BIOENGINEERING
FOR RARE DISEASES TREATMENTS

IBEC
Institute for Bioengineering of Catalonia

EXCELENCIA
SEVERO
OCHOA

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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.

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.

BIOENGINEERING FOR RARE DISEASES TREATMENTS

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.

Rare diseases are some of the maladies that can benefit most from the novel bioengineering approach. The field of rare diseases suffers from a deficit of medical and scientific knowledge. There is no cure for most rare diseases, or even diagnostic tools, but the appropriate treatment and medical care can improve the quality of life of those affected and extend their life expectancy.

IBEC researchers, in collaboration with international clinical groups and companies, are using their bioengineering expertise to develop novel therapies and diagnostic tools for rare diseases such as cystic fibrosis, muscular dystrophy and lysosomal storage disorders, to name only a few.

Bioengineering is used at IBEC in a multidisciplinary way to fight rare diseases: biosensors, microfluidic devices, organ-on-a-chip and organoids for disease modelling and drug screening, targeted drug delivery, high-throughput mutagenesis and light-regulated molecular prostheses.

Out of the 22 groups presently working at IBEC, 9 are currently involved in projects related to rare diseases. Since 2018, our researchers have published more than 40 publications focusing on rare diseases, including contributions in top impact journals such as Nature Communications, Nature Cell Biology, EMBO Journal, or

Science Translational Medicine. In the last years, our research on rare diseases has attracted competitive funding, including ERC grants, and national grants from the Ministry of Science and the Spanish Network of Neurodegenerative diseases (Ciberned) as well as private funding from Fundació “La Caixa”, Fundació Joan Ribas Araquistain or the Catalan Association of Cystic Fibroses.

At an institutional level, IBEC has signed a collaboration agreement with the Federación Española de Enfermedades Raras (FEDER), a non-profit organization that represents the three million people suffering from rare diseases throughout the country. The aim of this collaboration is to connect the institute with patients’ associations to develop projects together that have a direct application according to the needs of sufferers. IBEC has also collaborated with specific patient associations such as the Myotonic Muscular Dystrophy Patients Association, the Catalan Association of Cystic Fibroses and the Spanish Federation of Retinitis Pigmentosa Associations (FARPE).

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 rare diseases. Among other initiatives, since 2019, IBEC organizes in collaboration with Hospital Sant Joan de Déu the Nano Rare Diseases Day.

Bioengineering for Rare diseases 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.

There are over 300 million people living with one or more of over 6,000 identified rare diseases around the world. Through the research and innovation activities described in the following pages and in collaboration with its international network of partner institutions, IBEC aims to contribute, as stated in the Rare Disease Day campaign (https://www.rarediseaseday.org/), to achieve equitable access to diagnosis, treatment, health and social care and social opportunity for people affected by a rare disease and give hope to millions of patients and their families.

Protein phase transitions in health and disease

Benedetta Bolognesi

We aim to understand how protein sequences can become toxic upon mutation. We are particularly interested in amino acid sequences that can adopt different conformations and undergo a process of self-assembly which results in distinct physical states. In order to understand how mutations affect these delicate equilibria and when and why a sequence becomes toxic for the cell in the context of different types of disease, our lab integrates experimental and computational approaches in different model systems.

Currently we focus mainly on classical amyloids, such as the amyloid-beta peptide found in Alzheimer's disease brains, but we are also exploring prion-like domains. Prion-like domains are frequently mutated in several rare neurodegenerative conditions, such as Amyotrophic Lateral Sclerosis. Just like most disordered protein regions, prion-like domains are particularly difficult to study in vitro. In this perspective, in vivo approaches such as the ones we develop, can provide a unique opportunity to investigate these sequences in a systematic way.

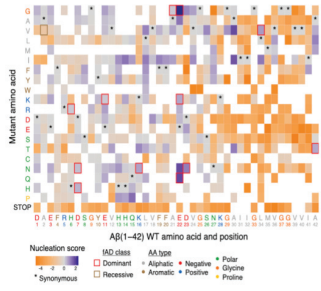
"We developed a deep mutational scanning strategy that allows to quantify the toxicity of thousands of mutations in TDP-43, a protein involved in inherited forms of amyotrophic lateral sclerosis."

Recent activities related to rare diseases

In collaboration with the CRG, we used high-throughput mutagenesis to study Amyotrophic Lateral Sclerosis (ALS). Amyotrophic lateral sclerosis is a devastating and incurable nervous system disease that affects nerve cells in the brain and spinal cord, causing loss of muscle control and normally death within a few years of diagnosis. We focused on TDP-43, a protein that aggregates in the motor neurons of nearly all ALS patients. We made over 50,000 mutants of TDP-43 and tracked their toxicity to yeast cells. The results showed that mutant forms that aggregated were, actually, less toxic than other versions of the protein which instead were forming unusual liquid species in the cells. We have also succeeded in determining the structure that this putatively disordered protein domain adopts inside the cell. The group is currently studying if the aggregation of TDP-43 is also protective in mammalian cells and neurons. If this proves to be the case, the way in which ALS is therapeutically addressed will have to be entirely changed.

Development of a massively parallel assay for amyloid nucleation and application to amyloid beta.

We have now developed a new high throughput method to quantify the effects of thousands of mutations in parallel on the nucleation of amyloid fibrils. In a pilot project we applied the method to the amyloid beta peptide (AB), which forms insoluble plaques in the brains of Alzheimer's disease patients. We could quantify how more than 15,000 mutations alter its aggregation. Remarkably, our preliminary map (Figure 1) identifies all of the known familial Alzheimer's disease mutations which cause horrific rare forms of dementia. Our work also provides many mechanistic insights into the process of amyloid nucleation which we are extending to other amyloid diseases. A manuscript is under review with the preprint available at:



https://www.biorxiv.org/content/10.1101/2020.09.22.308429v1.full

The amyloid nucleation propensity of amino acid substitutions in the amyloid beta peptide mapped by combining deep mutagenesis to our nucleation assay. Familial AD mutations are highlighted by red squares.

Funded projects related to rare diseases

PRIOMUT ESCANEADO EXHAUSTIVO DE MUTACIONES EN UN DOMINIO PRIÓNICO PARA ENTENDER LA TOXICIDAD INDUCIDA POR PROTEÍNAS	MICIU, RETOS INVESTIGACIÓN: PROYECTOS I+D

Main recent publications related to rare diseases

Bolognesi, B.; Faure, A.J.; Seuma, M.; Schmiedel, J.M.; Tartaglia, G.G.; Lehner, B. (2019). The mutational landscape of a prion-like domain Nature Communications 10, 4162

Seuma, M.; Faure, A.; Badia, M.; Lehner, B.; Bolognesi, B. The genetic landscape for amyloid beta fibril nucleation accurately discriminates familial Alzheimer's disease mutations. Under Review. https://www.biorxiv.org/content/10.1101/2020.09.22.308429v1.full

Molecular and cellular neurobiotechnology

José Antonio del Río

The Molecular and cellular neurobiotechnology group is made up of researchers developing their activities in developmental biology, neurobiology, and neurodegeneration.

Our research interests are focused on three main aspects of developmental neurobiology and neurodegeneration: 1) Development of new lab on chip devices for neurobiological research; 2) New strategies to avoid □-synuclein and tau transport in neurons; 3) New approaches to enhance axon regeneration after spinal cord lesion.

The main objective for the coming years is to focus on specific processes in tissue/organ regeneration also pointing to the development and application of new 3D in vitro platforms for the analysis of tissue/organ development and regeneration.

"We study the biology of neurodegenerative diseases, among them different rare diseases, such as Lafora, Gerstmann-Straussler-Scheinker syndrome, GGT, PART or Creutzfeldt-Jakob, to understand their pathogenesis and determine new biomarkers and putative therapeutical approaches."

Recent activities related to rare diseases

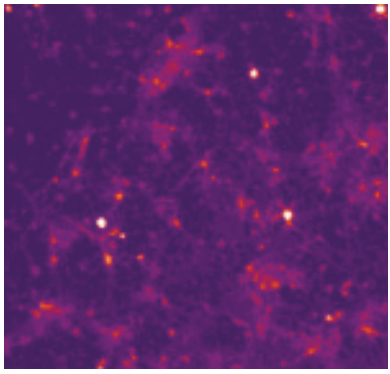
In the last years, we have been working in creating a lab on chip devices to analyse and to reproduce Amyotrophic lateral sclerosis (ALS) models (in collaboration with Biodonostia Hospital). The aim of these models is to mimic the developing and neurodegenerating nervous system in order to understand the disease pathogenesis in particular neuromuscular diseases.

We are also studying the interaction between □-synuclein, a key player in the pathogenesis of synucleinopathies, including Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy and PrPc a new receptor for □-synuclein involved in their spreading and propagation. Our objective is to block this interaction to reduce the neuropathological transport of □-synuclein. Current experiments are aimed to block the advance of particular tauopathies including Alzheimer´s disease.

As indicated, similar experiments are also developed in the case of tau, one of the hallmarks of Alzheimer´s disease and other tauopathies, since tau also binds to PrPC during its inter-neuronal propagation.

Another aspect of our research is related to spinal cord lesion in order to recapitulate some of the current strategies with new approaches and methods (i.e., omics) in order to develop basic research to be applied in future therapeutical strategies.

Lastly, we have collaborated with several groups in order to enhance our knowledge related to some rare diseases: i.e., Lafora disease, neuroinplamatory diseases, CJD, etc. Particularly of interest our laboratory developed by first time an in vitro model of GSS using induced plutipotent stem (iPS) cells.



Calcium waves in cultured cortical neurons growing on compartimentalized lab on chip devices

Funded projects related to rare diseases

PRPSEM · NUEVAS APROXIMACIONES PARA ENTENDER LAS FUNCIONES DE LA PRPC Y MIEMBROS SECRETABLES DE SEMAFORINAS DURANTE EL DESARROLLO DEL HIPOCAMPO Y EN NEUROTRANSMISIÓN	MICIU (RETOS INVESTIGACIÓN: PROYECTOS I+D)
STOPTAUPATHOL · MODULATION OF TAU SEEDING AND PATHOLOGY IN TAUOPATHIES BY BBBNANOCARRIERS, EPITOPE SELECTIVE VACCINATION AND ECTOPRP TAU RECEPTOR BODIES	OBRA SOCIAL "LA CAIXA"
PRIONET-SPAIN · RED DE EXCELENCIA NACIONAL DE PRIONES	MICIU (REDES TEMÁTICAS DE INVESTIGACIÓN)
CNED2016/2 · MONITORING THE ONSET AND EVOLUTION OF NEURONAL DYSFUNCTIONS IN PROPAGATIVE NEURAL DISORDERS USING MICROFLUIDIC DEVICES AND TRANSLATIONAL APPROACHES	SPANISH NETWORK OF NEURODEGENERATIVE DISEASES (CIBERNED), INSTITUTE OF HEALTH CARLOS III.
CNED2018/2 · ANÁLISIS CELULAR Y MOLECULAR DE LA SIEMBRA Y PROGRESIÓN DE TAU EN MODELOS ANIMALES Y CELULARES DE DISTINTAS TAUOPATIAS HUMANAS.	SPANISH NETWORK OF NEURODEGENERATIVE DISEASES (CIBERNED), INSTITUTE OF HEALTH CARLOS III.

Main recent publications related to rare diseases

Duran, J.; Brewer, M.K.; Hervera, A.; Gruart, A.; Del Rio, J.A.; Delgado-García, J.M.; Guinovart, J.J. (2020). Lack of astrocytic glycogen alters synaptic plasticity but not seizure susceptibility. Molecular Neurobiology. 57:4657-4666.

Del Rio, J.A.; Ferrer, I. (2020). Potential of microfluidics and lab-on-chip platforms to improve understanding of "prion-like" protein assembly and behavior. Frontiers in Bioengineering and Biotechnology 8:1057, doi: 10.3389/fbioe.2020.570692.

Ferrer, I.; Andrés-Benito, P.; Zelaya, M.V.; Aguirre, M.; Carmona, M.; Ausín, K.; Lachén-Montes, M.; Fernández-Irigoyen, J.; Santamaría, E.; Del Rio J.A. (2020). Familial Globular Glial Tauopathy Linked to MAPT Mutations: Molecular Neuropathology and Seeding Capacity of a Prototypical Mixed Neuronal and Glial Tauopathy. Acta Neuropathologica. 139(4):735-771.

Ferrer, I.; Andres-Benito, P.; Sala-Jarque, J.; Gil, V.; Del Rio, J.A. (2020). Capacity for seeding and spreading of argyrophilic grain disease in a wild-type murine model; comparisons with primary age-related tauopathy. Frontiers in Molecular Neurosciences, 13:101, doi: 10.3389/fnmol.2020.00101.

Ferrer, I.; Zelaya, M.V.; Aguiló García, M.; Carmona, M.; López-González, I.; Andrés-Benito, P.; Lidón, L.; Gavín, R.; Garcia-Esparcia, P.; del Rio, J.A. (2020). Relevance of host tau in tau seeding and spreading in tauopathies. Brain Pathology 30, 298-318.

Ferrer, I.; García, M. A.; Carmona, M.; Andrés-Benito, P.; Torrejón-Escribano, B.; Garcia-Esparcia, P.; Del Rio, J. A. (2019). Involvement of oligodendrocytes in tau seeding and spreading in tauopathies. Frontiers in Aging Neuroscience 11, 112

Del Rio, J.A.; Ferrer, I.; Gavín, R. (2018). Role of cellular prion protein in interneuronal amyloid transmission. Progress in Neurobiology 165-167: 87-102.

Ferrer, I.; García, M.A.; González, I.L.; Lucena, D.D.; Villalonga, A.R.; Tech, M.C.; Llorens, F.; Garcia-Esparcia, P.; Martinez-Maldonado, A.; Mendez, M.F.; Escribano, B.T.; Bech-Serra, J.J.; Sabido, E.; de la Torre Gómez, C.; Del Rio, J.A. (2018). Aging-related tau astrogliopathy (ARTAG): not only tau phosphorylation in astrocytes. Brain pathology 28(6), 965–985. https://doi.org/10.1111/bpa.12593

Llorens, F.; Thüne, K.; Martí, E.; Kanata, E.; Dafou, D.; Vivancos, A.P.; Shomroni, O.; Zafar, S.; Schmitz, M.; Michel, U.; Fernandez-Borges, N.; Andreóletti, O.; Del Río, J.A.; Díez, J.; Fischer, A.; Bonn, S.; Sklaviadis, T.; Maria, J.; Ferrer, I.; Zerr, I. (2018) Regional and subtype-dependent miRNA signatures in sporadic Creutzfeldt-Jakob disease are accompanied by alterations in miRNA silencing machinery and biogenesis. Plos Pathogens 22;14(1): e1006802.

Matamoros-Angles, A.; Mayela-Gayosso, L.; Richaud, Y.; di Domenico, A.; Vergara C.; Hervera, A.; Sousa, A.; Fernández Borges, N.; Consiglio, A.; Gavín, R.; Lopez de Maturana, R.; Ferrer, I.; López de Munain, A.; Raya, A.; Castilla, J.; Sánchez-Pernaute, R.; Del Río, J.A. (2018). iPS cell cultures from a Gerstmann-Sträussler-Scheinker patient with the Y218N PRNP mutation recapitulate Tau pathology. Molecular Neurobiology 55(4):3033-3048.

Eixarch, H.; Calvo-Barreiro, L.; Costa, C.; Reverter-Vives, G.; Castillo, M.; Gil, V.; Del Rio, J.A.; Montalban, X.; Espejo, C. (2020). Inhibition of the BMP-signaling pathway ameliorated established clinical symptoms of experimental autoimmune encephalomyelitis. Neurotherapeutics, doi: 10.1007/s13311-020-00885-8.

Hervera, A.; Zhou, L.; Palmisano, I.; McLachlan, E.; Kong, G.; Hutson, T.; Danzi, M.C., Lemmon, V.P.; Bixby, J.L.; Matamoros-Angles, A.; Forsberg, K.; De Virgiliis, F.; Matheos, D.P.; Kwapis, J.; Wood, M.A.; Puttagunta, R.; Del Río, J.A.; Di Giovanni, S. (2019). PP4-dependent HDAC3 dephosphorylation discriminates between axonal regeneration and regenerative failure. EMBO J 1; 38(13):e101032. doi: 10.15252/embj.2018101032.

Hervera, A.; De Virgiliis, F.; Palmisano, I.; Zhou, L.; Tantardini, E.; Kong, G.; Hutson, T.; Danzi, M.C.; Perry, R.B.; Santos, C.X.C.; Kapustin, A.N.; Fleck, R.A.; Del Río, J.A.; Carroll, T.; Lemmon, V.; Bixby, J.L.; Shah, A.M.; Fainzilber, M.; Di Giovanni, S. (2018) Reactive oxygen species regulate axonal regeneration through the release of exosomal NADPH oxidase 2 complexes into injured axons. Nature Cell Biology. 20(3):307-319.

Hutson, T.H.; Kathe, C,; Palmisano, I.; Bartholdi, K.; Hervera, A.; De Virgiliis, F.; McLachlan, E.; Zhou, L.; Kong, G.; Barraud, Q.; Danzi, M.C.; Medrano-Fernandez, A.; Lopez-Atalaya, J.P.; Boutillier, A.L.; Sinha, S.H.; Singh, A.K.; Chaturbedy, P.; Moon, L.D.F.; Kundu, T.K.; Bixby, J.L.; Lemmon, V.P.; Barco, A.; Courtine, G.; Di Giovanni, S. (2019). Cbp-dependent histone acetylation mediates axon regeneration induced by environmental enrichment in rodent spinal cord injury models. S. Sci. Transl. Med. 2019 Apr 10;11(487). doi: 10.1126/scitranslmed.aaw2064.

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 "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.

"We have developed molecules that can be applied as light-regulated molecular prostheses to help restore vision in cases of retinal degeneration (e.g. retinitis pigmentosa)."

Recent activities related to rare diseases

Nanoprobes and nanoswitches group has developed molecules that can be applied as light-regulated molecular prostheses to help restore vision in cases of retinal degeneration. Preliminary data with an active compound show that degenerated retina can be rapidly photosensitized and that blind zebrafish larvae fully recover their visual acuity.

In the frame of DRUG4SIGHT project, the group aims to validate this therapeutic approach by photosensitizing degenerated human retinae in vitro and restoring sight to mammalian models of retinal degeneration, and identify a light-regulated drug candidate that is safe and subtype-selective, that responds to visible light, and that displays high efficacy to restore sight. The end goal is to recover the light sensitivity of a human retina under laboratory conditions.

Funded projects related to rare diseases

DRUG4SIGHT · LIGHT-REGULATED DRUGS TO RESTORE SIGHT	OBRA SOCIAL LA CAIXA

Main recent publications related to rare diseases

Izquierdo-Serra, M.; Bautista-Barrufet, A.; Trapero, A.; Garrido-Charles, A.; Diaz-Tahoces, A.; Camarero, N.; Pittolo, S.; Valbuena, S.; Perez-Jimenez, A.; Gay, M.; Garcia-Moll, A.; Rodriguez-Escrich, C.; Lerma, J.; De La Villa, P.; Fernandez, E.; Pericas, M. A.; Llebaria, A.; Gorostiza, P. (2016). Optical control of endogenous receptors and cellular excitability using targeted covalent photoswitches Nature Communications 7, 12221

Pluripotency for organ regeneration

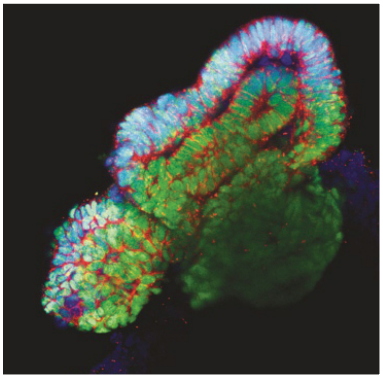
Núria Montserrat

The aims of the Pluripotency for organ regeneration group is to understand how tissues develop to tackle human disease gestation and progression. To do so, we rely in the inherent capacity of human pluripotent stem cells to respond to external stimuli and develop into cells of our body. Refining these methods, we have pioneered on the development of micrometre-size version of human organs, so called organoids. In our group we are combining organoid technology with gene-editing approaches. In this manner, we can generate hPSCs (including human embryonic stem cells and human induced pluripotent stem cells) carrying specific mutations capturing patient´s genetic background. Of equal importance we are also developing forefront approaches to generate genome-edited organoids through bioengineering. These approaches allow us to present external stimuli present in human tissues in a controlled fashion (i.e., microfluidic devices, 3D bioprinting, among others).

"We are developing in vitro disease models based on genome editing and hPSCs derived organoids to understand early biological programs accounting during renal ciliopathies and retinitis pigmentosa. These knowledge is crucial to develop therapeutic compounds targeting the malfunctioning processes accounting during these disorders."

Recent activities related to rare diseases

The kidney is comprised by thousands of nephrons that arise through reciprocal inductive interactions between the metanephric mesenchyme (MM) and the ureteric bud (UB)-derived cells. During development the UB extends into the MM and branches repeatedly to give rise to the collecting duct system, whereas the MM undergoes mesenchymal to epithelial transition (MET) to generate epithelial vesicles (EVs), the precursors for nephron assembly. Through growth, morphogenesis and patterning EVs transform into a highly elongated mature nephrons with distinct specialized cell types positioned along a proximal (glomerular) to distal (connecting segment) axis of functional organization. Like any tissue-scale morphogenetic event, nephron induction also occurs within the milieu of biophysical determinants including changes in shape, number, position, and force of cells. However, it remains undetermined how these tissue-scale morphogenetic changes work in concert with classic developmental signaling events mediated by diffusible signals for proper cell fate patterning.



Whereas initial stages of kidney formation are being elucidated in the mice animal model, much less is known about the genetic program that drives nephron morphogenesis in this system, and even less in humans. Of note, congenital anomalies of the kidney and urinary tract (CAKUT) are observed in three to six per 1000 live births and account for 40–50% of the etiology of chronic kidney disease (CKD) in children worldwide. Importantly, imbalances in the communication between the MM and the ureteric bud UB are believed to be central to the pathogenesis of CAKUT phenotypes. Despite large differences in clinical manifestation of CAKUT (it can be presented as an isolated renal condition or as part of a clinical syndrome) it is accepted that most of these conditions likely share a pathogenic origin in dysregulation of renal morphogenesis.

Based on all these findings the host laboratory is currently working in the development of conceptual and technical advances to mechanistically link how the presentation of controlled physical and metabolic constrains can be used to model early steps of CAKUT in kidney organoids. Through the generation of

The host laboratory has pioneered on the definition of procedures to generate miniaturized versions of human organs, so called organoids. This picture shows a detail of nascent tubular-like cells in kidney organoids generated from hPSCs-

hPSCs carrying specific mutations previously observed in CAKUT patients the host laboratory aims to develop unique platforms to understand the impact of these mutations during kidney organoid generation.

Renal ciliopathies (RCs) are human genetic disorders characterized by nephronophthisis, cystic kidneys or renal cystic dysplasia which are often accompanied by anomalies in other organs as retina, brain or liver. Once end-stage renal disease develops, patients with RCs currently depend on invasive therapies such as hemodialysis or renal transplantation. An important future challenge in the field resides in the need to develop human cellular models to understand these processes. Up to date these models are based in the generation of transgenic mice that in most of the cases do not fully capture ciliopathy-related phenotypes. In this regard, the host lab has developed vitro disease models with pluripotent stem cells (PSCs) derived organoids carrying specific mutations found in RCs patients.

To further identify therapeutic compounds restoring primary cilia function in renal ciliopathies we are working in two approaches:

1) The generation of high throughput three dimensional cellular systems (i.e: self-assembling organoids for kidney and retina) through the derivation of hPSCs carrying mutations in NPHP1 gene in the background of PSCs expressing fluorescent markers of primary cilia..

2) The identification of clinically evaluated compounds restoring primary cilia function through the screening of clinically evaluated compounds and marketed drugs in renal and retinal organoids.

Funded projects related to rare diseases

ENGINORG · ENGINEERING KIDNEY ORGANOIDS TO STUDY THE INTERPLAY BETWEEN TISSUE MECHANICS AND METABOLISM: FROM DEVELOPMENT TO DISEASE (LS9)	EUROPEAN RESEARCH COUNCIL

Main recent publications related to rare diseases

Garreta, E.; Prado, P.; Tarantino, C.; Oria, R.; Fanlo, L.; Martí, E.; Zalvidea, D.; 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

Hurtado Del Pozo, C.; Garreta, E.; Izpisúa Belmonte, J.C.; Montserrat, N. (2018). Modeling epigenetic modifications in renal development and disease with organoids and genome editing. Disease models & mechanisms, 11(11), dmm035048

Targeted therapeutics and nanodevices

Silvia Muro

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.

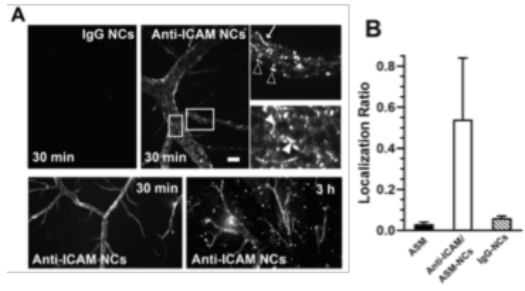
As such, through these studies, our lab generates knowledge and tools aimed to improve our ability to deliver therapeutic agents to specific disease sites. Focusing on endothelial cell adhesion molecules as examples of accessible targets and on genetic conditions which serve as models for metabolic, 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 during the last year, particularly focused on rare diseases, are described below.

"We designed polymer nanocarriers capable of transporting to the brain therapeutic enzymes aimed for replacement therapy for lysosomal disorders, overcoming a major hurdle of current strategies."

Recent activities related to rare diseases

The lysosomal storage disorders are a group of 60 different pathologies caused by genetic deficiencies affecting lysosomal components, mostly enzymes involved in degradation of macromolecules. As such, body cells accumulate aberrant amounts of undegraded substances in lysosomes, which alters their function. This affects both the central nervous system and peripheral organs, leading to severe neurological deterioration that leads to death within the first months/years of life and/or highly debilitating multiorgan disfunctions. An example is that of acid sphingomyelinase deficiency. While intravenous enzyme replacement therapy helps treat some peripheral tissues, neurological symptoms remains untreatable due to the blood-brain barrier (BBB) that hinders brain access for these therapeutics. To solve this problem, we designed polymer nanoparticles whose surface was coated with antibodies specific for ICAM-1, a protein expressed on the surface of endothelial cells lining blood vessels, including those of the brain, involved in leukocyte extravasation from the blood to the surrounding tissues during inflammation.

By targeting ICAM-1 these nanoparticles were able to cross the BBB both in cell culture models and in vivo in laboratory mice. To optimize their design, we compared particles with different number of antibodies on their surface (targeting valency) and, surprisingly, found that those with intermediate valency crossed the BBB faster than those with small or high valency: particles with low valency were worst at attaching to the BBB from the blood side, those with high valency were best at this but worst at being released from the BBB into the brain, and both processes were balanced for those with intermediate valency



Brain delivery of a therapeutic enzyme for treatment of acid sphingomyelinase deficiency by targeted nanocarriers. (A) Fluorescence microscopy of cortical brain vessels in brain specimens isolated from mice 30 min or 3 h after intravenous injection with green fluorescent nanocarriers targeted to ICAM-1 (anti-ICAM NCs) vs. control IgG NCs. Scale bar = 10 μm. Boxes = regions magnified 3-fold in the right panels. Arrows = NCs on the apical surface of the endothelium. Open arrowheads = NCs on the basolateral surface of the endothelium. Closed arrowheads = perinuclear NCs. (B) Amount of therapeutic acid sphingomyelinase (ASM) labeled with 125I, delivered to the brain in mice after intravenous injection in "naked" form or loaded in anti-ICAM NCs. IgG NCs are shown as a control. Data were calculated as the mean ± SEM of the localization ratio (brain-over-blood). Adapted from Manthe et al., (2020) J Control Rel. 324:181-193.

so that their BBB transport was faster. As such, nanoparticles with intermediate valency delivered higher amounts of a therapeutic protein for enzyme replacement therapy of acid sphingomyelinase deficiency, holding considerable translational potential.

Funded projects related to rare diseases

CROSSTARGET · DESARROLLO DE NUEVAS HERRAMIENTAS TRASLACIONALES MULTI-ESPECIE PARA EL DIRECCIONAMIENTO DE TERAPIAS CON PRECISIÓN DE ÓRGANO Y SUBCELULAR	MINISTERIO DE CIENCIA, INNOVACIÓN Y UNIVERSIDADES
NANOGABA · ASSESSING HOW GLUCOCEREBROSIDASE DEFECTS ALTER RECEPTOR MEMBRANE NANOARCHITECTURE TO DESIGN IMPROVED NANOMEDICINES	BARCELONA INSTITUTE OF SCIENCE AND TECHNOLOGY
HL098416 · TARGETED REPLACEMENT OF DEFECTIVE LYSOSOMAL ENZYMES IN THE LUNG AND BRAIN	U.S. NATIONAL INSTITUTES OF HEALTH
FUZYME · MULTIMODULAR ENZYMES FOR TARGETED TREATMENT OF GAUCHER'S AND PARKINSON'S	UNIVERSITY OF MARYLAND

Main recent publications related to rare diseases

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Biosensors for bioengineering

Javier Ramón

The development of a new drug takes years, even decades, from preclinical studies to reach the market. Preclinical research into the development of new therapeutic strategies is mostly based on animal models and cell cultures. Extrapolating data from these models is limited, and research on new drugs cannot be performed efficiently. Research in new drugs is especially dramatic in rare diseases, which are intrinsically very heterogeneous.

In our group, we focus on integrating biosensor technology and nanotechnology with tissue engineering. Engineered tissues are integrated with biosensing technology to obtain microdevices to detect cellular responses to external stimuli, monitor the microenvironment, and support diverse cellular requirements. Integration of fully functional tissues with biosensor technology allowed us to obtain 'organs-on-a-chip'. These devices could be a step toward in vitro drug testing.

"The 'organs-on-a-chip' developed in the lab are used as drug screening platforms to test novel drugs for muscular dystrophy treatments."

Recent activities related to rare diseases

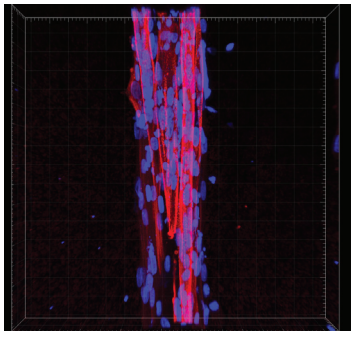
The Biosensors for bioengineering group have been working on the development of a 'muscle-on-a-chip' devices to study rare muscular diseases. 'Muscle-on-a-chip' devices would faster the study of disease progression as well as the analyses of the molecular pathways in human tissues and the discovery, development, and validation of new potential therapies for these rare diseases.

'Muscle-on-a-chip' has been adapted to integrate patient-derived cells to study myotonic dystrophy type 1 (DM1) and Duchenne muscular dystrophy (DMD). Although both disorders are considered rare diseases, DM1 and DMD are life-threatening and chronically debilitating disorders that significantly impact society. DM1 is the most common hereditary myopathy in the adult population affecting 1:8000 people worldwide, and DMD is the most common muscular dystrophy in childhood, affecting 1:5000 born boys. Unfortunately, at present, there is still no effective treatment for DM1 and DMD patients.

As well as modeling the diseases in a personalized way, these platforms also allow the study of different drugs or treatments in conditions that mimic the body as closely as possible and offer a more reliable alternative to animal models.

Part of this technology is currently being used in the TATAMI project to determine which of the 100 variant molecules developed for the treatment of DM1, produce a lighter inflammatory response and select the most effective. This selection is crucial in this drug development's preclinical step to identify the best "lead" molecule to begin the clinical phases with patients.

The DMD-Chip project aims to fabricate 'muscle-on-a-chip' devices using cells from DMD patients. Our goal is to develop a preclinical platform to test anti-DMD drug candidates more quickly and economically and reduce the time required for a candidate molecule to reach clinical practice and arrive with a greater probability of being a successful treatment.



Confocal microscopy image of an in vitro bioengineered skeletal muscle from Myotonic dystrophy patient-derived cells. Red (alpha-sarcomeric actinin), Blue (nuclei).

Funded projects related to rare diseases

THERAPEUTIC TARGETING OF MBNL MICRORNAS AS INNOVATIVE TREATMENTS FOR MYOTONIC DYSTROPHY [TATAMI]	FUNDACIÓ BANCARIA "LA CAIXA"
DEVELOPMENT OF A "MUSCLE-ON-A-CHIP" (MOC) PLATFORM FOR THE PRECLINICAL EVALUATION OF POTENTIAL THERAPIES FOR DUCHENNE MUSCULAR DYSTROPHY [DMD-CHIP]	DUCHENNE PARENT PROJECT SPAIN

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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 and rare diseases.

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 technology developed by the Nanobioengineering group combining, microfluidic devices and nanotechnology, is used to understand and find new treatments for rare diseases."

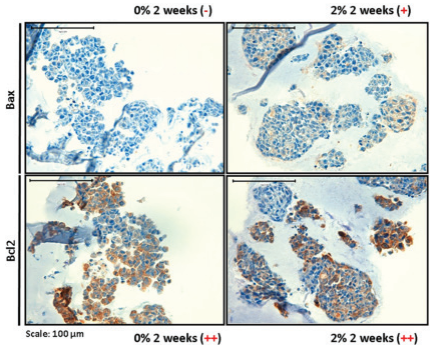
Recent activities related to rare diseases

We are working in the development of microfluidic devices to determine mechanical properties of red blood cells and the changes of these properties that appears in different anaemia diseases. Also, we develop biomimetic models of the spleen and analyse their interaction with blood rare diseases. In this sense, we participate in the European project, EVIDENCE, with the aim to explore the properties and behaviour of Red Blood Cells (RBCs) under flow conditions and in vivo to understand pathophysiology of rare anaemias and to design novel diagnostic devices. Theoretical models will help to understand these RBC properties and will enable the transfer of the gained knowledge into diagnostic devises in general and into the development of a spleen-on-the-chip, in particular.

Another focus of the lab is the biomimetic development of in-vitro models of neuromuscular disease as amyotrophic lateral sclerosis (ALS) or spinal muscular atrophy (SMA). We have in-vitro modelled neuromuscular circuit using iPSC derived from healthy and ALS patients. Also, we are working in 3D invitro muscular models obtained by bioprinting and in the analysis of properties 3D extracellular matrix of fibroblast obtained from patients with collagen VI deficiencies.

In the field of rare cancer diseases, we previously developed a novel functional 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. This technology has been successfully tested in vitro, in murine models and in-patient samples to predict therapy response. We have used this technology to study how driving signalling pathways control paediatric cancer cells survival and detect druggable targets. In collaboration with oncologists at Hospital Sant Joan de Déu we identified and tested optimal therapeutic strategies to effectively treat rhabdomyosarcoma, a rare but very aggressive cancer that affect mainly children.

Also, together with the INCLIVA Health Research Institute and the Hospital Clínico de Valencia, we have made further headway in understanding how neuroblastoma



Study of apoptosis and antiapoptosis. Immunohistochemistry images (40×) of Bax and Bcl2 markers. Optical microscopy analysis: – Negative (<1% positive cells); + Low positive (1–20% positive cells); ++ Intermediate positive (20–50% positive cells).

evolve by discovering how the rigidity of the tumour extracellular matrix affects the aggressiveness of the tumour. To carry out the study, we used a three-dimensional model obtained through 3D printing capable of generating different levels of stiffness to recreate simplified versions of tumours. Thanks to this new technology, we were able to see how the biomechanical properties of the tumour extracellular matrix affected the evolution of neuroblastoma.

Funded projects related to rare diseases

PERSONALIZING PEDIATRIC CANCER TREATMENT WITH KINOME ANALYSES, CELL-BASED FUNCIONAL ASSAYS AND MICROFLUIDICS	CELLEX
PERSONALIZING PEDIATRIC CANCER TREATMENT	FUNDACIÓN FERO
SISTEMA MICROFISIOLÓGICO PARA MIMETIZAR LAS BARRERAS HEMATO-SISTEMA NERVIOSO CENTRAL: APLICACIÓN A LA ESCLEROSIS LATERAL AMIOTRÓFICA	MICIU: RETOS INVESTIGACIÓN
EVIDENCE · ERYTHROCYTES PROPERTIES AND VIABILITY IN DEPENDENCE OF FLOW AND EXTRA-CELLULAR ENVIRONMENT	EUROPEAN COMISSION MARIE CURIE ITN

Main recent publications related to rare diseases

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Bacterial infections: antimicrobial therapies

Eduard Torrents

Infectious diseases constitute a persistent 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 these objectives: to establish the molecular basis for the regulation of genes involved in DNA synthesis and their importance in virulence and biofilm formation; to identify and screen new molecules for the inhibition of new antibacterial targets; to use nanomedicine techniques for the development of specific nanoparticles to deliver antibiotics to bacteria growing in biofilm; to study new methodologies to treat chronic bacterial infections in Cystic Fibrosis (CF) patients; to develop a new type of antibacterial vaccines; to develop new strategies for bacterial co-culture systems; 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 aim to investigate new antimicrobial therapies and strategies to combat bacterial infections in patients suffering from cystic fibrosis."

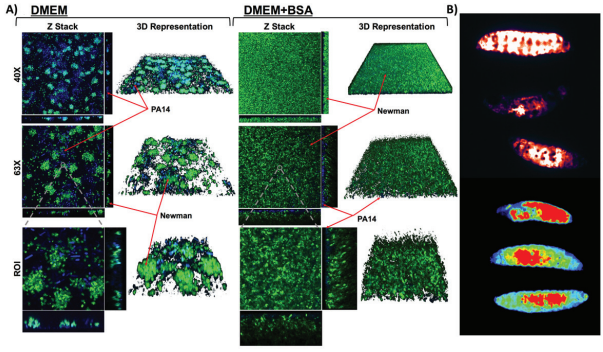
Recent activities related to rare diseases

Over 60% of all human infections treated by physicians are characterized by the formation of a biofilm, which is involved in a wide variety of pathological conditions. In the case of human biofilm infections, these are typically associated with major chronic diseases, such as Cystic Fibrosis (CF) being particularly complicated to treat. The control and treatment of biofilms remain an urgent unmet medical need, and it is occurring at the same time when there is a dearth of new and effective antibiotics available on the market or in late-stage development. These infections are not easily amenable to be treated with the current antimicrobial therapies or by using single "magic bullet" approaches.

Our group is totally focused on the identification of new antimicrobials and therapies specifically indicated to treat this chronic lung infection or with the capacity of removing pre-existing biofilms. We concentrate on this problem by applying basic research and more applied investigations to bring close to the market new technologies identified in our laboratory.

Firstly, we are investigating the molecular basis for bacteria to establish a chronic infection or a polymicrobial biofilm and how oxygen availability and bacterial strain type is crucial. At the same time, we are setting in vitro conditions to develop polymicrobial biofilms to resemble the real situations found in CF patients and useful for investigating new antibiofilm molecules. Furthermore, we are exploring new antibiofilm and antibacterial molecules to inhibit bacterial and biofilm proliferation as well as studying their potential bacterial or biofilm targets.

In our laboratory, we are bringing the nanotechnology close to the CF patients by developing new drug delivery systems based on nanoparticles with real capabilities to be used in CF patients with availability to degrade pre-existing biofilms and kill bacteria. Finally, we are optimizing different invertebrate animal model of infection and the developing of a new type of bacterial vaccine to be used primarily for the treatment of CF associated bacteria.



Simultaneous growth of Pseudomonas aeruginosa and Staphylococcus aureus populations with in a three-day- old mixed biofilm grown in continuous flow. B) Visualization of Galleria mellonella larvae, as an animal model of infection, infected with P. aeruginosa expressing lux genes.

Funded projects related to rare diseases

BIOVAC2 · ARTIFICIAL BACTERIA: A NOVEL GENERATION OF BIOINSPIRED VACCINES	BIST IGNITE PROGRAM
COMBATRNR · UNDERSTANDING DNA SYNTHESIS IN BACTERIAL PATHOGENS: NEW STRATEGIES FOR INFECTIOUS DISEASES TREATMENT	MINISTERIO DE CIENCIA, INNOVACIÓN Y UNIVERSIDADES
NOVES STRATEGIES ANTIMICROBIANES PEL TRACTAMENT DE LES ENFERMETATS INFECCIOSES EN MALALTS DE FIBROSIS QUÍSTICA	OBRA SOCIAL LA CAIXA
RESEARCH GRANT FROM THE CATALAN CYSTIC FIBROSIS FOUNDATION	ASSOCIACIÓ CATALANA DE FIBROSI QUÍSTICA
BIOFILMCHIP · PERSONALIZED TREATMENT FOR BIOFILM INFECTIONS	OBRA SOCIAL LA CAIXA

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