotron chambers in the I²SysBio.
- Technical support with the i²SysBio maintenance service.

Coordination and management is carried out by Consuelo Escrivá López (Laboratory technician, UV).

Administrative support

Francisca de la Iglesia Jordán (CSIC)

Pedro Guerrero García (UV)

Elena Navarro Marín (UV)

María Teresa Lobo Alcaide (CSIC)

Nissar Abbas (CSIC)

Alejandro Cuenca (CSIC)

Technical Staff

Julia Garzón García
(Laboratory officer, UV)

Cristina Fernández Fernández
(Laboratory technician, CSIC)

Alejandro Pérez Berna
(Laboratory officer, CSIC)

Jorge Blanco Roca
(Laboratory officer, “Garantía Juvenil”)

Transfer activities

Technology transfer brochure I²SysBio

Technological transfer offers at I²SysBio

The Institute for Integrative System Biology provides solutions to the problems that occur in different sectors linked with biological systems such as the pharmaceutical, biotechnological, biomedical, agro-industrial and environmental sectors. The researchers of the centre deal with these problems with systematic approaches by using biochemical tools, microbiology, genetic engineering, metabolic engineering, biology of systems and synthetic biology.

In order to make technological transfer easier, I²SysBio offers a new model of agreements between public and private organisations that allow private companies to develop their R&D projects in our laboratories within the research programmes of the institute. These agreements are based on the close interaction between the researchers of I²SysBio and the researchers of the companies in the laboratories of the institute.

The Innovation Unit “Sinnbiosis” of I²SysBio in close collaboration with the Units of Projects and Knowledge Transfer of the University of Valencia and CSIC will be in charge of promoting and facilitating the formulation of cooperation agreements between researchers and the companies and other entities of the socioeconomic environment.

Innovation Unit (Sinnbiosis)

The Innovation Unit “Sinnbiosis” (Innovative Solutions for Systems Biology) has been created thanks to the project (INNTA1 / 2020/9) granted for the Promotion of Innovation Agents (Innoagents) by the “Agencia Valenciana de Innovación” (AVI) within the Program for the Promotion of Talent of the Plan GenT 2020/21 call.

The Sinnbiosis Unit aims to promote the application of global and multidisciplinary approaches provided by Systems Biology for the generation of innovative biotechnological solutions to the social and economic challenges that are posed to the institute.

The objective of the Unit is to establish communication bridges with companies in the biotechnology sector that are interested in exploiting the results of the research developed at the institute or that require our help for the development of R&D&I projects, at regional, national or international levels. This attempts to respond to our vocation to manage all the human and technological resources at our disposal in the most efficient manner to speed up the generation of innovative solutions to the questions or needs that companies can propose.

Through the Sinnbiosis Innovation Unit we are able to channel different types of agree-

Driving biotechnological innovation through integrative system biology

ments of I²SysBio with public or private partners such as:

MATERIAL TRANSFER AGREEMENT (MTA)

An MTA allows parties to exchange a quantity of a unique material (natural or synthetic) for research purposes only. An MTA does not transfer title to the material, and at the conclusion of time-limited use, the material is either returned or destroyed.

TECHNICAL ASSISTANCE AGREEMENT

This agreement allows I²SysBio and its researchers to provide focused technical or research efforts to a party with or without reimbursement. Typically, the development of intellectual property is not anticipated. It requires that the project have a mission value to the I²SysBio and some technical or commercial significance for the partner. It can also be collaborative, with both parties providing technical or scientific expertise to accomplish a mutual objective.

COLLABORATIVE AGREEMENT

This agreement is similar to a Technical Assistance Agreement, except that it does not allow for the development of intellectual property and requires that all generated data be placed into the public domain.

COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT

This agreement allows parties (mainly companies) to share services, equipment, or other resources with I²SysBio to accomplish a mutually beneficial research and development project. The partner can provide funds to I²SysBio, but I²SysBio cannot provide funds to the partner. Parties may co-develop new intellectual property. Projects should have a mission value to the I²SysBio and commercial potential for the partner.

FACILITY USE/SERVICE AGREEMENT

This agreement allows a party to use unique I²SysBio laboratory facilities, equipment, or capabilities that are not available from the private sector.

LICENSE AGREEMENT

This agreement is a contract that authorizes one party to use solely or jointly developed patents or other intellectual property of I²SysBio in some commercial undertaking. It is a long-term contractual agreement that allows the I²SysBio (licensor) to give exclusive or nonexclusive use rights to the user (licensee) in exchange for express commitments to develop the technology, make annual and royalty payments based upon a negotiated formula, and undertake patent defence in the case of infringement.

CONTACT US:

The Sinnbiosis Innovation Unit is coordinated by Prof. José Luis García and has Dr. Araceli Lamelas as the Innovator Agent.

Contact Person: Dr. Araceli Lamelas.
E-mail: araceli.lamelas@csic.es
Location: I²SysBio. Parc Científic de la Universitat de València. Carrer del Catedràtic Agustín Escardino Benlloch, 46980 Paterna, Valencia.
PHONE: +34 963 54 48 10.
WEB: https://www.uv.es/institute-integrative-systems-biology-i2sysbio/en/transfer-services/transfer-services/serveis-tecnologics.html

Technological offer portfolio

COMPUTATIONAL BIOLOGY

I²SysBio has a new Data Processing Centre (CPD) designed on the principles of scalability and energetic efficiency. CPD has an excellent IT infrastructure for answering the IT demand of storing data for academic and business research groups.
This infrastructure does not only allow us to storage information online and having a powerful computer performance but it has a virtual environment that when used with the necessary administration systems can support the community of users. I²SysBio has a programme of Computational Biology in which the researchers can offer technological support services in many fields such as:

- Processing, analysis and quality of omics data (genomes, metagenomes, transcriptomes, metabolomes, etc.).
- Maintenance of large-scale data bases.
- Management and development of bioinformatics applications.
- Big data and artificial intelligence.

OMIC TECHNOLOGIES

We offer our support to any R&D project that requires the employment of omics technologies (genomics, transcriptomics, proteomics...) for the experimental approach to complex biological problems by using massive analysis tools. We offer help for interpreting the data and its possible application for resolving the problems set out in the projects. We pay special attention to the analysis of microbiomes in different human, animal or environmental niches.

PLANT CULTIVATION. STUDY OF PLANT DISEASES

I²SysBio has several R&D programmes for studying the interaction between plants and viral and sub-viral pathogens, as well as the answer of the plant to abiotic stress, including the creation and analysis of different types of omics data and its integration in models of response regulation of the plants that are subject to these stress conditions. We have the facilities for the cultivation of plants in vitro in controlled climate conditions. In the case of studying pathogens, the cultivation chambers have P2 containment conditions and biological security. Our research groups offer to the companies that are interesting in hiring our R&D services the possibility of developing projects in collaboration about the identification of the genes involved in the resistance of biotic and abiotic stresses, the development of transgenic plants, knock-out or knock-in genetically induced or edited in these genes and its phenotyping, as well as the definition of the possible collateral effects of these mutations. We also have the knowledge and experience for identifying new viral pathogens and for developing weakened viral strains for using them in cross protection.

VIROLOGY APPLIED TO HUMANS

I²SysBio, by means of the groups of its Programme of Biology of Systems of Pathogens, provides to academic and business researchers a wide number of technological tools for the manipulation and identification of human viruses and the development of techniques linked to applied virology in humans:

- Cultivation and purification of viruses increasing the number of human viruses known in cell cultivation and the preparation of high-title stocks purified in gradient.
- Metagenomics analysis of environmental or clinical samples for the detection of human viruses. Almost impartial enlargement of vi-

ral nucleoid acids in a sample provided by the user, sequencing the high performance and identification of viral sequences.

- Electronic microscopy of virus. Morphological analysis of viral particles in human tissues or the morphological analysis of purified viral preparations.
- Microscopy of automatized fluorescence in real time for the quantification of viral growth in cultivation. Infection of cell cultivation with virus marked with fluorescence provided by the user, quantification of the fluorescence in cultivations and analysis of the growth / viral expansion.
- Quantitative PCR in real time for the viral quantification of human samples. Extraction of DNA/ RNA, design of primers, qPCR and analysis of data.
- Research and characterisation of specific pathogen bacteria. Environmental samples and sample tests for detecting the presence of eaters that target the bacteria provided by the user (BSL-1 o BSL-2). Morphological (TEM) and genetic (NGS) characterisation of isolated eaters.
- Targeted evolution of viruses. Optimisation of a virus (infectiousness, growth rate, lithic capacity) by means of artificial selection in the laboratory. Characterisation of a developed virus (sequencing, infectiousness of the tests).

SYSTEMS BIOLOGY. SYNTHETIC BIOLOGY. METABOLIC ENGINEERING OF SYSTEMS

I²SysBio develops projects in which its researchers study biotechnological processes with tools of Biology of Systems and Synthetic Biology, applied to the improvement of different industrial processes by means of techniques of metabolic engineering. I²SysBio offers the possibility of developing R&D projects for implementations in the field of molecule with a high level of added value production such as medicines, biopolymers, enzymes...
I²SysBio offers the possibility of developing metabolic models in genomic scale with applications in Biotechnology and Synthetic Biology. The institute has several experts in reduced genomes and small cells, which can inspire the design of the chassis of synthetic cells with biomedical and technological applications.

R & D Services and Facilities

I²SysBio has some infrastructures and equipment that are available for the researchers for the development of R&D projects in public and private entities.

IT UNIT FOR THE PROCESSING AND STORAGE OF DATA (CPD)

I²SysBio has a new Data Processing Centre (CPD). Now I²SysBio has a data storage system globally distributed of 2.3 Petabytes (PB) of gross capacity formed by 13 nodes of interconnected storage by means of a network system of 70 Gigabit (Gb) added broadband. The computer performance is given by last generation 520 cores of Intel Xeon (Cascade Lake) processors and 16.2 Terabytes (TB) RAM. This allows analysing big data, mainly in the field of Biology of Systems and Computational Biology.
This infrastructure has been partially financed by the project EQC2018-004319-P of the Ministry of Science, Universities and Innovation co-financed by funds from the European Regional Development Program (ERDF)).

CLIMATIC CHAMBERS

I²SysBio has 9 climatic chambers with temperature, humidity and illumination control. 5 of them are intended for plant cultivation, 2 for insect cultivation and 2 for bacteria cultivation. In addition, it has 3 additional climatic chambers for works that require low temperatures (-20º C to 5º C)

VIROLOGY LABORATORY OF BIOLOGICAL CONTAINMENT NCB2 (LEVEL 2)

I²SysBio has a NSC2 fully equipped facility of 140 m² in which they can work with pathogenic viruses that require a level 2 of containment.

BACTERIOLOGICAL LABORATORY OF BIOLOGICAL CONTAINMENT NCB2 (LEVEL 2)

This lab is under construction and will be operative along 2021.

OPTICAL EQUIPMENT

I²SysBio has several optical equipment for biological work: Binocular loupe of fluorescence, Reader of plaques (fluorescence, UV-Vis), Reader of plaques for cultivation (UV-Vis), photo documentation machine (UV, chemiluminescence, visible), Bioanalyses, quantitative PCR, Nanodrop, inverted fluorescence microscope, double-beam UV-VIS spectrophotometer.

Current technological offer

PATENTS

The patents derived from the activities of the researchers of I²SysBio are the following:

1.- Inventor: J. Ferré Manzanero, M. Ferrandis Sebastiá, P. Caballero Murillo, J. Iriarte García, M. Porcar Miralles y Y. Bel Cortés. Title: Nueva cepa de Bacillus thuringiensis activa contra plagas de lepidópteros. Req. number: P200001716 Priority country: Spain Priority date: 04/07/2000. Patent holder: University of València. Countries to which it has spread: Spain. Company / s that are exploiting it: Industrias AFRASA S.A., Valencia (in the process of obtaining the registration for the exploitation).

2.- Inventor: P. Caballero Murillo, C. Martínez Rico, J. Ferré Manzanero, M. Porcar Miralles, C. Sara Hernández, J. González Cabrera. Title: Nueva cepa de Bacillus thuringiensis para el control de orugas de lepidópteros y en especial de la gardama, Spodoptera exigua. Req. number: P200101859 Priority country: Spain Priority date: 31/07/2001. Patent holder: University of València. Countries to which it has spread: Spain. Company / s that are exploiting it: AFRASA S.A. Industries (in the process of obtaining registration for exploitation).

3.- Inventor: Caballero, P., Martínez, C., y Porcar Miralles, M. Title: Nueva cepa de Bacillus thuringiensis con múltiples genes cry tóxica contra plagas de lepidópteros. Req. number: P200102916. Priority country: Spain Priority date: 31/03/2002. Patent holder: Universidad Pública de Navarra. Countries to which it has spread: Spain. Company / s that are exploiting it: UPNA.

4.- Inventor: Porcar Miralles, M, Rodríguez-Barreiro, R., Vilanova, C., Abendroth, C., Moya, A. Title: Dispositivo termoeléctrico microbiano y método asociado a dicho dispositivo. Req. number: P201200977. Priority country: Spain. Priority date: 28/09/2012. Patent holder: University of València. Países a los que se ha extendido: Spain. Empresa/s que la están explotando: Not being exploited now.

5.-Inventor: Cristina Vilanova, Joaquín Baixeras, Amparo Latorre, Manuel Porcar. Title: Cepas de Pseudomonas sp. y usos de las

mismas". Req. number OEPM: P201300612. Priority country: Spain Priority date: 04/07/2013. Patent holder: University of València. Countries to which it has spread: Spain. Company / s that are exploiting it: In negotiation.

6.- Inventors: A. Muñoz-Pomer, R. Futami, A. Moya, C. Llorens. Title: "CheckAlign 2.0". Patent registration number: V-2137-10. Objective: Source Code for Bioinformatic Analyses. Grant date: 2013. Owner entity: BiotechVana LS.

7.- Inventors: R. Futami, A. Muñoz-Pomer, J.M. Viu, L. Dominguez-Escribá, L. Covelli, G.P. Bernet, J.M. Sempere, A. Moya, C. Llorens. Title: "GPRO 1.0". Patent registration number: V-13-11. Objetive: Source code for bioinformatics analysis. Grant date: 2013. Owner entity: BiotechVana LS.

8.- Inventors: A. Muñoz-Pomer, R. Futami, L. Covelli, L. Dominguez-Escribá, G.P. Bernet, Gonzalo Fuster, A. Moya, C. Llorens. Title: "BiotechVana Time (Tool for in place Molecular Editing)". Patent registration number: V-1683-10. Objetive: Source code for bioinformatics analysis. Grant date: 2013. Owner entity: BiotechVana LS.

9.- Inventors: C. Llorens, R. Futami, L. Covelli, L. Dominguez-Escribá, A. Muñoz-Pomer, J.M. Viu, G. Fuster, A. Moya. Title: "The Gypsy Database (GyDB) of mobile genetic elements reléase 2.0". Patent registration number: V-1307-10. Objetive: Service oriented to biological research. Grant date: 2013. Owner entity: BiotechVana LS.

10.- Givert X, Sitjà M, Fenech MM, Elena SF, García S. 2018. Porcine reproductive and respiratory syndrome virus cDNA clone and uses thereof. WO 2018/024677 A1.

SPIN-OFF COMPANIES

The researchers of I²SysBio have participated in the foundation of the following corporate spin-offs:

DARWIN BIOPROSPECTING EXCELLENCE S. L.

This company is located in the Science Park of the Universitat de València and focuses on sampling and analysing microbiota associated to any type of habitat, using advance cultivation techniques and massive sequencing. It offers to companies all over the world microbial solutions and is specialised in microbial sequencing, food starters, probiotics, energetic and environmental solutions.

BIOTECHVANA S.L.

This company is located in the Science Park of the Universitat de València and provides solutions and tools in the field of IT and bioinformatics, especially designed for research. The company develops bioinformatics software for omics technologies and data bases, intranets, open access, wikis and servers for research, services and education in molecular biology.

Comprehensive Biotechnological Consultancy

I²SysBio offers thanks to its multidisciplinary composition a consultancy service that provide biotechnological solutions to the companies and the groups that require our help or technical opinion to deal with the projects, processes or any other R&D activity in the sector of biotechnology, especially in the fields of industrial and environmental biotechnology.

The experience of the researchers of I²SysBio in managing and developing projects and R&D initiatives alongside with cutting-edge knowledge and infrastructures of biotechnological research at regional, national and international level allow us to give advice comprehensively about how to address the development of a product or biotechnological service that requires a R&D activity for its implementation.

I²SysBio also offers the possibility of giving support to the companies in their negotiations with other companies or groups of research in terms of acquiring technology or implementing biotechnological processes or developing R&D activities, analysing the viability of the offers.

I²SysBio offers to the companies the possibility of brainstorming in order to address biotechnological solutions that are still in the first phases of research or need innovative or disruptive approaches.

Training and dissemination activities

Seminars

07/11/2018	The evolution of biological complexity: is there a trend?
14/11/2018	Feeding the world in 2030
26/11/2018	Intracellular traffic in the filamentous fungus Aspergillus nidulans : basic and applied interest
10/12/2018	Epigenetic and transcriptomic reprogramming during plant reproduction
10/12/2018	High throughput sequencing and the exploration of the virosphere
11/01/2019	Stability of the Human Microbiome. Health and disease related to the time variability in the Human Microbiome
13/01/2019	From symbiosis to synthetic biology: designing a minimal cell model based on Bartonella
10/02/2019	Interplay between stress response, metabolism and aging in wine yeasts
18/02/2019	Evolution of Mycobacterium tuberculosis: from basic biology to global control of the disease
28/02/2019	Engineering plant viruses to produce recombinant proteins and RNAs
20/03/2019	Longitudinal Metagenomics
20/03/2019	Molecular mechanisms involved in the adaptation of Saccharomyces yeasts to wine fermentations
26/03/2019	How mathematics can help us understand the complexity of the world of viruses
01/04/2019	Evolution of a transcriptional hub protein in plants
08/04/2019	Microbioma: el último órgano del cuerpo humano
17/04/2019	Exploring the different adaptive mechanisms in microbes: from endosymbiotic bacteria to yeast
06/05/2019	Genetic and epigenetic crosstalks in Alzheimer's disease: towards a more integrative analysis
13/05/2019	Drawing regulatory networks in plant development and secondary metabolism: from models to crops
17/05/2019	Zika, yellow fever, and pathogen X: analysing emerging epidemics in the genomic era
28/05/2019	A stylish story on carpel evolution
06/06/2019	Genetic canalisation and the context-dependent effect of mutations in cellular metabolism
12/06/2019	PhD Viva: Comparative genomics between two insect symbiotic models: Innate immune system and amino acid biosynthetic pathways of the rice weevil Sitophilus oryzae and the cedar aphid Cinara cedri
17/06/2019	Systems biology and artificial intelligence for the study and management of complex diseases
20/06/2019	Informal discussion on research integrity
27/06/2019	Ambrosia beetles complex "An emergency pest"
01/07/2019	Multiomics data for the new systems biology in development and disease
18/09/2019	Microbial dynamics of Xyleborus affinis during its cycle life
26/09/2019	Kick-off Meeting Associated Unit I²SysBio-CRM
14/10/2019	Discusión informal sobre: ¿Cómo podemos usar los plásmidos para intervenir en las microbiotas?
14/10/2019	Metabolic adaptation in the human gut microbiota during pregnancy and infancy
15/10/2019	Our Asgardian ancestry: increased genome diversity of Asgard archaea and the origin of Eukaryotes
21/10/2019	Regulación de la tasa de mutación en virus de DNA
30/10/2019	On the architecture of genotype spaces and the dynamics of molecular adaptation
04/11/2019	How chemistry computes: making a chemical Turing machine avoiding (but inspired by) biochemistry
18/11/2019	How molecular chaperones shape protein evolution: lessons from the world of RNA viruses
21/11/2019	Targeted manipulation of DNA methylation in plants
01/12/2019	Cheating on Mendel: The implementation of "Active Genetics" in plants, a novel Synthetic Biology strategy to fuel basic research and expedite agricultural biotechnology
04/12/2019	Systems Biology of Bugs: Bacteria, Beetles, and Bats
12/12/2019	Caracterización bioquímica y > de levaduras aisladas de bebidas fermentadas tradicionales de Ecuador
19/12/2019	Role of the microbiome in the defence against multidrug resistant pathogens
14/01/2020	Lipid biosynthesis in oleaginous actinobacteria: metabolism, regulation and biotechnological potential
15/01/2020	Statistical mechanics of cell metabolism
17/01/2020	Análisis de las rutas de señalización de nutrientes en cepas vínicas de Saccharomyces cerevisae en condiciones de vinificación
24/01/2020	Gene sharing networks, genetic parasites, and the evolution of microbial and viral genomes
03/02/2020	Biodiversity in an extreme environment characterized by a low water activity
14/02/2020	How to create healthier research labs in a hypercompetitive world
26/02/2020	Roundtable on the outbreak of coronavirus SARS-CoV-2
04/08/2020	Exceptions in protein synthesis: evolution of selenocysteine and stop codon readthrough
21/09/2020	Caracterización bioquímica de levaduras vínicas no-Saccharomyces y adaptación tecnológica de su producción industrial como levadura seca activa
28/09/2020	Epidemiological surveillance of COVID-19 in wastewater
06/11/2020	The cholesterol catabolon. Metabolic engineering for the industrial production of steroids
06/11/2020	Agente de innovación: Proyecto Sinnbiosis (AVI)
06/11/2020	Unravelling the spread of the gonococcus in different sexual networks using genomics
03/12/2020	What are phages talking about? Deciphering the molecular mechanism of the Arbitrium system

Outreach

08/02/2018	Dia de Darwin 2018
23/04/2018	Participants of Estalmat, of mathematical encouragement, visited the I²SysBio
24/05/2018	Ciència ARA at the I²SysBio Discovering Systems Biology
06/02/2019	L'11è DataBeers València divulga el paper de la dona en la ciència, demà dijous a l'Octubre
12/02/2019	València celebra el Dia de Darwin amb un bar de ciències sobre robòtica i una conferència sobre l'evolució dels cordats
25/03/2019	Presentació del llibre 'Editando genes: recorta, pega y colorea', de Lluís Montoliu
20/05/2019	Next Saturday, the 25th of May, the Universitat celebrates Expociència 2019
11/06/2019	I²SysBio participates in an educational program from Iowa State University
18/07/2019	Secondary and high school students visit the I²SysBio
13/12/2019	Emerging Science gives voice to I²SysBio's youngest research staff
07/02/2020	The University of Valencia and the Science Space of the Octubre Centre de Cultura Contemporània commemorate the figure of Charles Darwin Wednesday 12
02/03/2020	I²SysBio researchers participate in the "Family Talks" of the Girls4STEM project

Visiting Scientists

Alfonso Jaramillo
Professor, University of Warwick (United Kingdom)

Régis Lópes Corrêa
Associate Profesor, Universidade Federal do Rio de Janeiro (Brasil)

Martín Ramón Aluja Schuneman Hofer
Researcher, INECOL (México)

Luis José Delaye Arredondo
Researcher, CINVESTAV - Irapuato (México)

Araceli Lamelas Cabello
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Paul Banse. Researcher
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Rachel S. Whitaker
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Aleksandra Zarzyńska-Nowak
Researcher, NRI Plant Protection (Polonia)

A living logo

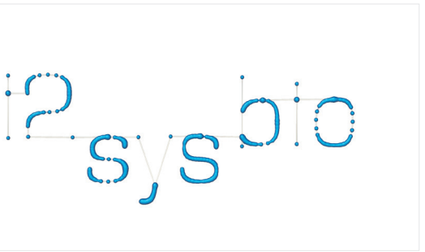
The image of the Institute for Integrative Systems Biology was a challenge for the L3C studio, as it had to respond to the philosophy behind the new center.

The development of the project began with the search for a visual metaphor that responded to the concept of network and composition of organic structures. The key to the proposal originates from placing the image and the evolution of its self-generative process on the same plane.

The graphic element of the brand is based on the comparison between the representation of the network nodes of a living system and the control points of the Bézier curves system that make up a vector image.

The logo is made from the application of the composite object modifier “blob mesh” of the 3DS MAX program on the typography. The effect of a living system is obtained by manipulating different configuration parameters of the modifier on a timeline that allows to observe the growth of the system. The progression of the fluid lattice manifests itself more intensely in the curved sections because they have a greater number of control points on the Bézier curve. On the contrary, in straight sections where there are no anchor points, the organic network does not develop in its entirety.

Due to the nature of the logo, the first application was made as a moving image: video and animated gif. Subsequently, it was interpreted in vector format in horizontal and vertical version. For the signage of the building, we proposed the objectual reproduction of the logo using current technology. In the garden of the Institute, an aluminum plate with laser-cut openwork lines was installed, and the pieces that make up the blue fluid were 3D printed using FDM technology with ABS filament.



I2SysBio Research and Innovation activities are funded by

European Commission
European Research Council
Horizon2020 Programme
European Regional Development Fund
European Social Fund+ (ESF+)
Marie Curie Actions
ERA CoBio Tech

European Society of Clinical Microbiology and Infectious Diseases ESCMID
National Centre for Replacement, Refinement and Reduction of Animals in Research, UK.
The French National Research Agency (ANR), France
National Institutes of Health (NIH), USA
Fondo Institucional de Fomento Regional para el Desarrollo Científico, Tecnológico y de Innovación (FORDECYT, CONACYT), Mexico
Programa Iberoamericano de Ciencia y Tecnología para el Desarrollo, CYTED

Ministerio de Ciencia e Innovación, Gobierno de España
Ministerio de Universidades, Gobierno de España
Agencia Estatal de Investigación (AEI)
Agencia Estatal Consejo Superior Investigaciones Científicas CSIC
Instituto de Salud Carlos III
CSIC-CRUE-Santander
Conselleria d'Innovació, Universitats, Ciència i Societat Digital, Generalitat Valenciana
Conselleria d'Educació, Generalitat Valenciana, Generalitat Valenciana
Agència Valenciana d'Innovació AVI, Generalitat Valenciana
Institut Valencià de Competitivitat Empresarial IVACE, Generalitat Valenciana

VLC-BIOMED
Programas de I+D en Biomedicina, Comunidad de Madrid

Parc Científic de la Universitat de València
ADM-Biopolis
HIPRA
SEQPLEXING
EVERIS
Darwin Bioprospecting Excellence
Fundació per al Foment de la Investigació Sanitària i Biomèdica de la Comunitat Valenciana FISABIO
Fundación AECC Investigación contra el Cáncer
Fundación MAPFRE