BIOENGINEERING
FOR CANCER DIAGNOSIS, PROGNOSIS AND PERSONALIZED THERAPY

IBEC
Institute for Bioengineering of Catalonia

EXCELENCIA
SEVERO
OCHOA

CONTENTS

ABOUT IBEC

The Institute for Bioengineering of Catalonia (IBEC) is an interdisciplinary research centre, based in Barcelona, that conducts excellent interdisciplinary research at the frontiers of engineering and life sciences in order to generate new knowledge by putting together fields like nanomedicine, biophysics, biotechnology, tissue engineering and the applications of health information technology.

The institute currently has 22 research groups and 350+ researchers and staff from 25 different countries.

The IBEC model represents an evolution from 20th-century biomedical institutes and is part of a new wave of research initiatives set up in the last decade, with shared interests and points of view concerning how to advance the frontiers of knowledge in experimental science to benefit clinical and biomedical research. The common denominator shared by these new initiatives is their focus on the enormous challenge of how to make life science quantitative on any scale, taking full advantage of the unprecedented power of the convergence between nano, bio and ICT.

At IBEC, frontier research is combined with specific transfer targets to produce new applied technologies to be used in life and health sciences. We have the versatility to generate excellent research and, at the same time, work with clinicians and industry to develop new diagnostic or treatment systems. The model envisaged by IBEC is inspired by a creative, innovative new ecosystem based on interaction between research experts in different enabling technologies (nano-bio-info-cogno) to generate new knowledge and engineering solutions in health technology.

Early diagnosis, new therapies based on regenerative medicine, better quality of life compatible with an ageing population, and technological advances to increase efficiency and make healthcare sustainable: these are some excellent examples of areas where IBEC can contribute with its cutting-edge research to generate new technological advances of key importance to innovation.

Collaboration across research groups with complementary skills is the key factor behind IBEC's uniqueness. This is achieved through the convergence of talented researchers with very diverse backgrounds, access to state-of-the-art laboratory facilities and effective leadership able to efficiently coordinate and maximise the benefits of such a complex environment.

IBEC excellence was recognized by the Spanish Ministry of Economy and Competitiveness by its award as Severo Ochoa Research Centre in the 2014 call, which labels IBEC as one of Spain top research centres at the highest international level in terms of research, training, human resources, outreach and technology transfer. The award was renewed in the Severo Ochoa 2018 call.

The knowledge that exists in IBEC is structured in 4 broad avenues of knowledge: nanomedicine, mechanobiology, cell engineering and ICT for health:

Nanomedicine: nanobiosensing; microfluidics; nanofabrication; beyond-AFM/ST microscopy tools to characterize biological samples at the nanoscale; nanorobotics; nanoscopy; drug delivery improvement; nano-scale characterization of bacterial-host interactions; organ/lab-on-chip.

Mechanobiology: new technologies to measure physical forces at the cell-cell and cell-matrix interface; optogenetics to control cell mechanics; molecular mechanism that cells employ to sense and respond to rigidity.

Cell Engineering: cell reprogramming; control differentiation of stem cells; cell niches; biomaterials for regenerative medicine; cell-material interaction; biomimetics; cellular and molecular biology; antibacterial strategies.

ICT for Health: application of advanced information and communication technologies to healthcare, such as modelling; signaling processing; automatics/ control software for robotics; theory of mind and brain; cognition.

These are placed at the service of science and society to progress in three major research programmes:

BIOENGINEERING FOR FUTURE AND PRECISION MEDICINE, with the aim of developing technology that goes beyond the existing paradigm of medical care in hospital to incorporate new areas such as personalize medicine, tailoring diagnostic and therapies to the individual, optopharmacology, diagnosis and therapies based on mechanobiology and nanomedicine.

BIOENGINEERING FOR ACTIVE AGEING, with the aim of developing care and technology and improve the quality of life of an increasing older population. Assisted living technologies such as mobile health solutions, including home-based devices and services for remote monitoring, consultation and diagnosis, can help support independent living at home, keeping patients out of hospital and residential care for longer.

BIOENGINEERING FOR REGENERATIVE THERAPIES, with the aim of developing regenerative technologies to allow the creation of implants able to bring about the regeneration of damaged tissues or organs and to develop cell therapies.

FIGHTING CANCER WITH BIOENGINEERING

Bioengineering enables society to define, understand and solve highly complex problems in medicine, bringing together fields such as nanomedicine, biophysics, mechanobiology, biomaterials, biotechnology, tissue engineering, biosensors and the applications of ICT for health.

These are put at the service of the understanding and quantification of all the mechanisms involved in human physiology and health.

One of the pathologies that can benefit most from the novel bioengineering approach is cancer. IBEC researchers, in collaboration with international clinical groups and companies, are using their bioengineering expertise to develop novel therapies and diagnostic tools against cancer.

Bioengineering is used at IBEC in a multidisciplinary way to fight cancer and metastasis: Liquid biopsies, Tumour on chip, Tumour Organoids, Mechanobiology, Metabolomics, Immunotherapies, Imaging and Targeted drug delivery.

Cancer treatment has benefited in recent years from the implementation of personalized therapeutic drugs targeting specific mutations in signalling pathways. However, even with the use of such personalized drugs, tumours still develop resistance and progress. We therefore require a better fundamental understanding of how biochemical signalling interacts with additional factors, such as mechanical ones to drive tumour dormancy and progression. Advanced drug delivery strategies are being developed using modular multivariant nanomaterials and nanorobots allowing for functionalization with multiple targeting ligands and photoactivated antimetabolites for chemotherapy with high efficacy and low side effects. Model in chip of relevant tumours will allow to test these novel therapies *in vitro*, reducing animal experiments and time to the patient. At the same time, liquid biopsies and metabolomics have the potential to dramatically improve the diagnosis and prognosis of cancer. Immunotherapy based on adoptive T cell transfer, requires bioengineering to improve the production and reduces the costs of the treatments. Microfluid technologies for T cell screening using single cell droplet microfluidics or artificial designer biomaterials to enhance T cell immunotherapy are some clear examples.

Out of the 22 groups presently working at IBEC, 13 are currently involved in projects related to cancer. Since 2018, our researchers have published more than 80 publications addressing cancer, including contributions in top impact journals such as Nature Materials, Nature Physics, Clinical cancer research, or PNAS. In the last years,

our research against cancer has attracted competitive funding, including ERC grants, FET Open and other H2020 collaborative projects, as well as private funding from La Caixa or the Spanish Association against Cancer (AECC).

At an institutional level, IBEC co-coordinates an institutional project together with the MIT (USA) entitled "Bioengineering against cancer" to foster transoceanic collaborations.

Moreover, as coordinator of the Spanish Platform of Nanomedicine, which gathers universities, research centres, companies and other stakeholders applying bioengineering and nanotechnology to health, IBEC fosters the use of nanomedicine to tackle cancer. Among other initiatives, IBEC organizes every year, together with the European Technology Platform for Nanomedicine, the HealthTech World Cancer Day.

IBEC has organized an international workshop on "Bioengineering and Medtech against cancer" on 24 and 25th November 2020. The event was part of the ToHealth project (https://eithealth.eu/project/tohealth/) funded by EIT Health and involving Biocat (Biocat.cat), La Caixa (https://obrasociallacaixa.org/) and Medicen Paris (https://medicen.org/). The workshop served to review novel approaches that bioengineering can bring to cancer and identify and address the barriers to uptake these novel technologies. It also included a pitch session to showcase the most promising European start-up and projects related to cancer.

Cancer diagnosis and prognosis is one of the Advanced Societal Health Challenges of the Severo Ochoa Strategic Plan of IBEC 2019-2023, designed to capitalize on IBEC's potential to apply a novel, non-conventional paradigm of bioengineering to contribute to the most acute challenges of medicine today.

Through the research and innovation activities described in the following pages, IBEC aims to be a main player in the EU Mission "Conquering Cancer: Mission Possible" recently launched by the European Commission and contribute, in collaboration with its international network of partner institutions, to defeat this main burden for human health worldwide and give hope to millions of patients and their families.

Nanoscopy for nanomedicine

Lorenzo Albertazzi

The understanding of materials-cell interactions is key towards the development of novel nanotechnology-based therapies for treatment of cancer and infectious diseases. The nanoscopy for nanomedicine group aims to use a multidisciplinary approach, at the interface of chemistry, physics and biology, to develop novel nanomaterials for these diseases. The main goal of the group is to use Super Resolution Microscopy (nanoscopy) to visualize and track in living cells and tissues self-assembled nanomaterials with therapeutic potential (nanomedicine).

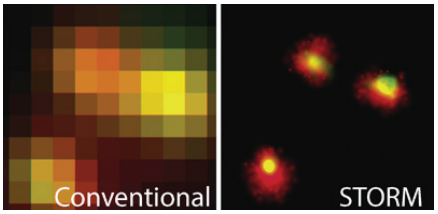
A key point towards the development of novel nanotechnology-based therapies is the understanding of the behaviour of nanomaterials in the complex biological environment. Using a variety of super resolution techniques based on single molecule detection we achieve a resolution down to few nanometres and we can track nanomaterials in the biological environment and visualize the interactions with blood components, immune system and target cells.

"Super resolution microscopy provides a molecular picture of structure-activity relations and represent a guide towards the design of innovative therapies against cancer."

Recent activities related to cancer

In the framework of the ERC Starting Grant "Design of Nanomaterials for Targeted Therapies Guided by Super Resolution Imaging" we use super resolution microscopy to examine nanomaterials that have potential as therapies for cancer, and understand their interactions with their target: the diseased cells. Doing so will help identify the key principles that are needed to rationally design the next generation of targeted, super-efficient cancer treatments.

We are using our Stochastic Optical Reconstruction Microscope (STORM) which offers unprecedented high-resolution imaging, even at the nanoscale to image new, synthesized nanomaterials in the biological environment, unveiling their interactions with healthy and tumorous tissues at the single molecule level for the first time ever.



We are also coordinating the Marie Curie ITN "Bio-orthogonal catalysis for cancer therapy" on the development of therapeutic catalysts. In this strategy, materials bearing a catalytic unit are delivered to the tumour and subsequently non-active prodrugs are administered. The prodrugs are non-toxic and therefore generate limited side effects. Only at the tumour site the catalytic particles convert the prodrugs into active compounds that generate a therapeutic effect. This approach presents several advantages on the classical drug delivery paradigm including limited side effects and prolonged efficacy.

We are also working on the development of Nanofibres and immunotherapies for cancer treatment. With our tools we are testing the toxicity, stability, and cell internalization of the nanofibers in cancer cells. We can also obtain super-resolution imaging of the fibres structure and functionality.

Funded projects related to cancer

UNDERSTANDING AND MEASURING MECHANICAL TUMOR PROPERTIES TO IMPROVE CANCER DIAGNOSIS, TREATMENT, AND SURVIVAL: APPLICATION TO LIQUID BIOPSIES	OBRA SOCIAL LA CAIXA
NANOVAX · NANOVACUNAS DISEÑADAS PARA INMUNOTERAPIA ANTITUMORAL	EURONANOMED (ERA-NET)
NANOSTORM · DESIGN OF NANOMATERIALS FOR TARGETED THERAPIES GUIDED BY SUPER RESOLUTION IMAGING	ERC – STARTING GRANT
THERACAT · BIO-ORTHOGONAL CATALYSIS FOR CANCER THERAPY	MARIA CURIE ITN

Main recent publications related to cancer

Brugada-Vila P., Cascante A., Lazaro M.A., Castells-Sala C., Fornaguera C., Rovira-Rigau M., Albertazzi L., Borros S., Fillat C. (2020). Oligopeptide-modified poly(beta-amino ester)s-coated AdNuPARmE1A: Boosting the efficacy of intravenously administered therapeutic adenoviruses. Theranostics 10, 2744-2758.

De Coen R., Nuhn L., Perera C., Arista-Romero M., Risseeuw M.D.P., Freyn A., Nachbagauer R., Albertazzi L., Van Calenbergh S., Spiegel D.A., Peterson B.R., De Geest B.G. (2020). Synthetic Rhamnose Glycopolymer Cell-Surface Receptor for Endogenous Antibody Recruitment. Biomacromolecules 21, 793-802.

Uroz M., Garcia-Puig A., Tekeli I., Elosegui-Artola A., Abenza J.F., Marín-Llauradó A., Pujals S., Conte V., Albertazzi L., Roca-Cusachs P., Raya Á.I, Trepat X., (2019). Traction forces at the cytokinetic ring regulate cell division and polyploidy in the migrating zebrafish epicardium. Nature Materials 18, 1015-1023

Krivitsky, A., Polyak, D., Scomparin, A., Eliyahu, S., Ofek, P., Tiram, G., Kalinski, H., Avkin-Nachum, S., Feiner Gracia, N., Albertazzi, L., Satchi-Fainaro, R., (2018). Amphiphilic poly(⍰)glutamate polymeric micelles for systemic administration of siRNA to tumors Nanomedicine: Nanotechnology, Biology, and Medicine 14, 303-315.

Liu, Y., Pujals, S., Stals, P.J.M., Paulöhrl, T., Presolski, S.I., Meijer, E.W., Albertazzi, L., Palmans, A.R A. (2018). Catalytically active single-chain polymeric nanoparticles: Exploring their functions in complex biological media Journal of the American Chemical Society 140, 3423-3433.

Delcanale, P., Porciani, D., Pujals, S., Jurkevich, A., Chetrusca, A., Tawiah, K. D., Burke, D. H., & Albertazzi, L. (2020). Aptamers with Tunable Affinity Enable Single-Molecule Tracking and Localization of Membrane Receptors on Living Cancer Cells. Angewandte Chemie (International ed. in English), 59(42), 18546–18555. Advance online publication. https://doi.org/10.1002/anie.202004764

Molecular Bionics

Giuseppe Battaglia

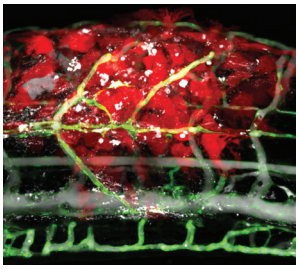
In our lab, we design bionic units that mimic specific biological functions and introduce operations that do not exist in nature. We apply a constructionist approach where we mimic biological complexity in the form of design principles to produce functional units from simple building blocks and their interactions. We call such an effort, Molecular Bionics, and it involves inputs from physical science and engineering from one side and biomedical science.

We are particularly interested in how molecules, macromolecules, viruses, vesicles and whole cells traffic across our body barriers. We combine novel microscopic tools with theoretical and computational physics to study biological transport from the single molecules, cell membrane, to the whole organism. We thus translate the acquired knowledge to bioengineer novel nanomedicines, combining soft matter physics with synthetic chemistry.

"Biological transport taught us to engineer nanomedicines that follow the cancer metabolic trail via chemotaxis, bind only to cancer cells unique phenotypes, and enter cells via endocytosis."

Recent activities related to cancer

We developed a unique approach to reach cancer cells and deliver drugs. We exploit the cancer anomalous metabolic profiles using chemotactic targeting and selectively targeting cancer cells exploiting their unique receptors composition or phenotype.



Chemotactic targeting. Tumours consume more metabolites than their healthy neighbours and express more proteins to capture as much metabolite as possible form their surroundings. Such a voracious nature creates pools of glucose, amino acids, acetates around and within the tumour areas effectively generating chemical trails around them. We exploit these chemical gradients using asymmetric vesicles capable of chemotaxis. That is the ability to move toward the high concentration of the given chemicals effectively argument diffusion toward actual locomotion. Such an approach allows for augmented selectivity across distance orders of magnitude larger than single cell size.

See more: Joseph et al. Science Adv. 2017, 3, 8, e1700362 and and I. Williams et al Proc. Natl. Acad. Sci. USA 2020, 17, 25263-25271

Phenotypic targeting. Each cell of our body exerts a unique function as a consequence of its distinctive phenotype, i.e. the cell's proteins and genes collective that defines its identity. Each cell so 'expresses' a unique combination of proteins on their membrane that distinguish them from their neighbours.

We use such information to engineer multivalent and multiplexed nanomedicines that comprise unique ligands combinations. We tune each ligand/receptor interaction to be weak enough that only when combined, they can bind to its complementary phenotype. Ergo, each nanomedicine interacts with a high level of precision, enabling to target defined cell populations. Such a precision nanomedicine increases anticancer drugs therapeutic efficiency of several orders of magnitude allowing for personalised treatment down to the single cell level to compensate for tumour heterogeneity and patient to patient variations.

See more: Tian et al. Science Adv. 2020, 6,4, eaat0919 and M. Liu et al Nature Comm. 2020 11, 4836

Funded projects related to cancer

THE DEVELOPMENT OF MICRORNA THERAPY FOR PAEDIATRIC TUMOURS	BRAIN TUMOUR RESEARCH
PHENOTYPIC MAPPING OF GLIOMAS	CANCER RESEARCH UK CITY OF LONDON CANCER CENTRE
PRECISION NANOMEDICINE FOR NEURO-ONCOLOGY APPLICATIONS	EPSRC
CHEMOTACTIC SUPERSELECTIVE TARGETING FOR GLIOMA	ERC CONSOLIDATOR GRANT
THE DEVELOPMENT OF NANOMEDICINE TO TARGET PAEDIATRIC GLIOMAS	CHILDREN WITH CANCER UK
DEVELOPMENT OF IMMUNE-THERAPY USING SYNTHETIC VIRUSES	ESPRC ENGD/BTG.
ON THE DESIGN OF PRECISION NANOMEDICINES	EPSRC ESTABLISHED FELLOWSHIP

Main recent publications related to cancer

Kocere, A., Resseguier, J., Wohlmann, J., Skjeldal, F. M., Khan, S., Speth, M., Dal, N. K., Ng, M., Alonso-Rodriguez, N., Scarpa, E., Rizzello, L., Battaglia, G., Griffiths, G., & Fenaroli, F. (2020). Real-time imaging of polymersome nanoparticles in zebrafish embryos engrafted with melanoma cancer cells: Localization, toxicity and treatment analysis. EBioMedicine, 58, 102902. https://doi.org/10.1016/j.ebiom.2020.102902

L Ruiz-Pérez, L. Rizzello, J. Wang, N. Li, G. Battaglia* and Y. Pei * Polypyrrole and polyaniline nanocomposites with high photothermal conversion efficiency Soft Matter 2020 10.1039/d0sm00306a

U. C. Oz, Z. B. Bolat, A. Poma, L Guan, D. Telci, F. Sahin, G. Battaglia* , and A. Bozkır* Prostate cancer cell-speciic BikDDA delivery by targeted polymersomes Appl. Nanosci 2020 10.1007/s13204- 020-01287-0

X. Tian, S. Angioletti-Uberti, G Battaglia* On the design of precision nanomedicines. Science Adv. 2020, 6, 4 , eaat0919

L. Luo, F. Xu,H. Peng,Y. Luo,X. Tian,G. Battaglia,H. Zhang, Q. Gong, Z. Gu, K. Luo Stimuli-responsive polymeric prodrug-based nanomedicine delivering nifuroxazide and doxorubicin against primary breast cancer and pulmonary metastasis J. Control. Release 2020, 318, 124-135

R. Rahman, E. Campbell, H. Brem, M. Pearl, J. Green, M. Janowski, P. Walczak, B. Tyler, K. Warren, W. Singleton, A. Mullen, M. Boyd, G. Veal, D. Hargrave, D. van Vuurden, S. Powell, G. Battaglia, I. Vivanco, K. Al-Jamal, D. Walker Children's Brain Tumour Drug Delivery Consortium (CBTDDC) Neuro-Oncology 2019, 24, vi274-vi274

Y. Zhu, M. Zhang,L. Luo, M.R. Gill, C. DePace,G. Battaglia,Q. Zhang,H.Zhou,J. Wu,Y. Tian and X. Tian NF-κB hijacking theranostic Pt(II) complex in cancer therapy Theranostics, 2019, 9, 2158-2166.

Y. Zhu, A. Poma, L. Rizzello, V. Goueveia, L. Ruiz-Perez, G. Battaglia*, and C.K. Williams* Metabolic active fully hydrolysable polymersomes Angew. Chem. Int. Ed. 2019, 8, 4581 –4586

X Tian, S Hussain, C de Pace, L Ruiz-Perez, G Battaglia ZnII Complexes for Bioimaging and Correlated Applications Chemistry– Asian J 2019,14, 509-526

L. Luo, Q Zhang, Y Luo, Z He, X Tian*, G Battaglia* Thermosensitive nanocomposite gel for intratumoral two-photon photodynamic therapy J. Control. Release, 2019, 298, 99-109

L Rodriguez-Arco, A Poma, L Ruiz-Perez, E Scarpa, K Ngamkham, and G. Battaglia* Molecular bionics–engineering biomaterials at the molecular level using biological principles Biomaterials 2019, 192, 26-50

X Tian, D Moreira-Leite, E Scarpa, S Nyberg, G Fullstone, J Forth, D Lourenco-Matias, A Apriceno, A Poma, A Duro-Castano, M Vuyyuru, L Harker-Kirschneck, A Saric, Z Zhang, P Xiang, B Fang, Y Tian, L Luo, L Rizzello, G Battaglia On the shuttling across the blood-brain barrier via tubules formation: mechanism and cargo avidity bias Science Adv. 2020 DOI: 10.1126/sciadv.abc4397

E. Scarpa ,C. De Pace ,A. S. Joseph,S. Campos de Souza,A. Poma,E. Liatsi-Douvitsa,C. Contini,V. De Matteis, J. Samitier Martí, G. Battaglia ,L. Rizzello Tuning cell behavior with nanoparticle shape PLoS ONE 2020 15(11): e0240197

B. Sola-Barrado, D. Moreira-Leite, E. Scarpa, A. Duro-Castano, G. Battaglia, Combinatorial Intracellular Delivery Screening of Anticancer Drugs Mol. Pharmac. 2020, on line, 10.1021/acs.molpharmaceut.0c00791

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C. Z. Bueno, A. C. Apolinário, A. Duro-Castano, A. Poma, A. Pessoa Jr,C. O Rangel-Yagui, G. Battaglia I-Asparaginase Encapsulation into Asymmetric Permeable Polymersomes ACS Macro Lett. 2020, 9, 1471-1477

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M. Liu, A. Apriceno, M. Sipin, E. Scarpa,L. Rodriguez-Arco, A. Poma, G. Marchello,G. Battaglia*, S. Angioletti-Uberti* Combinatorial entropy behaviour leads to range selective binding in ligand receptor interactions Nature Comm. 2020 11, 4836

X Tian , C. De Pace, L. Ruiz-Perez, D. Chen, R. Su, M. Zhang, R. Zhang, Q. Zhang, Q. Wang, H. Zhou, J. Wu, , Z. Zhang, Y. Tian, G. Battaglia A Cyclometalated Iridium (III) Complex as a Microtubule Probe for Correlative Super-Resolution Fluorescence and Electron Microscopy Adv. Mater., 2020, 32, 2003901

Synthetic Morphogenesis

Vito Conte

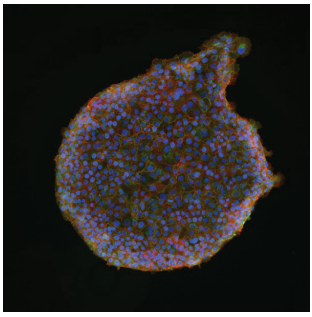
The research group Synthetic Morphogenesis advances cross-disciplinary research at the interface between biology, physics and engineering by studying the mechanical biology and the biological mechanics of pathological development and disease progression. The group is interested in understanding what mechanical rules need to be rationally synthetized and deployed within cellular epithelia so that these cellular monolayers may morph into a predetermined shape – morphogenesis comes from the Greek for generation of shape. This is important for the rational design of organotypic constructs in regenerative medicine. Understanding how epithelia acquire shapes also paves the way to understanding how certain epithelial shapes can be prevented to form. This is important because phenomena of neoplastic morphogenesis have been reported to be instrumental to the progression of some aggressive carcinomas to their metastatic stage. Ultimately, researching and understanding the processes by which a tissue takes or lose shape will open a pathway to identify new mechanical hallmarks of cancer progression and define principles of tissue design for organ regeneration.

The group focusses on developing new multidisciplinary methods to quantify cell and tissue mechanics in 2D and 3D environments by hybridising physical, computational and biological approaches. These techniques are used to extract mechanical information from large amounts of experimental data *in vitro*, *in vivo* and *ex vivo*, which are later mined 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.

"The Synthetic morphogenesis group combines in vitro experimentation with the most classical laws of physics and the most modern computer-science approaches to tap the full potential of cancer biology."

Recent activities related to cancer

The group has been recently investigating whether the cancer progression in human tissues exploits the alterations that the cancer disease itself induces in the material properties and intercellular forces of normal healthy tissues.



Human breast epithelium undergoing malignant transformation. Red – phalloidin, Green – E-cadherin and Blue – DAPI.

Research investigated the interplay between cell malignant transformation and cell mechanical alterations by resorting to a multidisciplinary research program combining *in vitro* experimentation, biophysical techniques and computational modelling. The group has identified a new physical mechanism that relies on collective extrusion and contractility to steer the 2D-to-3D transition of a healthy cellular monolayer that undergoes a progressively-malignant oncogenic transformation (in preparation for publication).

Funded projects related to cancer

CANCERMECHREG · REGULACION BIOMECANICA DE LA PROGRESION DEL CANCER	MINECO, PROYECTOS I+D EXCELENCIA

Main recent publications related to cancer

Uroz M., Garcia-Puig A., Tekeli I., Elosegui-Artola A., Abenza J.F., Marin-Llaurado A., Pujals S., Conte V., Albertazzi L., Roca-Cusachs P., Raya A., Trepat X. (2019). Traction forces at the cytokinetic ring regulate cell division and polyploidy in the migrating zebrafish epicardium. Nature Materials 18, 1015–1023.

Uroz M., Wistorf S., Serra-Picamal X., Conte V., Sales-Pardo M., Roca-Cusachs P., Guimerà R. and Trepat X. (2018) Regulation of cell cycle progression by cell–cell and cell–matrix forces. Nature Cell Biology 20, 646–654.

Biomaterials for regenerative therapies

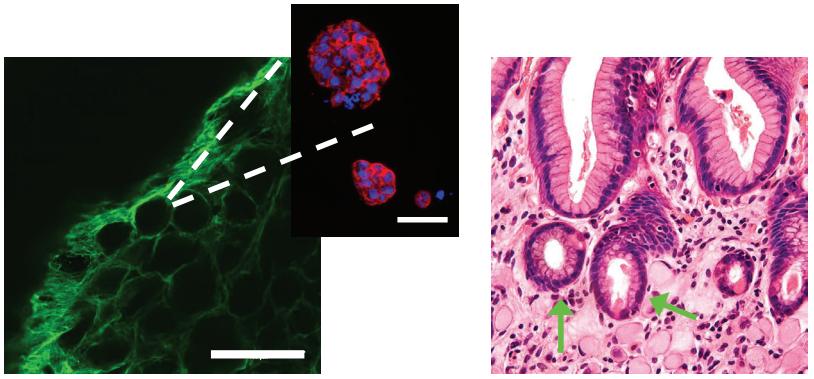
Elisabeth Engel

Research in the Biomaterials for Regenerative Therapies group is devoted to the development and knowledge transfer for biomedical applications. They design, fabricate and characterize bioactive and biodegradable materials and investigate their interactions with biological entities, both in terms of fundamental research aspects and as specific applications for tissue engineering and disease modelling purposes in mind. The aim is to repair and restore tissue and organ functions, as well as closely replicate 3D disease microenvironments such as cancer, for a better and personalized diagnose and treatment. By means of combining 3D scaffolds, cells, their generated extracellular matrix and their own signalling cues, researchers pretend to engineer innovative biomaterials and cell-derived scaffolds that mimic complex human structures and their biochemical properties, with promising industrial applications.

"The Biomaterials for Regenerative Therapies group is developing 3D models for tumour research based on cells self-produced extracellular matrix."

Recent activities related to cancer

We are developing 3D models for tumour research based on cells self-produced extracellular matrix as natural scaffolds that mimic human tissues' architecture, biochemical and mechanical properties. To achieve this, we are creating cell-derived matrix (CDM) scaffolds using poly (lactic acid) microparticles as sacrificial templates. These CDMs cultured with cancer cells and other cell types from the tumour microenvironment (TME) simulate an ex vivo tumour generation and progression to closely resemble the human TME (cell populations, extracellular matrix proteins in a 3D structure, cytokines and cancer biomarkers expression, mechanical properties, etc.). Hidrogels and decellularized matrices are also being used as scaffolds. All together, these models can be used for basic cancer research in tumour development, progression and metastasis, as promising platforms for patient specific diagnose and treatment and for new drug screening purposes and the identification of potential therapeutic targets.



Colorectal cancer cell-derived matrices (CDMs). A) Fibronectin (green) staining of CDMs (scale bar = 100mm). B) Cytokeratin (red) and nuclei (blue) staining of colorectal cancer cell spheroids (HT29; scale bar = 50mm). C) Histological section of a colorectal Signet ring carcinoma.

The tumour microenvironment plays an essential role in the tumour generation, progression and metastasis. It is formed by a three-dimensional extracellular matrix (ECM), cells and non-cellular components such as cytokines, chemokines and other signalling molecules. The ECM is a complex nanofibrous network involved in several cellular functions. During cancer progression ECM physico-chemical properties are altered due to its remodelling and stiffening, which results into changes in the different cell populations behaviour avoiding cell death and immune suppression mechanisms. The main scientific aims of this project are obtaining cancer CDMs and evaluate them as 3D colorectal and breast cancer physiological models for cancer therapeutics screening and to decipher the properties of the matrix that lead this disease progression, metastasis and resistance to existing therapies.

Funded projects related to cancer

MATRICELL	MICIN
LYMPH NODE-INSPIRED 3D PRINTED HYDROGELS FOR ADOPTIVE CELL THERAPY	VALORIZACIÓN CIBER
GELS4ACT · LYMPHA NODE-INSPIRED 3D PRINTED HYDROGELS FOR ADOPTIVE CELL THERAPY	CIBER-BBN

Main recent publications related to cancer

Rubi-Sans G., Castano O., Cano I., Mateos-Timoneda M.A., Perez-Amodio S., Engel E. (2020). Engineering Cell-Derived Matrices: From 3D Models to Advanced Personalized Therapies. Advanced Functional Materials 2020, 30, 2000496

Barbara Blanco-Fernandez, Irene Cano, Cristina Garrido, Gerard Rubi-Sans, Lourdes Sanchez-Cid, Marta Guerra-Rebollo, Nuria Rubio, Jeronimo Blanco, Miguel A. Mateos-Timoneda, Soledad Perez-Amodio and Elisabeth Engel. Engineering cell-based microtissues for prostate cancer bystander therapies. (Submitted)

Gerard Rubí-Sans, Soledad Pérez-Amodio, Agata Nyga, Elena Rebollo, Jordi Otero, Daniel Navajas, Miguel Ángel Mateos-Timoneda, Elisabeth Engel. In vitro development of 3D cell-derived extracellular matrices. (Submitted)

Blanco-Fernandez, B., Gaspar, V.M., Engel, E., Mano, J.F. Bioengineering the tumor microenvironment with protein and peptide-based ECM-mimetic hydrogels. Accepted for publication in Biotechnology Advances.

Nanoprobes and nanoswitches

Pau Gorostiza

The nanoprobes and nanoswitches research group focuses on developing nanoscale tools to study biological systems. These tools include instrumentation based on proximity probes applied to investigate individual redox proteins.

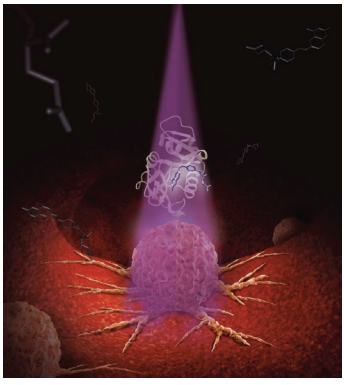
Another set of nanotools that we are developing is based on molecular actuators that can be switched with light, such as azobenzene, which can be chemically attached to biomolecules in order to optically control their activity. We have demonstrated for the first time two-photon stimulation of neurons and astrocytes with azobenzene-based photoswitches. We have also developed several bioactive compounds that have been engineered to be regulated by light. These "photopharmacological" 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.

"The optopharmacology expertise of the nanoprobes and nanoswitches group can be used to design anticancer photoswitchable drugs to reduce side effects, as drugs are only activated on demand."

Recent activities related to cancer

We have developed phototrexate, the first photoswitchable inhibitor of the human dihydrofolate reductase (DHFR), as a photochromic analogue of methotrexate, a widely prescribed chemotherapeutic drug to treat cancer and psoriasis. Quantification of the light-regulated DHFR enzymatic activity, cell proliferation, and *in vivo* effects in zebrafish show that phototrexate behaves as a potent antifolate in its photoactivated cis configuration and that it is nearly inactive in its dark-relaxed trans form. Phototrexate constitutes a proof-of-concept to design light-regulated cytotoxic small molecules and a step forward to develop targeted anticancer photochemotherapies with localized efficacy and reduced adverse effects. During 2019, we have been working in the valorization of this technology to transfer it to the market.

The second approach with photoswitchable drugs has focused on peptide-based drugs, which are highly specific, non-immunogenic, and can be designed to cross the plasma membrane. In order to combine target specificity and remote control of drug action, we designed a versatile strategy based on a generalized template to design nanoswitchable peptides that modulate protein–protein interactions upon light activation. This approach promotes photomodulation of two important targets involved in apoptosis (the interactions Bcl-xL–Bak and MDM2–p53), but can be also applied to a large pool of therapeutically relevant protein–protein interactions mediated by α-helical motifs.



Rational structural modifications of the chemotherapy agent methotrexate enabled control of cytotoxic efficacy with light.

Funded projects related to cancer

ADME STUDIES AND PRELIMINARY SAFETY PHARMACOLOGY OF A LIGHT- REGULATED LEAD COMPOUND FOR TARGET-SPECIFIC PHOTODYNAMIC THERAPY OF SKIN DISEASES	CIBER-BBN VALORIZACIÓN

Main recent publications related to cancer

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Signal and information processing for sensing systems

Santiago Marco

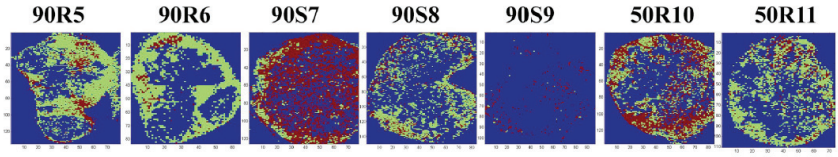
Current smart instrumentation using multi-sensors and/or spectrometers provides a wealth of data that requires sophisticated signal and data. The Signal and information processing for sensing systems group is interested in intelligent chemical instruments for the detection of volatile compounds and smells. These systems can be based on an array of nonspecific chemical sensors with a pattern recognition engine, inspired from the olfactory system. Some spectrometries 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. The group develops algorithmic solutions for the automatic processing of Gas Sensor Array, Ion Mobility Spectrometry and Gas Chromatography – Mass Spectrometry data for food samples and metabolomics, including applications to cancer theranostics.

"We are developing algorithms to study the heterogeneity in colorectal cancer tissues and its metabolites."

Recent activities related to cancer

We are developing algorithms for the analysis of mass spectrometry images for the study of heterogeneity in colorectal cancer tissues. The multivariate data processing pipeline relies on three steps: (a) multiset multivariate curve resolution (MCR) to separate biological contributions from background; (b) multiset K-means segmentation using MCR scores of the biological contributions to separate between tumour and necrotic parts of the tissues; and (c) partial-least squares discriminant analysis (PLS-DA) applied to tumour pixel spectra to discriminate between R and S tumour populations. If previously labelled tissue is available, the multistep modelling strategy proposed constitutes a good approach for the identification and characterization of highly similar phenotypic tumour subpopulations that could be potentially applicable to any kind of cancer tissue.

Moreover, we are also looking for alternatives for colorectal cancer diagnosis using urine metabolites. We are using computational tools to analyse LC-MS and GC-IMS data to identify novel biomarkers.



Distribution of R (green) and S (red) tumour populations in the heterogenous images obtained from xenografs.

Funded projects related to cancer

TENSOMICS DEVELOPMENT OF TENSORIAL SIGNAL PROCESSING AND MACHINE LEARNING TOOLS TAILORED TO THE ANALYSIS OF URINE METABOLOMICS	MINECO

Main recent publications related to cancer

Mas S, Torro A, Fernández L, Bec N, Gongora C, Larroque C, Martineau P, de Juan A, Marco S. (2020) MALDI imaging mass spectrometry and chemometric tools to discriminate highly similar colorectal cancer tissues. Talanta 208,120455.

Mas S., Torro A., Bec N., Fernández L., Erschov G., Gongora C., Larroque C., Martineau P., de Juan A., Marco S. (2019). Use of physiological information based on grayscale images to improve mass spectrometry imaging data analysis from biological tissues. Analytica Chimica Acta 1074, 69-79.

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. However, they rely on two dimensional monolayer cellular cultures, which fail to replicate the complexity of living systems.

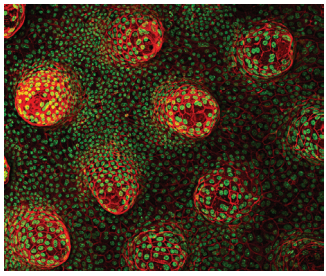
The biomimetic systems for cell engineering group proposes to combine engineering microfabrication technologies, tissue engineering concepts and recent advances in stem cell research, to create cell culture microenvironments that will go beyond current 3D *in vitro* models. Resulting *in vitro* tissue 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 will be compatible with conventional cell culture assays and high-throughput testing.

"Our knowledge on engineering microfabrication technologies, tissue engineering and stem cell can be used to help in the development innovative devices for cancer diagnosis and therapy monitoring."

Recent activities related to cancer

In the framework of an ERC Consolidator Grant we are developing functional, *in vitro* models of the intestinal epithelium, which protects the area against physical, chemical and microbial damage. As this is one of the most actively renewing tissues in the body, as well as a major site of carcinogenesis, achieving working models of the intestinal epithelium would be invaluable for basic and clinical research into intestinal disease modelling, including cancer, drug discovery and tissue replacement, among other things, as well as providing essential tools for adult stem cell research.

We also participated in a European H2020 project "Glass Laser Multiplexed biosensors" with the aim to develop an innovative device for personalized diagnosis and therapy monitoring for genitourinary cancers. It capitalized on the unprecedented sensitivity achieved using laser microring resonators to detect key biomarkers in tumour development and treatment. We participated in various tasks including the micro-ring design and chemical functionalisation of the micro-ring, taking into account the selectivity, as well as establishing the specifications for the detection of biomarkers. Also, we contributed to the fabrication of multiplexed micro-ring resonator arrays and chip packaging.



Mimicking small intestinal tissue by culturing intestinal-organoid derived cells on poly(ethylene glycol) diacrylate (PEGDA) microstructures. Cell nuclei are stained in green and actin cytoskeleton in red.

Funded projects related to cancer

GLAM · GLASS-LASER MULTIPLEXED BIOSENSOR	EUROPEAN COMMISSION (H2020) – PHC-10-2015
COMIET · ENGINEERING COMPLEX INTESTINAL EPITHELIAL TISSUE MODELS	ERC CONSOLIDATOR GRANT
METASTARG · TARGETED MULTIFUNCTIONAL NANOEMULSIONS TO INTERRUPT METASTASIC PROGRESSION	EURONANOMED (ERANET).
PROMISE · BIOPRINTED HYDROGEL MICROFLULDICS TO MIMIC PATIENT-SPECIFIC TUMOR METASTATIC MICROENVIRONMENT	OBRA SOCIAL LA CAIXA

Main recent publications related to cancer

De Goede, M.; Chang, L., Mu, J.; Dijkstra, M.; Obregón, R.; Martínez, E.; Padilla, L., Mitjans, F.; García-Blanco, S. Al2O3:Yb3+ integrated microdisk laser label-free biosensor, Optics Letters 2019, 27(13); 18508-18520.

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Macedo, M.H., Araújo, F., Martínez, E., Barrias, C., Sarmento, B. (2018). iPSC-Derived enterocyte-like cells for drug absorption and metabolism studies. Trends in Molecular Medicine 24, 696-708

Patent

European Patent Application No. EP19382327.5. SELF-REFERENCED SENSOR. Filed 30th April 2019.

Pluripotency for organ regeneration

Núria Montserrat

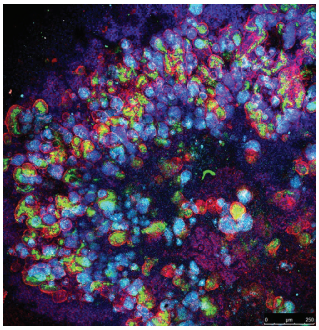
The aims of the Pluripotency for organ regeneration Group is to generate human pluripotent stem cells incorporationg disease-specific mutations for disease modelling and drug screening. The combination of gene-editing based methodologies together with the development of novel protocols for cell differentiation into relevant organoids, provides a unique scenario for modelling disease progression. In an effort to fully exploit these model systems the research team is focused in the development of reporter cell lines for different transcription factors essential for tissue-specific commitment and differentiation. Furthermore, the possibility to combine pluripotent stem cell lines together with decellularized matrices, functionalized biomaterials and microfluidic devies offers and unprecedented opportunity for the generation of patient-specific organoids, including tumour organoids to understand tumor initiation and cancer progression.

"The 3D models developed in our group are used to study how cells react when other changes take place, such as the development of cancer, as well as platforms for anti-cancer drug screening."

Recent activities related to cancer

In the framework of a project funded by the AECC, the group is working on the development of human model to study clear cell renal cancer (ccRCC), the most common type of kidney cancer. To develop the disease model, they are creating a 3D-organoid – a kidney-on-a-chip – from human pluripotent stem cells, which will demonstrate how the tissue in the organ develops, as well as how it reacts when other changes take place, such as disease. Within this model, the researchers will be able use a gene editing method, CRISPR-Cas9, to manipulate those genes related to the appearance of disease and identify possible early signs that cancer might develop.

Clear cell renal cancer engineered kidney organoids or mini-kidneys and their derived xenograft models are also being developed for the identification of new pathways and targets for ccRCC progression. This knowledge will allow to further implement these molecules as tools for treatment of advanced ccRCC in the clinical setting. Although this type of cancer has been extensively studied there is an important lack of targeted effective therapies that are effective for this disease. Therefore, there is an important unmet medical need to identify new pathways and markers of this in order to improve the therapeutic efficacy and prognosis for this disease.



Confocal image of a kidney organoid generated in vitro by hPSC differentiation in 3D culture. Proximal tubule-like structures (in green) and the Laminin (in red) is found in the basement membrane of the renal structures. Nuclei are detected by DAPI staining (in blue).

Funded projects related to cancer

GENERATION OF ISOGENIC MODELS OF CLEAR CELL RENAL CELL CARCINOMA (CCRCC) USING CRISPR-ENGINEERED KIDNEY ORGANOIDS, FOR THE IDENTIFICATION OF DIAGNOSTIC BIOMARKERS.	ASOCIACIÓN ESPAÑOLA CONTRA EL CÁNCER (AECC)
IDENTIFICATION OF KIDNEY CANCER PROGRESSION TARGETS AND BIOMARKERS THROUGH CRISPR-ENGINEERED ORGANOIDS AND XENOGRAFT MOUSE MODELS	FUNDACIÓ LA MARATÓ DE TV3

Main recent publications related to cancer

Garreta E, Prado P, Tarantino C, Oria R., Fanlo L., Martí Elisa Z., Dobryna, Trepat X., Roca-Cusachs P., Gavaldà -Navarro A., Cozzuto L., Campistol J.M., Izpisúa Belmonte J.C., Hurtado del Pozo C., Montserrat N. (2019). Fine tuning the extracellular environment accelerates the derivation of kidney organoids from human pluripotent stem cells. Nature Materials 18, 397-405.

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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. The cellular and molecular mechanobiology group 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, biophysical techniques like magnetic tweezers, Atomic Force Microscopy, traction microscopy, and microfabricated force sensors with molecular biology, advanced optical microscopy, and theoretical modelling are combined.

"The cellular and molecular mechanobiology group studies how tissue stiffness and mechanical forces activate cancer."

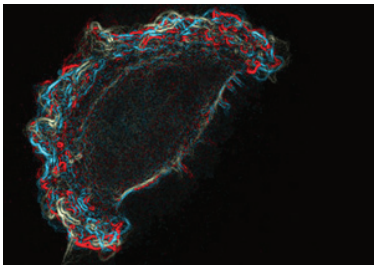
Recent activities related to cancer

We are coordinating a FET-proactive project called MECHANOCOTROL that focuses on understanding and controlling how cells transmit and detect mechanical forces in order to come up with new therapeutic or diagnostic approaches for cancer and other diseases. We are developing technologies from the molecular to the organoid scale to control, characterize, and mechanistically define the role of molecular adhesion and mechanics in breast cancer.

To evaluate the crosstalk between mechanical factors, cancer diagnosis, and treatment, we have begun analyzing samples from breast tumors provided by Vall d'Hebron Institute of Oncology. We are currently carrying out initial immune-staining analyses, with the aim of determining whether our findings in cell culture systems are also translated to patient samples.

We are also working on the development of drugs for the treatment of solid tumours based on interfering with cell sensing of mechanical forces.

We have started a project entitled "Understanding YAP-mediated mechanotransduction in pancreatic cancer" funded by la Marató de TV3, in collaboration with Miguel Ángel del Pozo Barriuso (CNIC) The project aims to understand how tissue stiffness affects pancreatic cancer. Specifically, will put its focus on the role of a molecule called YAP, which activates specific genes and is known to play a role both in pancreatic cancer and in cell response to stiffness. We will develop tools to understand the molecular mechanisms by which pancreatic tumours respond to stiffness through YAP, and what the implications are in order to be able to design novel drugs against pancreatic cancer. Pancreatic cancer is the fourth cause of cancer-related deaths across the world. Once it is diagnosed, it also has the lowest survival rate of all major cancers, as only 2-10% of diagnosed people survive after five years.



Visualization of the movement of the structures that cells use to exert force on their environment.

Funded projects related to cancer

UNDERSTANDING AND MEASURING MECHANICAL TUMOR PROPERTIES TO IMPROVE CANCER DIAGNOSIS, TREATMENT, AND SURVIVAL: APPLICATION TO LIQUID BIOPSIES	OBRA SOCIAL LA CAIXA
TALVIN · INHIBITING MECHANOTRANSDUCTION FOR THE TREATMENT OF PANCREATIC CANCER	EUROPEAN COMISSION – FET INNOVATION LAUNCHPAD
DESARROLLO DE UNA TERAPIA INNOVADORA PARA EL TRATAMIENTO DE LOS TUMORES SÓLIDOS MEDIANTE LA INHIBICIÓN DE LA MECANOTRANSDUCCIÓN	MINECO – RETOS COLABORACIÓN
MECHANO-CONTROL · MECHANICAL CONTROL OF BIOLOGICAL FUNCTION	EUROPEAN COMISSION – FET PROACTIVE
UNDERSTANDING YAP-MEDIATED MECHANOTRANSDUCTION IN PANCREATIC CANCER	FUNDACIÓ LA MARATÓ DE TV3
MECH4CANCER · ENABLING TECHNOLOGIES TO MAP NUCLEAR MECHANOSENSING: FROM ORGANOIDS TO TUMORS	OBRA SOCIAL LA CAIXA

Main recent publications related to cancer

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Uroz M., Garcia-Puig A., Tekeli I., Elosegui-Artola A., Abenza J.F., Marin-Llaurado A., Pujals S., Conte V., Albertazzi L., Roca-Cusachs P., Raya A., Trepat X. (2019). Traction forces at the cytokinetic ring regulate cell division and polyploidy in the migrating zebrafish epicardium. Nature Materials 18, 1015-1023.

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Kechagia J.Z., Ivaska J., Roca-Cusachs P. (2019). Integrins as biomechanical sensors of the microenvironment. Nature Reviews Molecular Cell Biology 20, 457-473.

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Elosegui-Artola, A., Trepat, X., Roca-Cusachs, P. (2018). Control of mechanotransduction by molecular clutch dynamics. Trends in Cell Biology 28, 356-367.

Nanobioengineering

Josep Samitier

The Nanobioengineering group is a 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 for main clinical problems, including cancer.

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.

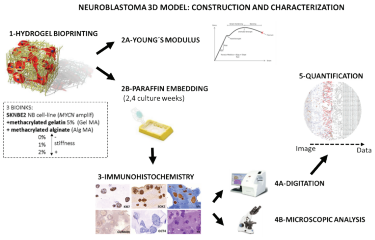
"The Nanobioengineering lab is developing novel bioengineering tools for in-vitro screening novel targets and test new drugs to fight cancers like neuroblastoma, melanoma, lung or paediatric cancers."

Recent activities related to cancer

Using a previously developed assay called dynamic BH3 profiling (DBP) that can rapidly detect early changes in the BCL-2 family of proteins preceding the activation of apoptosis and the cancer cell's commitment to death, we are working in collaboration with oncologists at Hospital Sant Joan de Déu to identify and test optimal therapeutic strategies to treat paediatric brain and spinal cord tumours. We intend to use DBP to study how driving signalling pathways control paediatric cancer cells survival and detect druggable targets. Once identified, we will explore new treatments, including drugs such as BH3 mimetics and immunotherapy, studying synergistic combinations of anticancer agents to treat different types of paediatric brain tumours.

Moreover, we are currently working on fabrication of three dimensional in-vitro cell-derived physio pathological matrices with controlled geometries and mechanical properties. This in-vivo-like microenvironment will be used to study malignant neuroblasts growth, migration, invasion and to guide the choice of therapy or to accurately predict the clinical efficacy. Also, building biomimetic models of neuroblastoma to investigate the resistance of tumours to different therapies, as well as the mechanisms that lead to the formation of vasculature in cancer.

On another hand, the characterization of circulating tumour cells (CTCs) is a key element to understand how they invade distant organs, settle in supportive niches and eventually overtake their host tissue. Their detection and characterization therefore require highly sensitive and specific methods combining enrichment (isolation) and detection (identification) strategies. At the moment, even though CTC isolation can be successfully achieved, the bulky instrumentation required for the subsequent detection and characterization remains a barrier to the development of CTC-based, point-of-care test. We are working on the development of microfluidic platforms for the separation and analysis of CTCs using nanotechnology combined with a lab-on-a-chip system, that will help to overcome this problem.



Scheme of the neuroblastoma in-vitro model: . 1. Hydrogel bioprinting; 2. Young's modulus measurement and paraffin embedding; 3. Immunohistochemistry; 4. Digitation and microscopic studies; 5. Analysis and quantification. From Scientific Reports 2020

Furthermore, we are also working on the development of nanovaccines based on degradable nanoparticles that target tumour associated antigens and activation stimuli to dendritic cells.

Funded projects related to cancer

PERSONALIZING PEDIATRIC CANCER TREATMENT	FUNDACIÓN FERO
ONCOKIDS	ONCOKIDS SERVEI D'ASSESSORAMENT
PERSONALIZING MELANOMA TREATMENT USING DYNAMIC BH3 PROFILING	DANA-FARBER CANCER INSTITUTE, INC.
UNDERSTANDING AND MEASURING MECHANICAL TUMOR PROPERTIES TO IMPROVE CANCER DIAGNOSIS, TREATMENT, AND SURVIVAL: APPLICATION TO LIQUID BIOPSIES	OBRA SOCIAL LA CAIXA
NANOVAX · NANOVACUNAS DISEÑADAS PARA INMUNOTERAPIA ANTITUMORAL	EURONANOMED (ERA-NET)
PREMED · DESARROLLO DE UN ENSAYO MICROFLUÍDICO FUNCIONAL EN CÉLULAS PARA EL TRATAMIENTO PERSONALIZADO CONTRA EL CÁNCER	MICIU: RETOS DE INVESTIGACIÓN
NEUROBLASTOMA EN UN CHIP PARA INVESTIGAR LA RESISTENCIA A FÁRMACOS Y EL USO DE NANOPARTÍCULAS TERAPÉUTICAS	ASOCIACIÓN ESPAÑOLA CONTRA EL CÁNCER (AECC)
3D *IN VITRO* MODELS FOR NEUROBLASTOMA MECHANOTHERAPY IDENTIFICATION	CIBER-ONC-CIBER-BBN -INSTITUTO DE SALUD CARLOS IIII

Main recent publications related to cancer

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Smart nano-bio-devices

Samuel Sánchez

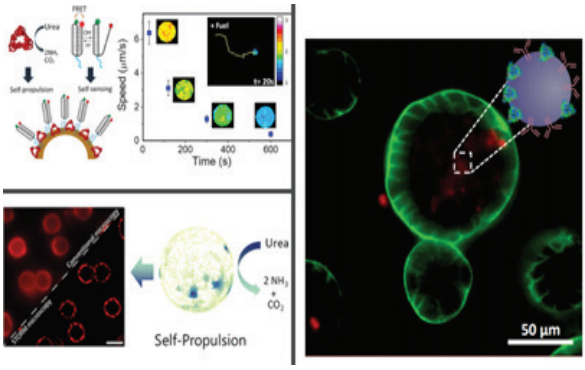
The smart nano-bio-devices group develops different bioengineering systems ranging from active nanoparticles (nanobots), 3D Bioprinted Actuators and 3D Bioprinted soft robotics. The group is interested in fundamental studies of active matter, the use of nanobots for future nanomedicine and environmental applications and the bioengineering of new devices based for robotics and medical purposes. The group has demonstrated the use of different enzymes, including urease and glucose oxidase, to generate active propulsion of nano– and microparticles, paving the way towards new applications in biomedicine. They have demonstrated that using enzyme-powered nanomotors can enhance anti-cancer drug delivery *in vitro*, improve the targeting of 3D bladder cancer spheroids and sense their surrounding environment. Current studies are moving forward in vivo imaging of nanobots and their target in patient-derived samples to demonstrate enhanced tumor targetting and delivery.

"The smart nano-bio-devices group is working on the design of the self-propelled nanomotors to enhance drug delivery to cancer cells to improve efficacy."

Recent activities related to cancer

In the field of bladder cancer, the group has been working on the development of nanomotors that are able to attack 3D bladder cancer spheroids *in vitro*. The nanomotors carry anti-FGFR3 on their outer surface, an antibody that not only enables cancerous cells to be specifically targeted, but also inhibits the fibroblast growth factor signalling pathway, suppressing tumour growth. Crucially, the fuel that gives the nanomotors the capability of autonomous motion is urea, which is present at high concentrations in the bladder – making these particular nanomotors a promising avenue for this particular cancer.

The group is also working on medical micro- and nano-robots for molecular imaging. The project is developing biocompatible robots driven by enzymes with applications as drug release systems whose progress *in vitro* and *in vivo* can be traced using advanced molecular imaging techniques such as super-resolution microscopy. The idea is to take advantage of the chemical reaction that causes the propulsion of these nanoparticles as a contrast agent to improve the molecular image in cancer. The ultimate goal will be that lower quantities of a cancer drug would need to be administered, thus reducing the many side effects that can occur.



Smart micro- and nanorobots are able to swim, monitor their own activity, sense their environment and deliver drugs to 3D bladder cancer spheroids using biocompatible and bioavailable fuels such as urea..

Funded projects related to cancer

TERANOBOTS · NANOROBOTS FOR BLADDER CANCER THERANOSTICS	OBRA SOCIAL LA CAIXA
MEDIROBOTS · MEDICAL MICRO- AND NANO-ROBOTS FOR MOLECULAR IMAGING	FUNDACIÓN BBVA
INANOSWARMS · ERC-CONSOLIDATOR GRANT	EUROPEAN RESEARCH COUNCIL

Main recent publications related to cancer

Llopis-Lorente, A., García-Fernández, A., Murillo-Cremaes, N., Hortelão, A. C., Patiño, T., Villalonga, R., Sancenón, F., Martínez-Máñez, R., & Sánchez, S. (2019). Enzyme-Powered Gated Mesoporous Silica Nanomotors for On-Command Intracellular Payload Delivery. ACS nano, 13, 12171–12183.

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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.

The Bacterial infections: antimicrobial therapies group aims to investigate new antimicrobial therapies and strategies to combat bacterial infections. In a complementary way, our expertise with antimicrobials and the enzyme ribonucleotide reductase (RNR), critical for the formation of the building blocks needed for bacterial DNA synthesis and repair, has been used to test and find novel anticancer therapies based on existing antibacterial agents.

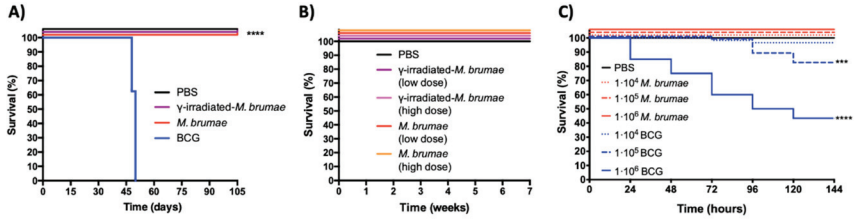
Also, the group is collaborating in the discovery of new molecules with antiproliferative activity in bacterial cells and eukaryotes. Finally, in close collaboration with the research group lead by Esther Julian at the Universitat Autònoma de Barcelona, we are working on the use of mycobacteria cells for the anti-tumor, and immunotherapy of bladder cancer.

"Our deep knowledge in antimicrobial therapies can be useful to study the effect of anticancer drugs on bacteria and antimicrobial drugs in cancer."

Recent activities related to cancer

On the one hand, New Water-Soluble Copper(II) Complexes with Morpholine-Thiosemicarbazone Hybrids have been studied. Insights into the processes controlling intracellular accumulation and mechanism of action have been investigated, including the role of ribonucleotide reductase (RNR) inhibition, endoplasmic reticulum stress induction, and regulation of other cancer signalling pathways.

On the other hand, we have studied the immunomodulatory effect of vaccines used against tuberculosis for the treatment of non-muscle-invasive bladder cancer. Intravesical Mycobacterium bovis Bacillus Calmette-Guérin (BCG) immunotherapy remains the gold-standard treatment for non-muscle-invasive bladder cancer patients, even though half of the patients develop adverse events to this therapy. On exploring BCG-alternative therapies, Mycolicibacterium brumae, a nontuberculous mycobacterium, has shown outstanding anti-tumor and immunomodulatory capabilities. We have shown that M. brumae constitutes a safe therapeutic biological agent, overcoming the safety and toxicity disadvantages presented by BCG in both mice and G. mellonella animal models.



*Kaplan–Meier survival curves after intravenous (IV)-infection and intravesical (IB)- inoculation in mice and intrahemacoelic infection in G. mellonella. (A) SCID mice (n = 8/group) received a single intravenous infection of live (red) or (purple) γ-irradiated M. brumae or Bacillus Calmette–Guérin (BCG) (blue), or PBS (black). BCG-infected mice survived for over 48 days, whereas the rest of mice groups survived until the end of the study. **** p < 0.0001 (Mantel–Cox test). (B) Balb/C mice (n = 8/group) received IB instillations with low (purple) or high doses (violet) of live γ-irradiated; low (red) or high doses (orange) of live M. brumae; or PBS (green). All animals survived until the end of the experiment; (C) G. mellonella larvae (n = 60/group) were infected with 1 × 104; 1 × 105 or 1 × 106 CFU/larvae of M. brumae or BCG, or PBS as control *** p < 0.0005; **** p < 0.0001 (Mantel–Cox test).*

Main recent publications related to cancer

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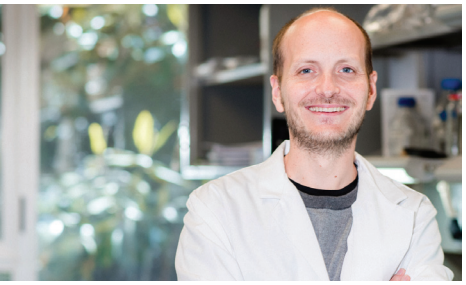


Integrative cell and tissue dynamics

Xavier Trepat

The Integrative cell and tissue dynamics group aims at understanding how physical forces and molecular control modules cooperate to drive biological function. It develops 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 the group explores the principles that govern the interplay between chemical and physical cues in living tissues and study how these principles are regulated in physiology and development, and how they are derailed in cancer and aging.

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

"The Integrative cell and tissue dynamics group studies how physical forces and molecular control are regulated in physiology and development, and how they are derailed in cancer."

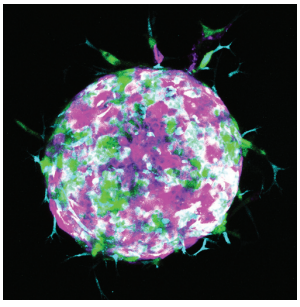
Recent activities related to cancer

We are working to unravel the molecular mechanisms by which cells detect and respond to tissue stiffness and how mechanical factors govern cancer invasion. We are analysing patient samples and data to shed light on how mechanical factors, cancer diagnosis, and treatments interfere or interact with each other. This will lead to the discovery of new biomarkers and develop targeted drug delivery strategies with maximum efficiency.

Cells are able to migrate along gradients of extracellular matrix stiffness, a process called durotaxis. The mechanisms underlying this type of directed migration, implicated in tumour progression, remain unknown. We are studying the molecular mechanisms governing durotaxis.

We have started a project on T-cell exclusion during cancer immune evasion and immunotherapy failure: cell types, transcriptional programs and biomechanics funded by La Marató de TV3. Together with Eduard Batlle from IRB Barcelona, and Holger Heyn from CRG, we are investigating the mechanisms used by the tumor cells to prevent migration and the function of immune cells in colorectal cancer. This will be used to improve immunotherapy.

In collaboration with Vall d'Hebron Institute of Oncology, we aim to characterize the mechanical regulation behind tumour invasion. We have developed new approaches to measure traction forces, intra-cellular forces and inter-cellular forces in the presence or absence of mechanical gradients. We have studied how induction of intercellular adhesion affects intercellular forces, traction forces and the invasive capacity of cellular clusters. We have also developed new algorithms to compute traction forces in three dimensions.



Cancer cells and cancer associated fibroblasts invade the extracellular matrix.

We are also participating in MECHANOCONTROL, a FET-proactive project, to understand and control how cells transmit and detect mechanical forces in order to come up with new therapeutic or diagnostic approaches for cancer and other diseases.

Together with Erik Sahai at the Francis Crick Institute we are studying the role of tumor-stroma interactions in cancer progression. We are analyzing how mechanical forces between cancer cells and cancer associated fibroblasts enable collective cancer cell invasion. We are also studying how forces between stromal cells remodel the extracellular matrix to shape tumors.

Funded projects related to cancer

UNDERSTANDING AND MEASURING MECHANICAL TUMOR PROPERTIES TO IMPROVE CANCER DIAGNOSIS, TREATMENT, AND SURVIVAL: APPLICATION TO LIQUID BIOPSIES	OBRA SOCIAL LA CAIXA
TENSIONCONTROL · MULTISCALE REGULATION OF EPITHELIAL TENSION	ERC CONSOLIDATOR GRANT
MECHANO-CONTROL · MECHANICAL CONTROL OF BIOLOGICAL FUNCTION	EUROPEAN COMISSION – FET PROACTIVE
EPIFOLD · ENGINEERING EPITHELIAL SHAPE AND MECHANICS: FROM SYNTHETIC MORPHOGENESIS TO BIOHYBRID DEVICES	ERC ADVANCED GRANT
T-CELL EXCLUSION DURING CANCER IMMUNE EVASION AND IMMUNOTHERAPY FAILURE: CELL TYPES, TRANSCRIPTIONAL PROGRAMS AND BIOMECHANICS	FUNDACIÓ LA MARATÓ DE TV3
MECH4CANCER - ENABLING TECHNOLOGIES TO MAP NUCLEAR MECHANOSENSING: FROM ORGANOIDS TO TUMORS -	OBRA SOCIAL LA CAIXA

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