20 Anniversary

CRG Centre for Genomic Regulation

Symposium
The value of fundamental research

23rd-24th MARCH 2023

Book of Abstracts

@CRGenomica / #CRG20Years

Texts: Invited speakers, Juan Valcárcel, CRG Department of Communications & PR

Graphics: Iris Joval

CRG 20th Anniversary Symposium: The value of fundamental research

PRBB Auditorium, Barcelona
23-24 March 2023

Organized by:

SYMPOSIUM PROGRAMME

THURSDAY, 23rd MARCH

09h00 WELCOME & OPENING

- Luis Serrano, Director of the CRG
- Jordi Camí, Director of the PRBB
- Ignasi López, Director of the Relations with Health and Research Institutions Area, 'la Caixa' Foundation
- Laia de Nadal, Rector of the Universitat Pompeu Fabra
- Manel Balcells, Catalan Minister of Health

09h30 CRG 20 YEAR'S CELEBRATION

- Miguel Beato, Founder and former Director of the CRG
- Andreu Mas-Colell, President of the Barcelona Institute of Science and Technology, and former Minister of Economy of the Government of Catalonia
- Carmen Vela, Director of Collaborative Projects, Gold Standards Diagnostics, and former State Secretary of Research, Development and Innovation of the Spanish Government

10h00 COLLOQUIUM: "The value of fundamental research"

- Moderator: Cristina Sáez, science journalist

1st part: Short talks about the experience of 5 local entrepreneurs

- Carlos Buesa, CEO, Oryzon Genomics
- Marie-Eve Beaulieu, Co-founder and Chief Scientific Officer of Peptomyc
- Maria Lluch, Founder and Chief Scientific Officer of Pulmobiotics and CRG Alumna
- Salvador Aznar-Benitah, Founder and Scientific Advisor of Ona Therapeutics, researcher at IRB Barcelona and CRG Alumni
- Evan Floden, CEO and Co-founder of Seqera Labs and CRG Alumni

2nd part: Debate with relevant stakeholders in the field of life sciences entrepreneurship

- Maria Leptin, President, European Research Council (ERC)
- Ion Arocena, Director, ASEBIO (Spanish Association of Biotech Companies)
- Carmen Vela, Director of Collaborative Projects, Gold Standards Diagnostics, and former State Secretary of Research, Development and Innovation of the Spanish Government
- Jordi Xiol, Partner, Ysios Capital
- Clara Campàs, Managing Partner and Co-founder, Asabys
- Bernhard Paetzold, Co-founder and Chief Scientific Officer, SBiomedic and CRG Alumni
- Xavier Aldeguer, Professor at the Universitat de Girona and Researcher at IDIBGI
- Phillip Zamore, Chair & Professor, RNA Therapeutics Institute; Investigator, HHMI, Gretchen Stone Cook Professor of Biomedical Sciences, University of Massachusetts Medical School
- Luis Serrano, Director, CRG

11h30 COFFEE BREAK

12h00 SCIENTIFIC TALKS
"Mechanism-based antisense therapeutics for genetic diseases and oncology"
Adrian Krainer, Cold Spring Harbor Laboratory, NY, US

13h00
"Understanding cellular reprogramming in vivo"
Manuel Serrano, Cambridge Institute of Science, Altos Labs, Cambridge, UK

14h00 LUNCH BREAK

15h00
"A single-cell isoform view of mouse and human brain OR progress through 12 years of failure in long-read sequencing"
Hagen Tilgner, Weill Cornell's The Feil Family Brain and Mind Research Institute, NY, US

15h30
"Engineering a bacterial chassis to treat respiratory diseases"
Maria Lluch, Pulmobiotics, Barcelona, Spain

16h00
"Adventures with Argonautes"
Phillip Zamore, HHMI, RNA Therapeutics Institute, University of Massachusetts Medical School, Worcester, MA, US

17h00 COFFEE BREAK

17h30
"Organoids to study regeneration and cancer"
Merixell Huch, Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany

18h00 Online talk
"The Src oncoprotein; from avian model systems to human disease"
Sara A. Courtneidge, Oregon Health & Science University, Portland, OR, US

19h00 CLOSING

- Dr. Cristobal Belda, Director of the Instituto de Salud Carlos III, representing the Spanish Ministry of Science and Innovation

FRIDAY, 24th MARCH

09h00 Online talk
"Mechanism of a cold-induced epigenetic switch"
Caroline Dean, John Innes Centre, Norwich, UK

10h00
"Mechanism of insulin granule biogenesis"
Julia von Blume, Yale School of Medicine, New Heaven, CT, US

10h30
"Targeting PI 3-Kinase in Women's Cancers- The Insulin Complication"
Lewis Cantley, Harvard Medical School, Dana Farber Cancer Institute, Boston, US

11h30 COFFEE BREAK

12h00 Online talk
"Lgr5 Stem Cell-based organoids in human disease"
Hans Clevers, Roche Pharma Research & Early Development, Roche Innovation Center Basel, F. Hoffman-La Roche Ltd, Basel, Switzerland

13h00
"Complex Systems: from CRG to EMBL..."
James Sharpe, EMBL Barcelona, Barcelona, Spain

13h30
"Engineering Synthetic Circuits with CRISPR-mediated gene regulation"
Yolanda Schaerli, University of Lausanne, Lausanne, Switzerland

14h00 LUNCH BREAK

15h00
"Systemic temporal regulation of tissue physiology by circadian rhythms during health and aging"
Salvador Aznar-Benitah, IRB Barcelona, Spain

15h30
"Seqera Labs: A Multiomics Data Analysis Business Based on Open Science"
Evan Floden, Seqera Labs, Barcelona, Spain

16h00
"A harmonious journey from fundamental research to nuts and bolts - the Solexa story"
Nick McCooke, Founding CEO of Solexa

17h00 WRAP-UP / CONCLUSIONS

- Mafalda Dias and Jonathan Frazer, Computational Biology and Health Genomics, CRG, Barcelona, Spain

ABSTRACTS / Invited Speakers

(in order of appearance in the Programme)

Mechanism-based antisense therapeutics for genetic diseases and oncology

Adrian Krainer

Cold Spring Harbor Laboratory, NY, US

Short Bio: Adrian R. Krainer discovered factors and mechanisms of alternative splicing regulation and designed small RNA splicing modulators that provided the first effective treatment for Spinal Muscular Atrophy.

Abstract: We are developing mechanism-based therapeutics, combining knowledge about RNA-splicing mechanisms and regulation with antisense technology. In collaboration with Ionis Pharmaceuticals and Biogen, we previously developed nusinersen (Spinraza), an antisense oligonucleotide (ASO) that modulates alternative splicing of SMN2 exon 7, restoring normal levels of functional SMN protein in the context of a genetic motor-neuron disease, spinal muscular atrophy (SMA). Nusinersen was approved at the end of 2016 as the first drug to treat SMA; it is a disease-modifying therapy and it can prevent the onset of SMA if treatment is initiated pre-symptomatically, following genetic diagnosis. To date, more than 13,000 SMA patients are being treated with nusinersen in over 50 countries.

In the area of oncology, we are developing ASOs to downregulate a somatic gain-of-function mutation in a histone H3 variant that causes a lethal pediatric brain cancer, diffuse intrinsic pontine glioma (DIPG). This dominant mutation results in replacement of lysine 27 with methionine (K27M) in the histone protein, causing a global reduction of tri-methylation on K27 of all wild-type histone H3 proteins—a driving event in gliomagenesis. To reduce the expression of the toxic mutant protein, we designed ASOs that either promote degradation of the mutant mRNA or cause incorrect splicing of the pre-mRNA, and tested them in patient-derived-neurosphere and mouse models of DIPG.

ASO treatment restored K27 trimethylation of histone H3 proteins and significantly reduced tumor growth, promoted neural-stem-cell differentiation, and increased survival in two different DIPG mouse models. These results demonstrate the involvement of the H3.3 K27M oncohistone in tumor maintenance, and the reversibility of the aberrant epigenetic changes it promotes, in addition to providing preclinical proof-of-concept for DIPG antisense therapy.

Understanding cellular reprogramming in vivo

Manuel Serrano

Cambridge Institute of Science, Altos Labs, Cambridge, UK

Short Bio: Manuel Serrano discovered key molecular mechanisms of tumor suppression, cellular senescence and organismal ageing, including the generation of mouse models resistant to cancer and for cellular reprogramming in vivo.

Abstract: An emerging theme in response to tissue injury is the acquisition of plasticity and progenitor properties by some cells. To study cell plasticity in vivo in a controllable manner, we have generated "reprogrammable" mice where it is possible to switch on-and-off the Yamanaka factors (Oct4, Sox2, Klf4 and Myc). We are using our "reprogrammable" mice to learn how to control in vivo cellular plasticity. The acquisition of OSKM-driven plasticity and the reversion to the original cell identity is known to reset molecular features of aging. In vivo, this process increases the capacity of tissues to repair a subsequent injury. Understanding the basis of this cellular and organismal rejuvenation is a challenge that we are trying to unravel. We have found that damaged cells secrete factors, like IL6, that strongly promote cellular reprogramming in vivo. I will present a novel intervention that greatly improves reprogramming by simply supplementing the diet with a particular vitamin. I will also present data on the identification of reprogramming intermediate states in vivo.

A single-cell isoform view of mouse and human brain OR progress through 12 years of failure in long-read sequencing

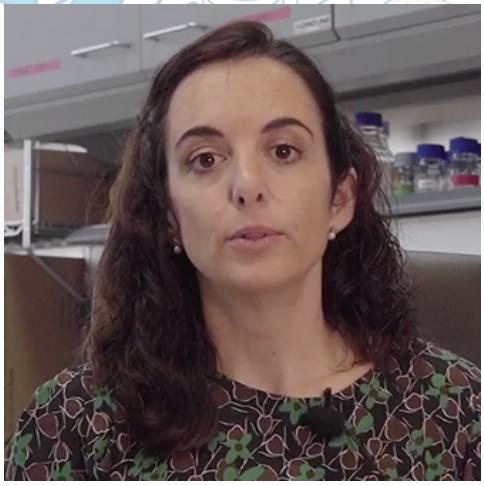
Hagen Tilgner

Weill Cornell's The Feil Family Brain and Mind Research Institute, New York, NY, US

Most mammalian genes encode multiple distinct RNA isoforms and the brain harbors especially diverse isoforms. Complex tissue, including the brain, often include highly divergent cell types and these cell types employ distinct isoforms for many genes. To untangle the distinct cell-type specific isoform profiles of the brain, we developed Single-cell isoform RNA sequencing (ScISOr-Seq1) for fresh tissues as well Single-nuclei isoform RNA sequencing (SnISOr-Seq2). To add spatial resolution, we developed Slide-isoform sequencing3. Collectively, these long-read approaches reveal a striking difference between coordinated pairs of exons with in-between exons ("Distant coordinated exons") and without in-between exons ("Adjacent coordinated exons"): The former show strong enrichment for cell-type specific usage of exons, whereas the latter do not in mouse1 and human brain2. Of note, coordinated TSS-exon pairs and exon-polyA-site pairs follow the same trend as distant coordinated exon pairs2. Simultaneously, autism-associated exons are among the most highly variably used exons across cell types2. Differences in isoform expression between hippocampus and prefrontal cortex are most often explained by differences arising between the two regions in one specific cell type (e.g., excitatory neurons), but for a smaller program of genes brain regions can override cell-type identity3. Spatially barcoded isoform sequencing revealed that often region-specific isoform differences correlate with precise boundaries of brain structures (e.g., from the choroid plexus to the hippocampus). However, genes including Snap25 go against this trend, using a steady gradient of exon inclusion as one traverses the brain3. Moreover, choroid plexus epithelial cells show a dramatically distinct isoform profile, which originates from distinct exon and poly(A) site usage, but most strongly from distinct TSS usage3.

Most recently, we have made advances in understanding the error sources of Pacific Biosciences and Oxford Nanopore long-read sequencing technologies4 and have implemented a highly accurate long-read interpretation pipeline5.

1. Gupta*, Collier* et al, Nature Biotechnology, 2018
2. Hardwick*, Hu*, Joglekar* et al, Nature Biotechnology, 2022
3. Joglekar et al, Nature Communications, 2021
4. Mikheenko*, Prjibelski*, et al, Genome Research, 2022
5. Prjibelski*, Mikheenko*, et al, Nature Biotechnology, 2023



Engineering a bacterial chassis to treat respiratory diseases

Maria Lluch

Pulmobiotics SL, Barcelona, Spain

Carlos Piñero-Lambea, Rocco Mazzolini, Samuel Miravet, Javier Delgado, Raul Burgos, Elisabet Aguilera, Eva García-Ramallo, Victoria Garrido, Bernard Paetzold, Tony Ferrar, Irene Rodríguez-Arce, Laia Fernández, Marguerita Scarpa, Nuria Buxons, Maria Jesús Grilló, Luis Serrano*, Maria Lluch*.

Abstract: The use of genetically programmed microorganisms (known as live biotherapeutics; LBPs) opens the door to alternative therapies based on a continuous or regulated targeted release of therapeutic molecules in a desired location. In the past years, many of the new drugs used in the clinics were biomolecules such as antibodies, interleukins or enzymes that are often administered systemically. Production of these biomolecules is expensive and systemic administration in some cases prevents their use due to toxicity. Alternatively, local production of these biomolecules by a living system (i.e. bacteria) represents an attractive approach to reduce the production costs and possible undesired effects associated with systemic administrations.

LBPs have the potential to become key players in healthcare over the coming years; acting as a chassis from which therapeutic platforms can be plugged into to activate new functions.

We have characterized Mycoplasma pneumoniae, a minimal lung pathogen, by systems biology approaches to identify its virulence factors. By developing innovative genetic tools, we rationally edit its genome to obtain an attenuated strain able to destroy biofilms formed by Staphylococcus aureus and Pseudomonas aeruginosa.

Biofilms are complex structures associated to resistance to antibiotics treatment. Biofilms formed by P. aeruginosa in endotracheal tubes (ETTs) of intubated patients are associated to a mortality rate that can rise the 14%. We have shown that our engineered strains are able to eliminate the infections caused by S. aureus and P. aeruginosa in vivo in mice models and more interestingly that it can eliminate biofilms formed in ETTs from intubated patients.

This chassis and genetic tools are the base of the technological platform of Pulmobiotics, the first Spanish Biotech company focused on engineering live biotherapeutics for treating respiratory diseases. Different products are being developed to assess the potential of the platform as novel strategy to treat additional complex respiratory diseases like asthma and lung cancer.

Adventures with Argonautes

Phillip Zamore

HHMI, RNA Therapeutics Institute, University of Massachusetts Medical School, Worcester, MA, US

Short Bio: Phillip D. Zamore discovered molecular mechanisms of RNA interference and helped to develop the first FDA-approved RNAi drug, used for the treatment of hereditary transthyretin-mediated amyloidosis.

Organoids to study regeneration and cancer

Meritxell Huch

Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany

In vitro 3D organoid cultures are emerging as novel systems to study tissue development, organogenesis and stem cell behavior ex-vivo. Organoids are multicellular structures that (1) self-assemble and can be clonally expanded, (2) resemble the corresponding tissues-of-origin and (3) allow the study of some aspects of tissue development and tissue physiology in a dish.
Over the past decade we have developed organoid cultures from healthy and diseased, human and mouse, adult and embryonic tissues for a range of organs including stomach, liver and pancreas. These, have allowed, for the first time, the long-term expansion of adult (stomach, liver and pancreas) tissues in a dish, thus defying the Hayflick limit, by which only cancer cells with aberrant ploidy and unstable genomes would expand in culture
Here, I will present our organoid work and summarize our findings on how this culture system is amenable for the study of adult tissue regeneration and disease across different biological scales. At the cellular scale, we have recently found that heterotypic cellular interactions between stromal and epithelial cells dictate the behavior of the liver epithelia, thus reconciling the apparent dichotomy between a pro-regenerative and a pro-quiescent stromal niche. At the molecular scale, we have found that a transient, genome-wide remodeling, of the cells' epigenome (DNA methylome/ hydroxymethylome), licenses adult differentiated liver cells to reprogram into bi-potent liver progenitors, both during organoid initiation and in vivo, following tissue damage. Our results indicate that adult tissue derived organoid cultures represent novel, reductionist in vitro models, that enable gaining mechanistic understanding of basic biological principles of human tissue regeneration and cancer.

The Src oncoprotein; from avian model systems to human disease

Sara A. Courtneidge (ONLINE TALK)

Oregon Health & Science University, Portland, OR, US

Short Bio: Sara A. Courtneidge made seminal contributions to dissect the functions of Src tyrosine kinase on cellular transformation, cancer invasion and metastasis and led efforts to discover novel kinases in oncology.

Abstract: The study of the Src oncoprotein provides a compelling example of how the pursuit of basic science research can lead to important insights into human disease, and ultimately to new treatment strategies and therapeutics. The beginnings of oncogene research was centered around the study of murine and avian retroviruses that caused cancer in their hosts. These model systems allowed us to ask: how does the action of a single protein change a normal cell into a cancer cell? Indeed, the study of viral Src, the oncogenic component of the chicken Rous sarcoma virus, precipitated many important discoveries, including that retroviral oncogenes originate in our own genomes, and that the kinase activity of viral Src creates phosphotyrosine. In the following years, attention turned to the normal form of Src (referred to as cellular Src or cSrc). Key findings of this era include the observation that cSrc activity is tightly regulated by C-terminal sequences lacking in viral Src, and that cSrc is involved in the response of cells to growth factors and cytokines, and during the transition from G2 to M phase of the cell cycle. And the discovery of many key cSrc substrates increased our understanding of the mechanisms by which cSrc exerts its effects. The observation that cSrc is frequently overexpressed or hyperactivated in human tumors led to the search for Src inhibitors, several of which are now on the market, although I believe their full potential has yet to be realized.

After leaving the Pharma sector I decided to focus my own research on the relatively understudied topic of the role of Src and its substrates in invasion and metastasis, rather than on cell cycle control. I recognize that therapeutic intervention in the ongoing process of metastasis is a very ambitious and difficult clinical path, but if it is ever to be achieved, we will need a better understanding of the processes involved, which in turn requires more fundamental research in this area. I will describe some of our more recent research on this topic, focusing on how Src and its substrate Tks5 controls the formation of membrane protrusions called invadopodia, and the role invadopodia play in tumor growth and metastasis.

Mechanism of a cold-induced epigenetic switch

Caroline Dean (ONLINE TALK)

John Innes Centre, Norwich, UK

Short Bio: Caroline Dean made outstanding contributions to the study of developmental timing in plants and the mechanisms behind the control of flowering and was instrumental to establish Arabidopsis as a genetically tractable model organism.

Abstract: Through the study of how plants time their development with respect to the seasons, we have been led into the study of conserved transcription and chromatin silencing mechanisms. The Arabidopsis FLC gene has become the evolutionary node for flowering time variation in Arabidopsis relatives (many of your vegetables!) and its homologues are emerging as important developmental regulators in cereals. In the warm, FLC expression is quantitatively modulated by a chromatin mechanism linked to transcriptional termination/anti-termination in a process involving antisense transcription. Upon winter exposure, transcription is down-regulated enabling a low probability, cis-based switch to a Polycomb-mediated epigenetic silenced state. This maintains the silenced state though subsequent growth, promoting flowering in spring. A major determinant of flowering time adaptation of Arabidopsis across wide latitudes is non-coding SNPs at FLC, which influence different aspects of these transcriptional and epigenetic mechanisms. The study of spring flowering has thus provided mechanistic surprises relevant to gene regulation in many organisms, but also essential to generate climate-proof varieties of our crops.

Mechanism of insulin granule biogenesis

Julia von Blume

Yale School of Medicine, New Haven, CT, US

Although type-2 diabetes (T2D) presents a significant clinical burden, globally, the **molecular mechanisms** of how b-cells route proinsulin to insulin granules remain obscure. No cargo receptor for proinsulin in the Golgi apparatus has been identified. Chromogranin proteins (CGs) are central regulators of insulin granule biogenesis, and it was proposed that their aggregation is critical for this process. However, the molecular mechanism by which these molecules facilitate sorting at the TGN is poorly understood. Our recent work has shown that CGs undergo liquid–liquid phase separation (LLPS) at low pH independently of divalent cations. Liquid CG condensates, but not aggregates, recruit, and sort proinsulin and its processing enzymes into immature secretory granules at the TGN. The client selectivity is independent of sequence or structural elements but is based on the size and concentration of the client molecules in the lumen of the TGN. Finally, electrostatic interactions and the N-terminal intrinsically disordered domain of chromogranin B facilitate LLPS and are critical for granule biogenesis. We propose that phase-separated CGs form client scaffolds within the TGN lumen, gathering proinsulin and its processing enzymes into the condensate independently of specific sequence- or structural elements, facilitating receptor-independent sorting. Interfering with CG condensation in insulin-secreting cells leads to a release of unprocessed, metabolically inactive proinsulin upon glucose stimulation, a hallmark of T2D. These findings challenge the canonical sorting models and provide a new model of insulin granule biogenesis.

Profiling the substrate motifs of Tyrosine Kinases: A software for predicting what kinase phosphorylates every Tyr in a tumor or cell line

Lewis Cantley

Harvard Medical School, Dana Farber Cancer Institute, Boston, US

Short Bio: Lewis C. Cantley discovered the growth factor-regulated enzyme PI-3-kinase and its key roles in metabolic regulation, cancer and diabetes. Inhibitors of this enzyme are in clinical use for the treatment of leukemias and lymphomas.

Abstract: Recently we published a technology that we developed to determine the substrate specificity of essentially all the human protein kinases (referenced below). We have subsequently applied this same technology. We have subsequently applied this same approach to determine the substrate specificity of the human protein-Tyr kinases. Including the 15 non-canonical protein kinases including pyruvate dehydrogenase kinase, WEE1 and PINK1, there are a total of 93 protein-Tyr kinases in humans. We obtained the expected result that highly related protein-Tyr kinases, such as the Src family kinases, have nearly identical substrate specificities and are distinguished, in regard to what protein they phosphorylate, based on the proteins in the cell type where each of these kinases is expressed. In contrast the various receptor-family protein-Tyr kinases and non-canonical protein-Tyr kinases have relatively unique substrate specificities that insure that they target distinct substrates to provide specific responses to different growth factors. This technology and the insight it provides in regard to signal transduction and protein-Tyr kinase driven cancers will be discussed in detail.

An atlas of substrate specificities for the human serine/threonine kinome.
Johnson JL, Yaron TM, Huntsman EM, Kerelsky A, Song J, Regev A, Lin TY, Liberatore K, Cizin DM, Cohen BM, Vasan N, Ma Y, Krismer K, Robles JT, van de Kooij B, van Vlimmeren AE, Andrée-Busch N, Käufer NF, Dorovkov MV, Ryazanov AG, Takagi Y, Kastenhuber ER, Goncalves MD, Hopkins BD, Elemento O, Taatjes DJ, Maucuer A, Yamashita A, Degterev A, Uduman M, Lu J, Landry SD, Zhang B, Cossentino I, Linding R, Blenis J, Hornbeck PV, Turk BE, Yaffe MB, Cantley LC.*Nature*. 2023 Jan 11. doi: 10.1038/s41586-022-05575-3. Online ahead of print.PMID: 36631611

Lgr5 Stem Cell-based organoids in human disease

Hans Clevers (ONLINE TALK)

Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Basel, Switzerland

Short Bio: Hans Clevers pioneered the development and study of organoids from adult stem cells, from a variety of tissues and cancer types, a technology that has been applied in personalized medicine and drug screening.

Abstract: The intestinal epithelium is the most rapidly self-renewing tissue in adult mammals. We originally defined Lgr5 as a Wnt target gene, transcribed in colon cancer cells. Two knock-in alleles revealed exclusive expression of Lgr5 in cycling, columnar cells at the crypt base. Using lineage tracing experiments in adult mice, we found that these Lgr5+ve crypt base columnar cells (CBC) generated all epithelial lineages throughout life, implying that they represent the stem cell of the small intestine and colon. Lgr5 was subsequently found to represent an exquisitely specific, yet 'generic' marker for active epithelial stem cells, including in hair follicles, kidney, liver, mammary gland, inner ear tongue and stomach epithelium.

Single sorted Lgr5+ve stem cells can initiate ever-expanding crypt-villus organoids, or so called 'mini-guts' in 3D culture. The technology is based on the observation that Lgr5 is the receptor for a potent stem cell growth factor, R-spondin. Similar 3D cultures systems have been developed for the Lgr5+ve stem cells of human stomach, liver, pancreas, prostate and kidney. Using CRISPR/Cas9 technology, genes can be efficiently modified in organoids of various origins. Organoid technology opens a range of avenues for the study of development, physiology and disease, for drug development and for personalized medicine. In the long run, cultured mini-organs may replace transplant organs from donors and hold promise in gene therapy.

Complex Systems: from CRG to EMBL...

James Sharpe

EMBL Barcelona, Barcelona Spain

X

Engineering Synthetic Circuits with CRISPR-mediated gene regulation

Yolanda Schaerli

University of Lausanne, Lausanne, Switzerland

Synthetic gene circuits allow us to govern cell behaviour in a programmable manner for user-defined tasks. Transcription factors constitute the 'classic' tool for synthetic circuit construction but some of their inherent constraints, such as insufficient modularity, orthogonality and programmability, limit progress in realizing more ambitious designs. CRISPR (clustered regularly interspaced short palindromic repeats) technology offers new and powerful possibilities for synthetic circuit design.

I will present how we used CRISPR interference to build synthetic circuits such as an oscillator, ("CRISPRlator"), bistable network (toggle switch) and incoherent feed-forward loop in *Escherichia coli*. I will also show how we can easily interface those circuits with the host genome to control endogenous gene expression. We demonstrated that our designs also work in other bacterial species by building a CRISPRlator in *Streptococcus pneumoniae*. Finally, I will present how we can combine CRISPRi with CRISPR activation (CRISPRa) in the same circuits.

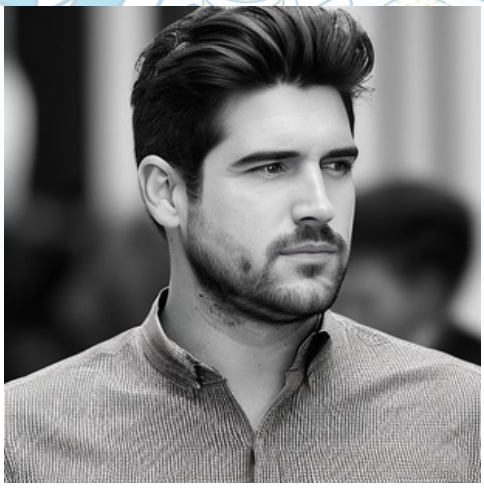
Systemic temporal regulation of tissue physiology by circadian rhythms during health and aging

Salvador Aznar-Benitah

Institute for Research in Biomedicine, Barcelona, Spain

Our body´s circadian clock allows cells to "know" the time of the day and to function according to it. This incredible mechanism ensures that all tissues function in a synchronized manner, which is essential for remaining healthy. Importantly, our clock progressively fails as we age, significantly contributing to neural, heart, and muscle degeneration, obesity, arthritis, loss of vision, infections, and cancer. Within the brain, a region known as the suprachiasmatic nuclei detects changes in light and communicates this information to all tissues in our body, which then communicate between each other to perform their daily functions in a concerted manner. How does this communication network happen? Why is it lost during aging? How does the misalignment of clocks of different tissues contribute to age-related pathologies?

In a collaborative effort of several labs, we are mapping all systemic nodes that govern clock communication between the central clock in the brain and tissues, and between peripheral tissues, and determine targetable nodes for anti-aging efforts. We have generated different mouse models in which we can restore the clock in any tissue of choice, or combinations of thereof. I will present data obtained from these models that is allowing us to obtain an atlas of the connections that ensure a coherent daily physiology, and of the critical clock nodes that "fail" during aging and that can be targeted to promote a healthier aging.



Seqera Labs: A Multiomics Data Analysis Business Based on Open Science

Evan Floden

Seqera Labs, Barcelona, Spain

The open science movement emphasizes the importance of accessibility, efficiency, and quality in scientific research through the use of collaborative tools, data sharing, and open-source software. The "omics" fields in particular have seen significant growth in recent years, driven by the development of open source software such as Nextflow. Developed at the CRG from 2013 to 2020, Nextflow has become the industry standard for scientific computational workflows and was the foundational technology in the formation of Seqera Labs, a company founded at CRG in 2018. Seqera Labs specializes in accelerating discovery through the use of foundational software that enables collaborative data analysis. To date, the company has raised 27 million EUR in funding, has 50 employees, and now supports over 150 life sciences organizations, including 8 of the top 15 pharmaceutical companies, with software for data management, data orchestration, infrastructure, and reporting. This talk looks back over the past decade of learnings from spinning out a company from a research organization.

A harmonious journey from fundamental research to nuts and bolts - the Solexa story

Nick McCooke

Founding CEO of Solexa

Short Bio: Nick McCooke is a pioneer in the development of Next Generation Sequencing (NGS) technologies that have revolutionized research in Molecular Biology, including Illumina's world leading DNA sequencing products.

Abstract: Next Generation Sequencing (NGS) has had a massive impact at the scientific and societal levels. Solexa was a pioneer of NGS and the technology it developed is still the basis of the Illumina platform. The speaker will describe the Solexa journey from basic research at the University of Cambridge to a working platform. It will be an insider's view of an amazing journey, laying bare the moments of despair and triumph along the way.

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