IBEC
Institute for Bioengineering of Catalonia

EXCELENCIA SEVERO OCHOA

IBEC ANNUAL REPORT 2017

Research and Services

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Research and Services


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Research
Groups at a glance

In 2017, IBEC had 21 research groups. Group leaders are listed here together with their group name and a top or representative publication from 2017.

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Nanoscopy for nanomedicine – Lorenzo Albertazzi

- Duro-Castano, A. et al (2017). Capturing "extraordinary" soft-assembled charge-like polypeptides as a strategy for nanocarrier design. *Advanced Materials* 29, (39), 1702888

Molecular dynamics at cell-biomaterial interface – George Altankov

- Nedjari, S. et al (2017). Three dimensional honeycomb patterned fibrinogen based nanofibers induce substantial osteogenic response of mesenchymal stem cells. *Scientific Reports*, 7 (1): 15947

Mechanics of development and disease – Vito Conte

- Perez-Mockus, G. et al. (2017). Spatial regulation of contractility by Neuralized and Bearded during furrow invagination in Drosophila. *Nature Communications* 8, (1), 1594

Biomaterials for regenerative therapies – Elisabeth Engel

- Oliveira, H.et al (2017). The proangiogenic potential of a novel calcium releasing composite biomaterial: Orthotopic *in vivo* evaluation. *Acta Biomaterialia*, 54 377-385

Nanomalaria (joint group IBEC/ISGlobal) – Xavier Fernandez-Busquets

- Moles, E. et al (2017). ImmunoPEGliposomes for the targeted delivery of novel lipophilic drugs to red blood cells in a *falciparum* malaria murine model. *Biomaterials*, 145 178-191

Nanoscale bioelectrical characterization – Gabriel Gomila

- Biagi, M. C. et al (2017). Direct mapping of the electric permittivity of heterogeneous non-planar thin films at gigahertz frequencies by SMM. *Phys. Chem. Chem. Phys*, 19 (5): 3884-3893

Nanoprobes and nanoswitches – Pau Gorostiza, Fausto Sanz

- Ruiz, M. P. et al (2017). Bioengineering a single-protein junction. *Journal of the American Chemical Society* 139, (43), 15337–15346

Biomedical signal processing and interpretation – Raimon Jané

- Sarlabous, L. et al (2017). Inspiratory muscle activation increases with COPD severity as confirmed by non-invasive mechanomyographic analysis. *PLoS ONE*, 12 (5): e0177730

Signal and information processing for sensing systems – Santiago Marco

- Pomareda, V. et al (2017). Chemical source localization fusing concentration information in the presence of chemical background noise. *Sensors*, 17 (4): 904

Biomimetic systems for cell engineering – Elena Martínez

- Ojosnegros, S. et al. (2017). Eph-ephrin signaling modulated by polymerization and condensation of receptors. *Proceedings of the National Academy of Sciences* 114, (50), 13188-13193

Cellular and respiratory biomechanics – Daniel Navajas

- Hernández-Vega, A. et al (2017). Polarized cortical tension drives zebrafish epiboly movements. *EMBO Journal*, 36 (1): 25-41

Cellular and molecular mechanobiology – Pere Roca-Cusachs

- Oria, R. et al (2017). Force loading explains spatial sensing of ligands by cells. *Nature*, 552 (7684), 219-224

Bacterial infections: antimicrobial therapies – Eduard Torrents

- Crespo, A. et al (2017). Regulation of ribonucleotide synthesis by the *Pseudomonas aeruginosa* two-component system AlgR in response to oxidative stress. *Scientific Reports*, 7 (1): 17892

iPSCs and activation of endogenous tissue programs for organ regeneration – Núria Montserrat

- Garreta, E. et al (2017). Tissue engineering by decellularization and 3D bioprinting. *Materials Today* 20, (4), 166-178

Biosensors for bioengineering – Javier Ramón

- Mohammadi, M. H. et al (2017). Engineered muscle tissues for disease modeling and drug screening applications. *Current Pharmaceutical Design*, 23 (20): 2991-3004

Nanobioengineering – Josep Samitier

- Gállego, I. et al (2017). DNA-origami-driven lithography for patterning on gold surfaces with sub-10 nm resolution. *Advanced Materials* 29, 1603233

Integrative cell and tissue dynamics – Xavier Trepat

- Rodríguez, P. et al (2017). Long-lived force patterns and deformation waves at repulsive epithelial boundaries. *Nature Materials* 16, 1029–1037

Targeted therapeutics and nanodevices – Silvia Muro

- Garnacho. C. et al (2017). Endothelial delivery and effects of acid sphingomyelinase by ICAM-1 targeted nanocarriers in type B Niemann-Pick disease. *Mol. Ther.* 25(7):1686-1696

Molecular and cellular neurobiotechnology – José A. Del Río

- Mata, A. et al (2017). Reelin expression in Creutzfeldt-Jakob disease and experimental models of transmissible spongiform encephalopathies. *Molecular Neurobiology*, 54 (8): 6412-6425

Smart nano-bio-devices – Samuel Sánchez

- Katuri, J. et al (2017). Designing micro- and nanoswimmers for specific applications *Accounts of Chemical Research* 50, (1), 2-11

Synthetic, Perceptive, Emotive & Cognitive Systems (SPECS) – Paul Verschure

- Maffei, G. et al (2017). The perceptual shaping of anticipatory actions. *Proceedings of the Royal Society B*, 284 (1869)

Nanoscopy for nanomedicine

Lorenzo Albertazzi

The main goal of our group is to use Super Resolution Microscopy (nanoscopy) to visualize and track in living cells and tissues self-assembled nanomaterials with therapeutic potential (nanomedicine).

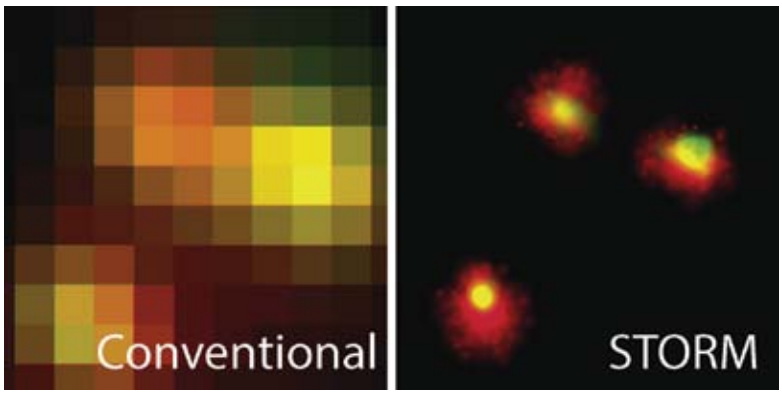
The understanding of materials-cell interactions is the key towards the development of novel nanotechnology-based therapies for treatment of cancer and infectious diseases.

Our group aims to use a multidisciplinary approach, at the interface of chemistry, physics and biology, to develop novel nanomaterials for the treatment of cancer and infectious diseases.

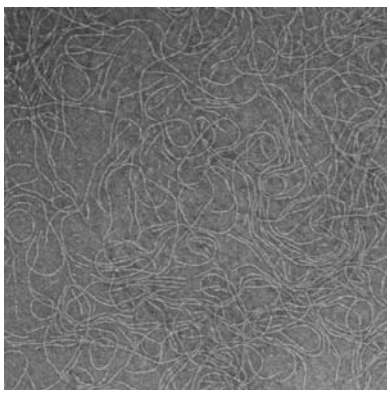
We aim at the development of novel nanocarriers for drug delivery based on self-assembly, i.e. able to build themselves. Molecular self-organization is ubiquitous in the biological world and represents for us a source of inspiration for the design of nanostructures with biomedical potential. In particular we focus on the development of self-assembled nanoparticles and nanofibers able to selectively target diseased cells and deliver locally therapeutic moieties such as drugs and genetic material (e.g. DNA, siRNA, mRNA).

A key point towards the development of novel nanotechnology-based therapies is the understanding of the behavior of nanomaterials in the complex biological environment. Here we use super resolution microscopy to track nanomaterials during their voyage in the biological environment and to visualize the interactions with blood components, immune system and target cells. We make use of a variety of super resolution techniques based on single molecule detection such a stochastic optical reconstruction microscopy (STORM), photoactivated localization microscopy (PALM), point accumulation for imaging in nanoscale topography (PAINT), and single particle tracking (SPT). These methods allow to achieve a resolution down to few nanometers and are therefore ideal to visualize nanosized synthetic objects in the biological environment. Super resolution microscopy provides a molecular picture of structure-activity relations and represent a guide towards the design of innovative materials for nanomedicine.

Nanoparticles interactions with blood components imaged with conventional optical microscopy (left) and super resolution STORM microscopy (right).



TEM image of novel self-assembled nanofibers synthesized in the group.



Postdocs
Silvia Pujals
Pietro Delcanale

PhD students
Roger Riera
Adrianna Glinkowska
Maria Arista
Natàlia Feiner

Research assistant
Edgar Fuentes

Research projects

- **NANOSTORM** Design of Nanomaterials for Targeted Therapies Guided by Super Resolution Imaging
  PI: **Lorenzo Albertazzi**
  ERC Starting Grant
- **TARGETSTORM** Nanomateriales para terapias dirigidas contra el cáncer visualizados con microscopia de súper resolución STORM (2016-2019)
  PI: **Lorenzo Albertazzi**
  MINECO Retos investigación: Proyectos I+D
- Novel approaches for Pandemic Virus Targeting Using Adaptive Polymers (2015-2017)
  PI: **Lorenzo Albertazzi**
  AXA Research Fund
- **NANOVAX** Nanovacunas diseñadas para inmunoterapia antitumoral MINECO Acciones de Programación Conjunta Internacional
  PI: **Lorenzo Albertazzi**/Josep Samitier
  MINECO Retos investigación: Proyectos I+D
- Understanding and measuring mechanical tumor properties to improve cancer diagnosis, treatment, and survival: Application to liquid biopsies (2017-2020)
  PI: **Lorenzo Albertazzi**
  Obra Social La Caixa

Collaborations

- **Roey Amir,** Tel Aviv University, Israel
- **Mika Linden,** Ulm University, Germany
- **Ilja Voets,** Eindhoven University of Technology, The Netherlands
- **Giovanni Pavan,** SUPSI, Switzerland
- **Bruno De Geest,** University of Ghent, Belgium
- **Salvador Borros,** IQS Barcelona

Publications

- Oria, R., Wiegand, T., Escribano, J., Elosegui-Artola, A., Uriarte, J. J., Moreno-Pulido, C., Platzman, I., Delcanale, P., Albertazzi, L., Navajas, D., Trepat, X., García-Aznar, J. M., Cavalcanti-Adam, E. A. and Roca-Cusachs, P. (2017). Force loading explains spatial sensing of ligands by cells. *Nature*, 552 219-224
- Labernadie, A., Kato, T., Brugués, A., Serra-Picamal, X., Derzsi, S., Arwert, E., Weston, A., González-Tarragó, V., Elosegui-Artola, A., Albertazzi, L., Alcaraz, J., Roca-Cusachs, P., Sahai, E. and Trepat, X. (2017). A mechanically active heterotypic E-cadherin/N-cadherin adhesion enables fibroblasts to drive cancer cell invasion. *Nature Cell Biology*, 19 (3): 224-237
- Duro-Castano, A., Nebot, V. J., Niño-Pariente, A., Armiñán, A., Arroyo-Crespo, J. J., Paul, A., Feiner-Gracia, N., Albertazzi, L. and Vicent, M. J. (2017). Capturing "extraordinary" soft-assembled charge-like polypeptides as a strategy for nanocarrier design. *Advanced Materials*, 29 (39): 1702888

- Feiner-Gracia, N., Buzhor, M., Fuentes, E., Pujals, S., Amir, R. J. and Albertazzi, L. (2017). Micellar stability in biological media dictates internalization in living cells. *Journal of the American Chemical Society*, 139 (46): 16677-16687
- Feiner-Gracia, N., Beck, M., Pujals, S., Tosi, S., Mandal, T., Buske, C., Linden, M. and Albertazzi, L. (2017). Super-resolution microscopy unveils dynamic heterogeneities in nanoparticle protein corona. *Small*, 13 (41): 1701631
- Van Onzen, A. H. A. M., Albertazzi, L., Schenning, A. P. H. J., Milroy, L. G. and Brunsveld, L. (2017). Hydrophobicity determines the fate of self-assembled fluorescent nanoparticles in cells. *Chemical Communications*, 53 (10): 1626-1629
- Pujals, S., Tao, K., Terradellas, A., Gazit, E. and Albertazzi, L. (2017). Studying structure and dynamics of self-Assembled peptide nanostructures using fluorescence and super resolution microscopy. *Chemical Communications*, 53 (53): 7294-7297
- Caballero, D., Blackburn, S. M., de Pablo, M., Samitier, J. and Albertazzi, L. (2017). Tumour-vessel-on-a-chip models for drug delivery. *Lab on a Chip*, 17 3760-3771

Equipment and techniques

- Nikon NSTORM Super Resolution Microscope
- Super Resolution microscopy
- Single particles tracking
- TIRF fluorescence imaging

Molecular dynamics at cell-biomaterial interface

George Altankov (ICREA Research Professor)

We are interested in cell–biomaterials interaction, and more specifically, on the dynamic formation of the provisional extracellular matrix (ECM) – the thin protein layer that cells recognize, produce, and remodel at the materials interface.

We aim to learn how this process affects the biocompatibility of materials, and if it can be controlled by engineering the surface properties of materials. For this purpose, we perform systematic studies in the following directions:

Remodelling of ECM proteins at cell-biomaterials interface

Upon adsorption at material interfaces, proteins may assemble spontaneously and this interaction has significant consequences for their biological activity. The cells can also actively rearrange these proteins presumably as an attempt to organize a provisional ECM. We anticipate that materials that bind proteins loosely will support the arrangement of a provisional ECM, while stronger binding provokes its degradation, i.e. their proteolytic remodeling. ECM remodelling is a fundamental proces that occurs in various physiological and pathological conditions, such as normal development, wound healing and angiogenesis, but also in atherosclerosis, fibrosis, ischemic injury and cancer. It is dynamic and consists of two fundamental processes: assembly and degradation. Although matrix remodelling is a subject of extensive biomedical research, the way it is related to the biocompatibility of materials is poorly understood and is therefore a hot topic of our research.

ECM organization at the biomaterial interface depends on the allowance of cells to rearrange adsorbed matrix proteins – a process strongly dependent on proper functioning of integrin receptors. We anticipate that materials that bind proteins loosely will support the arrangement of a provisional ECM, while stronger binding provokes its degradation.

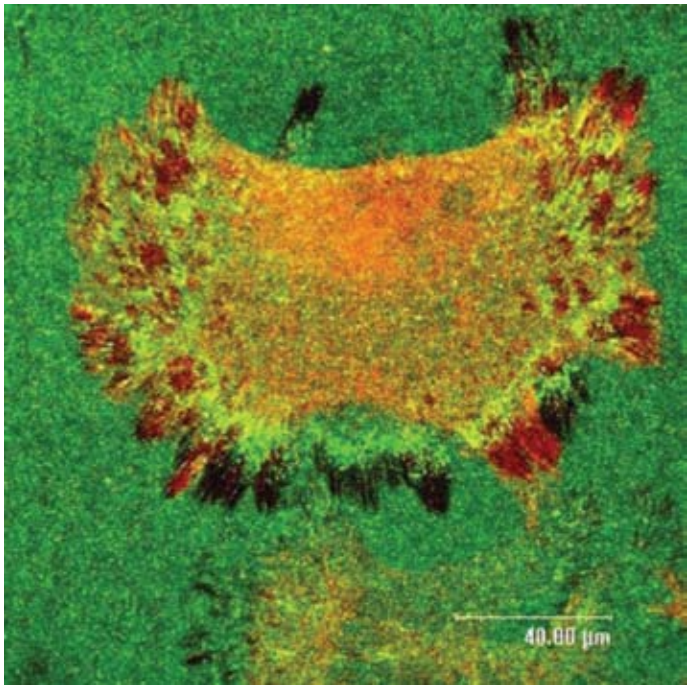


Fig. 1: Dynamic behaviour of ECM proteins at cell-biomaterials interface: Fibroblast remodelling of adsorbed collagen IV (green) depend on α2 integrin (red) function. Colocalization is in orange. Dark zones represents the mechanical removal of adsorbed protein followed by fibri-like organization (arrow).

Molecular dynamics at cell-biomaterial interface

Senior postdoc
Firas Awaja

Postdoc
Salima Nedjari

PhD student
Dencho Gugutkov

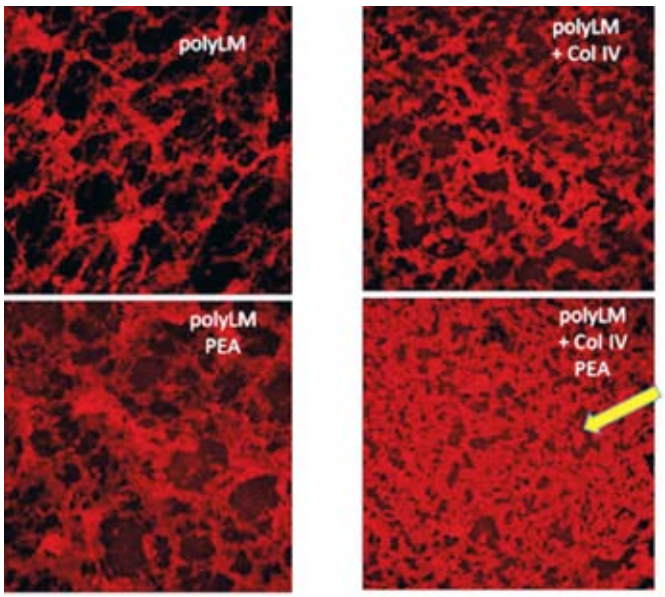


Fig. 2: Fluorescent confocal images of poly-laminin and poly-laminin/Col IV composite matrices showing the "condensation" effect of PEA surface resembling the physiological basement membrane

Biomaterials surface-driven assembly of ECM proteins at the nanoscale

Upon adsorption at material interfaces, proteins may assemble spontaneously and this interaction has significant consequences for their biological response. Recently we have employed distinct silane-inspired chemistries and polymer compositions to create model substrates with tailored densities of -OH, -COOH, $-NH_2$ and $-CH_3$ groups, thus varying the chemistry, charge and hydrophilic/ hydrophobic balance. In a series of communications combining AFM and other nanoindentation techniques, we have described a novel phenomenon of substratum-driven protein assembly depicting the fate of various matrix proteins such as fibronectin, collagen IV, vitronectin and fibrinogen at the above model biomaterials interfaces.

Specifically, we show that by varying the density of chemical functions one can tailor both the assembly and degradation of proteins. Following those findings we aim to control ECM remodelling by engineering specific material properties. Understanding the behavior of ECM proteins on flat biomaterials interface further boosts an important bioengineering target – the biohybrid organ technologies based on two-dimensional protein layers that mimic the arrangement of the natural basement membrane.

Development of artificial basement membrane

Understanding the behavior of ECM proteins on flat biomaterials interface further boosts an important bioengineering target – the biohybrid organ technologies based on two-dimensional protein layers that mimic the arrangement of the natural basement membrane. With this project we aim to develop a synthetic basement membrane (BM) to be used as a supportive lining for cellularized implants, with specific focus on the design of a bioengineered blood vessel. Taking advantage of the self-assembly properties of the two principal components of the BM, laminin and collagen IV, composite matrices of these molecules are produced by mixing them before or during the polymerization of laminin under acidic conditions.

Selected composites will be deposited on scaffolds produced using electronspun nanofibers preferentially made of polyethyl acrilate (PEA), which additionally favour networking of laminin and collagen IV. The resemblance to natural BM will be evaluated in terms of their morphological features and ability to properly induce the formation of biomimetic monolayers of endothelial cells. This project is driven involving joint efforts of our Lab and this of Prof Tatiana Coelho-Sampaio's from the Federal University of Rio de Janeiro, Brazil.

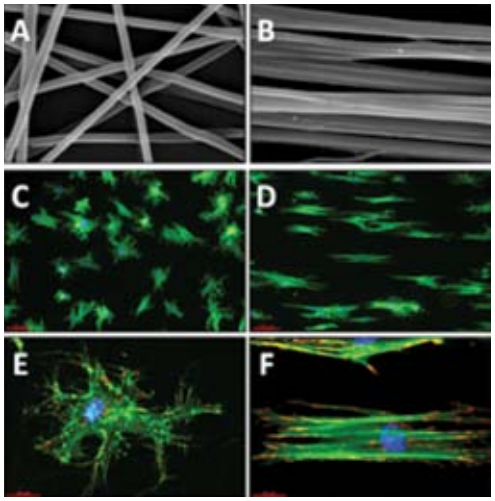


Fig. 3: Hybrid PLA/fibrinogen nanofibers deposited in random (A) and aligned (B) configurations. Human mesenchymal stem cells adhere to the fibers and acquire a stellate-like (C & E) or elongated (D & F) morphology, depending on the fiber orientations (staining: vinculin in red and actin in green).

Electrospinning of nanofibers from natural and synthetic polymers for guiding cellular behaviour

In solution, proteins can form structures of various shapes, including fibers with a diameter of only a few nanometers and with lengths up to centimeters. A fascinating possibility to mimic similar ECM structures is to engineer protein-like or matrix protein-containing nanofibers via electrospinning technology. For this purpose we are developing electrospun nanofibers from natural (e.g., fibrinogen) and synthetic polymers (e.g. PLA, PEA) in order to direct the desired cellular response via spatially organized cues (e.g. fiber size and geometrical organization) as well as by tailoring their chemical and mechanical properties.

Nanofibers-based 3D constructs for culturing of stem cells with spatially organized stimuli

Examining hierarchical biology in only two dimensions (i.e., cells confined to a monolayer) is in most cases insufficient as cells typically exhibit unnatural behavior if excised from native three-dimensional (3D) tissues. Therefore, within the European FIBROGELNET project (under our coordination) we are developing 3D biohybrid

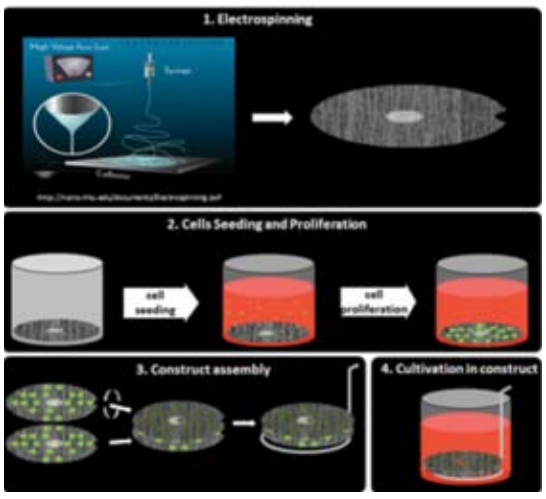


Fig. 4: Schematic illustration of the STRUCTGEL concept.

Publications

- Nedjari, S., Awaja, F. and Altankov, G. (2017). Three dimensional honeycomb patterned fibrinogen based nanofibers induce substantial osteogenic response of mesenchymal stem cells. *Scientific Reports*, 7 (1): 15947
- Bianchi, M. V., Awaja, F. and Altankov, G. (2017). Dynamic adhesive environment alters the differentiation potential of young and ageing mesenchymal stem cells. *Materials Science and Engineering C*, 78 467-474
- Gugutkov, D., Gustavsson, J., Cantini, M., Salmeron-Sánchez, M. and Altankov, G. (2017). Electrospun fibrinogen-PLA nanofibres for vascular tissue engineering. *Journal of Tissue Engineering and Regenerative Medicine*, 11 (10): 2774-2784
- Gugutkov, D., Awaja, F., Belemezova, K., Keremidarska, M., Krasteva, N., Kuyrkchiev, S., GallegoFerrer, G., Seker, S., Elcin, A. E., Elcin, Y. M. and Altankov, G. (2017). Osteogenic differentiation of mesenchymal stem cells using hybrid nanofibers with different configurations and dimensionality. *Journal of Biomedical Materials Research - Part A*, 105 (7): 2065-2074
- Hristova-Panusheva, K., Keremidarska-Markova, M., Altankov, G. and Krasteva, N. (2017). Age-related changes in adhesive phenotype of bone marrow-derived mesenchymal stem cells on extracellular matrix proteins. *Journal of New Results in Science*, 6 (1): 11-19

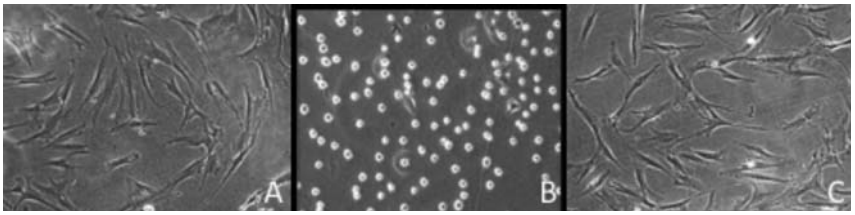


Fig. 6: Reversible attachment/detachment of human mesenchymal stem cells from thermo-responsible PNIPAM substrata: Cells were cultured at 37ºC for 5 h on PNIPAM (A) and left to detach at room temperature for 2 hours (B), then switched again to 37ºC overnight (C).

constructs that combine the structural and biological properties of electrospun nanofibers with the optimized mechanical properties of specific hydrogels in order to provide stem cells with relevant spatial orientation in three dimensions.

Creating dynamic stem cell niches using stimuli-responsive biomaterials

In addition to engineering the spatial configuration of cellular microenvironments, we are also interested in addressing the dynamic (i.e., temporal) aspects of the stem cell niche. To do that we take advantage of stimuli-responsive polymers to obtain control over an artificial cell-adhesive environment via dynamically altering either cell-cell (using cadherin-like ligands) or cell-matrix (using ECM proteins) interactions. By modulating the strength of adhesive protein-to-substratum interactions we aim to control the stem cell adhesive machinery, and which allows us to mimic the dynamic conditions of the stem cell niche.

Research projects

- **FIBROGELNET** Network for development of soft nanofibrous construct for cellular therapy of degenerative skeletal disorders (2013-2017).
  PI: **George Altankov** (coordinator)
  EU - FP7-PEOPLE-2012-IAPP
- **MYOHEAL** Muscle regeneration after injury. Engineered biodegradable ion–loaded scaffolds to promote muscle regeneration (2015-2017).
  PI: **George Altankov**
  MINECO, MAT 2015 – 69315 –C3
- **MYOREM** Remodelación Por Mioblastos de la Matriz Extracelular en la Interfaz Celula-Biomaterial (2016-2018)
  PI: **George Altankov**
  MINECO, Retos investigación: Proyectos I+D

Collaborations

- Center for Biomaterials, Technical University of Valencia, Spain
- Institute of Pharmacy, Martin Luther University, Halle, Germany
- Institute of Biomedical Science, Federal University of Rio de Janeiro, Brazil
- Institute for Biophysics and Biomedical Engineering, Bulgarian Academy of Sciences, Sofia, Bulgaria
- Institute of Solid State Physics, Bulgarian Academy of Sciences, Sofia, Bulgaria
- Division of Biomedical Engineering, School of Engineering, University of Glasgow, United Kingdom

Industrial collaborations:

- Bio-Elpida, France
- BulGen, Bulgaria

Equipment and techniques

- Laser scanning confocal microscope equiped for performing dynamic studies with living cells
- Full facilities for cell culturing
- Electrospinning device designed for the production of nanofibers from natural and synthetic polymers
- Laboratory freeze-dryer (Telstar Cryodos)
- Spectrofluorometer Fluormax 4 (Horiba, Jobin Yvon)
- Chromatographic and electrophoretic equipment
- Flow chamber setup for measuring the strength of cell adhesion
- Programmable compact spin coater

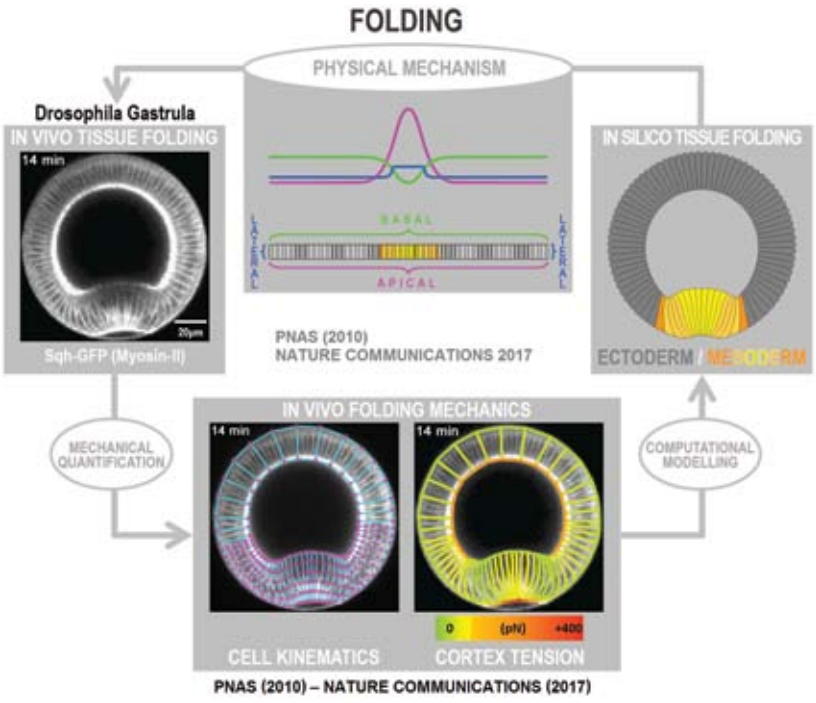
Mechanics of development and disease

Vito Conte

In the group we advance cross-disciplinary research at the interface between biology, physics and engineering by studying the mechanical biology and the biological mechanics of pathological development and disease progression. Specifically, we focus on soft tissue morphogenesis – the process by which a tissue takes or lose shape.

Deciphering the physical mechanisms of tissue morphogenesis is a powerful expedient to identify new mechanical hallmarks of cancer progression and define principles of tissue design for organ regeneration. This is so because both healthy and pathological tissues take or lose their shape through processes such as folding, segregation, growth, remodelling and invasion. These are biological processes involving mechanical events that require cells to deform, bear or develop forces as well as to fine-tune their material properties. Deciphering these processes in normal and pathological conditions provides experimental data that can be directly translated into therapeutics targeting diseased cells and tissues at the physical level.

To that end, we are developing new multidisciplinary methods to quantify cell and tissue mechanics in arbitrary 2D and 3D environments that have physiologically-relevant properties. These methods hybridise physical, computational and biological approaches to extract mechanical information from large amounts of experimental data *in vitro*, *in vivo* and *ex vivo*. This data is utilised to identify what mechanical quantities can determine and/or predict cells and tissues dynamics in normal and pathological conditions such as those of carcinogenesis and tumour progression.



Postdoc
Agata Nyga

Research projects

- **CancerMechReg** Regulacion biomecanica de la progresion del cancer (2016-2019)
  PI: **Vito Conte**
  MINECO, Proyectos I+D Excelencia

Collaborations

- **François Schweisguth** (Pasteur Institute, France)
- **Jose Muñoz** (UPC, Spain)
- **Wayne Brodland** (UW, Canada)

Equipment and techniques

- Mechanical quantification *in vitro* and *in vivo*
- Experimental physical modelling *in silico*

Publications

- Rodriguez-Franco, P., Brugués, A., Marin-Llaurado, A., Conte, V., Solanas, G., Batlle, E., Fredberg, J. J., Roca-Cusachs, P., Sunyer, R. and Trepat, X. (2017). Long-lived force patterns and deformation waves at repulsive epithelial boundaries. *Nature Materials*, 16 (10): 1029-1036
- Roca-Cusachs, P., Conte, V. and Trepat, X. (2017). Quantifying forces in cell biology. *Nature Cell Biology*, 19 (7): 742-751
- Perez-Mockus, G., Mazouni, K., Roca, V., Corradi, G., Conte, V. and Schweisguth, F. (2017). Spatial regulation of contractility by Neuralized and Bearded during furrow invagination in *Drosophila*. *Nature Communications*, 8 (1): 1594

Biomaterials for regenerative therapies

Elisabeth Engel

Research in the Biomaterials for Regenerative Therapies group is devoted to the development and knowledge transfer to industry of innovative biomaterials and scaffolds for tissue regeneration.

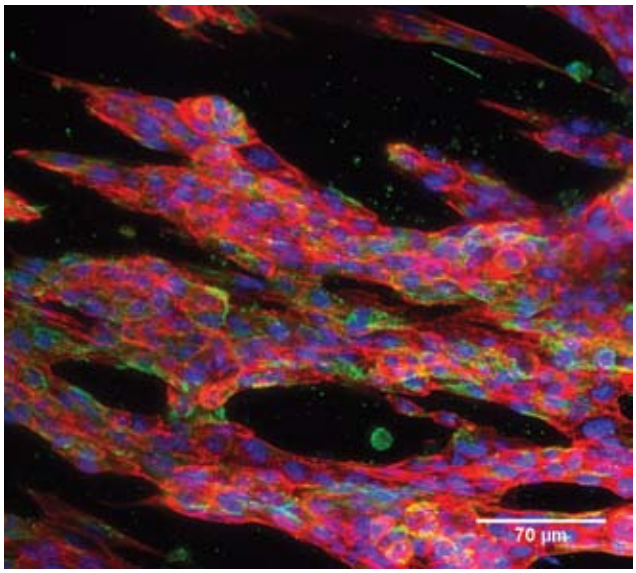
We design, fabricate and characterize bioactive and biodegradable materials and investigate their interactions with biological entities, both in terms of their fundamental aspects and with specific applications for tissue engineering purposes in mind. The aim is the repair and functional restoration of tissues or organs by means of 3D scaffolds, cells and signals.

Different research areas are being developed in the group:

The production of polymeric biomaterials using different fabrication techniques: by using a polymer organogelation/precipitation technique, the group produced 3D scaffolds with controlled architecture and mechanical properties (Punet et al, *Polymer* 2017)

We continued in the development of new materials for 3D (bio)printing in collaboration with the groups of Prof. G. Subra (Montpellier, France) and Prof. S. Catros (Bordeaux, France) (Echalier et al, *RSC Advances* 2017) (Guduric et al, *J Mat Sci Mat Med* 2017) and Prof. Carlos Semino (IQS, Barcelona)

The production of structured bioactive nanocomposites that can enhance vascularization, bone and skin regeneration, either by electrospinning, rapid prototyping or micro-particles production. Following the projects awarded by a CAIXAIMPULSE first edition project to bring our “Dermoglass” project to a closer commercialization stage and within the IBEC-LaCaixa Joint program, we continued to develop new nanoparticles that have an antimicrobial effect to add this property to the dressing. This project also obtained an award by EIT Health PoC to enhance IP protection (patent submitted) and scalability for further commercialization. During this year, we started *in vivo* studies in large animal models with very promising results.



Cardiac cell line HL1 on aligned electrospun PLGA fibers (Jesús Ordoño)

Senior researchers
Soledad Pérez
Miguel Angel Mateos
Oscar Castaño

PhD students
Jesús Ordoño
Irene Cano
Gerard Rubí

Masters students
Celia Ximenes
Carla Cofiño
Michel Augustin

Technicians
Sergi Rey

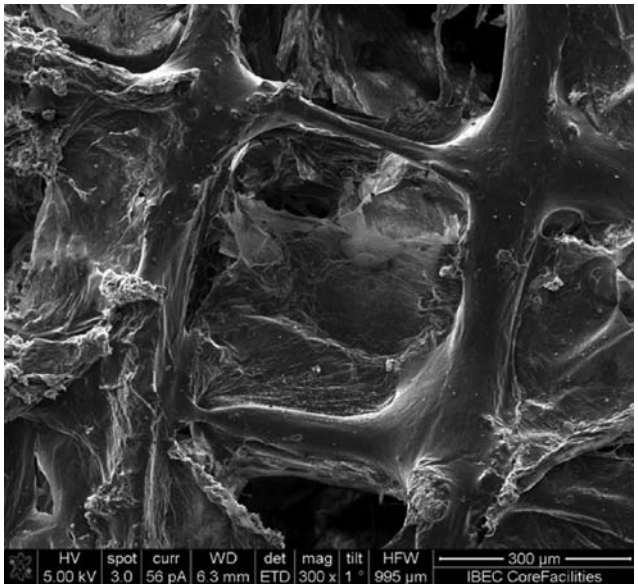
In collaboration with Prof. Kevin Healy at Berkeley, we focused in the fabrication of customized biomaterials and/or microfluidics based platforms for the fundamental study of biological systems related to angiogenesis processes. We have used signalling gradients of concentration to address progenitor cells to the desired target.

Following the project MATRICELL (awarded by MINECO), we started a new line of research on the production of microtissues that can be further processed to obtain new bioinks to print organs such as bone, and produce models for pathologies like cancer. In this line, we have started a collaboration with Prof. Alberto Muñoz (Ciberonc) in order to develop models to study colon cancer progression and the role of vitamin D. Moreover, these microtissues can be created inside a bioreactor, which can be used to decellullarize and recellularize them with the appropriate cells, and can be controlled by means of bioluminescence. Microtissues have been used as a Glioma tumor therapy (collaboration with Prof. J. Blanco, IQAC).

Another new line of research of the group is the development of instructive matrices to activate cardiac cells to promote cardiac regeneration.

Several works with industry and clinicians started during 2017: an industrial collaboration with Avinent Implant System S.L., a Barcelona-based company that is an internationally recognized reference in dental implantology and medical devices for fixing or replacing bone. The project aims to produce 3D-printed bioactive substitutes to develop a new model for 3D printing applications for bones in the maxillofacial region. With Dr. Velez at the Vall d'Hebron Hospital, we have developed a synthetic periosteum to enhance vascularization and bone formation.

We are new members of the Red de Terapia Celular (Tercel) to collaborate with the cell therapy groups in tissue and organ regeneration.



SEM capture of cartilage ECM and cell cluster formation from 4 weeks cultured hMSCs in 3D printed PCL scaffolds (Gerard Rubi)

Publications

- Oliveira, H., Catros, S., Castano, O., Rey, S., Siadous, R., Clift, D., Marti-Munoz, J., Batista, M., Bareille, R., Planell, J., Engel, E. and Amédée, J. (2017).The proangiogenic potential of a novel calcium releasing composite biomaterial: Orthotopic *in vivo* evaluation. *Acta Biomaterialia*, 54 377-385
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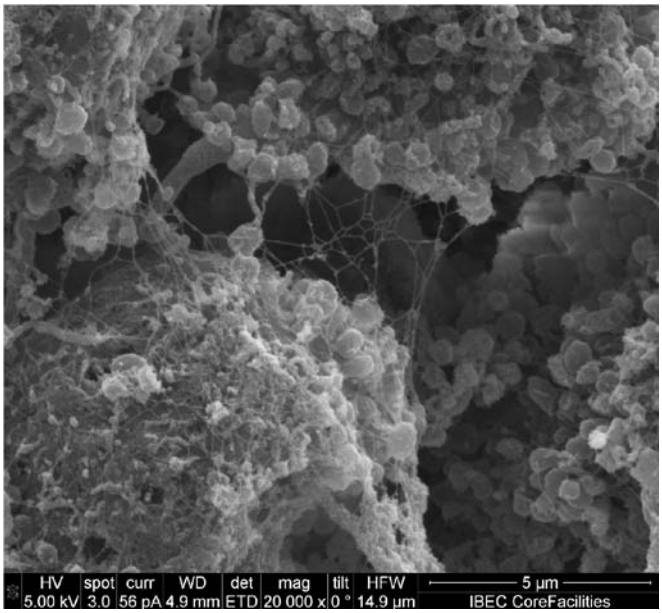


SEM picture of a microtissue formed by AMSCs after 10 days of culture in PLA microcarriers (Michel Augustin)

Filed patents

- Patent Number: EP17382325. **Patent in the field of wound healing**
  Assignees: IBEC, Universitat Politècnica de Catalunya
  Authors: Elisabeth Engel, Oscar Castaño, Joan Martí, Josep Anton Planell

Research projects

- **MatriCell** Desarrollo de partículas poliméricas para generar matrices extracelulares *in vitro* (2016-2018)
  PI: **Elisabeth Engel**
  MINECO Retos investigación: Proyectos I+D
- Nous models de bioimpressió 3D d'os per a ús maxil·lofacial (2017-2019)
  PI: **Elisabeth Engel**
  MINECO Retos investigación: Proyectos I+D
- State of the Art Research on Expandable Materials (2017-2018)
  PI: **Miguel Ángel Mateos**
  TUCSE, S.L.
- **DERMOGLASS** Smart dressing for the treatment of chronic wounds (2016-2017)
  PI: **Elisabeth Engel**
  Caixaimpulse / EIT Health / Obra Social La Caixa

Collaborations *cont.*

- **Dr. Ernest Mendoza** Applied Nanomaterials Laboratory, Research Centre in Nanoengineering, Technical University of Catalonia (UPC, BarcelonaTech), Spain
- **Dr. Izabella Rajzer** Institute of Textile Engineering and Polymer Materials, University of Bielsko-Biala, Poland
- **Dr. José María Mora** Servei de cirurgia ortopédica i traumatológica, Consorci Hospital de Terrassa, Spain
- **Dr. Mercè Alsina** Servicio de Dermatología, Hospital Clínic de Barcelona, Spain
- **Prof. Didier Letourneur** Laboratoire de Bioingénierie Cardiovasculaire, INSERM, University Denis Diderot-Paris 7, Paris, France
- **Prof. Dirk Grijpma**, Department of Biomaterials Science and Technology, University of Twente, Twente, the Netherlands
- **Prof. Francesco Serino** Department of Vascular Surgery, Istituto Dermatologico dell'Immacolata (IDI), Rome, Italy
- **Dr. Jerónimo Blanco** Institut de Ciències Cardiovasculars de Catalunya and CSIC, Barcelona, Spain
- **Dr. Joelle Amedee** INSERM, University of Bordeaux Segolen, Bordeaux, France
- **Dr. Margarita Calonge** Institute of Ophthalmobiology (IOBA), Universidad de Valladolid, Spain
- **Dr. José Becerra Ratia** Dept. Biología Celular, Genética y Fisiología, Universidad de Málaga, Spain
- **Dr. José Carlos Rodríguez-Cabello** Dept. de Física de la Materia Condensada, Universidad de Valladolid, Spain
- **Prof. Kevin Healy** Biomaterials & Tissue Engineering Laboratory, University of California at Berkeley, USA
- **Prof. Jaume Veciana** NANOMOL, Institut de Ciència de Materials de Barcelona (ICMAB-CSIC), Spain
- **Dr. Diego Gutiérrez de la Iglesia (MD)** Pediatric orthopaedic surgery, San Juan de Dios Hospital, Spain
- **Prof. Wouter J.A. Dhert & Dr. Jos Malda** Department of Orthopaedics, University Medical Center Utrecht, The Netherlands
- **Prof. Andrés J. García, F.B.S.E.** Petit Institute for Bioengineering and Bioscience, Georgia Institute of Technology, Atlanta, GA
- **Prof. Alberto Muñoz** Instituto de Investigaciones Biomédicas "Alberto Sols", CSIC-UAM
- **Dr. Luigi Ambrosio** Institute of Polymers, Composites & Biomaterials National Research Council, Naples, Italy
- **Prof. Carlos Semino** Grupo de Insuficiencia Cardíaca y Regeneración Cardíaca (ICREC), IQS School of Engineering, Universitat Ramon Llull

- Guduric, V., Metz, C., Siadous, R., Bareille, R., Levato, R., Engel, E., Fricain, J. C., Devillard, R., Luzanin, O. and Catros, S. (2017). Layer-by-layer bioassembly of cellularized polylactic acid porous membranes for bone tissue engineering. *Journal of Materials Science: Materials in Medicine*, 28 (5): 78
- Barbeck, M., Serra, T., Booms, P., Stojanovic, S., Najman, S., Engel, E., Sader, R., Kirkpatrick, C. J., Navarro, M. and Ghanaati, S. Analysis of the *in vitro* degradation and the *in vivo* tissue response to bi-layered 3D-printed scaffolds combining PLA and biphasic PLA/bioglass components – Guidance of the inflammatory response as basis for osteochondral regeneration. *Bioactive Materials*, 2 (4): 208-223

Book Sections

- Planell, J. A., Navarro, M. and Engel, E. (2017). Developing targeted biocomposites in tissue engineering and regenerative medicine. In: *Biomedical Composites* (ed. Ambrosio, L.). Duxfor, UK, Woodhead Publishing. Biomaterials: 569-587
- Castaño, O., Pérez, S., Mateos-Timoneda, M. A. and Engel, E. (2017).Cell Interactions with Calcium Phosphate Glasses. In: *RSC Smart Materials* (ed. Boccaccini, A. R., Brauer, D. S. and Hupa, L.). London, UK, Royal Society of Chemistry. Bioactive Glasses: Fundamentals, Technology and Applications: 303-315

Equipment and techniques

- Surface characterization equipment (contact angle, Z potential, nanoindenter)
- Cell culture facilities
- Molecular Biology equipment: protein and DNA electrophoresis
- Thermocycler (PCR)
- Rapid prototyping tool (part of the Production of Biomaterials and Nanoparticles platform of the CIBER-BBN) (http://www.ciber-bbn.es/programas/plataformas/equipamiento/biomateriales?nodo=nodo2&locale=en)
- Peptide synthetiser
- Combustion furnace
- Electrospinning device
- Spin-coater
- Vibrational viscosimeter

Nanomalaria (IBEC/ISGlobal joint unit)

Xavier Fernàndez-Busquets

The current activity of the Nanomalaria group is focused on the development of nanomedicine-based systems to be applied to malaria prophylaxis, diagnosis and therapy.

Malaria is arguably one of the main medical concerns worldwide because of the numbers of people affected, the severity of the disease and the complexity of the life cycle of its causative agent, the protist *Plasmodium spp*. The clinical, social and economic burden of malaria has led for the last 100 years to several waves of serious efforts to reach its control and eventual eradication, without success to this day. With the advent of nanoscience, renewed hopes have appeared of finally obtaining the long sought-after magic bullet against malaria in the form of a nanovector for the targeted delivery of antimalarial drugs exclusively to *Plasmodium*-infected cells. Nanotechnology can also be applied to the discovery of new antimalarials through single-molecule manipulation approaches for the identification of novel drugs targeting essential molecular components of the parasite. Finally, methods for the diagnosis of malaria can benefit from nanotools applied to the design of microfluidic-based devices for the accurate identification of the parasite's strain, its precise infective load, and the relative content of the different stages of its life cycle, whose knowledge is essential for the administration of adequate therapies. The benefits and drawbacks of these nanosystems have to be considered in different possible scenarios, including economy-related issues that are hampering the progress of nanotechnology-based medicines against malaria with the dubious argument that they are too expensive to be used in developing areas. Unfortunately, it is true that the application of nanoscience to infectious disease has been traditionally neglected, with most research resources overwhelmingly biased towards other pathologies more prominent in the developed world. Thus, extra ingenuity is demanded from us: malaria-

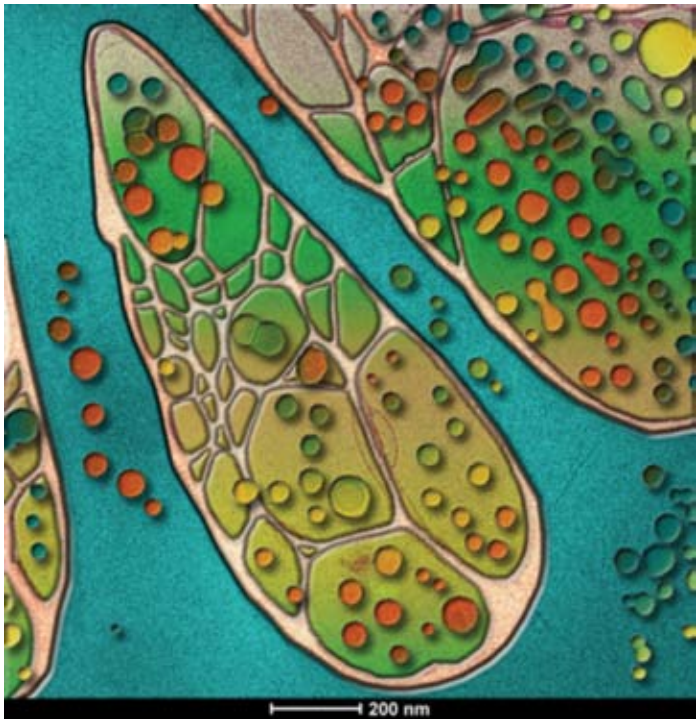


Figure 1. Cryo-transmission electron microscope image of liposomes being assayed for the encapsulation of drugs specifically targeted to red blood cells infected by the malaria parasite *Plasmodium falciparum*. CryoTEM image artistic editing by Marc Cirera, www.marccirera.com.

Postdocs
Livia Neves Borgheti
Ernest Moles

PhD students
Elisabet Martí
Elena Lantero
Arnau Biosca

Lab technicians
Alexandros Belavilas-Trovas
Lucía Gutiérrez

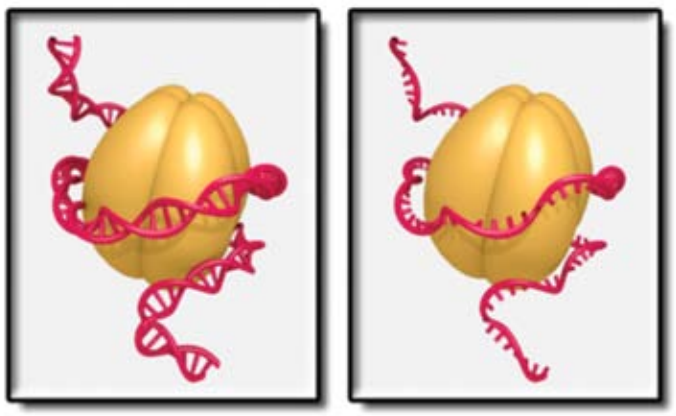
Publications

- Moles, E., Galiano, S., Gomes, A., Quiliano, M., Teixeira, C., Aldana, I., Gomes, P. and Fernàndez-Busquets, X. (2017). ImmunoPEGliposomes for the targeted delivery of novel lipophilic drugs to red blood cells in a *falciparum* malaria murine model. *Biomaterials*, 145 178-191
- Grice, L. F., Gauthier, M. E. A., Roper, K. E., Fernàndez-Busquets, X., Degnan, S. M. and Degnan, B. M. (2017). Origin and evolution of the sponge aggregation factor gene family. *Molecular Biology and Evolution*, 34 (5): 1083-1099
- Marques, J., Valle-Delgado, J. J., Urbán, P., Baró, E., Prohens, R., Mayor, A., Cisteró, P., Delves, M., Sinden, R. E., Grandfils, C., de Paz, J. L., García-Salcedo, J. A. and Fernàndez-Busquets, X. (2017). Adaptation of targeted nanocarriers to changing requirements in antimalarial drug delivery. *Nanomedicine: Nanotechnology, Biology, and Medicine*, 13 (2): 515-525
- Caddeo, C., Manca, M. L., Matos, M., Gutierrez, G., Díez-Sales, O., Peris, J. E., Usach, I., Fernàndez-Busquets, X., Fadda, A. M. and Manconi, M. (2017). Functional response of novel bioprotective poloxamer-structured

oriented nanomedicines not only need to work spotless; they have to do so in a cost-efficient way because they will be deployed in low-income regions.

The driving force of the Nanomalaria group is our personal commitment to applying nanomedicine to infectious diseases of poverty through several research lines: (i) Exploration of different types of encapsulating structure (liposomes, synthetic and natural polymers), targeting molecule (protein, polysaccharide, nucleic acid), and antimalarial compound (e.g. new structures derived from marine organisms and antimicrobial peptides) for the assembly of nanovectors capable of delivering their drug cargo with complete specificity to diseased cells. (ii) Study of metabolic pathways present in *Plasmodium* but absent in humans, with the aim of identifying specific enzymes as therapeutic targets. (iii) Use of glycosaminoglycans for innovative antimalarial strategies. (iv) Design of new methods for the targeted drug delivery to *Plasmodium* stages in the mosquito vector. (v) Investigation of novel drugs against insect-borne diseases working through radically new mechanisms. (vi) Extension of our activities to new pathologies (leishmaniasis).

Figure 2. Scheme depicting the proposed interaction of ssDNA with core histones. This hypothetical model is consistent with the observed interaction of a fixed histone mass (here represented in yellow as a core particle octamer) with equal lengths of dsDNA and ssDNA.



Research projects

- **NANOpheles** Development of nanovectors for the targeted delivery in *Anopheles* mosquitoes of agents blocking transmission of *Plasmodium* parasites (2017-2020).
  Coordinator: **Xavier Fernàndez-Busquets**
  EURONANOMED III. European innovative research & technological development projects in nanomedicine
- **NANOMISSION** Engineering of nanovectors for the delivery of antimalarial drugs to *Plasmodium* transmission forms (2015-2017).
  PI: **Xavier Fernàndez-Busquets**
  Biotechnology Programme, MINECO, Spain (BIO2014-52872-R)
- Amphoteric polyamidoamines as innovative tools to selectively direct antimalarial drugs towards *Plasmodium*-infected red blood cells (2014-2017).
  PI: **Xavier Fernàndez-Busquets**
  Fondazione CARIPLO call Science and Technology Research on Advanced Materials (2013-0584)
- Research agreement for the study of heparin-related molecules in new antimalarial strategies (2016-2018).
  PI: **Xavier Fernàndez-Busquets**
  BIOIBERICA
- Group for the study of self-aggregating proteins (2014-2017).
  Coordinator: Salvador Ventura Zamora
  Consolidated Research Group certified by the Generalitat de Catalunya, Spain (2014-SGR-938)

Equipment and techniques

- Zeiss Primostar microscope
- Shake 'N' Stack (Thermo Hybaid) hybridization oven
- Rotatory evaporator RS 3000-V (Selecta)
- *Plasmodium falciparum* cell cultures

vesicles on inflamed skin. *Nanomedicine: Nanotechnology, Biology, and Medicine*, 13 (3): 1127-1136

- Valls-Comamala, V., Guivernau, B., Bonet, J., Puig, M., Perálvarez-Marín, A., Palomer, E., Fernàndez-Busquets, X., Altafaj, X., Tajes, M., Puig-Pijoan, A., Vicente, R., Oliva, B. and Muñoz, F. J. (2017). The antigen-binding fragment of human gamma immunoglobulin prevents amyloid β-peptide folding into β-sheet to form oligomers. *Oncotarget*, 8 (25): 41154-41165
- Caddeo, C., Pons, R., Carbone, C., Fernàndez-Busquets, X., Cardia, M. C., Maccioni, A. M., Fadda, A. M. and Manconi, M. (2017). Physico-chemical characterization of succinyl chitosan-stabilized liposomes for the oral co-delivery of quercetin and resveratrol. *Carbohydrate Polymers*, 157 1853-1861
- Aláez-Versón, C. R., Lantero, E. and Fernàndez-Busquets, X. (2017). Heparin: New life for an old drug. *Nanomedicine*, 12 (14): 1727-1744
- Wang, Y., van Merwyk, L., Tönsing, K., Walhorn, V., Anselmetti, D. and Fernàndez-Busquets, X. (2017). Biophysical characterization of the association of histones with single-stranded DNA. *Biochimica et Biophysica Acta (BBA) - General Subjects*, 1861 (11): 2739-2749
- Moles, E., Marcos, J., Imperial, S., Pozo, O. J. and Fernàndez-Busquets, X. (2017). 2-picolylamine derivatization for high sensitivity detection of abscisic acid in apicomplexan blood-infecting parasites. *Talanta*, 168 130-135 (2017).

Vitonyte, J., Manca, M. L., Caddeo, C., Valenti, D., Peris, J. E., Usach, I., Nacher, A., Matos, M., Gutiérrez, G., Orrù, G., Fernàndez-Busquets, X., Fadda, A. M. and Manconi, M. (2017). Bifunctional viscous nanovesicles co-loaded with resveratrol and gallic acid for skin protection against microbial and oxidative injuries. *European Journal of Pharmaceutics and Biopharmaceutics*, 114 278-287

Collaborations

- **Prof. Dario Anselmetti**, Universität Bielefeld, Germany
- **Prof. Maria Antònia Busquets**, Universitat de Barcelona, Spain
- **Prof. Elisabetta Ranucci**, Università degli Studi di Milano, Italy
- **Prof. José Manuel Bautista**, Universidad Complutense de Madrid, Spain
- **Dr. Matthias Rottmann**, Swiss Tropical and Public Health Institute, Basel, Switzerland
- **Prof. Robert Sinden**, Imperial College London, UK
- **Dr. Israel Molina**, Hospital Universitari Vall d'Hebron, Barcelona
- **Prof. José Luis Serrano**, Instituto de Nanociencia de Aragón, Zaragoza
- **Prof. Johan Engbersen**, University of Twente, The Netherlands
- **Dr. Santiago Imperial**, University of Barcelona, Spain
- **Dr. Eduardo Prata Vilanova**, Universidade Federal do Rio de Janeiro, Brazil
- **Prof. Maria Manconi**, Università di Cagliari, Sardinia, Italy
- **Dr. Krijn Paaijmans**, ISGlobal, Barcelona, Spain
- **Dr. Ellen Faszewski**, Wheelock College, Boston, USA
- **Prof. Bernard Degnan**, University of Brisbane, Australia
- **Dr. Francisco J. Muñoz**, Parc de Recerca Biomèdica de Barcelona, Spain
- **Dr. Inga Siden-Kiamos**, FORTH Institute of Molecular Biology & Biotechnology, Greece
- **Prof. Salvador Ventura**, Universitat Autònoma de Barcelona, Bellaterra, Spain
- **Dr. Juan José Valle-Delgado**, Aalto University, Helsinki, Finland
- **Prof. Mats Wahlgren**, Karolinska Institutet, Stockholm, Sweden
- **Dr. Fatima Nogueira**, Instituto de Higiene e Medicina Tropical, Lisboa, Portugal
- **Prof. Christian Grandfils**, University of Liège, Belgium

Nanoscale bioelectrical characterization

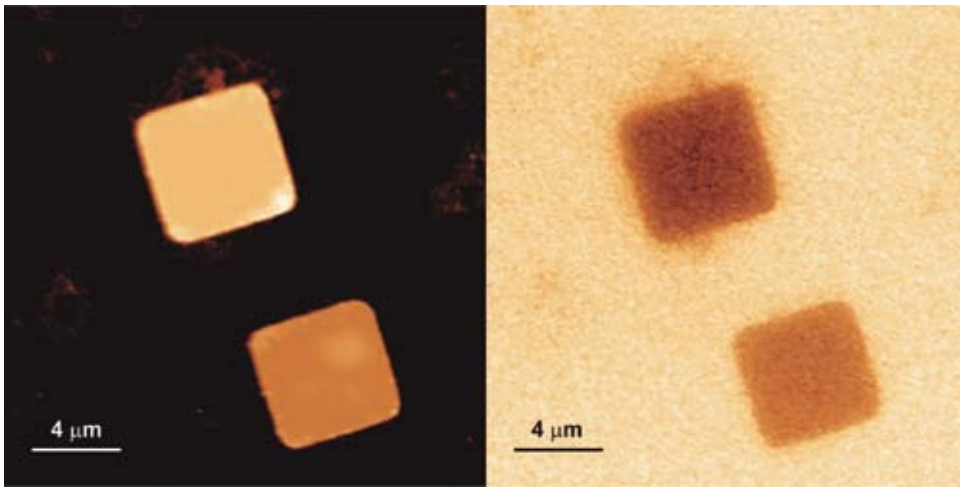
Gabriel Gomila (ICREA Academia Awardee)

The main goal of the Nanoscale bioelectrical characterization group is to develop new experimental setups based on atomic force microscopy and new theoretical frameworks enabling the quantification of the electrical properties of biological systems at the nanoscale (including biomembranes, single viruses, single bacteria cells and eukaryotic cells).

Our main objective is to contribute to develop new label-free biological nanoscale characterization methods and new electronic biosensors.

During 2017 we have completed our studies on the measurement of the local electromagnetic properties of materials in the high frequency range (>GHz) with the use of the Scanning Microwave Microscope. In particular, we have developed a method to map directly the electric permittivity of non-planar heterogeneous samples by means of a Scanning Microwave Microscope, and, contributed to the development of a full electromagnetic modelling of this microscope. On the other side, we have made experimental and theoretical advances towards extending the use of Electrostatic Force Microscopy in the liquid environment, in order to be able to probe the dielectric properties of biosamples in physiological conditions. Finally, we have developed methods to probe the dielectric properties of small scale filamentous protein structures and applied them to the dielectric characterization of bacterial polar flagella. During this year, also, we have optimized sample preparation and imaging methods to image protein-DNA complexes with the Atomic Force Microscope, and started new research projects devoted to the study of the electrical properties of electrogenic bacteria, nanopore systems, single neurons and organic electronic devices, which are currently under development.

Atomic Force Microscopy Topographic (left) and Electrostatic Force Microscopy dielectric (right) images of two microfabricated pillars of Al3O2 (95 nm thick, top) and of SiO2 (60 nm thick, bottom) on a gold substrate, obtained in a liquid environment. The dielectric image (right) shows an inverted contrast (higher electric force on the substrate than on the pillars) due to the higher electric permittivity of the surrounding liquid medium (water) with respect to that of the pillars.



Research

Nanoscale bioelectrical characterization

Postdocs
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Adrica Kyndiah
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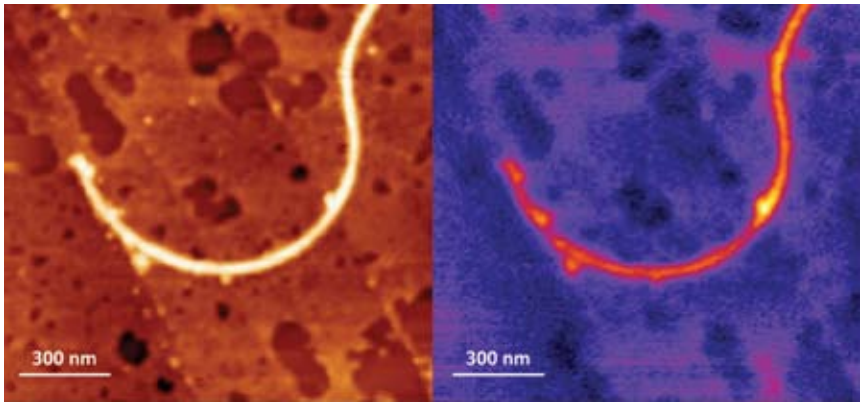
PhD students
Harishankar Balakrishnan
Martina Di Muzio
Helena Lozano
Martí Checa

Lab technician
Rubén Millán

Publications

- Wu, B.-Y., Sheng, X.-Q., Fabregas, R. and Hao, Y. (2017). Full-wave modeling of broadband near field scanning microwave microscopy. *Scientific Reports*, 7 (1): 16064
- Crespo, A., Pedraz, L., Van Der Hofstadt, M., Gomila, G. and Torrents, E. (2017). Regulation of ribonucleotide synthesis by the *Pseudomonas aeruginosa* two-component system AlgR in response to oxidative stress. *Scientific Reports*, 7 (1): 17892
- Biagi, M. C., Badino, G., Fabregas, R., Gramse, G., Fumagalli, L. and Gomila, G. (2017).Direct mapping of the electric permittivity of heterogeneous non-planar thin films at gigahertz frequencies by scanning microwave microscopy. *Physical Chemistry Chemical Physics*, 19 (5): 3884-3893



Atomic Force Microscopy topographic (left) and Electrostatic Force Microscopy dielectric (right) images of a bacterial polar flagellum of 10 nm in diameter obtained in air. The use of 3D finite element numerical simulations enables the quantification of the dielectric image and the extraction of the dielectric constant of the proteins composing the bacterial polar flagellum (sample prepared by Eduard Torrents' group at IBEC).

Research projects

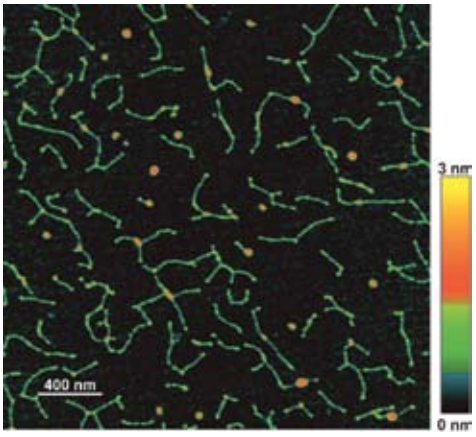
- **SPM2**.0 Scanning probe microscopies for nanoscale fast, tomographic and composition imaging. (2017-2020)
  Coordinator: **Gabriel Gomila**
  European H2020-MSCA-ITN project
- **NANOELECTOMOGRAPHY** Electrical nanotomography based on scanning probe microscopy for nanomaterials and biological samples (2014-2017)
  PI: **Gabriel Gomila**
  MINECO (TEC2013-48344-C2-1-P)
- **NANOELECTROPHYS** Scanning Electric Force Microscope for Electrophysiological Recordings at the Nanoscale (2016-2019)
  PI: **Gabriel Gomila**
  MINECO (TEC2016-79156-P)
- **BIOWIRESENSE** Universal platform for biomarker detection based on conducting bacterial nanowires (2017-2019)
  PI: **Gabriel Gomila**
  MINECO (TEC2015-72751-EXP)

Collaborations

- **Dra. Laura Fumagalli**, University of Manchester, United Kingdom
- **Dr. Ferry Kienberger**, Keysight Technologies Austria, Linz, Austria
- **Prof. Marco Sampietro**, Politecnico di Milano, Italy
- **Dr. Jordi Borrell**, University of Barcelona, Spain
- **Dr. Filip Meysman,** Vrije Universiteit Brussel, Belgium
- **Prof. Antonio Juárez**, University of Barcelona, Spain
- **Prof. Fabio Biscarini**, Universita di Modena e Regio Emilia, Italy
- **Dr. Manel Puig**, University of Barcelona, Spain

Equipment and techniques

- Cypher Atomic Force Microscope (Asylum Research)
- Nanowizard 4 Bio-Atomic Force Microscope (JPK)
- Cervantes Atomic Force Microscope (Nanotec Electronica)
- Easy Scan 2 Atomic Force Microscope (Nanosurf)
- AxioImager A1m Reflection Optical Microscope equipped with a AxioCam ERc5s (Zeiss)
- CompactStat portable electrochemical interface and impedance analyzer (Ivium Technologies)
- Palmsens 4, 8 channel Potentiostat (Palmens)
- 2 eLockIn204 4-phase Lock-In amplifiers (Anfatec)
- Keithley 6430 sub-femtoAmp remote sourcemeter (Keithley)
- Keysight B2912A precision Source/Measure Unit, 2 channels (Keysight)
- Keysight N9310A RF Signal Generator 9 kHz to 3.0 GHz (Keysight)



Atomic Force Microscopy image of DNA molecules complexed with AlgR proteins. The DNA molecules are 2 nm high and appear as green, while the proteins are around 3 nm high and appear as red spots in the DNA molecules. The DNA molecules tend to bent around the positions where the proteins are complexed with the DNA (sample prepared by the group of Dr. E. Torrents, IBEC).

Nanoprobes and nanoswitches

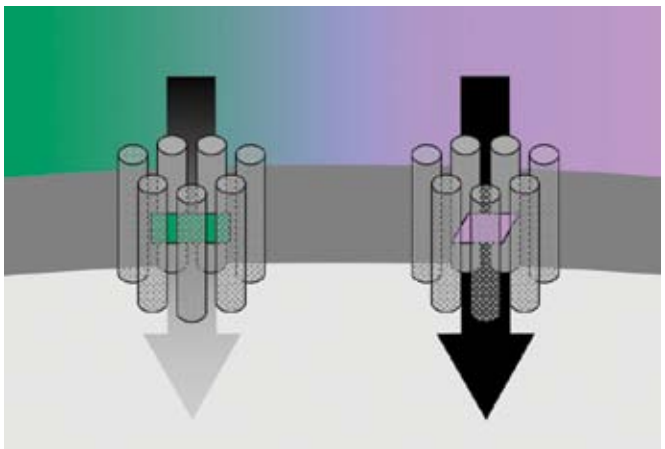
Pau Gorostiza (ICREA Research Professor), Fausto Sanz

The group's research focuses on developing nanoscale tools to study biological systems. These tools include instrumentation based on proximity probes, such as electrochemical tunnelling microscopy and spectroscopy, that we apply to investigate electron transfer in metal oxides and individual redox proteins.

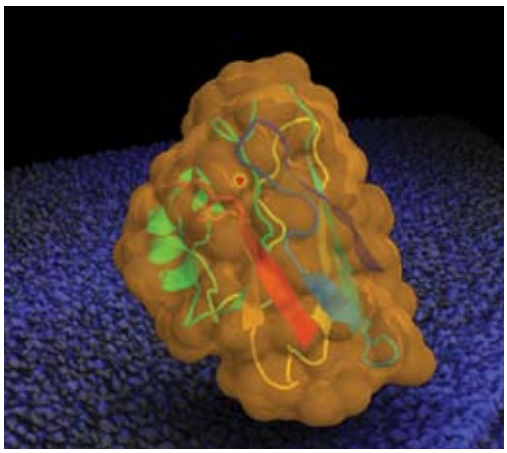
These studies are relevant to the development of biosensors and molecular electronics devices. In particular, based on our development of nanoscale field-effect transistors using individual redox protein, we have recently published a method to measure conductance switching in single redox proteins "wired" between two electrodes.

Another set of nanotools that we are developing is based on molecular actuators that can be switched with light, such as azobenzene, which can be chemically attached to biomolecules in order to optically control their activity. We have demonstrated for the first time two-photon stimulation of neurons and astrocytes with azobenzene-based photoswitches. We have also developed several bioactive compounds that have been engineered to be regulated by light. These "optopharmacological" compounds include peptide inhibitors of protein-protein interactions involved in clathrin-mediated endocytosis, and two ligands of G protein-coupled receptors (adenosine and metabotropic glutamate receptors), which are important therapeutic targets.

Schematic representation of a light-regulated drug bound to a 7-transmembrane receptor. Under violet illumination, the drug is inactivated and the receptor produces normal intracellular signaling. In the dark or under green light, the drug inhibits the receptor and interferes with signaling in a reversible way. (Pittolo, S. *et al,* 2014).



Crystal structure of redox protein azurin (Protein Data Bank entry: 1AZU) displaying its solvent accessible surface (gold) superimposed on the tertiary structure (rainbow) and a red sphere indicating the copper ion. When an atomically flat gold electrode is coated with azurin, the protein can be imaged under potentiostatic control by electrochemical tunneling microscopy (3D rendering of a 100x100nm^2 area shown in blue), and its electron transfer properties can be investigated by current-distance spectroscopy (Juan Manuel Artés *et al.*, 2011, *ACS Nano*).



Senior researchers
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Marina Inés Giannotti
Mireia Oliva

Postdocs
Núria Camarero
Miquel Bosch
Rossella Castagna
Gertrudis Perea
Carlo Matera

PhD students
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Alejandro Martín
Marta Pozuelo
Hyojung Lee
Rosalba Sortino
Fabio Riefolo
Alexandre Gomila

Davia Prischich
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Berta Gumí

Master students
Marta Masó

Lab technicians
Pablo Calvé

Filed patents

- Patent Number: EP17382894.8. **Patent in the field of photoactivated drugs**
  Assignees: IBEC, Universitat de Barcelona, ICREA, CIBER
  Authors: Pau Gorostiza, Concepció Soler, Carlo Matera, Núria Camarero, Michela Libergoli, Alexandre Gomila.

Collaborations

- **Prof. Amadeu Llebaria** Institut de Química Avançada de Catalunya (IQAC-CSIC)
- **Prof. Ernest Giralt** Dept. de Química Orgànica, Universitat de Barcelona
- **Prof. Miquel Àngel Pericàs** Institut Català d'Investigació Química (ICIQ), Tarragona
- **Dr. Piotr Bregestovski** Institut de Neurobiologie de la Mediterraneé (INMED), Marseille
- **Dr. Mireia Oliva** Dept. de Farmàcia i Tecnologia Farmacèutica, Universitat de Barcelona
- **Dr. Artur Llobet** Dept. Patología y Terapéutica Experimental, Universitat de Barcelona
- **Dr. Joan Torrent** Escola Universitària d'Òptica i Optometria de Terrassa, Spain
- **Prof. Dirk Trauner** Chemistry Dept., UC Berkeley, USA
- **Prof. Carles Solsona** Pathology and Experimental Therapeutics Dept, UB
- **Prof. Francisco Ciruela** ICREA / Universitat de Barcelona, Spain
- **Prof. Jesús Giraldo** & **Dr. Jordi Hernando** Universitat Autònoma de Barcelona, Spain

Publications

- Ruiz, M. P., Aragones, A. C., Camarero, N., Vilhena, J. G., Ortega, M., Zotti, L. A., Perez, R., Cuevas, J. C., Gorostiza, P. and Díez-Pérez, I. (2017). Bioengineering a single-protein junction. *Journal of the American Chemical Society*, 139 (43): 15337–15346
- Aragonès, A. C., Aravena, D., Valverde-Muñoz, F. J., Real, J. A., Sanz, F., Díez-Pérez, I. and Ruiz, E. (2017). Metal-controlled magnetoresistance at room temperature in single-molecule devices. *Journal of the American Chemical Society*, 139 (16): 5768-5778
- Carini, M., Ruiz, M. P., Usabiaga, I., Fernández, J. A., Cocinero, E. J., Melle-Franco, M., Diez-Perez, I. and Mateo-Alonso, A. (2017).High conductance values in π-folded molecular junctions. *Nature Communications*, 8 15195
- Aragonès, A. C., Darwish, N., Ciampi, S., Sanz, F., Gooding, J. J. and Díez-Pérez, I. (2017).Single-molecule electrical contacts on silicon electrodes under ambient conditions. *Nature Communications*, 8 15056
- López-Martínez, M., Artés, J. M., Sarasso, V., Carminati, M., Díez-Pérez, I., Sanz, F. and Gorostiza, P. (2017). Differential electrochemical conductance imaging at the nanoscale. *Small*, 13 (36): 1700958

- Aragonès, A. C., Medina, E., Ferrer-Huerta, M., Gimeno, N., Teixidó, M., Palma, J. L., Tao, N., Ugalde, J. M., Giralt, E., Díez-Pérez, I. and Mujica, V. (2017). Measuring the spin-polarization power of a single chiral molecule. *Small*, 13 (2): 1602519
- Gómez-Santacana, X., Pittolo, S., Rovira, X., Lopez, M., Zussy, C., Dalton, J. A. R., Faucherre, A., Jopling, C., Pin, J.-P., Ciruela, F., Goudet, C., Giraldo, J., Gorostiza, P. and Llebaria, A. (2017). Illuminating phenylazopyridines to photoswitch metabotropic glutamate receptors: From the flask to the animals. *ACS Central Science*, 3 (1): 81-91
- Santander-Nelli, M., Silva, C. P., Espinoza-Vergara, J., Silva, J. F., Olguín, C. F., Cortés-Arriagada, D., Zagal, J. H., Mendizabal, F., Díez-Pérez, I. and Pavez, J. (2017). Tailoring electroactive surfaces by non-template molecular assembly. Towards electrooxidation of L-cysteine. *Electrochimica Acta*, 254 201-213
- Gómez-Santacana, X., Dalton, J. A. R., Rovira, X., Pin, J. P., Goudet, C., Gorostiza, P., Giraldo, J. and Llebaria, A. (2017). Positional isomers of bispyridine benzene derivatives induce efficacy changes on mGlu5 negative allosteric modulation. *European Journal of Medicinal Chemistry*, 127 567-576
- Terni, B., Pacciolla, P., Masanas, H., Gorostiza, P. and Llobet, A. (2017). Tight temporal coupling between synaptic rewiring of olfactory glomeruli and the emergence of odor-guided behavior in Xenopus tadpoles. *Journal of Comparative Neurology*, 525 (17): 3769-3783
- Obiols-Rabasa, M., Oncins, G., Sanz, F., Tadros, T. F.,

Research projects

- **NANOPROSTHETICS** Prótesis moleculares para restablecer la visión basadas en fotoconmutadores covalentes dirigidos (2016-2019)
  PI: **Pau Gorostiza**
  MINECO, Retos investigación: Proyectos I+D
- **MODULIGHTOR** Moduladores fotoconmutables sintéticos para manipular remotamente proteínas endógenas: fotocontrol *in vivo* de canales iónicos pentaméricos (2015-2018)
  PI: **Pau Gorostiza**
  MINECO Nacional /Acciones de Programación Conjunta Internacional
- Inhibición fotoselectiva de interacciones proteína-proteína para el estudio de redes interactómicas y el desarrollo de nuevas terapias (2015-2018)
  PI: **Pau Gorostiza**
  Fundación Ramon Areces
- Fotoconmutadores covalentes para el control remoto de receptores endógenos (2017-2019)
  PI: **Pau Gorostiza**
  Convocatoria de Ayudas a la Investigación FUNDALUCE
- **WaveScalES** Human Brain Project Specific Grant Agreement 1 (2016-2018)
  PI: **Pau Gorostiza**
  European Commission, FET FLAGSHIPS, Tackling grand interdisciplinary science and technology challenges
- **OPTOFRAX** Optopharmacological brain mapping of autism mouse (2015-2017)
  PI: **Miquel Bosch**
  European Commission, MARIE CURIE - IF
- Milk fat globule membrane and periphera proteins: lipid-protein interactions (2016-2017)
  PI: **Fausto Sanz**
  INRA
- **nanoET-leukemia** Nanoconductance of electron transfer proteins of the respiratory chain. Direct measurement at the single molecular level and therapeutic regulation in cancer stem cells (2015-2018)
  PIs: Anna Lagunas (page 68)/**Marina Inés Giannotti**
  MINECO, Proyectos RETOS 2015 / CIBER

Equipment and techniques

- iMic molecular imaging system
- Electrochemical scanning tunnelling microscope (STM) for molecular imaging
- Asylum Research Molecular Force Probe
- Multimode SPM Nanoscope III (SCT-UB)
- Autolab potentiostat
- Patch clamp setup with Heka EPC10 amplifier
- Molecular Imaging Electrochemical STM

Solans, C., Levecke, B., Booten, K. and Esquena, J. (2017). Investigation of the elastic and adhesion properties of adsorbed hydrophobically modified inulin films on latex particles using Atomic Force Microscopy (AFM). *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, 524 185-192

- Calvé, P. and Gorostiza, P. (2017). Estrategias optogenéticas y fotofarmacológicas para restablecer la visión. *Visión*, 51 6-13

Conference Papers

- Quadri, M., Matera, C., Silnović, A., Pismataro, M. C., Horenstein, N. A., Stokes, C., Papke, R. L. and Dallanoce, C. (2017). Identification of α7 nicotinic acetylcholine receptor silent agonists based on the spirocyclic quinuclidine-Δ2 -isoxazoline scaffold: Synthesis and electrophysiological evaluation. XXIV National Meeting in Medicinal Chemistry (NMMC 2016). Perugia, Spain. Published by Wiley Online Library (2017/08/22)

Book Section

- Bosch, M., Castro, J., Sur, M. and Hayashi, Y. (2017). Photomarking relocalization technique for correlated two-photon and electron microcopy imaging of single stimulated synapses.In: *Synapse Development - Methods and Protocols (Methods in Molecular Biology)* (ed. Poulopoulos, A.). New York, USA, Humana Press. 1538: 185-214

Biomedical signal processing and interpretation

Raimon Jané

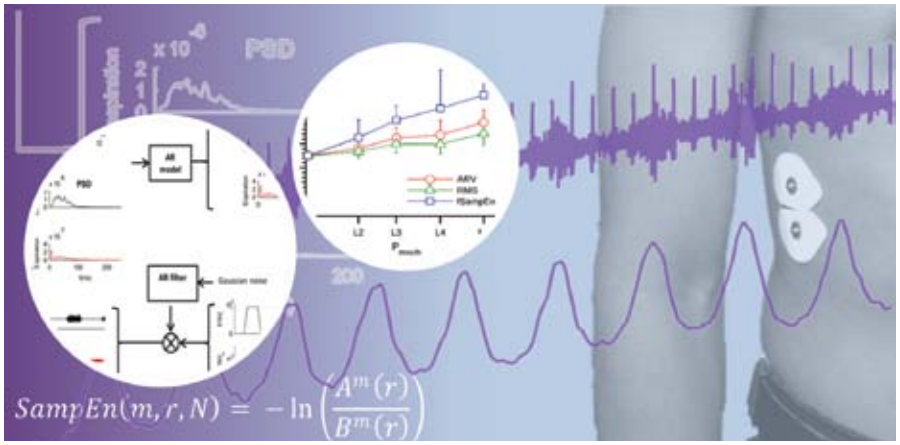
The group's research addresses the design and development of advanced signal processing techniques and the interpretation of biomedical signals to improve non-invasive monitoring, diagnosis, disease prevention and pathology treatment.

Our main objective is to improve diagnosis capability through the characterization of physiological phenomena and to enhance early detection of major cardiac and respiratory diseases and sleep disorders. We propose and design new signal processing algorithms and develop new biosignal databases, with the collaboration of our hospital partners. To validate the clinical information of new surface signals, we have developed specific invasive/non-invasive protocols and animal models. The group focuses its research in a translational way to promote the transfer of our scientific and technological contributions. Currently, our prototypes are used in hospitals for research purposes and for future industrial developments.

Highlights in 2017

Obstructive Sleep Apnea and Sleep Disorders

- Novel estimation of muscle respiratory effort for sleep studies using fixed sample entropy of surface diaphragm electromyography (*Entropy* 2017, 19, 460).
- Characterization of microphones for snoring and breathing events analysis (*IEEE-EMBC* 2017, 1547-1550) and novel mHealth tools for monitoring OSA patients at home (*IEEE-EMBC* 2017, 1555-1558).
- Characterization of a tooth microphone coupled to an oral appliance device: a new system for monitoring OSA patients (*IEEE-EMBC* 2017, 1543-1546), with Audiodontics, Bethesda, USA.
- Study of relationship between heart rate excursion and apnea duration in patients with Obstructive Sleep Apnea (*IEEE-EMBC* 2017, 1539-1542), with the Hospital Germans Trias i Pujol, Badalona.



Improvement in Neural Respiratory Drive Estimation from Diaphragm Electromyographic Signals using Sample Entropy of non-invasive EMG signals (Estrada *et al.*, 2016, *IEEE Journal of Biomedical and Health Informatics*).

Senior researchers
José Antonio Fiz
Beatriz Giraldo
Jordi Solà
Abel Torres

Postdocs
Luis Estrada
Manuel Lozano-Garcia
Leonardo Sarlabous

PhD students
Dolores Blanco
Ignasi Ferrer
Javier Rodríguez

Research assistants
Yolanda Castillo
Borja Pérez
Magdalena Ràfols

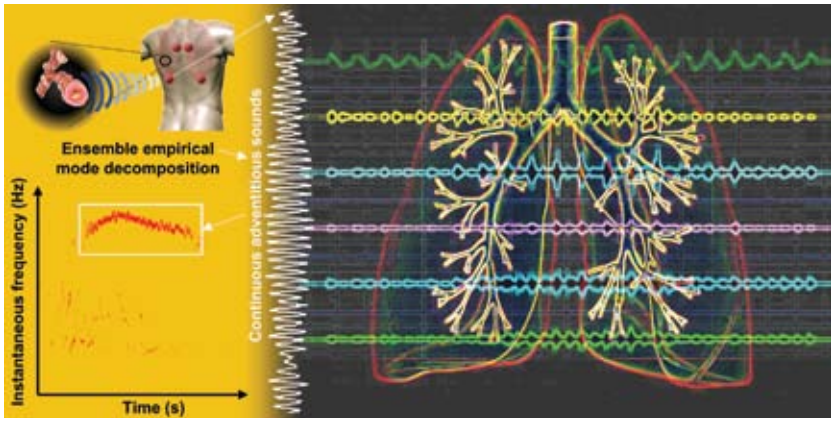
Chronic Obstructive Pulmonary Disease and Asthma

- Novel approach to continuous adventitious respiratory sound analysis for the assessment of bronchodilator response (*PLoS ONE* 2017, 12(2)), with the Hospital Germans Trias i Pujol, Badalona.
- A new non-invasive mechanomyographic analysis confirms that inspiratory muscle activation increases with COPD severity (*PLoS ONE* 2017, 12(5)), with the Hospital del Mar, Barcelona, and the Germans Trias i Pujol, Badalona.
- Evaluation of indirect measures of neural inspiratory time from invasive and noninvasive recordings of respiratory activity (*IEEE-EMBC* 2017, 341-344).

Cardiac and cardiorespiratory diseases and ageing

- Assessment of respiratory flow cycle morphology in patients with chronic heart failure (*Medical & Biological Engineering & Computing* 2017, 245-255), with Hospital Germans Trias i Pujol, Badalona, Hospital de Sant Pau, Barcelona, Lund University, Sweden, and University of Zaragoza.
- Characterization and classification of patients with different levels of cardiac death risk by using Poincaré plot analysis (*IEEE-EMBC* 2017, 1332-1335), with Hospital Germans Trias i Pujol, Badalona, and University of Jena, Germany.
- Nonlinear dynamic analysis of the cardiorespiratory system in patients undergoing the weaning process (*IEEE-EMBC* 2017, 3493-3496), with the Autonomous University of Bucaramanga, Colombia.

Novel method for differentiating normal from adventitious respiratory sounds (RS) to improve the diagnosis of pulmonary diseases. Particularly, continuous adventitious sounds (CAS) are of clinical interest because they reflect the severity of certain diseases. The new method is based on the multi-scale analysis of instantaneous frequency (IF) and envelope (IE) calculated after ensemble empirical mode decomposition (EEMD) of respiratory sounds. (Lozano *et al.*, 2016, *IEEE Journal of Biomedical and Health Informatics*)



Publications

- Sarlabous, L., Torres, A., Fiz, J. A., Martínez-Llorens, J. M., Gea, J. and Jané, R. (2017). Inspiratory muscle activation increases with COPD severity as confirmed by non-invasive mechanomyographic analysis. *PLoS ONE*, 12 (5): e0177730
- Lozano-Garcia, M., Fiz, J. A., Martínez-Rivera, C., Torrents, A., Ruiz-Manzano, J. and Jané, R. (2017). Novel approach to continuous adventitious respiratory sound analysis for the assessment of bronchodilator response. *PLoS ONE*, 12 (2): e0171455
- Garde, A., Sörnmo, L., Laguna, P., Jané, R., Benito, S., Bayés-Genís, A. and Giraldo, B. F. (2017). Assessment of respiratory flow cycle morphology in patients with chronic heart failure. *Medical and Biological Engineering and Computing*, 55 (2): 245-255
- Estrada, L., Torres, A., Sarlabous, L. and Jané, R. (2017). Influence of parameter selection in fixed sample entropy of surface diaphragm electromyography for estimating respiratory activity. *Entropy*, 19 (9): 460

Conference Papers

- Rodríguez, J. C., Arizmendi, C. J., Forero, C. A., Lopez, S. K. and Giraldo, B. F. (2017). Analysis of the respiratory flow signal for the diagnosis of patients with chronic heart failure using artificial intelligence techniques. VII Latin American Congress on Biomedical Engineering (CLAIB 2016). Springer (Santander, Colombia) 60, 46-49

Research projects

- Study on software comparison of audio recordings and correlation to SAHS events (2015-2018)
  PI: **Raimon Jané**
  R+D contract with Audiodontics in the framework of a SBIR project "System for Monitoring Dental Device Compliance and Efficacy in Treatment of Obstructive Sleep Apnea", funded by the NIH (USA)
- **M-Bio4Health** Multimodal physiological biomarkers for non-invasive monitoring and home healthcare of COPD patients with comorbidities (2016-2018)
  PI: **Raimon Jané**
  MINECO, Retos investigación: Proyectos I+D
- Novel m-Health tools for unobtrusive sensing and management improving of Obstructive Sleep Apnea patients at home (2016-2017)
  PI: **Raimon Jané**
  Obra Social La Caixa
- Non-invasive multimodal physiological biomarkers for monitoring COPD patients with comorbidities (2017-2018)
  PI: **Raimon Jané**
  With King's College London, funded by the European Respiratory Society (ERS-LTRF 2017)

Equipment and techniques

- Research laboratory with full equipment for acquisition and processing of biomedical signal to test new sensors and to define clinical protocols (preliminary tests and control subjects)
- Non-invasive Vital Signs Monitor for small lab animals (mice and rats) (Mouse-Ox Plus)
- BIOPAC system for multichannel cardiac and respiratory biomedical signal acquisition
- Databases of biomedical signals from hospitals and animal laboratories
- Snoring analyzer equipment (SNORYZER)
- Sensors, electrodes and microphones to obtain cardiac, respiratory, neural, muscular and sleep biomedical signals
- Polisomnographic equipment available in the Sleep Laboratory of collaborator hospital
- Beat to beat arterial blood pressure and haemodynamic monitor equipment
- Computing server for high performance biomedical signals
- Threshold™ IMT (Inspiratory Muscle Trainner) for respiratory muscle training (Phillips™)
- Robust wearable wireless sensor device Shimmer3 (Shimmer Research Ltd., Dublin, Ireland).

Collaborations

- **Dr. J. Mark Ansermino** Department of Anesthesiology, Pharmacology and Therapeutics, University of British Columbia, Vancouver, Canada
- **Prof. Antonio Bayes Genis** Grup ICREC, Servei Cardiología Hospital Universitari Germans Trias i Pujol, Barcelona
- **Dr. Salvador Benito** Hospital de la Santa Creu i Sant Pau, Barcelona
- **Prof. Dr. Konrad Bloch** Pulmonary Division, University of Zurich, Switzerland
- **Prof. Armin Bolz** Institute of Biomedical Engineering, University of Karlsruhe, Germany
- **Prof. Manuel Doblaré** Grupo de Mecánica Estructural y Modelado de Materiales, Universidad de Zaragoza, Spain
- **Prof. Guy Dumont** Department of Electrical and Computer Engineering, University of British Columbia, Vancouver, Canada
- **Prof. Ramon Farré** Unitat de Biofísica i Bioenginyeria, Facultat de Medicina, Barcelona
- **Dr. Javier García-Casado** Instituto Interuniversitario de Investigación en Bioingeniería y Tecnología Orientada al Ser Humano, Universidad Politécnica de Valencia
- **Dr. Joaquim Gea** Servei Pneumologia, Hospital del Mar-IMIM, Barcelona
- **Dr. Alfredo Hernández** Laboratoire Trataiment du Signal et de l'Image, Université de Rennes 1, Instituto Francés de Salud (INSERM), France
- **Dr. Eric Laciar** Departamento de Electrónica y Automática, Universidad Nacional de San Juan, Argentina
- **Prof. Pablo Laguna** Instituto de Investigación de Aragón (I3A), Universidad de Zaragoza, Spain
- **Dr. Barry Mersky** Audiodontics, LLC, Bethesda, Maryland, USA
- **Prof. Dr. Thomas Penzel** Interdisciplinary Sleep Center, Charité University Hospital, Berlin, Germany
- **Dr. Josep Morera Prat** Servicio de Neumología, Hospital Germans Trias i Pujol, Badalona, Spain
- **Prof. Winfried J. Randerath** Institut für Pneumologie, Klinik Bethanien, Solingen, Germany
- **Dr. Juan Ruiz** Servei de Pneumología de l'Hospital Germans Trias i Pujol de Badalona
- **Dr. Matthias Schwaibold** MCC-Med GmbH & Co. KG, Karlsruhe, Germany
- **Prof. Dr. Lotfi Senhadji** Laboratoire Traitement du Signal et de l'Image (LTSI), Université de Rennes 1, Institut National de la Santé et de la Recherche Médicale (INSERM), France
- **Prof. Leif Sörnmo** Signal processing group, Lund University, Sweden
- **Prof. Dr. Jaume Veciana** Grupo de Nanociencia Molecular y Materiales Orgánicos del Instituto de Ciencia de Materiales de Barcelona (NANOMOL-CSIC), Barcelona

- Camara, M. A., Castillo, Y., Blanco-Almazan, D., Estrada, L. and Jane, R. (2017). MHealth tools for monitoring Obstructive Sleep Apnea patients at home: Proof-of-concept. 39th Annual International Conference of the IEEE. IEEE (Seogwipo, South Korea), 1555-1558
- Castillo, Y., Blanco-Almazan, D., Whitney, J., Mersky, B. and Jane, R. (2017). Characterization of a tooth microphone coupled to an oral appliance device: A new system for monitoring OSA patients. 39th Annual International Conference of the IEEE. IEEE (Seogwipo, South Korea)
- Castillo, Y., Camara, M. A., Blanco-Almazan, D. and Jane, R. (2017). Characterization of microphones for snoring and breathing events analysis in mHealth.39th Annual International Conference of the IEEE. IEEE (Seogwipo, South Korea), 1547-1550
- Garcia-Castellote, D., Torres, A., Estrada, L., Sarlabous, L. and Jane, R. (2017). Evaluation of indirect measures of neural inspiratory time from invasive and noninvasive recordings of respiratory activity. 39th Annual International Conference of the IEEE. IEEE (Seogwipo, South Korea), 341-344
- Rodriguez, J., Voss, A., Caminal, P., Bayes-Genis, A. and Giraldo, B. F. Characterization and classification of patients with different levels of cardiac death risk by using Poincaré plot analysis. 39th Annual International Conference of the IEEE. IEEE (Seogwipo, South Korea), 1332-1335

- Schulz, S., Legorburu Cladera, B., Giraldo, B., Bolz, M., Bar, K. J. and Voss, A. (2017). Neuronal desynchronization as marker of an impaired brain network. 39th Annual International Conference of the IEEE. IEEE (Seogwipo, South Korea), 2251-2254
- Sola-Soler, J., Giraldo, B. F., Fiz, J. A. and Jane, R. (2017). Relationship between heart rate excursion and apnea duration in patients with Obstructive Sleep Apnea. 39th Annual International Conference of the IEEE. IEEE (Seogwipo, South Korea), 1539-1542
- Trapero, J. I., Arizmendi, C. J., Gonzalez, H., Forero, C. and Giraldo, B. F. (2017). Nonlinear dynamic analysis of the cardiorespiratory system in patients undergoing the weaning process. 39th Annual International Conference of the IEEE. IEEE (Seogwipo, South Korea), 3493-3496

Collaborations *cont.*

- **Prof. Andreas Voss** University of Applied Sciences, Jena, Germany
- **Dr. Pierluigi Casale** Laboratory for advanced research in microelectronics (IMEC), Eindhoven, The Netherlands
- **Dr. Francky Catthoor** Laboratory for advanced research in microelectronics (IMEC), Leuven, Belgium
- **Dr. Miquel Domenech** Dep. of Social Psychology, Universitat Autònoma de Barcelona
- **Dr. Caroline Jolley / Dr. John Moxham** King's College London, UK

Signal and information processing for sensing systems

Santiago Marco

Current smart instrumentation using multi-sensors and/or spectrometers provides a wealth of data that requires sophisticated signal and data processing approaches to extract the hidden information.

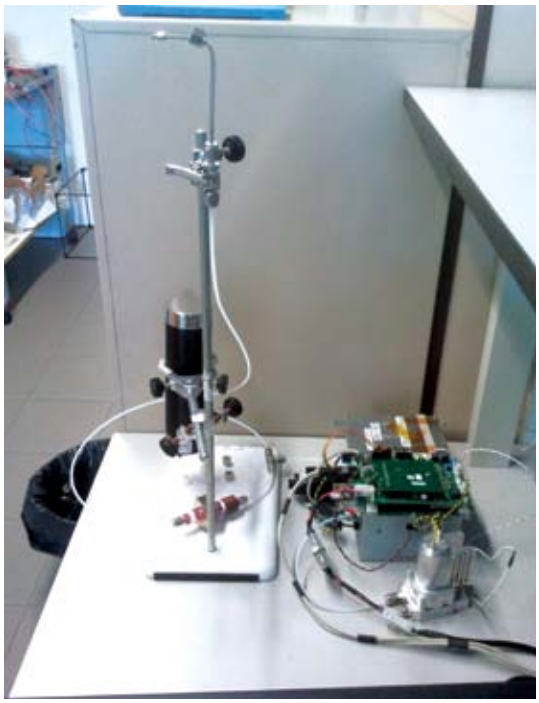
In this context, we are interested in intelligent chemical instruments for the detection of volatile compounds and smells.

These systems can be based on an array of nonspecific chemical sensors with a pattern recognition engine, taking inspiration from the olfactory system. Some spectrometries, e.g. Ion Mobility Spectrometry, are capable of very fast analysis with good detection limits but poor selectivity. These technologies have been proposed for the fast determination of the volatolome (volatile fraction of the metabolome), instead of the reference technique of gas chromatography – mass spectrometry.

Our group develops algorithmic solutions for the automatic processing of Gas Sensor Array, Ion Mobility Spectrometry (IMS) and Gas Chromatography – Mass Spectrometry (GC-MS) data for metabolomics and food samples.

Our research in 2017 included the following:

1. We have studied calibration transfer methods among chemical sensor arrays to reduce calibration costs.
2. We have studied the impact of low power operation modes in the performance of Metal Oxide Sensors.



Field Asymmetric Ion Mobility Spectrometer (Owlstone).

Autonomous Robot fitted with chemical sensor array for chemical source localization (in collaboration with University of Lleida)

Signal and information processing for sensing systems

Senior researcher
Agustín Gutiérrez

Postdocs
Silvia Mas
Jia Yan
Jordi Fonollosa

PhD students
Javier Burgués
Ana Maria Solórzano

Undergraduates
Suhyung Park
Marta Pérez

Lab technicians
Sergio Oller
Lluís Fernández

3. We have designed methodologies to estimate the limit of detection in chemical sensors inspired in the IUPAC recommendations.
4. We have been working in the detection of toxic emissions from fires to improve building occupant's safety.
5. In collaboration with Universitat de Lleida (Dr. J. Palacin) and University of Örebro (Prof. A. Lilienthal) we are testing chemical source localization algorithms with autonomous robots.
6. We have been studying the use of Volatile Fingerprints for the differentiation of food products such as Iberian Ham or Bitter Oranges.
7. We are developing algorithms for the analysis of mass spectrometry imaging data applied to colorectal cancer tissues.

Tag cloud of the group's research interests

Nanodrone to test bioinspired chemical source localization algorithms

Research projects

- **SIGVOL** Mejora de la señal para instrumentación química: aplicaciones en metabolómica de volátiles y en olfacción (2015-2017)
  PI: **Santiago Marco**
  MINECO
- **SAFESENS** Sensor Technologies for Enhanced Safety and Security of Buildings and its Occupants (2014-2017)
  PI: **Santiago Marco**
  ENIAC project (European project with a mix of public-private funding)
- Development of Data Processing Algorithms for Temperature Modulated Sensors
  PI: **Santiago Marco**
  Industrial Project with BSH Electrodomesticos, Spain
- Computational Metabolomics (2017-2019)
  PI: **Santiago Marco**
  Industrial Project with Nestlé Institute of Health Sciences, Switzerland

Publications

- Pomareda, V., Magrans, R., Jiménez-Soto, J., Martínez, D., Tresánchez, M., Burgués, J., Palacín, J. and Marco, S. (2017). Chemical source localization fusing concentration information in the presence of chemical background noise. *Sensors*, 17 (4): 904

Conference Papers

- Fernandez, L., Martin-Gomez, A., Mar Contreras, M., Padilla, M., Marco, S. and Arce, L. (2017). Ham quality evaluation assisted by gas chromatography ion mobility spectrometry. ISOCS/IEEE International Symposium on Olfaction and Electronic Nose (ISOEN), Montreal, Canada. Published by IEEE (2017/05/28)
- Burgues, J., Fonollosa, J. and Marco, S. (2017). Discontinuously operated MOX sensors for low power applications. ISOCS/IEEE International Symposium on Olfaction and Electronic Nose (ISOEN), Montreal, Canada. Published by IEEE (2017/05/28)
- Solorzano, A., Fonollosa, J., Fernandez, L., Eichmann, J. and Marco, S. (2017). Fire detection using a gas sensor array with sensor fusion algorithms. ISOCS/IEEE International Symposium on Olfaction and Electronic Nose (ISOEN), Montreal, Canada. Published by IEEE (2017/05/28)

Collaborations

- **Dr. Lourdes Arce**, Dept. Química Analítica, Universidad de Córdoba, Spain
- **Prof. J. W. Gardner**, Microsensors and Bioelectronics Lab, Dept. of Electric and Electronic Engineering, University of Warwick, UK
- **Prof. Achim Lilienthal**, Mobile Robotics and Olfaction Lab, University of Örebro, Sweden
- **Dr. Ivan Montoliu and Dra. Sofia Moço**, Nestlé Institute of Health Sciences, Laussane, Switzerland
- **Dr. Jordi Palacín**, Robotics Lab, Universitat de Lleida, Spain
- **Dra. Cristina Castro**, Sensors Technology, BSH-Zaragoza, Spain
- **Dr. Jens Eichman**, MINIMAX, Bad Oldesloe, Germany
- **Dr. Ulf Struckmeier,** AMS sensors, Reutlingen, Germany
- **Dr. Fernando Azpiroz**, Dept. Digestive Diseases, Vall d'Hebron, Barcelona, Spain
- **Dra. Anna de Juan**, Dept. Química Analítica i Enginyeria Química, Universitat de Barcelona, Spain

Equipment and techniques

- Gas chromatograph/mass spectrometer (Thermoscientific) with robotic head-space sampler
- Gas Chromatograph/ Thermal Conductivity Detector (Thermoscientific) with robotic head-space sampler
- 2 Infusion pumps K-systems
- 6 channel vapor generator plus humidity control (Owlstone, UK)
- Ion Mobility Spectrometer: Gas Detector Array (Airsense Analytics GmbH)
- Computing and General Purpose Electronic Instrumentation
- Field Asymmetric Ion Mobility Spectrometer (Owlstone, UK)
- Corona Discharge Ion Mobility Spectrometer (3QBD, Israel)
- Ultraviolet Ion Mobility Spectrometer (Gas Dortmund, Germany)
- Fast Photo Ionization Detector (Aurora Scientific, Canada).

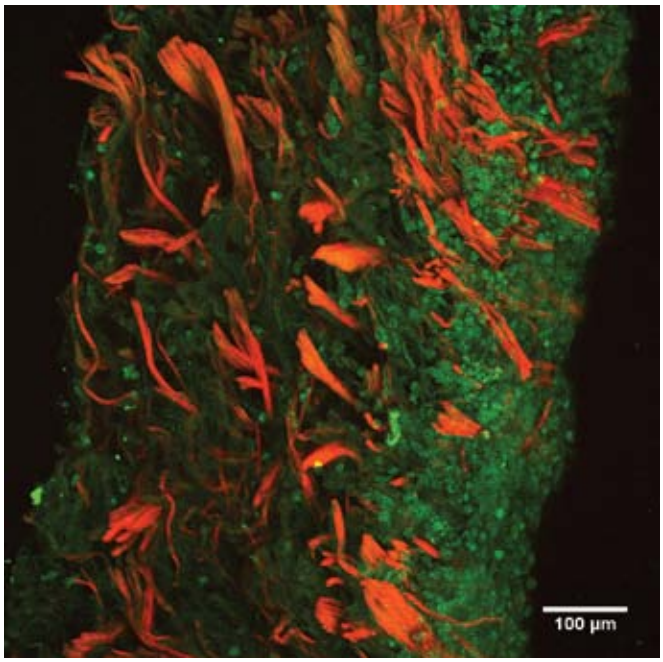
Biomimetic systems for cell engineering

Elena Martínez

In vitro assay platforms involving human cells are increasingly important to study tissue development, tissue regeneration, construct models of disease or develop systems for therapeutic screening that predict the human *in vivo* context.

The main conceptual problem of the standard *in vitro* cell-based assays is that they rely on two dimensional monolayer cellular cultures, which fail to replicate the complexity of living systems. There is an urgent need to create technological platforms with complex cell culture systems that mimic better the tissue-like cellular microenvironment.

We propose to combine engineering microfabrication technologies, tissue engineering concepts and recent advances in stem cell research, exploiting stem cell unique properties, to create cell culture microenvironments that will go beyond current 3D *in vitro* models. Resulting *in vitro* tissue equivalents aim at recapitulating *in vivo* cell functionality, cell renewal and migration, multicell-type differentiation and cell-matrix and cell-cell interactions. The cell culture platforms proposed will provide physiologically relevant and highly reproducible data, and they will be compatible with conventional cell culture assays and high-throughput testing. The new organotypic cell culture platforms will aim to advance the *in vitro* modelling of diseases, the preclinical screening for drug toxicity, the understanding of organ development and the regenerative medicine applications. Current main projects are: (i) to engineer and validate a complex *in vitro* model of small intestinal epithelium and (ii) to engineer and validate a novel *in vitro* model of engineered cardiac tissue.



Cross-section of a cardiac tissue construct cultured in a perfusion bioreactor with electrical stimulation. A primary culture of neonatal rat cardiomyocytes was seeded in a 3D collagen-elastin matrix. Collagen fibers (orange) were imaged using two-photon second harmonic generation (SHG), and elastin fibers (green) using autofluorescence. As cells have a high degree of autofluorescence they are also shown in green, densely packed in the right part of the image.

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Research projects

- **COMIET** Engineering Complex Intestinal Epithelial Tissue Models (2015-2020)
  PI: **Elena Martínez**
  ERC Consolidator Grant
- **GLAM** Glass-Laser Multiplexed Biosensor (2015-2019)
  PI: **Elena Martínez**
  European Commission (H2020) – PHC-10-2015
- **INDUCT** Dispositivo de multitejido intestinal para la monitorización de la comunicación entre epitelio y músculo en condiciones patológicas (2018-2021)
  PI: **Elena Martínez**
  MINECO
- Cardiopoesi amb biomatrius per regenerar la cicatriu post infart: From bench to bedside (first-in-man trial) (2017-2019)
  PI: Daniel Navajas (page 54)
  Pla Estratègic de Recerca i Innovació en Salut (PERIS)
- Ajuts per a grups de recerca consolidats (2014-)
  PI: Josep Samitier (page 68)
  Agència de Gestió d'Ajuts Universitaris i de Recerca. Generalitat de Catalunya. AGAUR 2014SGR1442
- **REPROMICRO** Reprogramación y regeneración tisular a partir de microvesiculas derivadas de células madre de pluripotencia inducida (2017-2018)
  PI: Nuria Montserrat (page 46)
  MINECO (EXPLORA)
- **MINAHE5** (Bio)funcionalización de Micro- y NanoHerramientas en Suspensión para Aplicaciones en Células Vivas (2015-2017)
  PI: Maria Lluïsa Pérez
  MINECO

Publications

- Ojosnegros, S., Cutrale, F., Rodríguez, D., Otterstrom, J. J., Chiu, C. L., Hortigüela, V., Tarantino, C., Seriola, A., Mieruszynski, S., Martínez, E., Lakadamyali, M., Raya, A. and Fraser, S. E. (2017). Eph-ephrin signaling modulated by polymerization and condensation of receptors. *Proceedings of the National Academy of Sciences*, 114 (50): 13188-13193

Collaborations

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- **Dr. Elisabeth Engel**, IBEC (page 16)
- **Prof. Raimon Jané**, IBEC (page 32)
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- **Dr. Matthew Dalby**, University of Glasgow (UK)
- **Prof. Jordi Martorell**, Institut de Ciències Fotòniques (ICFO), Castelldefels (Spain)
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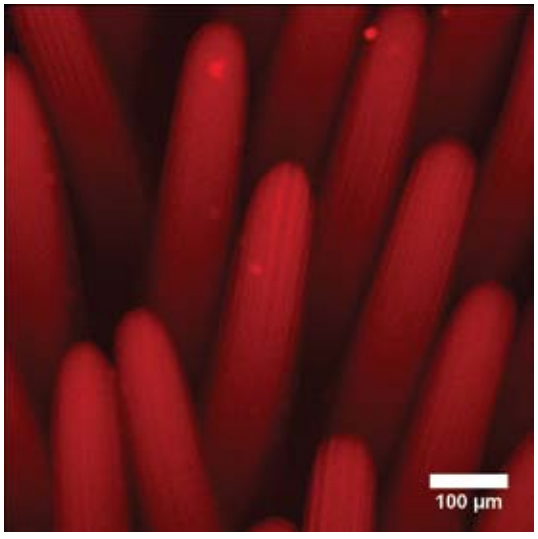
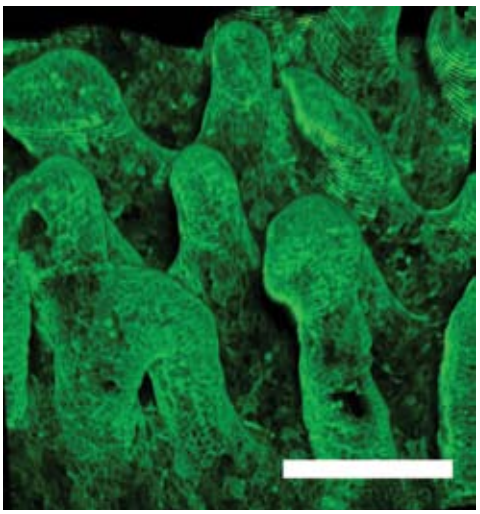


Hydrogel microstructures mimicking villi of the small intestinal tissue. They have been fabricated of PEGDA polymer and functionalized with labelled protein (in red).

Equipment and techniques

- Micro and nanofabrication techniques:
  - Biomolecule gradients produced by microfluidics
  - Large-area nanostructured polymer surfaces produced by diblock copolymers
  - 3D microstructures on hydrogel materials
  - Multistimuli mini-bioreactor for 3D cell culture
- Characterization techniques:
  - Surface Plasmon Resonance (SPR) measurements on polymer materials
  - Atomic Force Microscope (AFM) expertise
  - Optical Microscopes (white light/epifluorescence)
  - Focused Ion Beam (FIB) / Scanning Electron Microscopy (SEM) of biological specimens
- Equipment:
  - Biological safety cabinet (class II)
  - High precision syringe pumps
  - Peristaltic pumps
- Access to the Nanotechnology Platform (IBEC Core Facilities): equipment for hot embossing lithography, polymer processing and photolithography, chemical wet etching, e-beam evaporation and surface characterization (TOF-SIMS)
- Access to the Scientific and Technological Centers (University of Barcelona): equipment for surface analysis (XPS, AFM, XRD) and microscopy techniques (SEM, TEM, confocal)



3D rendering of villi-like microstructures fabricated of an hydrogel and seeded with Caco-2 cells. Scale bar = 200 µm.

Pluripotent stem cells and activation of endogenous tissue programs for organ regeneration

Nuria Montserrat

The generation of induced pluripotent stem cells (iPSCs), especially the generation of patient-derived pluripotent stem cells suitable for disease modelling *in vitro*, opens the door for the potential translation of stem-cell related studies into the clinic.

Successful replacement, or augmentation, of the function of damaged cells by patient derived differentiated stem cells would provide a novel cell-based therapy for diseases. Since iPSCs resemble human embryonic stem cells (hESCs) in their ability to generate cells of three germ layers, patient-specific iPSCs offer definitive solutions for the ethical and histo-incompatibility issues related to hESCs. Indeed human iPSC (hiPSC)-based autologous transplantation is heralded as the future of regenerative medicine.

One of our aims is to generate and correct disease-specific hiPSCs for disease modelling and drug screening. The combination of gene-editing based methodologies together with the development of novel protocols for cell differentiation into relevant tissues/organs, provides a unique scenario for modelling disease progression, and the identification of molecular and cellular mechanisms leading to organ regeneration (Figure 1). In this regard we are particularly interested in generation of transgene-free and disease free patient derived hiPSCs for disease modelling and the discovery of novel therapeutic targets.

We believe that the recovery of tissue function should not be restricted to the development of cell replacement therapies. In this regard, in our laboratory we take advantage of organisms that possess the ability to regenerate such as zebrafish, in order to understand which molecular and cellular pathways lead to organ regeneration. Surprisingly, studies in neonatal mice have demonstrated that soon after birth this organism posses the capability to regenerate its heart. Taking advantage of such preliminary observations we are translating such analysis in order to understand if the mammalian neonatal kidney still posses the capability to regenerate, and more importantly, if we are able to dissect the epigenetic and cellular mechanisms leading to those responses.

Lastly, and in an effort to fully develop *in vitro* and *ex vivo* platforms for organ regeneration, in our lab we are focused in the development of reporter cell lines for different transcription factors essential for tissue-specific commitment and differentiation (i.e: renal and cardiac lineages). The possibility to combine pluripotent stem cell lines together with decellularized matrices, functionalized biomaterials and *ex vivo* organoids offers and unprecedented opportunity for the immediate generation of patient-specific *in vitro* and *ex vivo* platforms for disease modelling and organ regeneration (Figure 2).

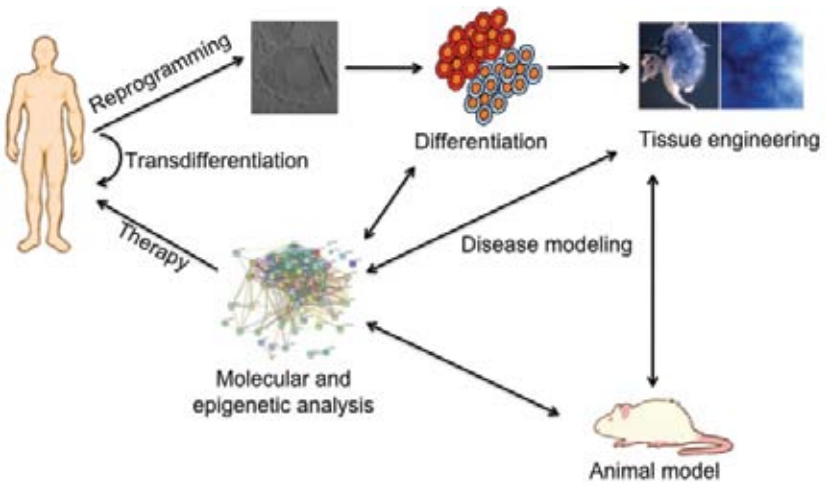


Figure 1: Patient induced pluripotent stem cells (iPSCs) represent an unprecedented tool for the generation of *in vitro* platforms for disease modelling and the definition of protocols for pluripotent stem cells differentiation. Transdifferentiation also offers the possibility to generate auto-compatible cells with no need to undergo to pluripotent stage. In these scenarios the correction of the genetic defect(s) leading to disease may help to understand the molecular and cellular mechanisms driving disease gestation and progression, and more importantly, to identify novel mechanisms leading to organ regeneration. The combination of gene editing methodologies with defined protocols for tissue differentiation helps us to generate *in vitro* systems for drug screening and disease modelling.

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Mireia Samitier

Visiting researcher
Blanca Molins

Research projects

- **REGMAMKID** How to regenerate the mammalian kidney (2015-2020)
  PI: **Núria Montserrat**
  ERC Starting Grant
- Generation of Isogenic Models of Clear Cell Renal Cell Carcinoma (ccRCC) using CRISPR-engineered Kidney Organoids, for the identification of diagnostic biomarkers (2017-2020)
  PI: **Núria Montserrat**
  Fundación AECC
- **TRATENFREN** Desarrollo de nuevas estrategias para el tratamiento de la enfermedad renal (2015-2017)
  PI: **Núria Montserrat**
  MINECO, Retos investigación: Proyectos I+D
- **CHONDREG** Identification of the epigenetic mechanisms preventing chondrocyte de-differentiation: generation of novel therapeutic strategies for the treatment of cartilage chronic osteochondral lesions
  PI: **Núria Montserrat**
  CIBER
- Infarto de miocardio en jóvenes. Factores epigeneticos y nuevos marcadores de riesgo cardiovascular. Efecto de la modulación de la expresión de microRNAs y long-non coding RNAs
  PI: Mercè Roque
  FIS, Instituto de Salud Carlos III
- Desarrollo de nuevas estrategias para el tratamiento de la enfermedad renal (2015-2017)
  PI: **Núria Montserrat**
  MINECO
- **REPROMICRO** Reprogramacion y regeneracion tisular a partir de microvesiculas derivadas de celulas madre de pluripotencia inducida (2017-19)
  PI: **Núria Montserrat**
  Ministerio de Economía y Competitividad, Explora Ciencia
- Red de Terapia Celular (Red TerCel) (2017-21)
  PI: Dr. Moraleda Jiménez (coordinator)
  Instituto de Salud Carlos III, Redes Temáticas de Investigación Cooperativa en Salud

Publications

- Garreta, E., Oria, R., Tarantino, C., Pla-Roca, M., Prado, P., Fernández-Avilés, F., Campistol, J. M., Samitier, J. and Montserrat, N. (2017). Tissue engineering by decellularization and 3D bioprinting. *Materials Today*, 20 (4): 166-178
- Garreta, E., Prado, P., Izpisua Belmonte, J. C. and Montserrat, N. (2017). Non-coding microRNAs for cardiac regeneration: Exploring novel alternatives to induce heart healing. *Non-coding RNA Research*, 2 (2): 93-99

Conference Papers

- Climent, A. M., Hernandez-Romero, I., Guillem, M. S., Montserrat, N., Fernandez, M. E., Atienza, F. and Fernandez-Aviles, F. (2017). High resolution microscopic optical mapping of anatomical and functional reentries in human cardiac cell cultures. Computing in Cardiology Conference (CinC2016), Vancouver, Canada. Published by IEEE (2017/03/02)

Book chapters

- Xia, Y., Montserrat, N., Campistol, J. M., Izpisua Belmonte, J. C., Remuzzi, G. and Williams, D. F. (2017). Lineage reprogramming toward kidney regeneration. In: *Kidney Transplantation, Bioengineering and Regeneration* (ed. Orlando, G., Remuzzi, G. and Williams, D. F.). London, UK, Academic Press: 1167-1175

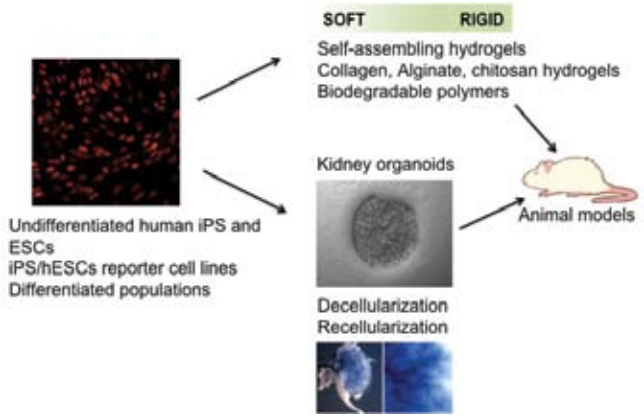

Figure 2: Induced pluripotent stem cells (iPSCs) resemble human embryonic stem cells (hESCs) in their ability to generate cells of the three germ layers of the embryo. This capacity can help us to understand the molecular and cellular cues driving cell fate. Our aim is to generate reporter cell lines from patient iPSCs in order to develop robust protocols for pluripotent stem cells differentiation. Moreover, the combination of patient differentiated populations together with functionalized biomaterials, *ex vivo* approaches (i.e: organoids), and decellularized tissue matrices, offers and unprecedented strategy for organ regeneration.

Collaborations

- **Prof. Juan Carlos Izpisua Belmonte**, Salk Institute for Biological Studies
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- **Dr. Peter Hohestein**, The Roslin Institute, University of Edinburgh
- **Dr. Pere Gascón Vilaplana**, Head of Oncology Service/Molecular and Translational Oncology Laboratory, IDIBAPS
- **Dr. Gloria Calderon**, President, Embryotools SL
- **Dr. Pura Muñoz Cánovas**, Departament de Ciències Experimentals i de la Salut, Universitat Pompeu Fabra
- **Dr. Pedro Guillén**, Director Clínica Cemtro, Madrid
- **Dr. Francisco Fernández Avilés**, Head of Cardiology Service, Hospital General Universitario Gregorio Marañón, Madrid
- **Dr. María Eugenia Fernández**, Unit of Cell Production, Hospital Gregorio Marañón, Madrid
- **Dr. Joaquin Gutiérrez Fruitós**, University of Barcelona
- **Dr. Pere Roca-Cusachs**, IBEC (page 64)
- **Dr. Cristina Eguizabal Argaiz**, Centro Vasco de Transfusion y Tejidos Humanos (CVTTH), Bizkaia
- **Dr. Antonio Alcaraz**, Head of Urology, Hospital Clínic, Barcelona
- **Dr. Oriol Casanovas**, Head of Tumour Angiogenesis Group, IDIBELL

Equipment and techniques

- Real Time QuantStudio 5
- SimpliAmp thermocycler
- Eppendorf 5415D centrifuge
- Allegra X-15 R centrifuge
- Gyrozen 1248 centrifuge
- BioUltra 6 Telstar culture Hood 2x
- AH-100 Telstar primary culture Hood
- Binder CB 60 incubators 2x
- Controltecnica ASTEC SCA 165 incubator
- Controltecnica ZC 180 incubator
- Bioruptor Pico sonicator
- Thermomixer C thermal block
- Leica DMS1000 and DMIL Led microscopes
- Leica DMi1 microscope
- Leica MZ 10F magnifying glass
- Safe Imager 2.0 transilluminator

Targeted therapeutics and nanodevices

Silvia Muro (ICREA Research Professor)

Our research sits at the interface between molecular-cellular biology and nanotechnology-drug delivery. We study the biological mechanisms ruling how our cells and tissues transport cargoes to precise destinations within our bodies, and apply this knowledge to the design of "biologically-controlled" nanodevices for improved delivery of therapeutic agents to specific disease sites (Figure 1).

A plethora of promising tools are becoming available to tackle health problems, such as new drug carriers or delivery systems, macromolecular assemblies within the nanoscale-size range which can be loaded with diagnostic and therapeutic agents to improve their solubility, dosage, circulation, biodistribution and, hence, overall performance and safety. However, despite such a great advance and promise, our ability to treat diseases such as neurological maladies, genetic syndromes, cancer, etc., remains a major challenge. One of the prime obstacles is our limited knowledge on the biological parameters that regulate the interaction of these systems with our tissues and, hence, our inability to gain non-invasive, efficient, and specific access within the body, its cells, and subcellular organelles. Our lab generates knowledge and tools aimed to improve our ability to deliver therapeutic agents to specific disease sites. Focusing on endothelial cell adhesion molecules as examples of accessible targets and on genetic conditions which serve as models for metabolic, neurodegenerative and cardiovascular syndromes, our ultimate goal is to enable effective treatment for these life-threatening disorders and other maladies characterized by similar pathological traits. Some of our main programmatic efforts are described below.

Biologically-Controlled Transport of Drug Carriers

How drug delivery systems are sensed, transported, and disposed of within the body, which is greatly dependent upon biological properties and processes, is far from being understood and much less controlled. Most targeted strategies are designed to achieve

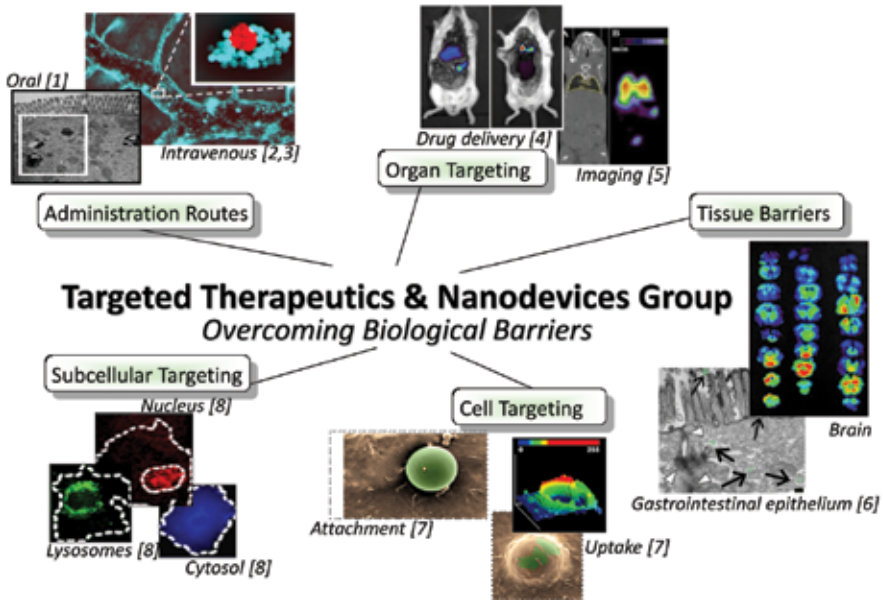

Figure 1. Targeted drug carriers for specific access within the body and its cells. Pictures are reproduced or adapted from the following sources (Copyrights reside on the respective publishers and associated professional societies): [1] Mane et al. (2012) *Int J Nanomedicine*, 7:4223-4237; [2] Garnacho et al. (2008) *J Pharm Exp Ther*, 325(2):400-408; [3] Finikova et al. (2008) *Chem Phys Chem*, 9(12):1673-1679; [4] Hsu et al. (2013) *J Biomed Nanotech*. 10(2):345-354; [5] Rosin et al. (2008) *J Nucl Med*, 49(1):103-111; [6] Ghaffarian et al. (2012) *J Control Release*, 163(1):25-33; [7] Serrano et al. (2012) *Arterioscler Thromb Vasc Biol*, 32(5):1178-1185; [8] Muro S. (2014) *Adv Funct Mat*, 24(19):2899-2906.

specific binding of drug delivery systems to cell-surface receptors, but then they simply depend on the signaling and transport processes the bound receptor regulates in nature. Instead, by deciphering the biological bases of these events, we impart the drug carrier control over biological signaling events independently from the receptor being bound, bypassing the mechanisms, kinetics, and destinations otherwise associated with these receptors. This provides a new and complementary avenue at the interface between the use of novel technological tools to decipher the biological mechanisms that regulate health and fail in disease, and the use of biological knowledge to optimize nanotechnology tools aimed to diagnose and treat human pathologies. For instance, we have shown how even using the same targeting or receptor, the kinetics, mechanism, and destination of a drug carrier can be modulated by: (a) varying its size, shape, and targeting valency; (b) varying the receptor epitope to which the carrier binds; (c) using auxiliary drugs to modulate the endocytic machinery; (d) coupling carriers to signaling molecules that can tune the uptake route independently from the receptor being used (Figure 2); (e) combining targeting to several receptors; or (f) coupling targeting moieties with anti-phagocytic moieties on the surface of drug carriers.

Transport of Drug Carriers Across Physiological Barriers

Crossing the linings that separate body and cellular compartments is paramount for efficient drug delivery. For instance, an epithelial barrier separates the gastrointestinal tract from the bloodstream, controlling uptake of orally ingested substances. While certain chemical entities are able to cross this barrier, many therapies do not and their successful utilization needs of means to bypass this obstacle. As for neurodegenerative conditions, they remain largely untreatable because the vast majority of available pharmaceuticals and drug carriers under development both fail to traverse the endothelial barrier that separates the bloodstream from the brain tissue. Another example is that of novel biological therapeutics, which have demonstrated potential to manipulate disease targets far more precisely than their small chemical counterparts. However, these large and fragile therapeutics fail to traverse the membranes that separate the extracellular environment from the intracellular milieu and those of intracellular organelles. We demonstrated that the ICAM-1 pathway (described in the next section) enables transcytosis across epithelial and endothelial linings, which we explore for oral delivery and delivery across the blood-brain barrier. We were also able to target DNA-

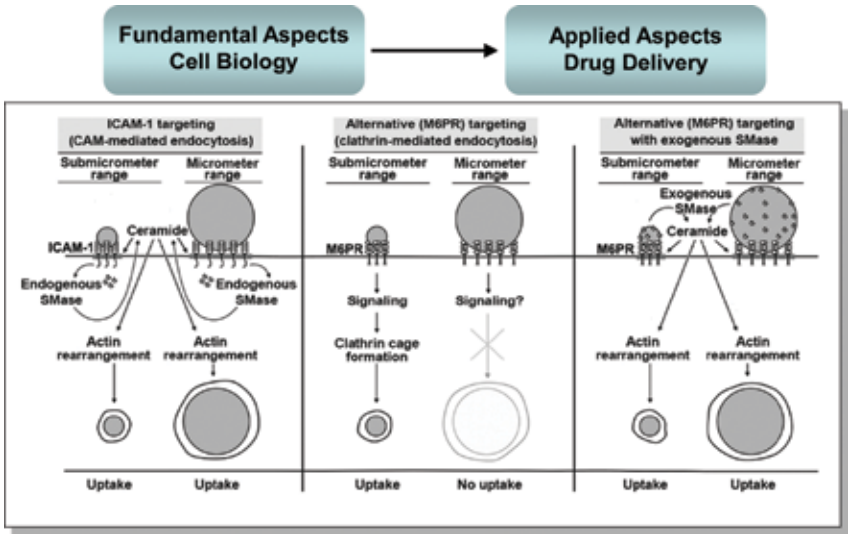

Figure 2. Enzyme-functionalization of drug carriers to improve their uptake by cells. ICAM-1-targeted nano- and micro-carriers are both internalized by cells due to natural sphingomyelinase (SMase)-dependent generation of ceramide at ICAM-1-binding sites. Ceramide improves carrier engulfment and membrane invagination, and acts as a second messenger toward actin re-organization, helping endocytic uptake (left panel). In contrast, targeting drug carriers to receptors associated with more size-restrictive pathways, e.g., clathrin-associated mannose-6-phosphate receptor (M6PR), often enables uptake of nano- but not micro-carriers (middle panel). Surface-functionalization of M6PR-targeted carriers with elements mimicking the ICAM-1 pathway, namely exogenous SMases (such as NSM), supplies the necessary ceramide and actin re-organization, improving endocytosis of nano- and micro-carriers even when targeted to receptors different from ICAM-1 (right panel). Reproduced from Ansar et al. (2013) *ACS Nano*, 7(12):10597-10611.

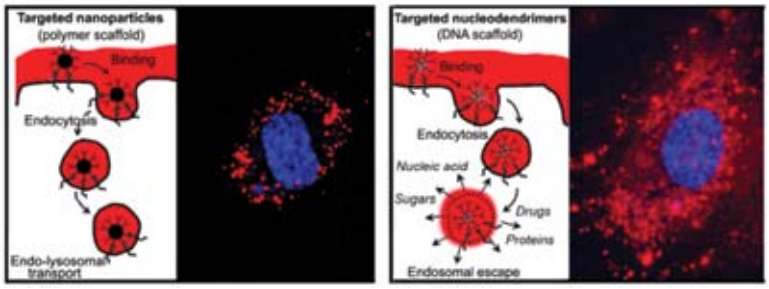

Figure 3. Subcellular distribution of cargo delivered by targeted DNA-built dendrimers. (Left) Illustrative cartoon and corresponding microscopy showing that fluorescent dextran delivered to cells via targeted polymer nanoparticles resides in vesicular compartments (bright red spots) around the cell nucleus (blue). (Right) Instead, much dextran can escape vesicular compartments and reach the cytosol (more diffuse red color) when delivered using similarly targeted "nucleodendrimers" (DNA-built dendrimers). Adapted from Muro (2014) *Adv Funct Mat*, 24(19):2899-2906.

built dendrimers to cells specifically, whereby these DNA dendrimers enabled endosomal escape and cytosol delivery of a variety of cargoes, including small toxins, carbohydrates (Figure 3), proteins, and nucleic acids.

Vesicular Transport of Endothelial Cell Adhesion Molecules

During my postdoctoral training, I helped to identify an endocytic pathway induced upon multivalent engagement of the endothelial cell-surface molecules ICAM-1 and PECAM-1. This new transport route is different from most others classically utilized for drug delivery, including clathrin-, caveolar-, macropinocytosis-, or phagocytosis-mediated pathways. My independent laboratory continues to unravel the regulation of this route, particularly focusing on ICAM-1 (Figure 4), and its implications in patho-physiology and drug delivery. The relevance of this new pathway is illustrated by the fact that ICAM-1 mediates extravasation of leukocytes during inflammation, signaling at the immune synapsis, and invasion by some pathogens (e.g., human rhinoviruses). The understanding of this fundamental route and its properties is also advancing diverse drug delivery applications by our group and many others.

Improving Treatment of Lysosomal Disorders

Monogenic pathologies due to genetic deficiency, such as the case of lysosomal disorders, are valuable models to study disease progression and therapeutic intervention because they have well-known etiology and defined molecular, biochemical and cellular effects, and because patient samples, diverse cell types, and small and large animal models are all readily available. Also, their unequivocal diagnosis enables the tracing of their progression from early to late stages. Since these diseases present with either acute or long-term effects depending on genetic severity, and associate with neurodegeneration, cardiovascular, metabolic, and cancer-like syndromes, they represent excellent disease models. The current lack of efficient therapies to treat these syndromes stems from problems similar to those described above, i.e. our inability to deliver therapeutics to disease sites in need. Consequently, we are applying targeted nanotechnology concepts to the treatment of genetic lysosomal disorders. Current therapies by i.v. enzyme infusion are only helpful for diseases where clearance cells and organs (liver, spleen, macrophages, etc.) are the main targets. Yet, delivery to other organs (brain, lungs, etc.) hinders translation for most diseases. Using types A and B Niemann-Pick (Figure 5), Fabry, and Gaucher diseases as examples, we have shown improved delivery of therapeutic enzymes to all affected organs in animal models, holding considerable translational potential.

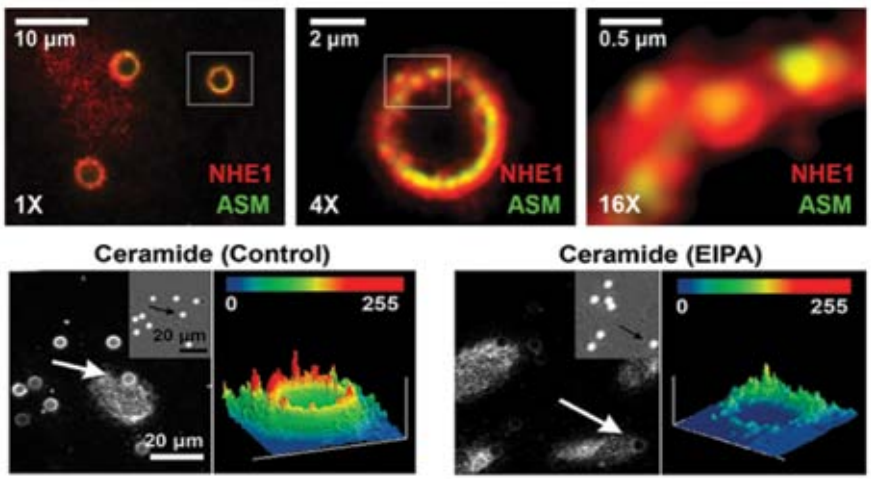

Figure 4. Cell adhesion molecule (CAM)-mediated endocytosis. (Top) Different magnifications of microscopy images showing precise co-localization of sodium-proton exchanger 1 (NHE-1; red) and acid sphingomyelinase enzyme (ASM; green) at plasmalemma areas where ICAM-1-targeted carriers are being engulfed by cells. (Bottom) Relative enrichment of ceramide in regions of binding of ICAM-1-targeted carriers to control cell versus cell treated with EIPA (an NHE-1 inhibitor) shows that NHE-1 function is needed for membrane engulfment of said carriers. Adapted from Serrano et al. (2012) *Arterioscler Thromb Vasc Biol*, 32(5):1178-1185.

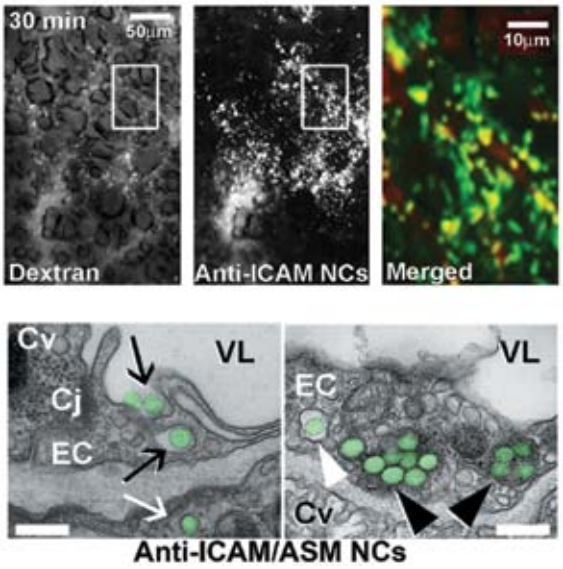

Figure 5. Endocytosis and lysosomal trafficking of anti-ICAM/ASM NCs in mouse lungs. (Top) Polymer nanocarriers (NCs) bearing therapeutic acid sphingomyelinase (ASM) and targeted to ICAM-1 were observed by fluorescent microscopy to abundantly reach the lungs, as observed 30 min after i.v. injection in mice (green spots). (Bottom) Transmission electron microscopy of lungs collected 3 h after i.v. administration confirmed the presence of NCs (green) interacting with endothelial cells (ECs). For instance, NCs can be seen being engulfed by cells (black arrows), within cell endosomes (white arrowheads) and lysosomes (black arrowheads), and transcytosed across the endothelium into subjacent epithelial cells (white arrow). VL = vessel lumen. Cv = caveolar vesicles. Cl = clathrin vesicles. Cj = cell junction. Scale bars = 300 nm. Reproduced from Garnacho et al. (2017) *Mol. Ther.* doi: 10.1016/j.ymthe.2017.05.014.

Collaborations

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- **Dr. Yu Chen**, University of Maryland College Park, MD, USA.
- **Dr. Mandy Esch**, National Institutes for Standards and Technology, Gaithersburg, MD, USA.
- **Dr. Robert Getts**, Genisphere LLC, Hatfield, PA, USA.
- **Dr. Hamid Ghandehari**, University of Utah, UT, USA.
- **Dr. Janet Hoenicka**, Sant Joan de Deu Hospital, Barcelona, Spain.
- **Dr. Christopher Jewell**, University of Maryland College Park, MD, USA.
- **Dr. Joe Kao**, University of Maryland Baltimore, MD, USA.
- **Dr. Peter Kofinas**, University of Maryland College Park, MD, USA.
- **Dr. Juan Marugan and Dr. Wei Zheng**, National Institutes of Health, Rockville, MD, USA.
- **Dr. Vladimir Muzykantov**, University of Pennsylvania, Philadelphia, PA, USA.
- **Dr. Gianfranco Pasut**, University of Padova, Padova, Italy.
- **Dr. Edward Schuchman**, Mount Sinai School of Medicine, New York, NY, USA.
- **Dr. Brigitte Stadler**, Aarhus University, Denmark.
- **Dr. Maria Jesus Vicent**, Principe Felipe Research Center, Valencia, Spain.

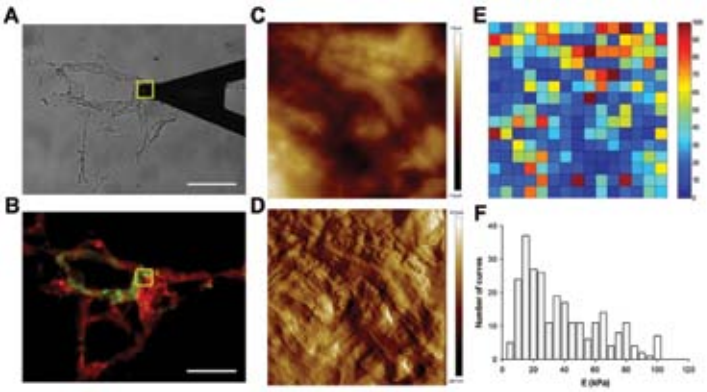
Cellular and respiratory biomechanics

Daniel Navajas

The goal of our research is to gain a deeper understanding of cellular and respiratory biomechanics to improve the diagnosis and treatment of respiratory diseases.

The work is organized in two interrelated areas, focused on respiratory mechanics at both the systemic and the cellular level. We use basic and translational approaches in a multidisciplinary framework involving close cooperation with clinical groups.

Our current research interest is focused on the study of cell-matrix mechanical cross-talk for tissue engineering and regenerative medicine. Cells sense and actively respond to the biophysical features of their microenvironment. Mechanical properties of the extracellular matrix regulate critical cell processes such as contraction, migration, proliferation, gene expression and differentiation. We use atomic force microscopy and other cutting-edge biophysical techniques to study the mechanical properties of the extracellular matrix and their impact in cell behavior. We have implemented protocols to decellularize different soft tissues. This innovative approach allowed us to reveal the local mechanical properties of the lung and heart extracellular matrix. By seeding cells in these scaffolds we study the impact of the mechanical features of the microenvironment on stem cell engraftment and differentiation onto lung and heart phenotypes. We produce lab-on-chip devices mimicking the native cell microenvironment to investigate mechanical signaling driving stem cell differentiation under precisely controlled conditions. Using 3D bioprinters we integrate stem cells into synthetic and extracellular matrix hydrogels to fabricate tissue patches as an innovative approach to regenerate ventricular scars resulting from heart infarct. Organ biofabrication reengineered from decellularized tissue scaffolds offers a promising alternative for transplantation. We develop improved bioreactors mimicking breathing and blood perfusion to biofabricate lungs by seeding stem cells into acellular lung scaffolds.



Mechanical mapping and imaging of the extracellular matrix of a slice of decellularized mouse lung obtained by the combination of bright field (A), immunofluorescence microscopy (B), and atomic force microscopy (C – F).

Cellular and respiratory biomechanics

Postdocs
Jordi Otero
Jordi Alcaraz

PhD students
Ignasi Jorba
Noelia Campillo

Lab technician
Maeba Polo

Research projects

- Precondicionamento biofísico de células madre mesenquimales para el tratamiento de la lesión pulmonar aguda provocada por sobreventilación en modelo animal (2015-2017)
  PI: **Daniel Navajas**
  Fondo de Investigación Sanitaria (FIS), MINECO (PI14/00280)
- Bench test on performance of portable automatic CPAP devices (2016-2017).
  PI: Ramon Farré (UB)
  RESMED (FBG2016A)

Collaborations

- **Prof. Ramon Farré** Unit of Biophysics and Bioengineering, Dept. Physiological Sciences, School of Medicine, University of Barcelona/ IDIBAPS, Barcelona, Spain
- **Prof. J. M. Montserrat** Service of Pneumology, Hospital Clinic/IDIBAPS, Barcelona, Spain
- **Prof. Antoni Bayés-Genis** Institut del Cor dels Germans Trias I Pujol, Badalona
- **Prof. Daniel Weiss** Department of Medicine, University of Vermont
- **Prof. A. Artigas** Intensive Care Service, Hospital Parc Taulí, Sabadell
- **Mauricio Rojas** Scientific Director of the Simmons Center for Interstitial Lung Diseases, University of Pittsburgh
- **David Gozal** Chair of the Department of Pediatrics, University of Chicago Medical Center. Chicago

Publications

- Oria, R. et al (2017). Force loading explains spatial sensing of ligands by cells. *Nature*, 552 219-224
- Elosegui-Artola, A. et al (2017). Force triggers YAP nuclear entry by regulating transport across nuclear pores. *Cell*, 171 (6): 1397-1410
- Hernández-Vega, A. et al (2017). Polarized cortical tension drives zebrafish epiboly movements. *EMBO Journal*, 36 (1): 25-41
- Schillers, H. et al (2017). Standardized nanomechanical atomic force microscopy procedure (SNAP) for measuring soft and biological samples. *Scientific Reports*, 7 (1): 5117
- Campillo, N. et al (2017). Role of cyclooxygenase-2 on intermittent hypoxia-induced lung tumor malignancy in a mouse model of sleep apnea. *Scientific Reports*, 7 44693
- Jorba, I., Uriarte, J. J., Campillo, N., Farré, R. and Navajas, D. (2017). Probing micromechanical properties of the extracellular matrix of soft tissues by atomic force microscopy. *Journal of Cellular Physiology*, 232 (1): 19-26
- Campillo, N. et al (2017). Frequency and magnitude

of intermittent hypoxia modulate endothelial wound healing in a cell culture model of sleep apnea. *Journal of Applied Physiology*, 123 (5): 1047-1054

- Jorba, I. et al (2017). Ageing and chronic intermittent hypoxia mimicking sleep apnea do not modify local brain tissue stiffness in healthy mice. *Journal of the Mechanical Behavior of Biomedical Materials*, 71 106-113
- Vilaseca, A. et al (2017). Intermittent hypoxia increases kidney tumor vascularization in a murine model of sleep apnea. *PLoS ONE*, 12 (6)
- Urbano, J. J. et al (2017). Effects of two different decellularization routes on the mechanical properties of decellularized lungs. *PLoS ONE*, 12 (6): e0178696
- Isetta, V. et al (2017). A New mHealth application to support treatment of sleep apnoea patients. *Journal of Telemedicine and Telecare*, 23 (1): 14-18
- Marsal, M. et al (2017). AFM and microrheology in the zebrafish embryo yolk cell. *Journal of Visualized Experiments, Developmental Biology* (129): e56224
- Giménez, A., Uriarte, J. J., Vieyra, J., Navajas, D. and Alcaraz, J. Elastic properties of hydrogels and decellularized tissue sections used in mechanobiology studies probed by atomic force microscopy. *Microscopy Research and Technique*, 80 (1): 85-96

Equipment and techniques

- Fluorescence resonance energy transfer (FRET) microscopy
- Confocal Microcopy
- Traction Microscopy
- Live cell fluorescence microscopy
- Cell stretching
- Cell culture
- Magnetic Tweezers
- Atomic Force Microscopy
- Surface Micro/Nano-patterning

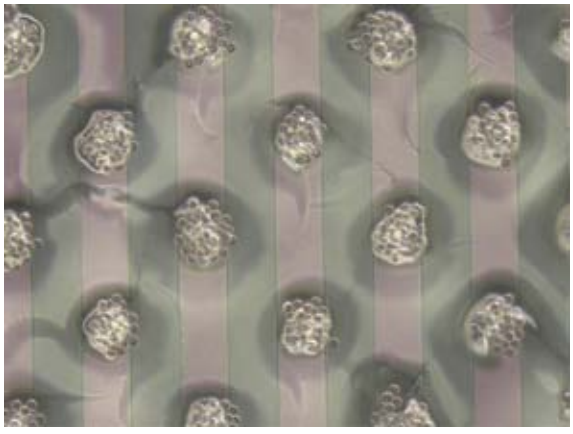
Biosensors for bioengineering

Javier Ramon

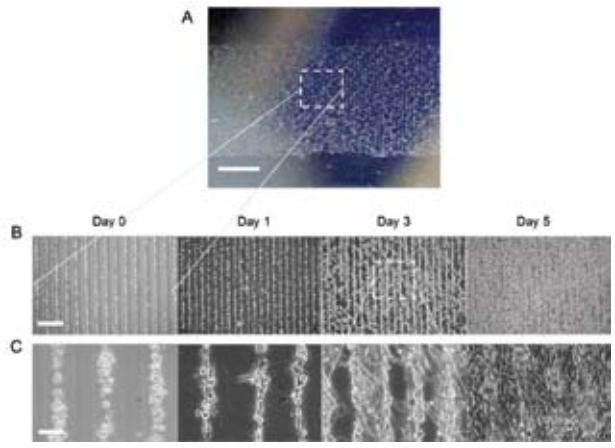
The drug discovery pathway relies heavily on *in vivo* animal models and *in vitro* cell mediums. In the case of animal models we have not only some ethical problems but also the ability to extrapolate data to human conditions is limited and *in vitro* platforms often do not simulate the complex cell–cell and cell–matrix interactions crucial for regulating cell behaviour.

The Biosensors for Bioengineering group is focused on a new line of research that has become of extreme importance in the last years. The idea is to integrate biosensor technology and nanotechnology with stem cell research and with tissue engineering. Engineered tissues are integrated with biosensing technology to obtain microdevices for detecting cellular responses to external stimuli, monitoring the quality of the microenvironment (e.g., metabolites, nutrients), and supporting diverse cellular requirements. This research on 3D-functional engineered tissues is expected to develop knowledge of tissue construction and their functions and relation with some human diseases. Integration of fully functional tissues with microscale biosensor technology allowed us to obtain "organs-on-a-chip". These chips could be used in pharmaceutical assays and could be a step toward the ultimate goal of producing *in vitro* drug testing systems crucial to the medicine and pharmaceutical industry.

Formation of 3D ESC aggregates in GelMA hydrogel using dielectrophoresis (DEP). The stem cells in the GelMA prepolymer were introduced into the 100 µm height chamber and localized by DEP forces to the low electric field regions within the microelectrodes. The GelMA prepolymer was then exposed to UV light, embedding the cells in a stable microscale organization. Aggregated ESCs within the GelMA hydrogel were removed from the top electrode and cultured. The ESCs were dielectrophoretically patterned within 15 sec. Scale bar show 100 µm.



Picture of aligned C2C12 muscle cells within hydrogel as obtained by the dielectrophoresis (DEP) technique using 50 µm electrode 50 µm gap device (A). Phase contrast images of the aligned C2C12 muscle cells within hydrogel at different culture times (B and C). Scale bar shows 0.25 cm, 400 µm, and 50 µm in A, B, and C, respectively.



Research

Biosensors for bioengineering

Postdoc
Maria Alejandra Ortega

PhD students
Ferran Velasco
Xiomara Gislen Fernández

Masters student
Pablo García

Lab technician
Albert Garcia

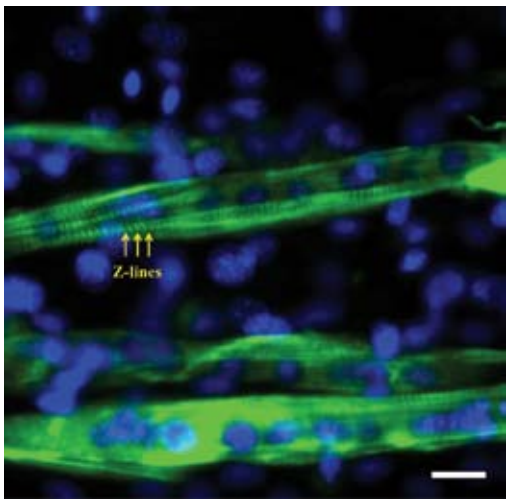
Research assistant
Alejandro Hernández

Publications

- Mohammadi, M. H., Obregón, R., Ahadian, S., Ramón-Azcón, J. and Radisic, M. (2017). Engineered muscle tissues for disease modeling and drug screening applications. *Current Pharmaceutical Design*, 23 (20): 2991-3004

Book chapter

- Obregón, R., Ramón-Azcón, J. and Ahadian, S. (2017). Nanofiber composites in blood vessel tissue engineering. In: *Nanofiber Composites for Biomedical Applications* (ed. Ramalingam, M. and Ramakrishna, S.), Elsevier, Duxford, UK. Woodhead Publishing Series in Biomaterials: 483-506



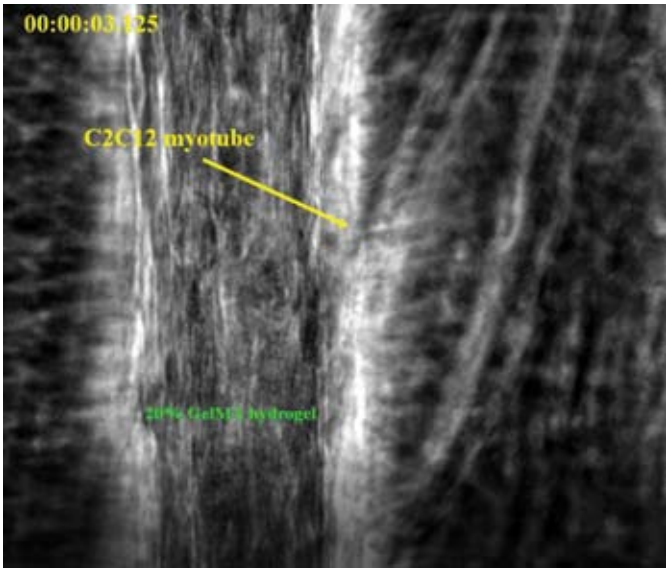
Myotubes differentiated in a groove-ridge topography GelMA-CNTs composite loaded with 0.3 mg/mL CNTs. Immunostaining of cell nuclei/myosin heavy chain showing the highly aligned C2C12 myotubes. Z-lines were also observed for the myotubes indicating high maturation of muscle myofibers. Scale bar show 20 µm.

Research projects

- **DAMOC** Diabetes Approach by Multi-Organ-on-a-Chip (2017-2021)
  PI: **Javier Ramón**
  ERC - StG

Collaborations

- **Prof. Josep Samitier**, IBEC (page 68)
- **Dr. Elena Martínez**, IBEC (page 42)
- **Dr. Anna Novials**, Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS)
- **Dr. Ramon Gomís**, IDIBAPS
- **Dr. Eduard Montanya**, The Bellvitge Biomedical Research Institute (IDIBELL)
- **Prof. Enric Bertran**, Physics and Engineering of Amorphous Materials and Nanostructures (FEMAN), Department of Applied Physics, University of Barcelona



Equipment and techniques

- Micro and nanofabrication techniques:
  - 3D microstructures on hydrogel materials
  - Mini-bioreactor for 3D cell culture
  - Microelectrodes fabrication
  - Synthesis and chemical modification of polymers and surfaces
  - Dielectrophoretic cells and micro particles manipulation
- Characterization techniques:
  - Optical Microscopes (white light/epifluorescence)
  - Electrochemical techniques (Potentiometric/Amperometric/Impedance spectroscopy)
  - Immunosensing techniques (Fluorescence ELISA/Colorimetric ELISA/ magneto ELISA)
- Equipment:
  - Microfluidic systems (High precision syringe pumps/Peristaltic pumps/ Micro valves)
  - Biological safety cabinet (class II)
  - Epifluorescence microscope for live-cell imaging
- Access to the Nanotechnology Platform (IBEC Core Facilities): equipment for hot embossing lithography, polymer processing and photolithography, chemical wet etching, e-beam evaporation and surface characterization (TOF-SIMS)
- Access to the Scientific and Technological Centers (University of Barcelona): equipment for surface analysis (XPS, AFM, XRD), organic structures characterization (NMR) and microscopy techniques (SEM, TEM, confocal)

Molecular and cellular neurobiotechnology

José Antonio del Río

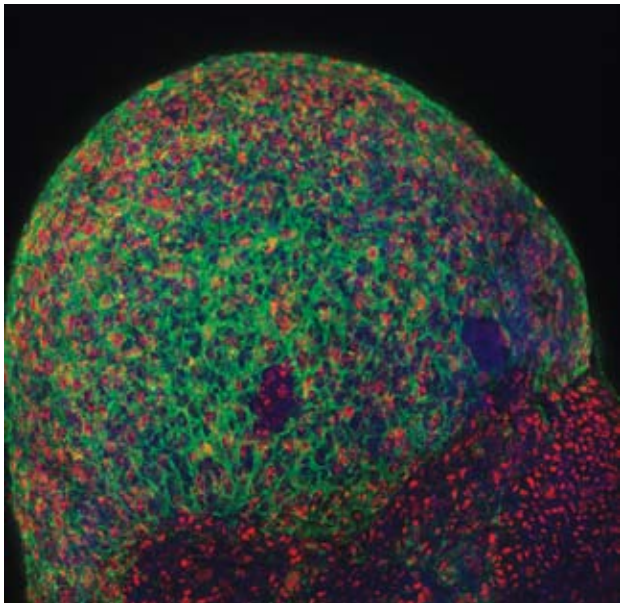
Our research interests are focused on three main aspects of developmental Neurobiology and regeneration:

1) IPS cell models for neurodegeneration

Our knowledge of many neurodegenerative diseases relies on the possibility of analysing samples only at very late stages of the disease. This drawback increases steadily the faster the progression of the neurodegeneration. Indeed, changes during asymptomatic stages of these diseases cannot be analysed, and, more relevantly, a prodromal study during illness evolution cannot be properly developed, hampering biochemical/molecular studies and drug-discovery. Gerstmann-Sträussler-Scheinker (GSS) syndrome is a rare autosomal dominant neurodegenerative prionopathy characterized clinically by a wide spectrum of manifestations including but not limited to ataxia, spastic paraparesis, extrapyramidal signs and dementia. In some cases patients also showed comorbid Tau hyperphosphorylatioon. Due to the above-mentioned restrictions, we developed an induced pluripotent stem (iPS) cell model using fibroblasts from an GSS patient harbouring the Y218N PRNP mutation and hyperphosphorylated Tau. Y218N iPS-derived cultures showed relevant astrogliosis, increased p-Tau and cell death.

2) New receptors for α-synuclein transport in neurons

α-Synuclein is a key player in the pathogenesis of synucleinopathies, including Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy. Transmission of synthetic α-synuclein aggregates has been demonstrated in several cellular and animal models. Several groups have reported that insoluble α-synuclein shows prion-like propagation in wild-type mice. However, the basis of the spreading process remains poorly understood although cell to cell transport via exocytosis has been proposed. Because of this, PrP^C is proposed as Aβ receptor, and in our current studies we aimed to explore whether PrP^C is involved in the propagation and spreading of a-synuclein.



A mass of neurons derived from GSS-affected pluripotent stem cells.

Senior researcher
Rosalina Gavín

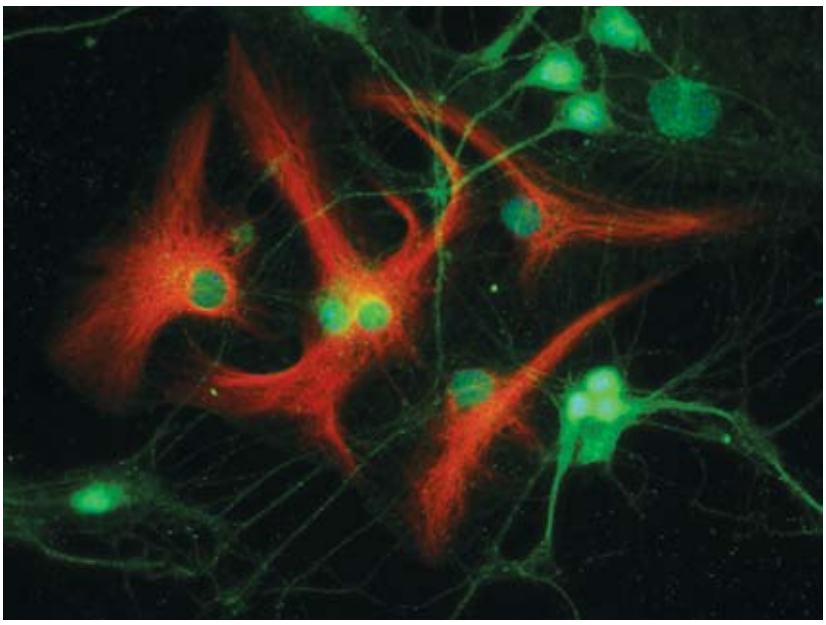
Postdocs
Vanessa Gil
Arnau Hervera

PhD students
Francina Mesquida
Ana López
Laia Lidón
Laura Urrea
Andreu Matamoros

Masters students
Amaia Mimenza
Júlia Sala
Marta Sánchez

Undergraduate
Alicja Kosiorowska

Lab technician
Miriam Segura



Primary neuronal culture from mouse embryo after 7 days *in vitro*. Neurons are labelled in green and astrocytes in red.

3) Development of new lab on a chip devices for neurobiological research

We recently developed a new device able to reproduce axon lesioning *in vitro* in a single chip. Current experiments of our group in collaboration with groups of IBEC and CIBER-BBN aimed at developing new lab on chip devices to mimics and modulate particular neurobiological processes. For example: cortico-spinal chips to develop genetic studies; molecular gradient generation for migrating neurons and *in silico* 3D modeling for neurodegenerative diseases (Alzheimer and Parkinson chip).

Publications

- Mata, A., Urrea, L., Vilches, S., Llorens, F., Thüne, K., Espinosa, J.-C., Andréoletti, O., Sevillano, A. M., Torres, J. M., Requena, J. R., Zerr, I., Ferrer, I., Gavín, R. and del Río, J. A. (2017). Reelin expression in Creutzfeldt-Jakob disease and experimental models of transmissible spongiform encephalopathies. *Molecular Neurobiology*, 54 (8): 6412-6425
- Gutiérrez-Franco, A., Eixarch, H., Costa, C., Gil, V., Castillo, M., Calvo-Barreiro, L., Montalban, X., Del Río, J. A. and Espejo, C. (2017). Semaphorin 7A as a potential therapeutic target for multiple sclerosis. *Molecular Neurobiology*, 54 (6): 4820-4831
- Frau-Méndez, M. A., Fernández-Vega, I., Ansoleaga, B., Blanco, R., Carmona, M., Antonio del Rio, J., Zerr, I., Llorens, F., Zarranz, J. J. and Ferrer, I. (2017). Fatal familial insomnia: Mitochondrial and protein synthesis machinery decline in the mediodorsal thalamus. *Brain Pathology*, 27 (1): 95-106
- Garcia-Esparcia, P., López-González, I., Grau-Rivera, O., García-Garrido, M. F.,

Konetti, A., Llorens, F., Zafar, S., Carmona, M., del Rio, J. A., Zerr, I., Gelpi, E. and Ferrer, I. (2017). Dementia with Lewy Bodies: Molecular pathology in the frontal cortex in typical and rapidly progressive forms. *Frontiers in Neurology*, 8 Article 89

- Urrea, L., Ferrer, I., Gavín, R. and del Río, J. A. (2017). The cellular prion protein (PrPC) as neuronal receptor for α-synuclein. *Prion*, 11 (4): 226-233

Research projects

- Role of the cellular prion protein as "cross-talk" protein between alpha syn/LRRK2 and p-Tau in sporadic and familiar Parkinson's disease (2015-2017)
  PI: **José A. Del Río**
  Fundació La Marató de TV3
- Red de Excelencia Nacional de Priones (2016-2018)
  PI: **José A. del Río**
  MINECO, Reference: AGL2015-71764-REDT
- Robots biológicos basados en el control de la union neuromuscular (2016-19).
  PI: Josep Samitier (page 68)
  MINECO, Programa EXPLORA, Reference: TEC2015-72718-EXP
- **ANGIODEVSNC** Funciones de genes implicados en angiogenesis y remodelación vascular durante el desarrollo cortical y en neurodegeneración (2016-19).
  PI: **José A. del Río**
  MINECO, Reference: BFU2015-6777-R
- Spanish Network of Neurodegerative Diseases of the Ministry of Heath (FIS) (2009-2017)
  PI: **José A. del Río**
  CIBERNED, Reference: P1-L14

Equipment and techniques

- Neural stem and iPS cell culture
- Microscopy facility (Olympus BX61 and Olympus IX71 with LCi culture and OKOlab systems)
- Electroporation system (BTX 600)
- Pressure microinjection system
- Protein expression and purification systems
- Technology of neuronal culture facilities (2D and 3D)
- Lentiviral and AVV production and characterization
- Protein and DNA electrophoresis
- In situ hybridization oven
- Optogenetic *in vitro* and *in vivo* stimulation system

Collaborations

- **Dr. Adolfo Lopéz de Munain**, Hospital de Donostia, San Sebastian, Spain
- **Dr. Joaquin Castilla**, CiC Biogune, Bilbao, Spain
- **Prof. Juan María Torres**, INIA-CISA CSIC, Valdeolmos, Madrid, Spain
- **Prof. José María Delgado and Prof. Agnest Gruart**, UPO, Sevilla, Spain
- **Prof. Jose Manuel García Verdugo**, Facultad de Ciencias, Universidad de Valencia, Spain
- **Prof. Jose Manuel García Aznar**, Nanotechnology Institute, Zaragoza, Spain
- **Prof. Fernando Albericio and Ernest Giralt**, Institute for Research in Biomedicine (IRB), Barcelona
- **Dr. Miriam Royo**, Institute for Research in Biomedicine (IRB), Barcelona
- **Dr. Elisabeth Engel** (page 16), **Prof. Josep Samitier** (page 68), **Prof. Xavier Trepat** (page 84) and **Prof. Daniel Navajas** (page 54), IBEC
- **Prof. Ángel Raya**, Center of Regenerative Medicine in Barcelona (CMRB)
- **Dr. Antonella Consiglio and Dr. Franc LLorens**, Institut d'Investigació Biomèdica de Bellvitge, University of Barcelona, Spain
- **Prof. Jesús Ávila and Prof. Francisco Wandosell**, Consejo Superior de Investigaciones Científicas (CSIC), Universidad Autónoma de Madrid, Spain
- **Prof. Isidro Ferrer**, Institut d'Investigació Biomèdica de Bellvitge, University of Barcelona, Spain
- **Dr. Alberto LLeó**, Hospital Sant Pau, Barcelona, Spain.
- **Prof. Miquel Vila**, VHIR, Barcelona, Spain.
- **Prof. Fanny Mann**, Developmental Institute of Marseille Luminy, Université de la Méditerranée, Marseille, France
- **Prof. Yutaka Yoshida**, Division of Developmental Biology, Cincinnati Children's Research Foundation, Cincinnati, Ohio, USA
- **Prof. Masato Hagesawa**, Faculty of Medicine, Tokyo
- **Prof. José Luis Lanciego**, CIMA, Navarra, Spain

Cellular and molecular mechanobiology

Pere Roca-Cusachs

Every time we blink, move a hand, draw a breath, or walk, cells in our body exert, transmit, withstand, and detect forces. This mechanical interaction with the environment determines how cells proliferate, differentiate, and move, and regulates development, tumorigenesis or wound healing.

Just like biochemical stimuli initiate signaling cascades, mechanical forces affect the links and conformation of a network of molecules connecting cells to the extracellular matrix. Our research aims precisely at unraveling the mechanisms that these molecules use to detect and respond to mechanical stimuli like forces or tissue rigidity, triggering downstream cell responses. To this end, we combine biophysical techniques like magnetic tweezers, Atomic Force Microscopy, traction microscopy, and microfabricated force sensors with molecular biology, advanced optical microscopy, and theoretical modelling.

Sensing rigidity: Using this multi-disciplinary approach, we have recently unveiled a molecular mechanism that cells employ to detect and respond to the rigidity of their environment, which could be crucial in breast tissue and breast cancer (Elosegui-Artola et al., 2016 *Nat. Cell Biol.*, and Elosegui-Artola et al. 2014, *Nature Mater.*). This mechanism is mediated by what is known as a "molecular clutch": in a surprising analogy with a car engine, cells can be understood as a molecular network that can engage and disengage from its environment, just as the clutch of a car. This affects force transmission from the environment to cells, and also within different cell components. Recently, we have begun to explore how force transmission to the nucleus affects the dynamics of transcriptional regulators, such as YAP (Elosegui-Artoal et al., 2017, *Cell*).

Sensing the environment: We are currently expanding on the idea of the molecular clutch, to explore how cell molecular engines sense not only mechanical rigidity, but other important parameters from their environment: for instance, the composition and distribution of ligands in the extracellular matrix, or other cells. In this regard, we recently uncovered that this concept can explain how cells sense the spatial distribution of ligands in the extracellular matrix (Oria et al., *Nature* 2017). We have also demonstrated that cell-cell force transmission, mediated by a molecular clutch, is essential for cells to sense gradients in stiffness (Sunyer et al., *Science* 2016, in collaboration with the group of Xavier Trepat).

The membrane as a mechanosensor: Due to its mechanical properties, the plasma membrane itself can respond to forces and act as a mechanosensor. Recently, we have shown that cell membranes can use purely physical principles to adapt their shape in response to mechanical forces (Kosmalska et al., 2015, *Nat. Commun.*). We are currently studying how cells harness this physical membrane behavior to respond to signals from their environment.

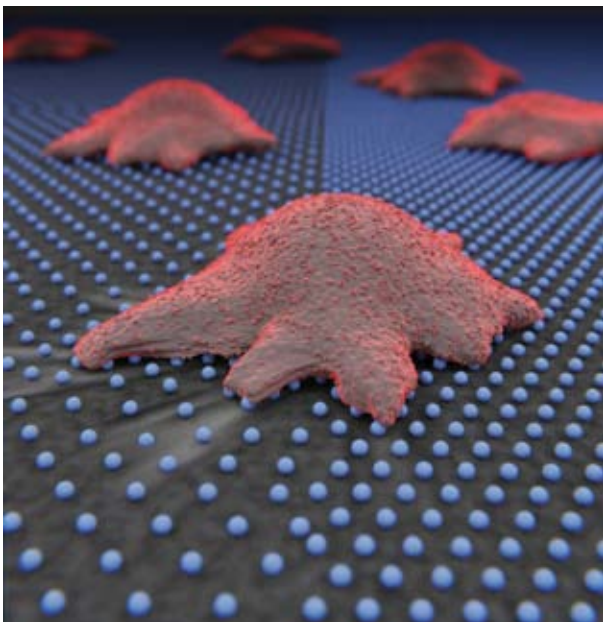
Ultimately, when we determine the molecular mechanisms that communicate cells with their environment, we will understand how forces determine development when things go right, and tumor formation when they go wrong.

Postdocs
Zanetta Zoi (Jenny) Kechagia
Anabel-Lise Le Roux
Laura Faure
Ion Andreu

PhD students
Víctor González
Xarxa Quiroga
Roger Oria

Masters students
Ignasi Granero
Marina Pavlova

Lab assistant
Oriol Mañé



Artistic rendering of a cell attaching to a substrate coated with a gold nano-pattern array, used to study how cells detect spatial cues (From Oria et al. 2017, *Nature*).

Collaborations

- **Dr. Nils Gauthier**, Mechanobiology Institute, Singapore
- **Prof. Miguel Ángel del Pozo**, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid
- **Prof. Marino Arroyo**, UPC, Barcelona
- **Prof. Ada Cavalcanti**, U. of Heidelberg, Germany
- **Dr. Satyajit Mayor**, National Centre for Biological Sciences, Bangalore, India
- **Dr. Sergi Garcia-manyes**, King's College, London, UK
- **Dr. Cheng Zhu**, Georgia Tech, Atlanta, USA
- **Dr. Louise Jones**, Barts Cancer Institute, London, UK

Publications

- Oria, R., Wiegand, T., Escribano, J., Elosegui-Artola, A., Uriarte, J. J., Moreno-Pulido, C., Platzman, I., Delcanale, P., Albertazzi, L., Navajas, D., Trepat, X., García-Aznar, J. M., Cavalcanti-Adam, E. A. and Roca-Cusachs, P. (2017). Force loading explains spatial sensing of ligands by cells. *Nature*, 552 219-224
- Rodriguez-Franco, P., Brugués, A., Marin-Llaurado, A., Conte, V., Solanas, G., Batlle, E., Fredberg, J. J., Roca-Cusachs, P., Sunyer, R. and Trepat, X. (2017). Long-lived force patterns and deformation waves at repulsive epithelial boundaries. *Nature Materials*, 16 (10): 1029-1036
- Elosegui-Artola, A., Andreu, I., Beedle, A. E. M., Lezamiz, A., Uroz, M., Kosmalska, A. J., Oria, R., Kechagia, J. Z., Rico-Lastres, P., Le Roux, A. L., Shanahan, C. M., Trepat, X., Navajas, D., Garcia-Manyes, S. and Roca-Cusachs, P. (2017). Force triggers YAP nuclear entry by regulating transport across nuclear pores. *Cell*, 171 (6): 1397-1410
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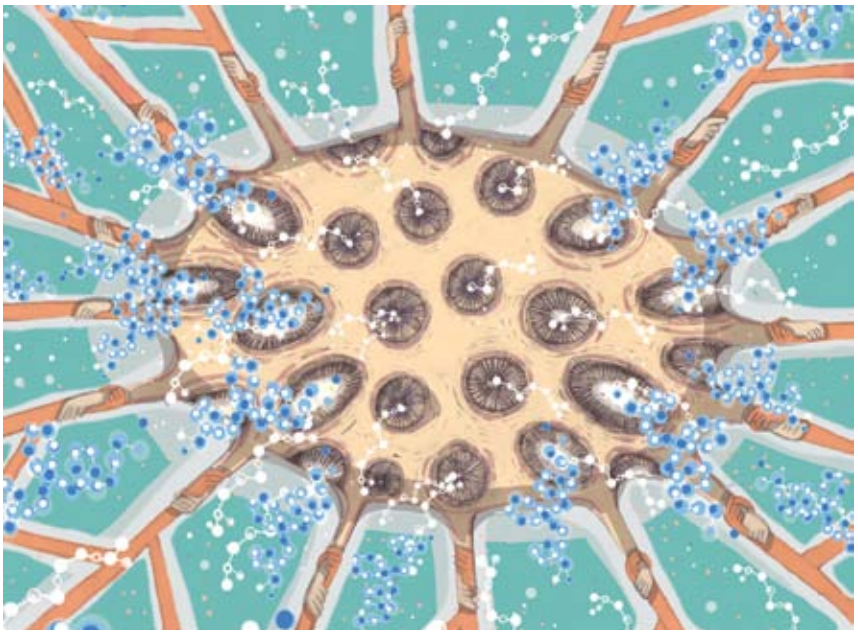
Tissue engineering by decellularization and 3D bioprinting. *Materials Today*, 20 (4): 166-178

- Roca-Cusachs, P., Conte, V. and Trepat, X. (2017). Quantifying forces in cell biology. *Nature Cell Biology*, 19 (7): 742-751
- Labernadie, A., Kato, T., Brugués, A., Serra-Picamal, X., Derzsi, S., Arwert, E., Weston, A., González-Tarragó, V., Elosegui-Artola, A., Albertazzi, L., Alcaraz, J., Roca-Cusachs, P., Sahai, E. and Trepat, X. (2017). A mechanically active heterotypic E-cadherin/N-cadherin adhesion enables fibroblasts to drive cancer cell invasion. *Nature Cell Biology*, 19 (3): 224-237
- Pontes, B., Monzo, P., Gole, L., Le Roux, A. L., Kosmalska, A. J., Tam, Z. Y., Luo, W., Kan, S., Viasnoff, V., Roca-Cusachs, P., Tucker-Kellogg, L. and Gauthier, N. C. (2017). Membrane tension controls adhesion positioning at the leading edge of cells. *Journal of Cell Biology*, 216 (9): 2959-2977
- Neri, L., Lasa, M., Elosegui-Artola, A., D'Avola, D., Carte, B., Gazquez, C., Alve, S., Roca-Cusachs, P., Iñarrairaegui, M., Herrero, J., Prieto, J., Sangro, B. and Aldabe, R. (2017). NatB-mediated protein N-α-terminal acetylation is a potential therapeutic target in hepatocellular carcinoma. *Oncotarget*, 8 (25): 40967-40981
- González-Tarragó, V., Elosegui-Artola, A., Bazellières, E., Oria, R., Pérez-González, C. and Roca-Cusachs, P. (2017). Binding of ZO-1 to α5β1 integrins regulates the mechanical properties of α5β1–fibronectin links. *Molecular Biology of the Cell*, 28 (14): 1847-1852

Research projects

- **MECHANOCONTROL** Mechanical control of biological function (2017-2021)
  PI: **Pere Roca-Cusachs**
  European Commission, FET Proactive
- **MECHANOMEMBRANE** Redes mecanoquímicas en la membrana plasmática (2017-2018)
  PI: **Pere Roca-Cusachs**
  MINECO, Subprograma Estatal de Generación de Conocimiento "EUROPA EXCELENCIA"
- **IMREG** El sistema acoplado entre integrinas y proteínas adaptadoras como regulador mecánico del comportamiento celular (2016-2019)
  PI: **Pere Roca-Cusachs**
  MINECO, Proyectos I+D Excelencia
- Understanding and measuring mechanical tumor properties to improve cancer diagnosis, treatment, and survival: Application to liquid biopsies (2017-2020)
  PI: **Pere Roca-Cusachs**
  Obra Social La Caixa
- Inhibiting mechanostransduction as a novel therapy in the treatment of solid tumors (2017-2018)
  PI: **Pere Roca-Cusachs**
  Obra Social La Caixa, Caixaimpulse
- Stromal stiffness in tumor progression (2014-2017)
  PI: **Pere Roca-Cusachs**
  Fundació la Marató de TV3
- Grup de recerca consolidat (2014-2017)
  PI: **Pere Roca-Cusachs**
  Agència de Gestió d'Ajuts Universitaris i de Recerca (AGAUR). Convocatòria d'ajuts per donar suport a les activitats dels grups de recerca de Catalunya



Cartoon depicting how force transmission to the nucleus affects nuclear pores, leading to nuclear protein import (from Elosegui-Artola et al. 2017, *Cell*).

Equipment and techniques

- Confocal Microcopy
- Traction Microscopy
- Live cell fluorescence microscopy
- Cell stretching
- Cell culture
- Magnetic Tweezers
- Atomic Force Microscopy
- Surface Micro/Nano-patterning
- Optical tweezers

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Nanobioengineering

Josep Samitier

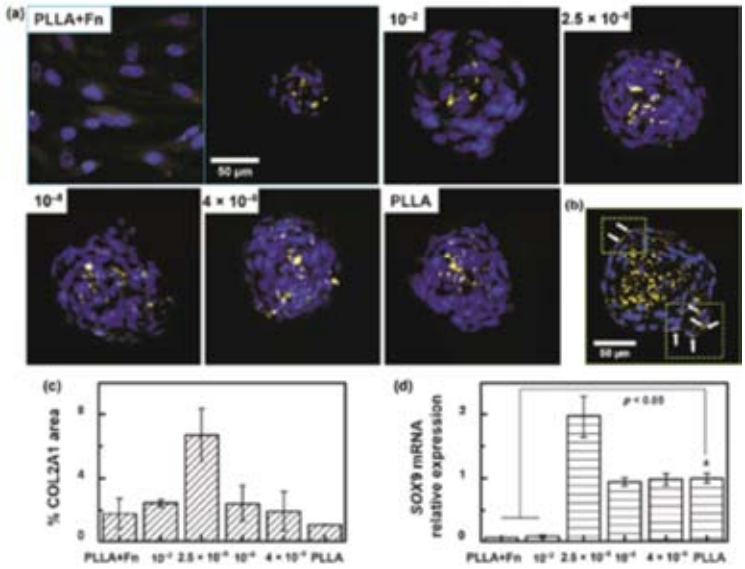
The Nanobioengineering group is a truly multidisciplinary team composed by researchers coming from very diverse backgrounds working together in applying nanotechnology for the development of new biomedical systems and devices, mainly for diagnostic purposes, and integrated microfluidic Organ-on-Chip devices for the study of organ physiology, disease etiology, or drug screening.

The main research activities of the group include the engineering and biochemical functionalization of biomaterials integrated with microfluidics systems. The bioengineered microdevices are used to study cell responses to biomolecular compounds applied to Organ-on-Chip devices, or for the development of new lab-on-a-chip based biosensors.

The goal is to fabricate microsystems containing living cells that recapitulate tissue and organ level functions *in vitro* and new portable diagnosis devices that can be used as Point-of-Care systems. The projects carried out by the group are focused on clinical and industrial problems and are related to three convergent research lines:

1. Biosensors and Lab-on-a-Chip devices for clinical diagnosis and food safety applications

- DNA sensors and platform arrays for cancer biomarker detection.
- Antibody-based sensors for pathogenic microorganisms' detection and neurodegenerative early detection
- Sensor array for *in vivo* hypoxia and ischemia monitoring.



Chondrogenesis improvement by using nanoparticles to control cell adhesion and migration

Senior researchers
Joan Montero
Anna Lagunas
Mònica Mir

Postdocs
Lourdes Rivas Torcates
Romén Rodríguez
Maria José López

PhD students
Ignasi Casanellas
Andrea García
Roberto Paoli
Maider Badiola

Masters students
Nord Oliver
Jessica Sierra
Marc Tarín

Undergraduates
Miguel Mir
Mariel Castillejos

Research technicians
Jennifer Maria Cruzado
Samuel Dulay
Sandrine Miserere

Lab technicians
David Izquierdo
Miriam Funes

Visiting researcher
Valeria Rizzuto

- 3D printing microfluidic technology.
- Microfluidic chip using hydrodynamic forces for cell counting and sorting. Application for detection of circulating tumors cells (CTC).

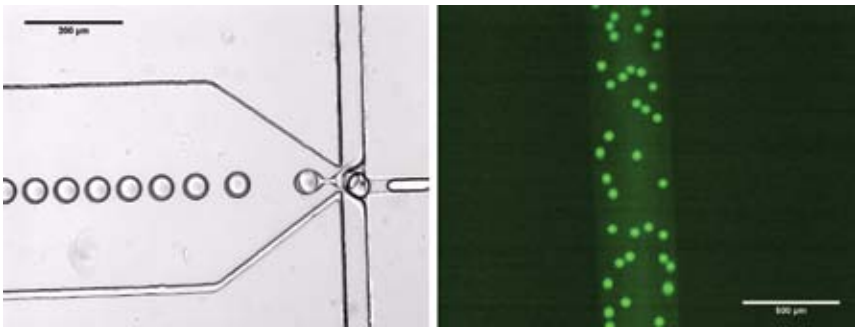
2. Nanotechnology applied to biomolecule interaction studies and micro/nano-environments for regenerative medicine applications

- Development of bioengineered 2D and 3D micro/nanoenvironments with a topography and chemical composition controlled at the nanoscale for cell behavior studies (adhesion, proliferation, differentiation). Study of Chondrogenesis and tenogenesis differentiation.
- Biophysical description of cellular phenomena (cell migration, differentiation) using micro/nanotechnologies, cell biology tools and soft matter physics.
- Study of magnetite nanoparticles - Amyloid-Beta interaction in Alzheimer disease.

3. Microfluidic systems for biological studies and Organ-on-Chip devices

- Microfluidic chip for blood/plasma filtering and anemia diseases characterization
- Spleen-on-a-chip development.
- Nanoporous-based systems for kidney-on–a-chip developments.
- Engineering microfluidic platforms for neurobiological studies.
- Development of 3D neuromuscular tissue models for soft robotics and clinical applications
- Microfluidic system to monitor cancer therapy response. Tumor Cancer on a chip *in vitro* development.
- Study of magnetite nanoparticles - Amyloid-Beta interaction in Alzheimer's disease.

Microfluid chip for droplet generation and encapsulation



Publications

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- Gállego, I., Manning, B., Prades, J. D., Mir, M., Samitier, J. and Eritja, R. (2017). DNA-origami-driven lithography for patterning on gold surfaces with sub-10 nm resolution. *Advanced Materials*, 29 1603233
- Caballero, D., Palacios, L., Freitas, P. P. and Samitier, J. (2017). An interplay between matrix anisotropy and actomyosin contractility regulates 3D-directed cell migration. *Advanced Functional Materials*, 27 (35): 1702322
- Agusil, J. P., Torras, N., Duch, M., Esteve, J., Pérez-García, L., Samitier, J. and Plaza, J. A. (2017). Highly anisotropic suspended planar-array chips with multidimensional sub-micrometric biomolecular patterns. *Advanced Functional Materials*, 27 1605912
- Caballero, D. and Samitier, J. (2017). Topological control of extracellular matrix growth: A native-like model for cell morphodynamics studies. *ACS Applied Materials and Interfaces*, 9 (4): 4159-4170
- Lagunas, A., Tsintzou, I., Vida, Y., Collado, D., Pérez-Inestrosa, E., Pereira, C. R., Magalhaes, J., Andrades, J. A. and Samitier, J. (2017). Tailoring RGD local surface density at the nanoscale toward adult stem cell chondrogenic commitment. *Nano Research*, 10 (6): 1959-1971

Research projects

- **NANOVAX** Nanovacunas diseñadas para inmunoterapia antitumoral (2016-2018)
  PI: **Josep Samitier**
  EuroNanoMed (ERA-Net)
- **BIOBOT** Engineered biological soft robots based on neuro-muscular junction control (2017-2018)
  PI: **Josep Samitier**
  MINECO, Proyectos EXPLORA Ciencia / Tecnología
- **MINDS** Plataforma MIcrofluídica 3D de cultivo Neuronal compartimentada para el estuDio de enfermedades neurológicaS (2016-2018)
  PI: **Josep Samitier**
  MINECO, Proyectos I+D Excelencia
- **Advancecat** Acceleradora pel desenvolupament de teràpies avançades
  PI: **Josep Samitier**
  ACCIÓ / Smart Specialization funds (RIS3)
- Understanding and measuring mechanical tumor properties to improve cancer diagnosis, treatment, and survival: Application to liquid biopsies (2017-2020)
  PI: **Josep Samitier**
  Obra Social La Caixa
- Personalizing pediatric cancer treatment with kinome analyses, cell-based funcional assays and microfluidics (2017-2020)
  PIs: **Josep Samitier** / **Joan Montero**
  Fundación CELLEX
- **ISCHEMSURG** Miniaturized electrochemical sensor for monitoring of free flap ischemia in post-surgery (2017-2018)
  PI: **Mònica Mir**
  CaixaImpulse
- Desarrollar un sistema de asistencia robótica para medicina y cirugía fetal (2016-2019)
  PI: **Josep Samitier**
  Fundación CELLEX
- Desarrollo de una nueva tecnología lab-on-a-chip para la detección y cuantificación de secuencias de ADN/ARN (2014-2016) (Joint Unit IBEC-Genomica)
  PI: **Josep Samitier**
  Genómica S.A.U
- Monitoring neurocognitive deficits in Alzheimer's and Parkinson's diseases using saliva or blood-derived biomarkers and a multiplexed approach (2016-2018)
  PIs: **Josep Samitier**/José A. del Río (page 60)
  Obra Social La Caixa
- **nanoET-leukemia** Nanoconductance of electron transfer proteins of the respiratory chain. Direct measurement at the single molecular level and therapeutic regulation in cancer stem cells (2015-2018)
  PIs: **Anna Lagunas**/Marina Inés Giannotti (page 28)
  MINECO, Proyectos RETOS 2015 / CIBER

Collaborations

- **Prof. Fernando Albericio** Institut de Recerca Biomédica (IRB), Barcelona, Spain
- **Dr. José Antonio Andrades** Universidad de Málaga, Spain
- **Prof. Ezequiel Pérez Inestrosa** Centro Andaluz de Nanomedicina y Biotecnología (BIONAND), Málaga, Spain
- **Prof. Joan Bausells** Centro Nacional de Microelectrónica (CNM-CSIC), Barcelona
- **Prof. Albert van den Berg** University of Twente, The Netherlands
- **Prof. Andre Bernard** Institut für Mikro- und Nanotechnologie (MNT-NTB), Buchs, Switzerland
- **Prof. H. Börner** Max Planck Institute of Colloids and Interfaces, Golm, Germany
- **Prof. Josep Maria Canals** University of Barcelona, Spain
- **Dr. Matthew Dalby** University of Glasgow, UK
- **Prof. Paolo Dario** Scuola Superiore Sant'Anna (SSSA), Pontedera, Italy
- **Prof. Ramón Eritja** Institut de Recerca Biomédica (IRB), Barcelona, Spain
- **Prof. E. Faszewski** Wheelock College, Boston, USA
- **Prof. G. Fuhr** FhG Biomedicine, St. Ingbert, Germany
- **Dr. Juan C. Izpisúa** Salk Institute for Biological Studies, La Jolla, California
- **Dr. Nicole Jaffrezic** Université Claude Bernard Lyon 1, France
- **Dr. Graham Johnson** Uniscan Instruments Ltd, Buxton, UK
- **Dr. Mª Pilar Marco** Institute of Chemical and Environmental Research, Barcelona
- **Prof. Jean-Louis Marty** Université de Perpignan Via Domitia, France
- **Prof. Barbara Mazzolai** IIT Center for Micro-BioRobotics (CMBR), Pontedera, Italy
- **Dr. Edith Pajot** Biology of Olfaction and Biosensors group (BOB) at INRA, Jouy-en-Josas, France
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- **Dr. Jaume Reventós** Hospital Vall d'Hebrón, Barcelona, Spain
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- **Prof. Daniel Riveline** Laboratory of Cell Physics ISIS/IGBMC, Strasbourg
- **Prof. M. Sampietro** Politecnico di Milano, Italy
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- **Dr. Christophe Vieu** Laboratoire d'analyse et d'architectures des systèmes (LAAS-CNRS), Toulouse, France
- **Prof. Pau Gorostiza** IBEC (page 28)

- Caballero, D., Blackburn, S. M., de Pablo, M., Samitier, J. and Albertazzi, L. (2017). Tumour-vessel-on-a-chip models for drug delivery. *Lab on a Chip*, 17 3760-3771
- Sanmartí-Espinal, M., Iavicoli, P., Calò, A., Taulés, M., Galve, R., Marco, M. P. and Samitier, J. (2017). Quantification of interacting cognate odorants with olfactory receptors in nanovesicles. *Scientific Reports*, 7 (1): 17483
- Ramos, E., Pardo, W. A., Mir, M. and Samitier, J. (2017). Dependence of carbon nanotubes dispersion kinetics on surfactants. *Nanotechnology*, 28 (13): 135702
- Zaffino, R. L., Mir, M. and Samitier, J. (2017). Oligonucleotide probes functionalization of nanogap electrodes. *Electrophoresis*, 38 (21): 2712-2720

Conference Papers

- Tezanos, E., Badiola, M. and Samitier, J. (2017). 3D Bioprinted muscle on a chip. XXXV Congreso Anual de la Sociedad Española de Ingeniería Biomédica (CASEIB 2017). Valencia, Spain. Published by Sociedad Española de Ingeniería Biomédica (2017/11/23)
- Badiola, M., Hervera, A., López, J., Segura-Feliu, M., del Río, J. A. and Samitier, J. (2017). In-vitro Peripheral Nervous System on a chip. XXXV Congreso Anual de la Sociedad Española de Ingeniería Biomédica (CASEIB 2017). Valencia, Spain. Published by Sociedad Española de Ingeniería Biomédica (2017/11/23)
- Gállego, I., Manning, B., Prades, J. D., Mir, M., Samitier, J. and Eritja, R. (2017). DNA-Origami-Aided Lithography for Sub-10 Nanometer Pattern Printing. Eurosensors 2017. Paris, France. Published by MDPI (2017/07/01)

Collaborations *cont.*

- **Prof. Irene Díaz Moreno** 3IIQ-cicCartuja, Universidad de Sevilla-CSIC, Spain.
- **Prof. Miguel A. de la Rosa** 3IIQ-cicCartuja, Universidad de Sevilla-CSIC, Spain
- **Dr. María del Mar Mañú Pereira** Josep Carreras Leukaemia Research Institute, Barcelona, Spain
- **Dr. Joan Lluis Vives** Josep Carreras Leukaemia Research Institute, Barcelona, Spain

Industry partners:

- **Biokit S.A. (Werfen group); Genomica S.A.U. (Zeltia group); Tallers Fiestas S.L.; Enantia S.L.; Microfluidic ChipShop GmbH; Minifab; Microliquid**

Equipment and techniques

- Nanofabrication and nanomanipulation
  - 3D Printing system for microfluidic devices
  - Graphtech
- Characterization
  - Potentiostates
  - Optical Waveguide Lightmode Spectroscope (OWLS)
  - Atomic Force Microscope (AFM)
  - Optical Microscopes (white light/epifluorescence)
  - Electrical Impedance spectroscopy (EIS)
  - Multi-frequency Lock-in Amplifier
  - Sub-femtoamp Remote SourceMeter Instrument
- Molecular/cell biology
  - Biological safety cabinet (class II)
  - Microwell plate readers
  - Protein and DNA electrophoresis systems
  - Microincubator Okolab
  - Nanodrop spectrophotometer
  - CO2 incubator for cells: Galaxy® 48 S, 48 L, 230 V/50/60 Hz, standard
  - Cell culture cabin: Bioii-Advance 3
- Microfluidics
  - High precision syringe pumps
  - Peristaltic pumps

Smart nano-bio-devices

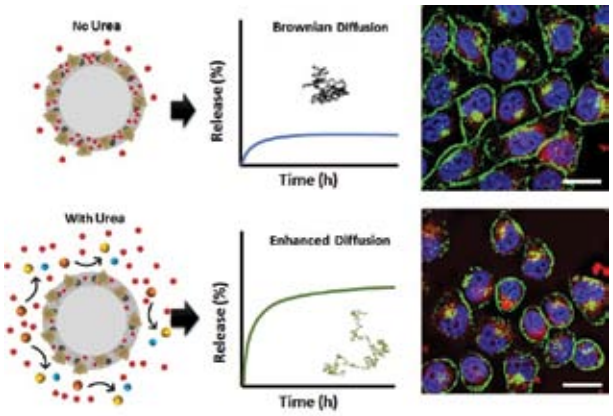
Samuel Sánchez (ICREA Research Professor)

Chemically powered micro- and nanomotors are small devices that are self-propelled by catalytic reactions in fluids.

These synthetic systems form a relatively new class of active matter, natural examples of which include flocks of birds, collection of cells and suspensions of bacteria. A number of promising applications have been envisioned for these micro-nano motors, such as targeted drug delivery, environmental remediation and as pick-up and delivery agents in lab-on-a-chip devices. These applications rely on the basic functionalities of self-propelled motors: directional motion, sensing of the local environment, and the ability to respond to external signals. Our group works on the design and study of new types of synthetic motors towards these applications and develops proof-of-concept studies to demonstrate their viability. Below are some of the projects that we are currently working on.

Enzyme powered motors: from fundamentals to biomedical applications

Enzymes trigger biocatalytic reactions, which can convert chemical energy into kinetic motion for bioprocesses, for example, intracellular protein transport. The use of enzyme catalysis is emerging as an attractive alternative to power micro- and nanomachines due to their unique features including biocompatibility, versatility and fuel bioavailability. Our group has pioneered the use of different enzymes, including urease and glucose oxidase, to generate active propulsion, opening the door to new applications in biomedicine. We have recently demonstrated that using enzyme-powered nanomotors can improve anti-cancer drug delivery *in vitro*. In addition, we are also interested in the fundamental aspects underlying the motion mechanism of biocatalytic microswimmers to be able to design efficient and safe nanomotors. (Xing Ma et al., 2016, *Journal of the American Chemical Society* 138; Xing Ma et al., 2016, *ACS Nano* 10; Ana C Hortelão et al., 2017, *Advanced Functional Materials*).



Enzymes can be coupled with synthetic nano and micro structures to create efficient, bio-compatible nanomotors.

Postdocs
Lei Wang
Mingjun Xuan
Diana Vilela
Tania Patiño
Katherine Villa
Agostino Romeo
Nerea Murillo

PhD students
Lucas Santiago Palacios
Jaideep Katuri
Ana Candida Lopes
Jemish Parmar
Rafael Mestre

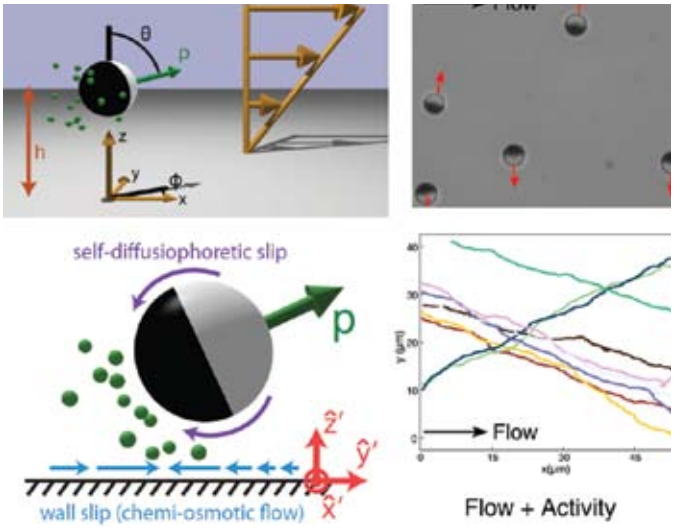
Master students
Xavi Barceló
Natàlia Salvat
Rafael Carrascosa

Lab technicians
Angel Blanco
Ariadna Pérez

Research assistants
Xavier Arqué
Albert Miguel
Shivesh Anand

Visiting researcher
DongPyo Kim

Artificial micro-swimmers respond to external shear flows.



Active matter near interfaces

We study colloidal suspensions of Pt-coated silica particles as a model system of synthetic active matter. These systems have mostly been studied in homogeneous environments until now. Our interest lies in observing these systems in more complex settings, such as near interfaces. We focus both on hard interfaces, like solid walls, and soft interfaces, such as an oil-water interface. Since the self-propelled particles generate chemical and hydrodynamic fields around them, they interact in complex ways with nearby surfaces that often leads to interesting behaviour. We could find, for instance, that close to solid surfaces they achieve a stable 'gliding' state which could be exploited to develop a system for guiding micro-nano motors using topographical features. In recent experiments we have also found that a surprising directional response emerges for these particles when exposed to an external shear flow. (Jaideep Katuri et al., 2018, *Science Advances* 4; Juliane Simmchen et al., 2016, *Nature Communications* 7; Claudio Maggi et al., 2016, *Small* 12).

Environmental applications of micro-nano motors

Artificial micromotors, based on bubble self-propulsion have demonstrated to be able to mix solutions and enhance chemical reactions while they swim. These micromotors are mostly based on two main structures, tubular and spherical.

First, we have designed tubular micromotors, which use hydrogen peroxide as a fuel, using different techniques such as, 'rolling-up' and electrodeposition. 'Rolling-up' microjets with a functional iron based layer can generate and actively transport free radicals in the solution performing the degradation of organic dyes via Fenton-like reactions in presence of hydrogen peroxide. On the other hand, electrodeposited microjets, which are smaller than their 'roll-up' counterparts, contain graphene-oxide on the outside working as 'heavy metal scrubbers'. In this case, the metal is adsorbed and removed from the contaminated water. The metal can thereafter be desorbed and the microjets used again.

In order to target other water pollution problems, such as microorganism contamination, we have developed spherical microbots that can kill bacteria while they swim. These microbots have a Janus structure based on spherical magnesium microparticles, able to dissolve in water producing hydrogen bubbles, covered in one of their faces by Fe, Au and AgNPs which provide magnetic, bacteria attachment and bactericidal properties to the microjets.

Publications

- Katuri, J., Ma, X., Stanton, M. M. and Sánchez, S. (2017). Designing micro- and nanoswimmers for specific applications. *Accounts of Chemical Research*, 50 (1): 2-11
- Stanton, M. M., Park, B.-W., Vilela, D., Bente, K., Faivre, D., Sitti, M. and Sanchez, S. (2017).Magnetotactic bacteria powered biohybrids target *E. coli* biofilms. *ACS Nano*, 11 (10): 9968-9978
- Stanton, M. M. and Sánchez, S. (2017).Pushing bacterial biohybrids to *in vivo* applications. *Trends in Biotechnology*, 35 (10): 910-913
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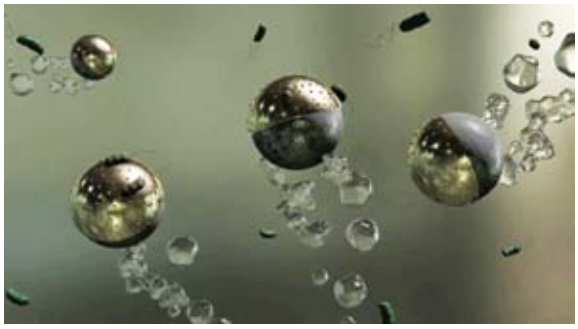
- Vilela, D., Stanton, M. M., Parmar, J. and Sánchez, S. (2017). Microbots decorated with silver nanoparticles kill bacteria in aqueous media. *ACS Applied Materials and Interfaces,* 9 (27): 22093-22100
- Vilela, D., Hortelao, A. C., Balderas-Xicohtencatl, R., Hirscher, M., Hahn, K., Ma, X. and Sanchez, S. (2017). Facile fabrication of mesoporous silica micro-jets with multi-functionalities. *Nanoscale*, 9 13990
- Ma, X. and Sánchez, S. (2017). Self-propelling micro-nanorobots: challenges and future perspectives in nanomedicine. *Nanomedicine*, 12 (12): 1363-1367
- Simmchen, J., Baeza, A., Miguel-Lopez, A., Stanton, M. M., Vallet-Regi, M., Ruiz-Molina, D. and Sánchez,

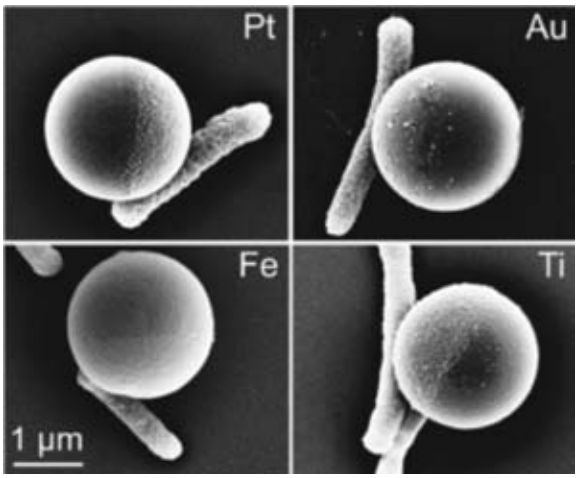


Micromotors can remove a wide variety of pollutants in contaminated water.

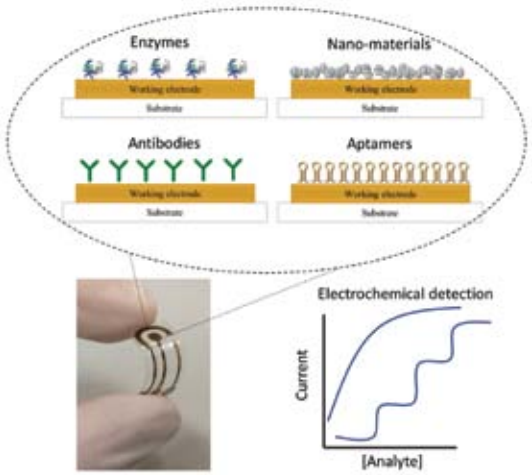
Recently, due to the necessity of scaling-up of the micromotor synthesis for cleaning large volumes of water, we have fabricated micromotors using exclusively chemical methods such as, precipitation, reduction and sol-gel chemistry. These micromotors are based on a silica microtubular structure which contains an inner-layer of a catalytic material (PtNPs or MnO2) capable of removing pollutants efficiently from water while they swim in the presence of hydrogen peroxide. The external decoration of these structures with magnetic nanoparticles provides for good magnetic control. Finally, magnetic and catalytic micromotors formed by the aggregation of cobalt ferrite nanoparticles were synthesized to remove anti-biotics from water. All these micromotors, due to their magnetic properties can be removed from the solution after finishing their targeting action by the application of an external magnetic field. (Lluís Soler et al., 2013, *ACS Nano* 7; Jemish Parmar et al., 2016, *Advanced Functional Materials* 26; Diana Vilela et al., 2016, *NanoLetters* 16; Diana Vilela et al., 2017, *ACS Appl. Mater. Interfaces* 9).

Bio-hybrid micro-nano motors

Bio-hybrid motors focus on the interaction of a motile cell with artificial materials to create a mobile system that is powered by cellular actuation. Bio-hybrids are not powered by toxic chemical fuels but by biological fluids, making them ideal for biomedical applications. They are responsive to their local environment (pH, temperature, and chemical gradients) and are capable of performing complex tasks that synthetic-only motors would not be capable of. We have coupled *E. coli* bacteria with metal capped 'Janus' colloids to create a multi-flagellated bio-hybrid system. *E.*



Bacteria can be selectively adhered to metal caps of 'Janus' colloids to create multi-flagellated bio hybrid systems.



Electrodes fabricated on flexible substrates are modified with a wide range of materials for selectivity towards biomarkers. Analytes are quickly quantified by electrochemical techniques.

S. (2017). Dynamics of novel photoactive AgCl microstars and their environmental applications. *ChemNanoMat*, 3 (1): 65-71

- Ma, X. and Sánchez, S. (2017). Bio-catalytic mesoporous Janus nano-motors powered by catalase enzyme. *Tetrahedron*, 73 (33): 4883-4886
- Parmar, J., Villa, K., Vilela, D. and Sánchez, S. (2017). Platinum-free cobalt ferrite based micromotors for antibiotic removal. *Applied Materials Today*, 9 605-611

coli adheres selectively to the metal cap of the Janus particle and the polystyrene side of the Janus particle can be used for localized drug attachment. We have also recently used tubular bio-hybrid motors powered by magnetotactic bacteria to target bio-films. (Morgan M. Stanton et al., 2017, *ACS Nano* 11; Morgan M. Stanton et al., 2017, *Small* 13; Morgan M. Stanton et al., 2016, *Advanced Materials Interfaces* 3).

Flexible bio-sensors for personalized diagnostics

Point-of-care diagnostics is a promising complementary approach to clinical diagnostics performed at hospital settings. Decentralized monitoring of health parameters allows to improve quality of life of patients, enhance therapeutic efficacy thanks to more frequent tests, and lower the overall cost of the health system. We develop flexible biochemical sensors for non-invasive, cost-effective and personalized monitoring of bio-analytes in biological fluids. We focus on sensors based on electrochemical detection, as they are particularly suited for low-cost, portable and user-friendly medical diagnostics. (Agostino Romeo et al., 2018, *Applied Materials Today* 10; Agostino Romeo et al., 2016, *Lab Chip*, 16; Diana Vilela et al., 2016, *Lab Chip* 16).

Soft hybrid bio-robotics

In the recent research line of soft hybrid bio-robotics, we explore the integration of biological tissue and artificial materials at larger length scales. In particular, we take advantage of the 3D bioprinting technique to develop bio-robotic systems composed of skeletal muscle cells embedded in biocompatible hydrogels, which can be 3D bioprinted alongside other artificial materials. These materials can act as scaffolds, support, or flexible parts, as well as be responsive upon certain stimuli. By controlling the contractions of skeletal muscle cells via electric fields, we can envisage different ways of actuation, paving the way for complex hybrid systems. (Tania Patino et al., 2016, *Lab Chip*, 1619).

Research projects

- **ENZWIM** Nanomotores de nanopartículas mesoporosas impulsados por enzimas
  PI: **Samuel Sánchez**
  MINECO Explora Ciencia / Tecnología
- **MicroDia** Sistemas Lab-on-a-chip basados en micro-nanomotores para el diagnóstico de enfermedades (2016-2018)
  PI: **Samuel Sánchez**
  MINECO, Retos investigación: Proyectos I+D
- **MICROCLEANERS** Active microcleaners for water remediation (2016-2018)
  PI: **Samuel Sánchez**
  European Research Council (ERC-PoC)
- **LT-NRBS** Lab-in-a-tube and Nanorobotic biosensors (2013-2017)
  PI: **Samuel Sánchez**
  European Research Council (ERC-StG)

Equipment and techniques

- Autolab Galvostat/potentiostat (Metrohm)
- Dynamic light scattering (Wyatt)
- Langmuir Blodgett (KSV NIMA)
- Inverted Fluorescent microscope with cell incubator, galvo stage for 3D tracking (Leica DMi8); Upright microscope (Leica)
- Video camera (1000+ fps) (Hamamatsu)
- High speed camera (10000+ fps) (Vision Research)
- CCD video camera (100fps) (Thorlabs)
- Centrifuge (Eppendorf)
- 3D BioPrinter Inkredible+ (CELLINK)
- UV- Visible spectrometer (Analytik Jena)
- 3D printer (Formlabs)
- Wave form source; Voltage amplifier (Tabor Electronics)
- DC power supply (Hameg)
- Oscilloscope (Rigol)
- Testtube heater; Eppendorf tube Shaker (Hach)
- Oxygen Plasma cleaner (Deiner Electronics)
- TOC Analyser (Analytik Jena)
- Spin coater (Laurell)
- High vacuum film deposition system (Leica Microsystems)

Equipment and techniques *cont.*

- UV irradiation system (Vilber Lourmat)
- Portable potentiostat-galvanostat and multiplexer (PalmSens)
- Sonicator (Branson)

Collaborations

- **Prof. D.P. Kim**, National Center of Applied Microfluidic Chemistry, Department of Chemical Engineering, POSTECH (Pohang University of Science and Technology), Korea
- **Prof. S. Dietrich, Dr. M. Popescu, M. Tasinkevych, Dr. W. Uspal**, Theory of Soft Condensed Matter, MPI for Intelligent Systems, Stuttgart, Germany
- **Prof. M. Sitti**, Physical Intelligence department, MPI for Intelligent Systems
- **Prof. R. Di Leonardo**, Universtità La Sapienza, Rome, Italy
- **Prof. J. Sort, Dr. Eva Pellicer**, Physics Department, Universitat Autònoma de Bellaterra (UAB), Spain
- **Dr. D. Esqué**, The School of Materials, The University of Manchester, UK
- **Dr. J. Llop**, CIC BiomaGUNE, San Sebastián, Spain
- **Prof. F. Ricci**, Dipartimento di Scienze e Tecnologie Chimiche Università di Roma Tor Vergata, Rome, Italy
- **Dr. Ll. Soler**, Institute of Energy Technologies (INTE), UPC (ETSEIB), Barcelona
- **Prof. E. Shäffer**, Center for Plant Molecular Biology (ZMBP), University of Tübingen, Germany
- **Dr. L. Albertazzi**, Nanoscopy for Nanomedicine group, IBEC (page 6)
- **Prof. J. Samitier**, Nanobioengineering group, IBEC (page 68)
- **Dr. D. Caballero**, University of Minho, Portugal
- **Prof. R. Voituriez**, CNRS/Université Pierre et Marie Curie, Paris, France
- **Dr. G. Gabriel and Prof. R. Villa**, Instituto de Microelectrónica de Barcelona, IMB-CNM (CSIC)
- **Dr. R. Artuch**, Laboratorio de enfermedades metabólicas hereditarias, Hospital Sant Joan de Déu, Barcelona.

Bacterial infections: antimicrobial therapies

Eduard Torrents

Infectious diseases constitute a tenacious and major public health problem all over the world. The emergence and increasing prevalence of bacterial strains that are resistant to available antibiotics demand the discovery of new therapeutic approaches.

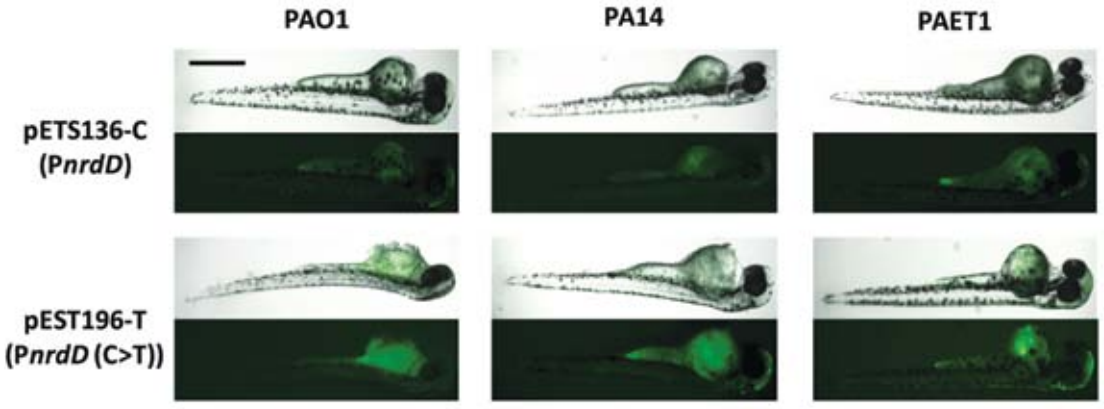
There is an urgent need for reliable and rapid detection of infecting bacteria and its pattern of resistance to antibiotics.

Our lab aims to investigate new antimicrobial therapies and strategies to combat bacterial infections with different objectives:

- to establish the molecular basis for the regulation of genes involved in DNA synthesis (ribonucleotide reductase genes), their importance in virulence and biofilm formation;
- the identification and screening of new molecules for the highly selective inhibition of new antibacterial targets (e.g. ribonucleotide reductases);
- the use of nanomedicine techniques for the development of novel and specific nanoparticles to deliver existing antibiotics or new identify antimicrobial drugs, especially when the bacteria are growing in biofilm, close to the physiological conditions of the disease and where the current chemotherapy fails;
- to study new methodologies to threat bacterial chronic infections in patients suffering cystic fibrosis;
- to develop a new type of antibacterial vaccines;
- the development of new strategies for bacterial co-culture systems;
- to study and develop models for wound healing infections and the search of novel treatments;
- the use of lab-on-a-chip technology to deeply elucidate mechanisms to combat bacterial forming biofilm as well as new approaches to identify multiresistant bacteria to different antibiotics.

We believe these projects will be beneficial to society since we explore the use of different bioengineering approaches to elucidate ways to diagnose and eradicate multi-drug resistant bacteria.

Elongated cell morphology of different *P. aeruginosa* strains under anaerobic conditions



Postdocs
Marija Vukomanovic
Maria del Mar Cendra

PhD students
Laura Moya
Maria Zimina
Núria Blanco
Lucas Pedraz
Aida Baelo

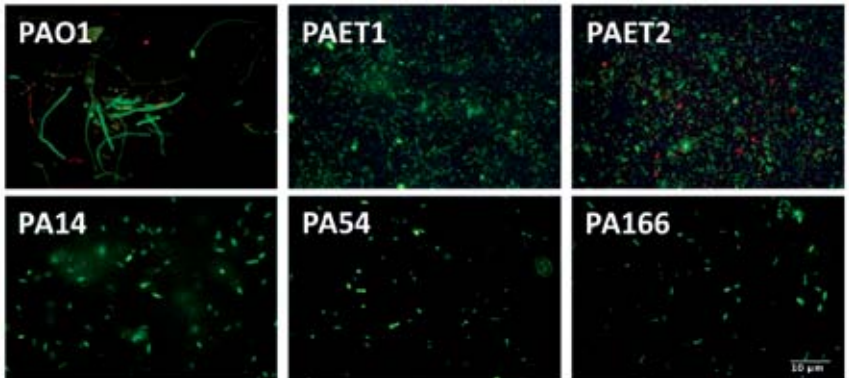
Masters students
Neus Sanfeliu
Paula Bellés
Núria Buxons
Laura De Cubas

Undergraduates
Johanna Binding
Abigayle Gill
Neus Gual

Research projects

- Ribonucleotide reductasas: una nueva diana terapéutica contra organismos patógenos en enfermos de fibrosis quística (2010-2017)
  PI: **Eduard Torrents**
  Asociación Española Fibrosis Quística/PABLO MOTOS Becas de Investigación "Pablo Motos"
- **inhibitRNR** Las ribonucleotido reductasas como una nueva diana terapéutica frente a patógenos bacterianos (2016-2018)
  PI: **Eduard Torrents**
  MINECO, Retos investigación: Proyectos I+D
- **RNRbiotic** A new strategy to combat bacterial infections (2015-2017)
  PI: **Eduard Torrents**
  Obra Social La Caixa "CAIXAIMPULSE"
- **BACTSHOT** Novel antimicrobial therapy (2016-2017)
  PI: **Eduard Torrents**
  EIT Health Head Start – Proof of Concept

Expression of different *Pseudomonas aeruginosa* ribonucleotide reductase genes in the zebrafish (*Danio rerio*) animal model of infection.



Publications

- Crespo, A., Pedraz, L., Van Der Hofstadt, M., Gomila, G. and Torrents, E. (2017). Regulation of ribonucleotide synthesis by the *Pseudomonas aeruginosa* two-component system AlgR in response to oxidative stress. *Scientific Reports*, 7 (1): 17892
- Crespo, A., Gavaldà, J., Julián, E. and Torrents, E. (2017). A single point mutation in class III ribonucleotide reductase promoter renders *Pseudomonas aeruginosa* PAO1 inefficient for anaerobic growth and infection. *Scientific Reports*, 7 (1): 13350

Conference Papers

- Morer, A., Basas, J., Colominas, S., Ratia, C., Gomis, X., Abellà, J., Torrents, E., Larrosa, N., Almirante, B. and Gavaldà, J. (2017).Actividad de la electrólisis con corriente eléctrica directa continua de bajo amperaje en infecciones por biopelículas y por microorganismos XDR Gram-negativos. XXI Congreso de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC). Málaga, Spain. Published by Elsevier (2017/05/11)

- Basas, J., Morer, A., Ratia, C., Rojo, E., Larrosa, N., Oliver, A., Cantón, R., Ferrer, R., Gomis, X., Grau, S., Vima, J., Torrents, E., Almirante, B. and Gavaldà, J. (2017).Eficacia *in vitro* e *in vivo* de distintas combinaciones antibióticas para el tratamiento nebulizado de neumonía aguda frente a clones de alto riesgo de *Pseudomonas aeruginosa*. Enfermedades Infecciosas y Microbiología Clínica. XXI Congreso de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC). Málaga, Spain. Published by Elsevier (2017/05/11)

Collaborations

- **Prof. Fernando Albericio**, Institut de Recerca Biomèdica (IRB), Barcelona, Spain
- **Dr. Elisabeth Engel**, IBEC (page 16)
- **Dr. Esther Julián**, Dept. de Genètica i de Microbiologia, Universitat Autònoma de Barcelona, Spain
- **Dr. Joan Gavaldà**, Infectious diseases, Vall d'Hebrón Hospital and Research Institute, Barcelona, Spain
- **Prof. Josep Samitier**, IBEC (page 68)
- Prof. Santiago Vazquez, Laboratori de química farmacèutica, Pharmacy Faculty, Barcelona University.
- **Prof. Gabriel Gomilla**, IBEC (page 25)
- **Prof. Vladimir Arion**, Department of Inorganic Chemistry, University of Vienna, Austria

Equipment and techniques

- Zeiss LSM 800 Confocal Laser Scanning Microscope
- Nikon Inverted Fluorescent microscope ECLIPSE Ti-S/L100
- Cell culture facilities for microbial infections
- Biological safety cabinet (class II)
- Characterization of nanoparticles/biomaterial antibacterial activity
- *Drosophila melanogaster* and *Galleria mellonella* as a model host for bacterial infections
- Continuous flow system model for bacterial biofilm development
- Single Channel Fiber-Optic Oxygen Meter with microsensor
- Gradient thermocycler (PCR)
- Molecular biology facilities
- Protein and DNA electrophoresis
- Bacterial expression systems for heterologous protein production
- Protein purification systems (FPLC; Biologic DuoFlow System; Bio-Rad)
- Technology of microbial culture facilities.
- Pressure microinjection system

Integrative cell and tissue dynamics

Xavier Trepat (ICREA Research Professor)

We aim at understanding how physical forces and molecular control modules cooperate to drive biological function.

We develop new technologies to map and perturb the main physical properties that determine how cells and tissues grow, move, invade and remodel. By combining this physical information with systematic molecular perturbations and computational models we explore the principles that govern the interplay between chemical and physical cues in living tissues.

We study how these principles are regulated in physiology and development, and how they are derailed in cancer and aging.

Making cellular forces visible

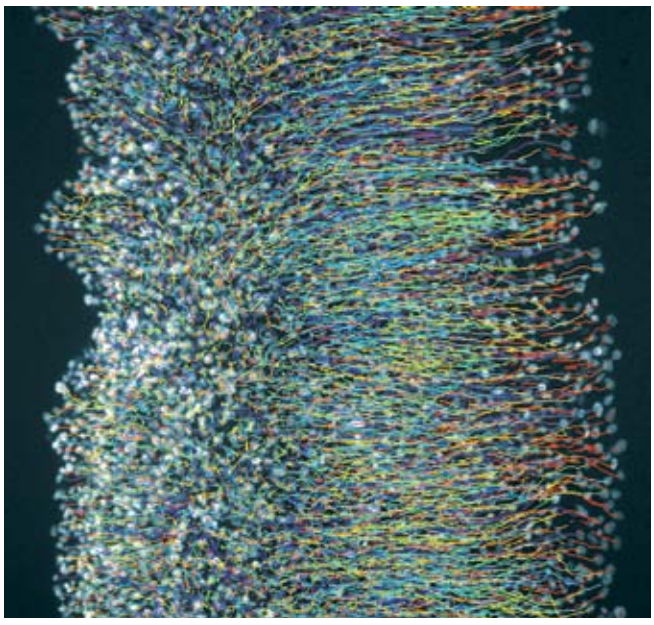
To study cell and tissue dynamics we develop new technologies to measure physical forces at the cell-cell and cell-matrix interface. By combining these technologies with computational analysis of cell shape and velocity we obtain a full experimental characterization of epithelial dynamics during tissue growth, wound healing and cancer cell invasion.

Tumour invasion by stromal forces

Cancer cell invasion and metastasis remain the leading cause of death in patients with cancer. Both processes are the result of a complex interaction between tumor cells and their microenvironment. One of our main lines of research is to study how tumours exploit the functions non-cancer cells in their microenvironment to invade and metasize. We focus on the interaction between epithelial cancer cells and Cancer Associated Fibroblasts (CAFs), the most abundant cell type in the tumour stroma. In a recent study we were able to demonstrate that CAFs guide the collective invasion of cancer cells through a physical force. This force enables CAFs to physically drag cancer cells into the surrounding tissue. Force transmission is mediated by a heterotypic interaction between two different proteins, one located on the surface of cancer cells called E-cadherin, and another expressed on the surface of fibroblasts, called N-cadherin.

Optogenetics to control cell mechanics

The recent development of optogenetic technologies offers promising possibilities to control signalling pathways with high spatiotemporal resolution. By expressing genetically encoded light-sensitive proteins, optogenetic technology enables the reversible perturbation of intracellular biochemistry with subcellular



A group of human mammary epithelial cells expands asymmetrically on a surface of increasing rigidity (towards the right of the image). Colored lines correspond to the tracks followed by each cell (gray dots) for 10h.

Senior researcher
Dobryna Zalvidea

Postdocs
Leone Rossetti
Manuel Gómez
Raimon Sunyer
Anna Labernadie

PhD students
Nimesh Chahare
Ariadna Marin
Sabrina Wistorf
Macià Esteve Pallares
Ernest Latorre
Carlos Pérez
Marina Uroz

Senior technician
Natalia Castro

Research assistants
Maria Eleni Naoum
Sefora Conti

Visiting researchers
Andrea Malandrino
Jonel Trebicka

resolution. We have developed optogenetic tools based on controlling the activity of endogenous RhoA to upregulate or downregulate cell contractility. We have shown that these tools enable rapid, local and reversible changes in traction forces, cell–cell forces, and tissue compaction. We have shown, further, that changes in cellular forces are paralleled by translocation of the transcriptional regulator YAP, indicating that our tools can be used to control mechanotransductory pathways.

Collective durotaxis: a mechanism for cellular guidance by mechanical cues

Directed cell migration is one of the earliest observations in cell biology, dating back to the late XIX century. Also known as taxis, directed cell migration has been commonly associated with chemotaxis, i.e. the ability of a broad variety of cell types to migrate following gradients of chemical factors. We recently demonstrated a new mode of collective cell guidance by mechanical cues, called collective durotaxis. This new migration mode emerges only in cell collectives and, strikingly, does not require isolated cells to exhibit gradient sensing. To study the mechanisms behind this phenomenon, we developed new tools to measure the forces that propel cells during durotaxis at the cell-matrix and cell-cell levels. Upon combining this new experimental technique with biochemical approaches and theoretical modelling, we concluded that collective durotaxis originates from long-range transmission of contractile intercellular forces. This mechanism is unique in that the very same machinery that senses the attractant -the actomyosin cytoskeleton- is responsible for propulsion towards it. As such, collective durotaxis appears to be the simplest and perhaps most primitive mechanism by which a collective system responds to a gradient.

Microfabrication and wound healing

Using microfabrication technologies, we designed new ways to decipher the mechanisms of wound healing. By doing so we uncovered a new understanding of how cells move and work together to close a gap in a tissue. We showed that a new mechanism applies in which cells assemble supracellular contractile arcs that compress the tissue under the wound. By combining experiments and computational modeling, we showed that contractions arising from these arcs make the wound heal in a quicker and more robust way.

Fracking epithelial layers

Epithelial sheets must be malleable enough to adopt functional shapes during morphogenesis and to quickly self-repair after damage. Yet, they must be resilient enough to ensure organ compartmentalization and to protect organisms against environmental pathogens. To study the mechanisms that regulate this fine balance between malleability and integrity we develop tools to map epithelial tension during tissue stretching. By combining these tools with computational modeling we determined the mechanisms of epithelial fracture. Intriguingly, one of such mechanisms is hydraulic fracturing or “fracking”.

Publications

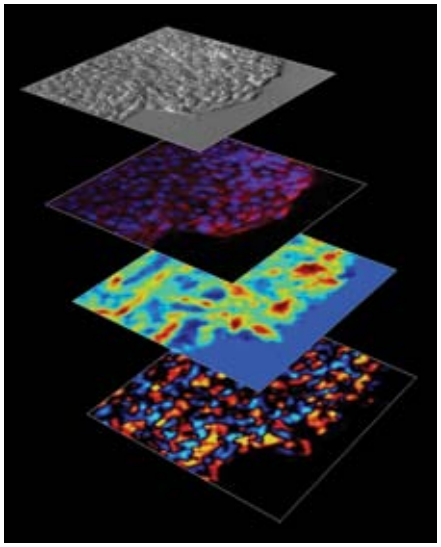
- Oria, R., Wiegand, T., Escribano, J., Elosegui-Artola, A., Uriarte, J. J., Moreno-Pulido, C., Platzman, I., Delcanale, P., Albertazzi, L., Navajas, D., Trepat, X., García-Aznar, J. M., Cavalcanti-Adam, E. A. and Roca-Cusachs, P. (2017). Force loading explains spatial sensing of ligands by cells. *Nature*, 552 219-224
- Rodriguez-Franco, P., Brugués, A., Marin-Llaurado, A., Conte, V., Solanas, G., Batlle, E., Fredberg, J. J., Roca-Cusachs, P., Sunyer, R. and Trepat, X. (2017). Long-lived force patterns and deformation waves at repulsive epithelial boundaries. *Nature Materials*, 16 (10): 1029-1036
- Malinverno, C., Corallino, S., Giavazzi, F., Bergert, M., Li, Q., Leoni, M., Disanza, A., Frittoli, E., Oldani, A., Martini, E., Lendenmann, T., Deflorian, G., Beznoussenko, G. V., Poulikakos, D., Ong, K. H., Uroz, M., Trepat, X., Parazzoli, D., Maiuri, P., Yu, W., Ferrari, A., Cerbino, R. and Scita, G. (2017). Endocytic reawakening of motility in jammed epithelia. *Nature Materials*, 16 587–596
- Elosegui-Artola, A., Andreu, I., Beedle, A. E. M., Lezamiz, A., Uroz, M., Kosmalska, A. J., Oria, R., Kechagia, J. Z., Rico-

Lastres, P., Le Roux, A. L., Shanahan, C. M., Trepat, X., Navajas, D., Garcia-Manyes, S. and Roca-Cusachs, P. (2017). Force triggers YAP nuclear entry by regulating transport across nuclear pores. *Cell*, 171 (6): 1397-1410

- Roca-Cusachs, P., Conte, V. and Trepat, X. (2017). Quantifying forces in cell biology. *Nature Cell Biology*, 19 (7): 742-751
- Labernadie, A. et al (2017). A mechanically active heterotypic E-cadherin/N-cadherin adhesion enables fibroblasts to drive cancer cell invasion. *Nature Cell Biology*, 19 (3): 224-237
- Valon, L., Marín-Llauradó, A., Wyatt, T., Charras, G. and Trepat, X. (2017). Optogenetic control of cellular forces and mechanotransduction. *Nature Communications*, 8 14396
- Arroyo, M. and Trepat, X. (2017). Hydraulic fracturing in cells and tissues: fracking meets cell biology. *Current Opinion in Cell Biology*, 44 1-6
- Blanch-Mercader, C., Vincent, R., Bazellières, E., Serra-Picamal, X., Trepat, X. and Casademunt, J. (2017). Effective viscosity and dynamics of spreading epithelia: a solvable model. *Soft Matter*, 13 (6): 1235-1243
- Castellanos, M. I. et al (2017). Functionalization of CoCr surfaces with cell adhesive peptides to promote HUVECs adhesion and proliferation. *Applied Surface Science*, 393 82-92

Publications by visiting researchers

- Trebicka, J. and Gluud, L. L. (2017). Reply to: "Adding embolization to TIPS implantation: A better therapy to control bleeding from ectopic varices?"



Our lab has developed techniques to simultaneously map cell velocities, cytoskeletal structure, intercellular stresses, and cell-substrate tractions (from top to bottom).

Research projects

- **TENSIONCONTROL** Multiscale regulation of epithelial tension (2015-2019)
  PI: **Xavier Trepat**
  European Research Council - CoG
- **DUROTAXIS** Mecanobiología de la durotaxis: de las células aisladas a los tejidos
  PI: **Xavier Trepat**
  MINECO /Nacional /Proyectos I+D Excelencia
- Understanding and measuring mechanical tumor properties to improve cancer diagnosis, treatment, and survival: Application to liquid biopsies (2017-2020)
  PI: **Xavier Trepat**
  Obra Social La Caixa
- **CAMVAS** Coordination and migration of cells during 3D Vasculogenesis (2014-2017)
  PI: **Xavier Trepat**
  MARIE CURIE - IOF

Collaborations

- Julien Colombelli / Eduard Batlle Institute for Research in Biomedicine (IRB) Barcelona
- Marino Arroyo Universitat Politècnica de Catalunya, Barcelona
- Guillaume Charras / Roberto Mayor University College London, UK
- Erik Sahai Cancer Research, UK
- Benoit Ladoux Université Paris 7, France
- Jim Butler / Jeff Fredberg Harvard University, Boston
- Danijela Vignjevic Institut Curie, Paris

Equipment and techniques

- Soft Lithography
- Micro/Nano fabrication
- Cell stretching
- Live Confocal Microcopy
- Magnetic Tweezers
- Magnetic Twisting Cytometry
- Monolayer stress microscopy
- Traction microscopy

Journal of Hepatology, 67 (1): 202-203

- Jansen, C., Thiele, M., Verlinden, W., Krag, A., Francque, S. and Trebicka, J. (2017). Prediction of presence of oesophageal varices just by shear-wave elastography of the liver and spleen. *Liver International*, 37 (9): 1406-1407
- Reiberger, T. and Trebicka, J. (2017). New liver – Fresh microbiome: Implications on brain function. *Liver Transplantation*, 23 (7): 873-874
- Schierwagen, R., Uschner, F. E., Magdaleno, F., Klein, S. and Trebicka, J. (2017). Rationale for the use of statins in liver disease. American *Journal of Physiology - Gastrointestinal and Liver Physiology*, 312 (5): G407-G412
- Beiert, T. et al (2017). Relaxin reduces susceptibility to post-infarct atrial fibrillation in mice due to anti-fibrotic and anti-inflammatory properties. *Biochemical and Biophysical Research Communications*, 490 (3): 643-649
- Schwab, S. et al (2017). Influence of genetic variations in the SOD1 gene on the development of ascites and spontaneous bacterial peritonitis in decompensated liver cirrhosis. *European Journal of Gastroenterology and Hepatology*, 29 (7): 800-804

Book Chapter

- Klein, S., Schierwagen, R., Uschner, F. E. and Trebicka, J. (2017). Mouse and rat models of induction of hepatic fibrosis and assessment of portal hypertension. In: *Fibrosis (Methods in Molecular Biology)* (ed. Rittié, L.). New York, USA, Humana Press. 1627: 91-116

Synthetic, Perceptive, Emotive and Cognitive Systems

Paul Verschure (ICREA Research Professor)

SPECS uses synthetic methods to study and synthesize the neuronal, psychological and behavioural principles underlying perception, emotion, and cognition.

SPECS activities are organized around three complementary dimensions:

- Theory of mind and brain
- Biomimetic real-world artefacts
- Brain repair and quality of life technologies

SPECS is also very much involved in the development of scientific co-operation in the field of Biomimetics and Neurotechnology, as well as in Educational and Outreach activities.

Cognitive Systems Laboratory

The Cognitive Systems Laboratory is a multidisciplinary environment that supports research in the following areas:

- Distributed Adaptive Control
- Multi-robot exploration and coordination
- Classical conditioning, operant conditioning and learning models based on the Distributed Adaptive Control framework, which has become a standard in the field of artificial intelligence and behavior-based robotics (McFarland and Bosser, 1993; Hendriks-Jansen, 1996; Arkin, 1998; Pfeifer and Scheier, 1999; Clancey 1996; Cordeschi, 2002).

Robotic Systems Laboratory

The Robotic Systems Laboratory is a multidisciplinary environment that supports research in the following areas:

- Classical conditioning, operant conditioning and learning models based on the Distributed Adaptive Control framework, which has become a standard in the field of artificial intelligence and behavior-based robotics

NeuroRobotics programme for secondary school students

Senior researcher
Anna Mura

Postdocs
Xerxes Arsiwalla
Riccardo Zucca

PhD students
Dina Urikh
Sock Low
Maria Blancas
Martina Maier

Masters student
Marlene Weller

Lab technicians
Sytse Baldwin
Wierenga

Research assistants
Giovanni Maffei
Daniel Pacheco
Diogo Pata

- Multi-robot exploration and coordination
- Navigation in human and animal behavior
- Implementation in robots of brain models of the hippocampus, cerebellum, thalamus/cortex
- Rule learning VR robots/avatars
- Fast and reliable insect-based visual navigation models for flying vehicles
- Investigation of the neuronal substrates of chemical sensing and their application to odor discrimination and localization

Hybrid Systems laboratory (HLB)

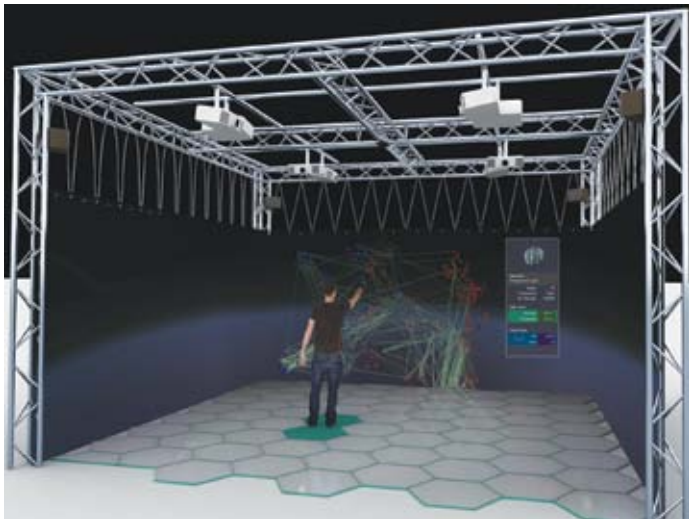
The HLB is primarily involved in the development, implementation, and analysis of machine-brain-machine interfaces. The interdisciplinary nature of the study of hybrid systems lies at the intersection of different research areas, namely:

- computational neuroscience
- electronics
- robotics
- artificial intelligence
- neuromorphic engineering

The HLB was involved in the ReNaChip FP7 project, whose overarching goal is to build s neuroprosthetic neuromorphic chip recovering a learning function lost in the aged cerebellum.

Digital Heritage

By using advanced digital humanities technologies, and making it accessible online, we can conserve, develop and preserve the



XIM - The eXperience Induction Machine

memory of Europe's cultural heritage, and in particular the Holocaust, for future generations.

Existing memorial sites or museums offer a traditional historiographical approach. We propose to use virtual and augmented reality techniques to reconstruct sites of WW-II crimes and their interrelated structures. SPECS's approach combines virtual and augmented reality with integrated databases of graphical reconstructions and historical sources to allow us to actively explore and try to comprehend the incomprehensible: the massive scale of the crimes Nazi Germany perpetrated on the world and the depth of the destruction and suffering it caused.

The SPECS research group has been pioneering this approach over the last 15 years and grounded it in its fundamental research in psychology and neuroscience. In collaboration with the Bergen-Belsen memorial site and Prof. Habbo Knoch, this paradigm has been elaborated to conserve and present the history of the Bergen Belsen concentration camp.

Educational Robotics

Technology evolves and advances faster than ever in all aspects of our society. Thus, it is important that the next generations of students learn as much as possible about emerging technology and stay competitive.

SPECS contributes to the education of the next generations by combining platforms for training and outreach activities, facilitating multidisciplinary education and innovation by sharing the value of convergent science, excellence, and societal impact. We have developed Educational Robotics programs for students of the primary and secondary school, as well as courses to train teachers and young adults.

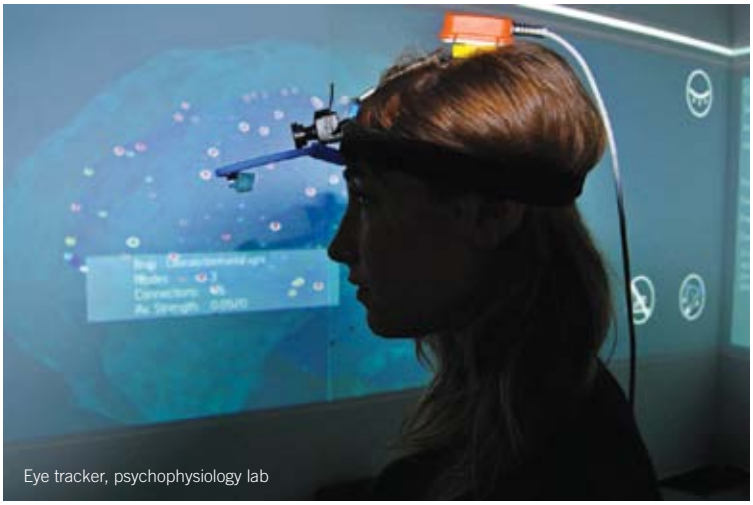
Interaction Technology

There is a growing interest in understanding creativity from a more neuroscientific point of view, so to say, to disclose the neural basis of creativity we will need great insights on how the brain elaborates the process of human thought.

Our approach to understanding the process of creativity is to use Art & Technology to create high impact, sophisticated man-machine interaction tools.

- Narrative in interactive mixed reality environment

A stroke patient training with SPECS' Rehabilitation Gaming System under the supervision of her physician/physiotherapist at Val d'Hebron Hospital in Barcelona



Eye tracker, psychophysiology lab

- Multimedia installations: affect-based self-generated media content

Mixed-reality lab

The Mixed-reality lab serves a threefold research agenda:

- Understand human behavior in a mixed-reality context
- Build mixed-reality applications based on neurobiological understanding and methodologies see iqr and Brainx3
- Test neurobiological models by deploying them in control of mixed-reality systems

Neuro-Rehabilitation

Over the past 15 years, SPECS has been developing science-based technology tools to drive perceptual, cognitive, affective and motor systems of the brain to facilitate functional recovery after damage. By means of novel interaction paradigms such as Virtual Reality or music therapy, and based on the Distributed Adaptive Control theory of mind and brain DAC developed by Paul Verschure, SPECS studies the brain and the mechanisms underlying loss of function and its rehabilitation and recovery after stroke, and other brain diseases (see Verschure *Conf Proc IEEE Eng Med Biol Soc*. 2011, Mónica S. Cameirão et al. *Restor Neurol Neurosci* 2011 and *Stroke* 2012)

Psychophysiology lab

The Psychophysiology lab studies how humans react to various uni- and multisensory signals – visual, auditory and tactile stimuli. We assess human responses at different levels using subjective ratings, behavioral data, physiological and brain wave recordings. This data helps us to understand human perception and cognition mechanisms, with particular stress on the novel methods for diagnosis and treatment of various brain disorders (chronic pain, migraine, autism, depression, Alzheimer's disease).

- affective chronometry (such parameters as the rise time to peak and the recovery time of the emotional waveform)
- multisensory perception (sound, vision, touch)
- multisensory interactions for emotional stimuli (custom sound and video databases are created)
- sonification of EEG signals
- neurofeedback using mixed reality environments processing of eye-gaze in autistic children

Publications

- Maffei, G., Herreros, I., Sanchez-Fibla, M., Friston, K. J. and Verschure, P. F. M. J. (2017). The perceptual shaping of anticipatory actions. *Proceedings of the Royal Society B*, 284 (1869)
- Pacheco, D., Sánchez-Fibla, M., Duff, A. and Verschure, P. F. M. J. (2017). A spatial-context effect in recognition memory. *Frontiers in Behavioral Neuroscience*, 11 Article 143
- Hindriks, R., Schmiedt, J., Arsiwalla, X. D., Peter, A., Verschure, P. F. M. J., Fries, P., Schmid, M. C. and Deco, G. (2017).Linear distributed source modeling of local field potentials recorded with intra-cortical electrode arrays. *PLOS ONE*, 12 (12): e0187490
- Santos-Pata, D., Zucca, R., Low, S. C. and Verschure, P. F. M. J. (2017). Size matters: How scaling affects the interaction between grid and border cells. *Frontiers in Computational Neuroscience*, 11 Article 65
- Ballester, R. B., Nirme, J., Camacho, I., Duarte, E., Rodríguez, S., Cuxart, A., Duff, A. and Verschure, F. M. J. P. (2017). Domiciliary VR-based therapy for functional recovery and cortical reorganization: Randomized controlled trial in participants at the chronic stage post stroke. *JMIR Serious Games*, 5 (3): e15

Conference paper

- Moulin-Frier, C., Puigbò, J.-Y., Arsiwalla, X. D., Martì Sanchez-Fibla, M. and Verschure, P. F. M. J. (2017). Embodied artificial intelligence through distributed adaptive control: An integrated framework. 7th Joint IEEE International Conference on Development and Learning and on Epigenetic Robotics (ICDL-Epirob 2017). Lisbon, Portugal. Published by IEEE (2017/09/18)

Book chapter

- Puigbò, J.-Y., Gonzalez-Ballester, M. Á. and Verschure, P. F. M. J. (2017). Behavior-state dependent modulation of perception based on a model of conditioning. In: *Biomimetic and Biohybrid Systems: Living Machines 2017 (Lecture Notes in Computer Science)* (ed. Mangan, M., Cutkosky, M., Mura, A.et al), Springer, Cham. 10384: 387-393

Spin-offs

- **Eodyne** is an R+D company specialised in advanced interactive systems and technologies for virtual and augmented reality, ambient and wearable sensors, robotics, machine perception, cognitive processes and user experience. Eodyne's flagship product is the Rehabilitation Gaming System (RGS), a science-based neuro-rehabilitation solution for the integrated treatment of deficits resulting from brain damage.

Research projects

- **CDAC** The role of consciousness in adaptive behavior: A combined empirical, computational and robot-based approach (2014-2019)
  PI: **Paul Verschure**
  ERC Advanced Grant
- **iC-ACCESS** Accessing Campscapes: Inclusive Strategies for Using European Conflicted Heritage (2016-2019)
  PI: **Paul Verschure**
  HERA Joint Research Programme Uses of the Past, REFLECTIVE-1-2014
- **socSMCs** Socialising Sensori-Motor Contingencies (2015-2018)
  PI: **Paul Verschure**
  Future Emerging Technologies (FET), H2020
- **WYSIWYD** What You Say Is What You Did (2014-2017)
  PI: **Paul Verschure**
  FP7-ICT-2013-10, grant agreement n° 612139
- **EASEL** Expressive Agents for Symbiotic Education and Learning (2013-2017)
  PI: **Paul Verschure**
  FP7-ICT-2013-10, grant agreement n° 611971
- DAC-CHM Distributed Adaptive Control of Consciousness in Humans and Machines (2017-2020)
  PI: **Paul Verschure**
  MINECO, Retos investigación: Proyectos I+D
- **INSOCO** Social interaction based on sensorimotor contingencies (2015-2018)
  PI: **Paul Verschure**
  MINECO
- **SANaR** Smart Autonomous Neuro-Rehabilitation System
  PI: **Paul Verschure**
  MINECO, Retos Investigación 2013
- **TECNIO** (2016-2019)
  PI: **Paul Verschure**
  Generalitat of Catalonia

Equipment and techniques

- EXperience Induction Machine (XIM), an immersive room equipped with a number of sensors and effectors that have been constructed to conduct experiments in mixed-reality.
- Robotics lab
- Codi-Bot, the musical robot that teaches you how to program
- iqr: simulator for large-scale neural systems
- Collective machine cognition: Autonomous dynamic mapping and planning using a hybrid team of aerial and ground-based robots
- Humanoid robots: iCub
- Quality of Life Technologies

Associated Researchers

Publications

Alícia Casals

- Aviles, A. I. et al (2017). Robust cardiac motion estimation using ultrafast ultrasound data: A low-rank topology-preserving approach. *Physics in Medicine and Biology*, 62 (12): 4831-4851
- Aviles, A. I. et al (2017). Towards retrieving force feedback in robotic-assisted surgery: A supervised neuro-recurrent-vision approach. *IEEE Transactions on Haptics*, 10 (3): 431-443

Maria-Pau Ginebra

- Hoyos-Nogués, M. et al (2017). Regenerating bone via multifunctional coatings: The blending of cell integration and bacterial inhibition properties on the surface of biomaterials. *ACS Applied Materials and Interfaces*, 9 (26): 21618-21630
- Barba, A. et al (2017). Osteoinduction by Foamed and 3D-Printed Calcium Phosphate Scaffolds: Effect of Nanostructure and Pore Architecture. *ACS Applied Materials and Interfaces*, 9 (48): 41722-41736
- O'Neill, R. et al (2017). Critical review: Injectability of calcium phosphate pastes and cements. *Acta Biomaterialia*, 50 1-19
- Maazouz, Y. et al (2017). Self-hardening and thermoresponsive alpha tricalcium phosphate/ pluronic pastes. *Acta Biomaterialia*, 49 563-574

Associated researchers are university professors seconded to IBEC with an agreement signed between their university and the institute who are based in the university premises and working on topics that are of interest or complementary to our research areas.

They participate in IBEC's scientific strategy, academic activities and support initiatives, and have the option to submit project proposals and papers with IBEC affiliation.

Recruitment is carried out according to several criteria such as scientific excellence and alignment with IBEC's institutional strategy. Associated researchers are approved by the International Scientific Committee, which evaluates their performance on a regular basis.

Marino Arroyo (UPC)

Marino Arroyo is Full Professor at the Universitat Politècnica de Catalunya (UPC), where he is a member of the Laboratory of Computational Methods and Numerical Analysis (LaCaN) group.

Before joining the UPC, he obtained a PhD from Northwestern University, was a postdoctoral scholar at the California Institute of Technology (Caltech) and a long-term visitor at the Institute for the Mathematics and its Applications (University of Minnesota). He has been awarded the O. C. Zienkiewicz Award for Young Scientists in Computational Engineering Sciences by ECCOMAS (2010), two ICREA Academia Awards (2009, 2015), and the ASME/BOEING Structures and Materials Award (2003). He has also been the Timoshenko Visiting Scholar at Stanford. He was awarded a ERC-Starting in 2009 and a ERC-Consolidator Grant in 2016. In 2016 he came third, alongside IBEC group leader and ICREA research professor Xavier Trepat, in the La Vanguardia Science Award for their groups' research that was published in Nature Materials.

His research goal is to develop theories and computational methods to understand the small-scale mechanics of materials and biological systems, with a recent emphasis on cell and tissue mechanobiology and bio-inspired materials.

Ralph G. Andrzejak (UPF) | Marino Arroyo (UPC) | Alícia Casals (UPC) | Maria-Pau Ginebra (UPC) | Antonio Juárez (UB)

Ralph G. Andrezejak (UPF)

Ralph G. Andrzejak is director of the Nonlinear Time Series Analysis Group at the Department of Information and Communication Technologies at the Universitat Pompeu Fabra, Barcelona. His department has recently been awarded as a "Maria de Maeztu Unit of Excellence" by the Spanish Ministry of Economy and Competitiveness (MINECO).

He pursues two parallel research tracks. On the one hand, he develops innovative nonlinear signal analysis techniques. These techniques aim, for example, at the detection of non-random structure in complex dynamics or the characterization of interactions in networks of dynamics. On the other hand, he applies these techniques to real-world biomedical signals. Here an emphasis is placed on different types of electrophysiological recordings from epilepsy patients.

Prof. Andrzejak was born in Germany and has a degree and PhD in physics (University Bonn, Germany). During his career he was affiliated with the Neurophysics group of K. Lehnertz and C.E. Elger (Department of Physics and Department of Epileptology, University Bonn, Germany), the Neurodynamics research group of S.J. Schiff (George Mason University, Fairfax, USA), the Complex Systems research group of P. Grassberger (Research Centre Jülich, Germany), and the Computational Neuroscience group of G. Deco at the Department of Information and Communication Technologies at the Universitat Pompeu Fabra. Since 2011, he is a tenured associate professor at this Department.

Some 60 publications of Ralph G. Andrzejak in leading journals of physics, neuroscience, neurology, and engineering are indexed in the ISI Web of Science. This work receives more than 2400 citations (h-index: 23; ISI Researcher ID: H-7923-2012). In Google Scholar the publications of Prof. Andrzejak reach more than 4500 citations (h-index: 30). He is principal investigator of several prestigious research projects receiving funding from Spanish, German and European Institutions.

- Diez-Escudero, A. et al (2017). *In vitro* degradation of calcium phosphates: Effect of multiscale porosity, textural properties and composition. *Acta Biomaterialia*, 60 81-92
- Ciapetti, G. et al (2017). Osteoclast differentiation from human blood precursors on biomimetic calcium-phosphate substrates. *Acta Biomaterialia*, 50 102-113
- Canal, C. et al (2017). Plasma-induced selectivity in bone cancer cells death. *Free Radical Biology and Medicine*, 110 72-80
- Schieber, R. et al (2017). Direct laser interference patterning of CoCr alloy surfaces to control endothelial cell and platelet response for cardiovascular applications. *Advanced Healthcare Materials*, 6 (19): 1700327
- Fraioli, R. et al (2017). Towards the cell-instructive bactericidal substrate: Exploring the combination of nanotopographical features and integrin selective synthetic ligands. *Scientific Reports*, 7 (1): 16363
- Sadowska, J. M. et al (2017). Biomimetic versus sintered calcium phosphates: The *in vitro* behavior of osteoblasts and mesenchymal stem cells. *Tissue Engineering Part A*, 23 (23-24): 1297-1309
- Diez-Escudero, A. et al (2017). Focus ion beam/scanning electron microscopy characterization of osteoclastic resorption

of calcium phosphate substrates. *Tissue Engineering Part C: Methods*, 23 (2): 118-124

- Castellanos, M. I. et al (2017). Functionalization of CoCr surfaces with cell adhesive peptides to promote HUVECs adhesion and proliferation. *Applied Surface Science*, 393 82-92
- Castellanos, M. I. et al (2017). Cell adhesive peptides functionalized on CoCr alloy stimulate endothelialization and prevent thrombogenesis and restenosis. *Journal of Biomedical Materials Research - Part A*, 105 (4): 973-983

Antonio Juárez

- Matalonga, J. et al (2017). The nuclear receptor LXR limits bacterial infection of host macrophages through a mechanism that impacts cellular NAD metabolism. *Cell Reports*, 18 (5): 1241-1255
- Juarez, A. et al (2017). Nutrient starvation leading to triglyceride accumulation activates the Entner Doudoroff pathway in Rhodococcus jostii RHA1. *Microbial Cell Factories*, 16 35
- Venkova, T. et al (2017). Editorial: Modulating prokaryotic lifestyle by DNA-binding proteins: Learning from (apparently) simple systems. *Frontiers in Molecular Biosciences*, 3 Article 86
- Espinosa, M., Juarez, A. and Venkova, T. Modulating prokaryotic lifestyle by DNA-binding proteins. Lausanne, Switzerland. *Frontiers in Molecular Biosciences*

Ralph G. Andrzejak

- Malvestio, I., Kreuz, T. and Andrzejak, R. G. (2017). Robustness and versatility of a nonlinear interdependence method for directional coupling detection from spike trains.

Alícia Casals (UPC)

From 2008-2015, **Alícia Casals** led the Robotics group at IBEC.

While at IBEC she began a spin-off company with the UPC, Rob Surgical Systems, which aims to develop a minimally invasive robotic station for surgery, Bitrack, and also worked alongside researchers at the Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau and at the UPC on the development of Surgitrainer, a training platform for laparoscopic surgery. The group was awarded European funding for projects such as HYPER, which aims to develop new treatments in neurorehabilitation and help with patients' mobility, and RecerCaixa funding for InHANDS ("Robòtica interactiva per a l'assistència humana en l'entorn domèstic") and "Desenvolupament d un sistema robòtic de baix cost d ajut a la rehabilitació de la marxa per a nens amb transtorns motors greus".

Alícia was recognized for her work as a research scientist in the "16 Científiques Catalanes" exhibition being organized by the Associació Catalana de Comunicació Científica in 2010, and immortalised as a notable representative of the field of industrial engineering in the educational card game "La paciència és la mare de la ciència" by IEC's Secció de Ciències i Tecnologia, and in 2015 she received a 2015 fem.talent Award at the fem. talent Fòrum in Barcelona.

Maria-Pau Ginebra (UPC)

Maria-Pau Ginebra is Full Professor in the Department of Materials Science and Metallurgy and director of the Biomaterials Division of the Research Centre for Biomedical Engineering at the Technical University of Catalonia (UPC) in Barcelona, Spain, where she leads the Research group on Biomaterials, Biomechanics and Tissue Engineering. She has received numerous awards, amongst them the ICREA Academia Award in 2008 and 2013 and the Narcis Monutriol Medal in 2012 from the Generalitat de Catalunya, and the Racquel LeGeros Award, from the International Society for Ceramics in Medicine, for her contribution to calcium phosphate research, in 2013.

Her research interests include the design and development of new biomaterials for bone regeneration, bone tissue engineering and drug delivery. Her research team has made significant contributions in the processing and characterisation of a new generation of calcium phosphate-based materials which mimic bone extracellular matrix, including calcium phosphate cements and foams, incorporating synthetic or natural polymers, and/or biologically active molecules. She is involved also in new biofabrication strategies, including injectable scaffolds for bone tissue engineering, bioinspired substrates and 3D printing of regenerative medical implants.

She has been involved in numerous national and European research projects and participated in the organisation of scientific events in the area of biomaterials and bioceramics. She is author of more than 150 articles in peer-reviewed International journals as well as of 9 patents. In 2013 she founded the spin-off company Subtilis Biomaterials.

Antonio Juárez (UB)

From 2007-2015, **Antonio Juárez** led the Microbial Biotechnology and Host-pathogen Interaction group at IBEC. The group's focus was the protein–protein and protein–DNA interactions that play key roles in the ability of virulent bacteria to adapt to the host environment and cause disease, with a particular interest in finding ways to tackle the resistance of bacteria to antibiotics.

During his time at IBEC, he and colleagues from the UB and IRB identified the strategy used by enterobacteria to acquire resistance and pathogenicity (Baños, R.C. et al. (2009), *PLoS Genet*), and worked together with IBEC's Nanoscale Bioelectrical Characterization group to demonstrate the potential of electrical studies of single bacterial cells (Esteban-Ferrer, D. et al., (2014), *ACS Nano*).

The group also embarked on a technology transfer venture together with two biopharmaceutical companies, CZV Veterinaria and MEVET, to obtain strains of Salmonella with weakened virulence, which can then be used to develop a vaccine to reduce the incidence of the infection in poultry farms.

Physical Review E, 96 (2): 022203

- Laiou, P. and Andrzejak, R. G. (2017). Coupling strength versus coupling impact in nonidentical bidirectionally coupled dynamics. *Physical Review E*, 95 (1): 012210
- Andrzejak, R. G., Ruzzene, G. and Malvestio, I. (2017). Generalized synchronization between chimera states. *Chaos: An Interdisciplinary Journal of Nonlinear Science*, 27 (5): 053114
- Leguia, M. G., Andrzejak, R. G. and Levnajić, Z. (2017). Evolutionary optimization of network reconstruction from derivative-variable correlations. *Journal of Physics A: Mathematical and Theoretical*, 50 (33): 334001

Services

Core Facilities

Core Facilities

Isabel Oliveira

IBEC provides its researchers with extensive research facilities and a scientific–technical infrastructure distributed over interdisciplinary open lab spaces. It is designed and managed to facilitate research and promote the cooperation and exchange of knowledge between IBEC scientists from different fields of expertise.

In this way, researchers share not only the space itself but also the equipment, bench space, and qualified technical staff, thereby helping to reduce research costs.

The fact of sharing spaces and resources shouldn't be an issue in the day-to-day of our researchers. An important part of the work of IBEC Core Facilities is to manage and facilitate this challenging and crucial point. To achieve this, the standardization of some of the daily operations and general organization of the laboratories of the Institute has been established.

During 2017, IBEC Core Facilities were reorganized into six blocks: Labs Layout and Logistics; Common Core Basics; BioSpace Lab; ChemSpace Lab; MicroFabSpace Lab; Microscopy Characterization Facility.

Labs Layout and Logistics

2017 has been a year of great growth of IBEC concerning wet and dry laboratory spaces. 1295m^2 – distributed between the Barcelona Scientific Park (PCB) and the Polytechnic University of Catalonia's Besòs Campus – have been designed and refurbished to receive new IBEC research groups, to expand the space of some of the actual groups and to open new common spaces.

- January – Xavier Trepat and Pere Roca-Cusachs' groups opened a new 83.66m^2 lab in the Hélix building (PCB).
- February – Javier Ramón, new junior group leader, opened his 103.8m^2 lab in the Clúster I building (PCB).
- March – Samuel Sanchez's group expanded to 95.41m^2 in a new lab prepared for intensive chemical research in the Clúster II building (PCB).
- May – Eduard Torrents's group expanded to a new 19.26m^2 space designed to receive culture experiments and a new confocal microscope.
- Also in May, we opened a co-working room (42.13m^2) in the Hélix building (PCB), created to provide space for students with specifics needs, such as finishing their PhD theses. It's an open space that offers users the chance to share ideas, spread creativity, collaborate and network. This new space is managed by the Core Facilities Unit.

IBEC'S new co-working room

Scientific Coordinator
Mateu Pla

Microfab & Microscopy Technicians
Marina Cazorla
Judit Linacero

Microfab Assistant
Alicia Nadal

Laboratory Technicians
Ramona Bravo
Laura Gómez
Miriam Funes
Inma Moreno

Administrative Assistant
Tania Bordoy

- July – we opened a new Core Facilities space (70.79m^2) to carry out "heavy" chemical synthesis – ChemSpace.
- December – a new IBEC location was opened at the UPC-Besòs Campus. 880.67m^2 distributed over three floors were refurbished to receive the new IBEC group leader and ICREA professor Paul Verchure's group and relocate Raimon Jané's group, and also expand our administrative support services.

Furthermore, with the purpose of installing new scientific equipment (e.g. microscopes), some refurbishments of several spaces has been carried out during the year.

Common Core Basics

At present we do the general maintenance and organization of 2100m^2 of IBEC's wet labs in the PCB. We are also in charge of the 'in-house shop', which has about 76 laboratory consumables available to be redistributed, on demand, throughout the IBEC groups. In addition, this year we have implemented a new lab coats laundry service.

Apart from routine laboratory equipment, IBEC's Core Facilities provide additional sophisticated, state-of-the-art equipment to support the groups' research.

- Small equipment available:

Scales; heating baths; thermoblocks; thermomixers; centrifuges; magnetic stirrers with or without heater; platform shakers; ultrasonic baths; pHmeters; conductimeter; incubators; ovens; water purification systems; UV tip cleaner; sterilize miniclave; puller machine, etc.

- Specific routine laboratory equipment available:
  - Chromatography System Biologic LP – Bio-Rad
  - Spectrophotometer – Nanodrop
  - Multimode microplate reader Infinite M200 Pro – Tecan
  - Spectrophotometer UV-Visible – Shimadzu
  - Microplate Reader Benchmark Plus – Bio-Rad
  - StepOnePlus Real Time PCR System – Applied Biosystems
  - DNA Engine Thermal Cycler – Bio-Rad
  - T100 Thermal Cycler – Bio-Rad
  - GeneAmp PCR System 9700
  - ImageQuant LAS 4000 mini – GE Healthcare
  - GelDoc XR+ System – Bio-Rad

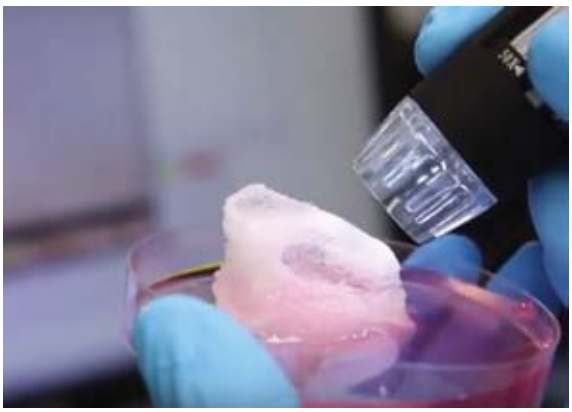
3D bioprinter (3D Discovery from RegenHU) located in the BioSpace

BioSpace Lab

IBEC's BioSpace Lab is a shared space dedicated to working with primary and cell line cultures and 3D bioprinting. It is equipped with several Class-II biosafety cabinets and CO_2 incubators, with one prepared for complex experiments with cells that include

extra equipment, and routine equipment for cell culture. Also, researchers have access to an inverted microscope and a stereomicroscope, both with epifluorescence option. During 2017, 116 IBEC researchers from 13 groups have used this space.

3D bioprinting continues to be a hot topic in the Strategic Plan of the Institute in the areas of regenerative medicine and tissue engineering. Our 3D bioprinter allows the printing of different types of biomaterials (polymers, abrasive viscous substances, hydrogels loaded with cells and solutions) in a coordinated way, generating complex multi-material 3D scaffolds and therefore closer to biological tissues. The applications of this 3D constructs span from 3D cellular models for drug screening (i.e. dermis), scaffolds for regenerative medicine or, at a more advanced stage, organ-printing. Apart from software upgrades, the 3D bioprinter system has been equipped with a temperature controlling jacket that allows to control the temperature of the materials being extruded from 4ºC to 37ºC, and a USB microscope that allows the recording and monitoring of the printing process.



3D printed scaffold of PCL generated using the thermopolymer extruder of the 3D bioprinting system

At present, 3D bioprinting is set up in the BioSpace, and 34 IBEC researchers from 8 groups have received training to work with the printer. The training consists of a theoretical and practical two-day session. Multiple companies and institutions has shown interest in our 3D bioprinter. Core Facilities have been giving support to the IBEC Technology Transfer Unit organizing and performing some demonstrations of its capabilities, and we expected that some collaborations will arise from these interactions.

Chemspace Lab

In July 2017, IBEC open a new shared space prepared to carry out 'heavy' chemical synthesis. It's an isolated space furnished with several chemical fume hoods, equipped with argon and nitrogen, gases necessary to perform chemical reactions in a controlled atmosphere. Also, routine specific equipment for chemical synthesis is available. This space responds to a new demand of the IBEC groups that are developing innovative bioactive compounds and biomaterials. Currently, two IBEC groups are using this space intensively.

IBEC'S ChemSpace Lab

Microfabspace Lab

Accessible and versatile research facility featuring 90m^2 of class 10,000 cleanroom space offering state-of-the-art equipment for the fabrication and characterization of microdevices and structures for biomedical applications. At the end of 2017, we have carried out a major refurbishment in our clean room to better define the spaces dedicated to photolithography processes and create a separated space for a new 3D printer (service to be opened in 2018).

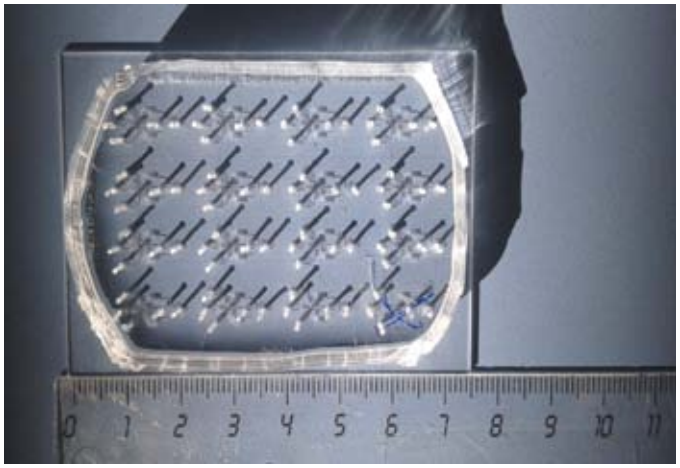
At present, the facility provides advanced research support that includes

MicroFabSpace and Microscopy Characterization external users in 2017:

- Advanced Nanotechnologies S.L.
- Bio-model
- BCN Peptides, S.A.
- Fundació Centre de Regulació Genòmica (CRG)
- Fundació IGTP - Ciencies de la Salut Germans Trias i Pujol
- GP-Pharm, S.A.
- Infinitec Activos S.L.
- Institut Català de Nanociència i Nanotecnologia (ICN2)
- Institut de Biologia Molecular de Barcelona (IBMB-CSIC)
- Institut de Quimica Avançada de Catalunya (IQAC-CSIC)
- Institut Químic de Sarrià (IQS)
- Universitat Autonòma de Barcelona (UAB)
- Universitat de Barcelona (UB)
- Universitat Politècnica de Catalunya (UPC)
- Max Planck Institute for Brain Research
- Stat-Diagnostica and Innovation S.L.

MicroFabSpace Lab users' publications in 2017:

- Biagi, Maria Chiara; Badino, Giorgio; Fabregas, Rene; Gramse, Georg; Fumagalli, Laura; Gomila, Gabriel, (2017). Direct mapping of the electric permittivity of heterogeneous non-planar thin films at gigahertz



Customized Microfluidic chip with 16 microfluidic units (with permission of the Centre de Regulació Genòmica – Unidad de Genómica).

the design, development and analysis of devices, materials and processes, so that researchers may use the facility to develop their innovative ideas in the fields of bioengineering, BioMEMS, materials science, tissue engineering and microfluidics.

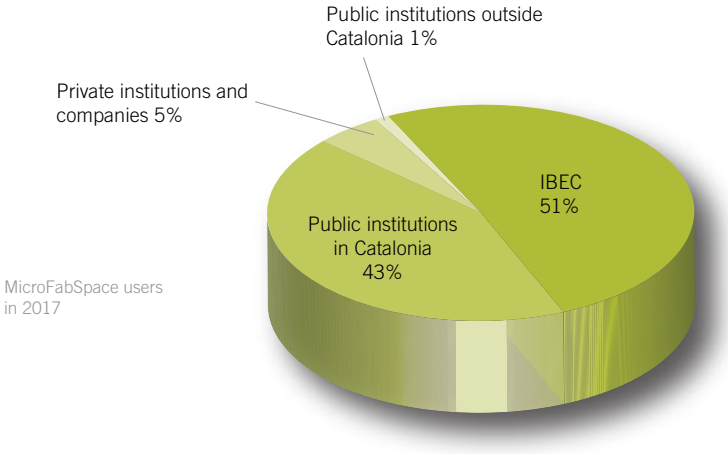
The facility is open to potential users from other public institutions and private companies.

Services

- Training as a self-user for the following equipment: interferometer, profilometer, optical microscope, spin-coater, plasma cleaner and mask aligner (photolithography)
- Training to use microfabrication equipment (self-user) or custom-made fabrication/ characterization (quotation required)
- Fabrication:
  - Design and fabrication of customized microfluidic chips using photolithography and replica molding (rapid prototyping in PDMS silicone)
  - E-beam lithography technique for the manufacture of micro- and nano-structures
  - Fabrication of Cr photomasks for photolithographic processes
  - Thin layer deposition of materials (Au, Al, Ti, Cr, SiO2, Al2O3, etc.)
  - Microelectrodes
  - Fabrication of SU-8 molds for microcontact printing and micromolding in capillaries
  - Medium density microarrays (proteins and DNA)
- Characterization:
  - Surface topographic analysis by using optical interferometry and mechanical profilometry
  - Optical characterization of samples with bright and dark field
  - Contact angle measurements of wettability properties of surfaces

Equipment

- E-beam Lithography (EBL) Elphy Puls - Raith
- UV-Photolithography Mask-aligner MJB4 – SÜSS Microtec
- Direct Write Laser 66FS – Heidelberg Instruments
- Thermal and E-beam metal evaporator Univex 450B – Oerlikin Leybold Vacuum



MicroFabSpace users in 2017

- Spin-coaters – Laurell Technologies Corporation (2 units)
- Plasma Cleaner PDC-002 – Harrick Scientific Corporation (2 units)
- Chemical Bath - Quimipol
- UV lamp - Omnicure
- Interferometer WYCO NT1100 – Veeco Instruments
- Profilometer DEKTAK 6M – Veeco Instruments
- Optical microscope equipped with camera for samples inspection BX51RF – Olympus
- Stereo microscope for samples inspection - Olympus
- Contact angle measure equipment OCA15Plus - Dataphysics
- Microarrayer SPOTBOT2 – Arrayit corporation

Some data related to MicroFabSpace Lab users

During the last year, 52 researchers from twelve IBEC groups, 45 researchers from 9 other public institutions, and 5 from 3 private companies have used as a self-user or order a service available at the MicroFabSpace facility. In 2017 the average of users and services performed by the platform was 37 and 234 per month respectively.

Microscopy Characterization

This facility is composed of several microscopes for very different ranges of applications, located in different spaces and managed separately. It is a combined service between microscopes managed centrally (Core Facilities Unit) and others managed by IBEC groups that have the obligation to facilitate the 30% of user time to other IBEC researchers.

During the last quarter of the year, a new Confocal Microscope was incorporated into the facility.

Equipment & Services

- Ultra-High Resolution Field Emission Scanning Electron Microscopy (SEM) – Nova NanoSEM FEI.
  - Training as a self-user on the use of the SEM microscope (only for IBEC researchers).
  - SEM morphological and topographical characterization.

This microscope is open to potential users from other public institutions and private companies.

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- Caballero, D.; Samitier, J., (2017). Topological control of extracellular matrix growth: A native-like model for cell morphodynamics studies. *ACS Applied Materials and Interfaces* 9, (4), 4159-4170
- Caballero, D.; Palacios, L.; Freitas, P. P.; Samitier, J., (2017). An interplay between matrix anisotropy and actomyosin contractility regulates 3D-directed cell migration. *Advanced Functional Materials* 27, (35), 1702322
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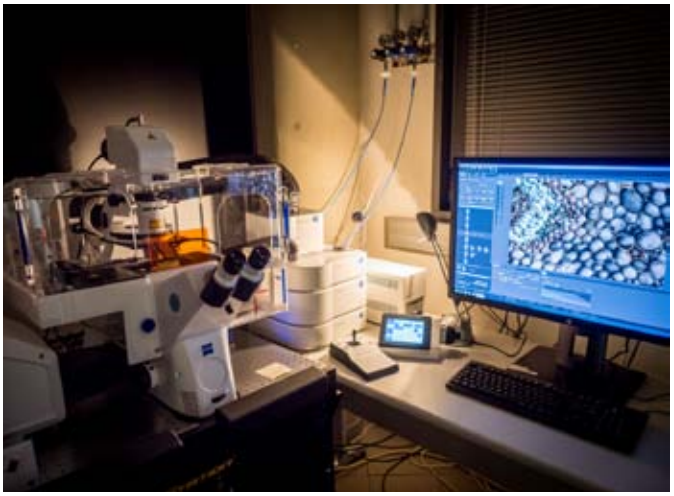
The MicroFabSpace Lab and Microscopy Characterization (only SEM) is also an active member of the ICTS (Infraestructuras Científicas y Técnicas Singulares) map as part of NANOBIOSIS (Infraestructuras Integradas de Producción y Caracterización de Nanomateriales, Biomateriales y Sistemas en Biomedicina), an integrated platform for research-oriented medical applications (U7 – Nanotechnology Unit).



Confocal Microscope

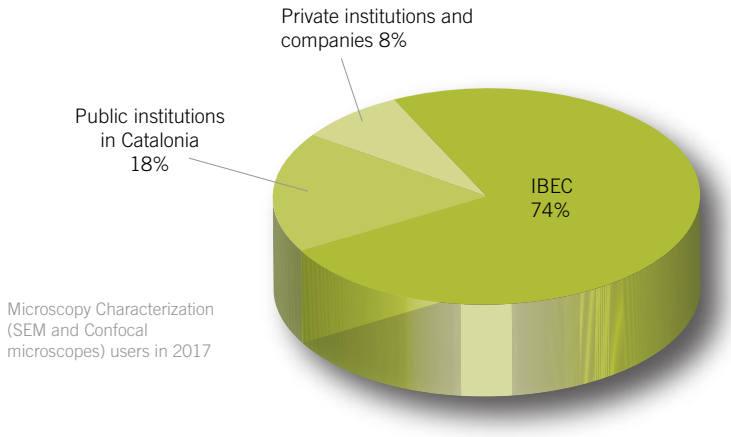
- Confocal Microscope with Spectral Detection LSM 800 – Zeiss
- Bio-Atomic Force Microscope (Bio-AFM) – JPK. Managed by Gabriel Gomila's group
- Stochastic Optical Reconstruction Super Resolution Microscope (STORM) – Nikon. Managed by Lorenzo Albertazzi's group.

Some data related to Microscopy Characterization users

During the last year, 80 researchers from twelve IBEC's groups, 20 researchers from 6 other public institutions, and 9 from 6 private companies have used the Microscopy Characterization facility as a self-user or ordered one of its services.

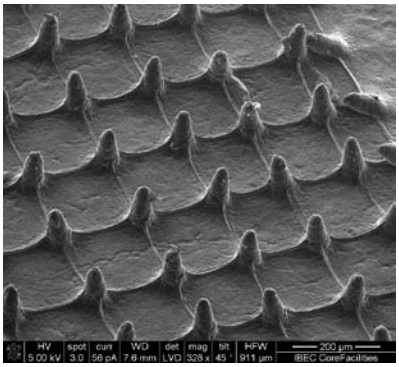
Activities during 2017

- Participation with a talk titled 'Photolithography microfabrication: from 2D designs to 3D structures' in the biotechnology degree at the University of Vic.
- Organization of the workshop 'Using a Scanning Electron Microscope (SEM)' held in IBEC. Aimed at all IBEC researchers and technicians who are potential users of our SEM.
- Invited talk at the Bioengineering Workshop organized by the Associació de Biotecnòlegs de Catalunya (ASBTEC) and IBEC, entitled '3D Bioprinting: Engineering Complex Tissues and Soft Materials' (Barcelona).



Microscopy Characterization (SEM and Confocal microscopes) users in 2017

Poly(ethylene glycol) diacrylate based 3D villi-like scaffolds (with permission from the Biomimetic Systems for Cell Engineering group)



- Invited talk at the X Conferencia Anual de las Plataformas Tecnológicas de Investigación Biomédica: Medicamentos Innovadores, Nanomedicina Tecnología Sanitaria y Mercados Biotecnológicos, organized by FarmaIndustria, entitled '3D Bioprinting: Engineering Complex Tissues and Soft Materials' (Madrid).
- Participation in 'Berripills', organized by the Organización Sanitaria Integrada Ezkerraldea-Enkarterri-Cruces, with a talk entitled 'Bioimpresión 3D de estructuras complejas blandas y sus aplicaciones en ingeniería de tejidos' (Bilbao).
- Participation in a 3D Printing Techniques Workshop, held in EURECAT Centre Tecnològic de Catalunya, with a talk entitled '3D Bioprinting: Engineering complex tissues with soft materials' (Cerdanyola del Vallès).
- Participation in the organization of the workshop 'Good practices in a multi-disciplinary laboratory' held at IBEC and aimed at young scientists and students at the institute. The objective was to acquire the good practices necessary in a laboratory to ensure the highest quality of results.
- Participated in two documentaries about 3D printing, giving support to the IBEC Communications and Outreach Unit.

Research projects

- **3D bioprinted tissue-like cores for cancer diagnostics.** The goal of the project, to take advantage of 3D bioprinters to create 3D tissue-like structures containing biomarkers that can be used as quality controls in histopathological analysis in companion diagnostics kits.
  PI: **Mateu Pla**
  CaixaImpulse 2017

Publications

- Garreta, E., Oria, R., Tarantino, C., Pla-Roca, M., Prado, P., Fernández-Avilés, F., Campistol, J. M., Samitier, J., Montserrat, N. (2017). Tissue engineering by decellularization and 3D bioprinting. *Materials Today* 20, (4), 166-178

Notes

Notes

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