BEYOND CANCER GENOMES

BARCELONA CONFERENCE ON EPIGENETICS AND CANCER

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October 13th and 14th , 2016

WELCOME

Dear Invited Speakers and Participants,

We are pleased to welcome you to Barcelona and to the meeting "Beyond Cancer Genomes. Barcelona Conference on Epigenetics and Cancer", co-organised by B·Debate International Centre for Scientific Debate Barcelona, an initiative of Biocat and "la Caixa" Foundation and the Institute for Research in Biomedicine of Barcelona (IRB Barcelona), with the collaboration of Molecular Biology Institute of Barcelona (IBMB,CSIC), Institut de Medicina Predictiva i Personalitzada del Càncer (IMPPC), Cancer Epigenetics and Biology Program (PEBC, IDIBELL) and the Center for Genomic Regulation (CRG).

Over the past few years, the genomes and transcriptomes of thousands of tumors have been sequenced. This information has revealed an enormous diversity of tumor genotypes and it is helping personalize the treatments of cancer patients. However, despite these advances, it remains a major challenge to predict fundamental aspects of tumor cell behavior such as resistance to therapy or metastatic dissemination.

In this conference world-leading experts in the fields of epigenetic regulation, RNA processing and translation, stem cell biology or tumor microenvironment will discuss how the information contained within the cancer genomes is being integrated with temporal and spatial gene regulation mechanisms to understand the complex cellular reprograming associated to cancer progression.

On behalf of IRB, IBMB-CSIC, IMPPC, PEBC-IDIBELL, CRG and B-Debate, we thank you for joining us in this exciting debate.

Yours sincerely,

Eduard Batlle, Salvador Aznar-Benitah and Raúl Méndez (Scientific Leaders), Scientific Committee and B-Debate

PROGRAM

Thursday, October 13th, 2016

9:00 **Welcome**
Jordi Portabella, Director, Area of Research and Knowledge, la Caixa Foundation
Marta Soler, Head of Research and Scientific Debate, Biocat
Joan Guinovart, Director, IRB Barcelona

9:15 **SESSION 1: EPIGENETIC CONTROL OF CELL STATES**
Chair: **Luciano di Croce,** Centre for Genomic Regulation, Barcelona, Spain

Gene regulation dynamics in stem cell and cancer
Luciano di Croce, Centre for Genomic Regulation, Barcelona, Spain

Cancer: the view from chromosome neighborhoods
Richard A.Young, Whitehead Institute and MIT, Cambridge, USA

Short talk from selected abstract:
Steroid receptors dependent conformation of enhancer domains determines cell-specific intra-TAD folding and transcriptional coordination
François Le Dilly, Centre for Genomic Regulation, Barcelona, Spain

Chromatin during epithelial to mesenchymal transition
Sandra Peiró, IMIM, Barcelona, Spain

11:20 **Coffee Break**

11:50 **SESSION 2: STEM CELLS AND CANCER**
Chair: **Michaela Frye**, University of Cambridge, UK

Epigenetic mechanisms governing stem cell function in homeostasis and cancer
Salvador Aznar, IRB-Barcelona, Barcelona, Spain

Short talk from selected abstract:
Defining the role of stem cells during tumour initiation and resistance to therapy
Adriana Sánchez-Danes, Université Libre de Bruxelles (ULB), Bruxelles, Belgium

Understanding epidermal cell plasticity
Giacomo Donati, University of Turin, Turin, Italy

RNA modifications in the stress responses and cancer
Michaela Frye, University of Cambridge, Cambridge, UK

13:55 **Lunch and poster session**

15:25 **SESSION 3: REGULATION OF RNA FUNCTIONS IN CANCER**
Chair: **Juan Valcárcel**, Centre for Genomic Regulation, Barcelona, Spain

Translating the Cancer Genome One Codon at a Time and its Therapeutic Implications
Davide Ruggero, University of California, San Francisco, USA

Short talk from selected abstract:
The dual role of the RNA binding protein CPEB1 in pancreatic cancer progression
Pilar Navarro, Fundació IMIM, Barcelona, Spain

RNA-binding proteins in cancer
Raúl Méndez, IRB Barcelona, Barcelona, Spain

16:55 **Coffee Break**

17:25 **Networks of alternative splicing regulation in cancer**
Juan Valcárcel, Centre for Genomic Regulation, Barcelona, Spain

Oncogenic splicing factors in breast-cancer pathogenesis
Adrian Krainer, Cold Spring Harbor Laboratory, New York, USA

Short talk from selected abstract:
Targeting GMP synthesis reveals a hierarchy of p53-cell cycle checkpoints in c-Myc driven CRCs
Joffrey Pelletier, IDIBELL, Barcelona, Spain

18:55 **Poster session and networking**

Friday, October 14th, 2016

9:00 **SESSION 4: ONCOGENIC AND NON-ONCOGENIC ADDICTIONS IN CANCER**
Chair: **Laura Soucek,** Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

Myc functions in stem cells and cancer
Andreas Trumpp, German Cancer Research Center (DKFZ), Heidelberg, Germany

Exploring and exploiting aberrant cell fate programs in leukemia
Johannes Zuber, Research Institute of Molecular Pathology (IMP), Vienna, Austria

The contribution of genomic instability to malignant growth in Drosophila
Cayetano González, IRB-Barcelona, Barcelona, Spain

10:45 **Coffee Break**

11:15 **SESSION 5: MODELING CANCER THERAPEUTICS**
Chair: **Laura Soucek,** Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

New first-in-class anti-Myc therapeutics
Laura Soucek, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

A p53-dependent checkpoint limits the viability of mammalian haploid cells
Oscar Fernández Capetillo, Spanish National Cancer Research Centre, Madrid, Spain

Short talk from selected abstract:
Molecular basis of breast cancer dormancy
Roger Gomis, IRB Barcelona, Barcelona, Spain

A stromal gene program drives metastasis in colorectal cancer
Eduard Batlle, IRB-Barcelona, Barcelona, Spain

13:20 **Lunch**

14:50 **SESSION 6: MINING GENOMICS TO UNDERSTAND CANCER**
Chair: **Oscar Fernández Capetillo,** Spanish National Cancer Research Centre, Madrid, Spain

Long-lasting trans-generational epigenetic memory of environmental change
Ben Lehner, Centre for Genomic Regulation, Barcelona, Spain

The genomic landscape of chronic lymphocytic leukemia: functional role of coding and non-coding mutations
Carlos López Otín, Universidad de Oviedo, Oviedo, Spain

Short talk from selected abstract:
Increased mutation rate in transcription factor binding sites across tumors
Radhakrishnan Sabarinathan, Universitat Pompeu Fabra, Barcelona, Spain

Linking stemness properties to therapy failure and disease recurrence
John Dick, University Health Network, Toronto, Canada

16:55 **Closing remarks**

SCIENTIFIC COMMITTEE

Salvador Aznar Benitah, Principal Investigator and ICREA Research Professor at the **Institute for Research in Biomedicine in Barcelona (IRB Barcelona)**, Barcelona, Spain.

Salvador Aznar Benitah obtained his Honours BSc at McGill University. He then did his postdoctoral work at the London Research Institute (Cancer Research UK) at the laboratory of Prof. Fiona Watt. At the age of 32 he established is own lab at the Center for Genomic Regulation (CRG) as a Junior ICREA researcher. In 2014 Salvador was promoted to ICREA Research Professor, and moved to the Institute for Research in Biomedicine (IRB) in Barcelona as a senior researcher. In 2015 he became a Foundation Botín Researcher. His lab aims at understanding the molecular mechanisms underlying adult stem cell function during homeostasis, ageing and cancer.

Eduard Batlle, ICREA Research Professor and Head of the Oncology Program, **Institute for Research in Biomedicine in Barcelona (IRB Barcelona)**, Barcelona, Spain.

Eduard Batlle (Barcelona, 1970) obtained a BSc degree in Biology and a PhD in Molecular Biology by the University of Barcelona. After his postdoctoral training in Hans Clevers lab (Utrecht, the Netherlands), he joined the Institute for Research in Biomedicine (IRB Barcelona) as ICREA Research Professor and Head of the Oncology Program. His research activity has focused on the mechanisms that drive colorectal cancer initiation and progression. Amongst other findings, his research originally identified the transcription factor Snail as a repressor of E-Cadherin gene expression during the Epithelial-to-Mesenchymal Transition (2000); the first connection between intestinal stem cells and colorectal cancer (2002-2011); and more recently a key role for TGF-beta signaling in stromal cells during metastatic colonization (2012-2015). His track record has been recognised through several awards/honours such as the Debiopharm Life Science Award (2006), an ERC starting Grant (2007), Banc de Sabadell Award for Biomedical Research (2010), Josef Steiner Cancer Research Award (2013), Drs. Diz-Pintado award (2013), ERC Advanced Grant (2013) and the Pezcoller foundation-EACR award (2014).

Raúl Méndez, ICREA Research Professor and Group Leader at Molecular Medicine at **the Institute for Research in Biomedicine (IRB Barcelona)**, Barcelona, Spain.

Raúl Méndez studied biology (biochemistry) in the Universidad Autónoma de Madrid. He obtained his PhD in 1993 for work carried out at the Centro de Biología Molecular Severo Ochoa under the supervision of César de Haro. He did postdoctoral work in the laboratory of Robert E. Rhoads at the Louisiana State University Medical Center (1994-1997) and then in the laboratory of Joel D. Richter (1997-2001) at the University of Massachusetts and in 2001 he joined the Centre de Regulació Genòmica of Barcelona as a group leader. In 2010 his group moved to the Institut de Recerca Biomèdica of Barcelona, where he is a senior scientist and ICREA Research Professor. Since the time of his PhD work, his research has focused on how mRNAs are translated into proteins and how this process is regulated during cell division and differentiation. EMBO member since 2012. His research interest is to understand the molecular mechanisms that dictate alternative 3' UTR formation and the temporal and spatial translational control of specific mRNAs during cell cycle progression and chromosome segregation to explore the contribution of these mechanisms in the reprogramming of gene expression in cancer.

Luciano di Croce, Group leader and ICREA Research Professor, **Center for Genomic Regulation (CRG)**, Barcelona, Spain.

Dr. Di Croce's laboratory is addressing the molecular basis of epigenetic alterations during the early phase of tumorigenesis, that is: how epigenetic modifications and chromatin changes are established and, once in place, how they affect gene expression, cell differentiation and transformation. His research focuses in particular in understanding the role of several protein complexes that are involved in chromatin dynamics and metabolism (Polycomb and others), which when altered could participate in the establishment and maintenance of the aberrant silencing of tumor suppressor genes during transformation.

Marcus Buschbeck, Principal Investigator at **Josep Carreras Leukaemia Research Institute**, Barcelona, Spain.

Marcus Buschbeck has been trained in molecular cancer research and chromatin biology at several institutions that include the Max-Planck-Institute of Biochemistry, the University of Oxford and the Center of Genomic Regulation. In 2009 he has combined the two fields to start his own lab at the IMPPC, a small institute embedded in the biomedical research Campus Can Ruti located in the oustkirts of Barcelona, Spain. By joining the Josep Carreras Institute in Leukemia Research on the same campus at the beginning of 2015 he has also started new lines of research focusing on the hematopoietic stem cell defects known as myelodysplastic syndromes and the blood cancer myeloid leukemia.

Antonio García de Herreros, Research Professor at **IMIM-Hospital del Mar and Universitat Pompeu Fabra**, Barcelona, Spain.

Researcher and Group Leader, Program for Cancer Research, IMIM-Hospital del Mar; Full Professor of Biochemistry ("Catedrático Serra-Hunter"), Department of Experimental Sciences, Universitat Pompeu Fabra; Barcelona, Spain. Current research: Regulation of E-cadherin function in epithelial cells: role of Snail1 transcriptional factor in epithelial-mesenchymal transition.
Author of 84 articles published in international journals (article most cited from his lab, Batlle, et al. The transcription factor Snail is a repressor of E-cadherin gene expression in epithelial tumour cells. Nat Cell Biol 2000, 2: 84-89, 698 citations-25/09/11).Supervisor of 16 doctoral theses. Current principal investigator of four grants.

Manuel Perucho, Director of the **Institute of Predictive and Personalized Medicine of Cancer (IMPPC)**, Barcelona, Spain.

Manuel Perucho studied a master in Biological Sciences at University of Madrid in 1971, where he also obtained his Ph.D. degree in Biological Sciences, in 1976. From 1977 to 1978, Perucho was a Postdoctoral Fellow at the Max-Plank-Institute für Molekulare Genetic, (Berlin, Germany) where he studied Isolation and characterization of m RNA for the tissue-specific histone

H5 from immature chicken erythrocytes. From 1979 to 1980, he did a postdoctoral work at Cold Spring Harbor Laboratory, where he became staff investigator during 1981 and 1982. In 1982 he moved to Dept. of Biochemistry at State University of New York, where he was Assistant Professor and, in 1987 Perucho became Associate Professor at the same university until 1988. From 1995 to 2007 he had been linked with California Institute of Biological Research (La Jolla, California) as a research program director (1988-1995) and professor and program director (1995-2007). Currently, Manuel Perucho is a Visiting Professor at Universitat Autònoma de Barcelona, Associate Investigator at Fundación Investigación Sanitaria Castilla-La Mancha, Member Advisory Board at Instituto Canario Investigación, Professor and Program Co-Director at Sanford-Burnham Medical Research Institute and Director of Institute of Predictive and Personalized Medicine of Cancer (Badalona, Spain). Perucho has also organized more than twenty meetings and courses and he has about 130 scientific publications.

Manel Esteller, Director of the **Cancer Epigenetics and Biology Prgram (PEBC-IDIBELL)**, Barcelona, Spain.

Manel Esteller graduated in Medicine from the Universitat de Barcelona, where he also obtained his Ph.D. degree specialising in molecular genetics of endometrial carcinoma. Dr. Esteller was a Postdoctoral Fellow and a Research Associate at the Johns Hopkins University and School of Medicine, (Baltimore, USA) where he studied DNA methylation and human cancer. His work was decisive in establishing promoter hypermethylation of tumour suppressor genes as a common hallmark of all human tumours. From October 2001 to September 2008 Manel Esteller was the Leader of the CNIO Cancer Epigenetics Laboratory. Since October 2008, Dr Esteller is the Director of the Cancer Epigenetics and Biology Program (PEBC) of the Bellvitge Institute for Biomedical Research (IDIBELL) in Barcelona, Leader of the Cancer Epigenetics Group, Professor of Genetics in the School of Medicine of the University of Barcelona, and an ICREA Research Professor. His current research is devoted to the establishment of the epigenome maps of normal and transformed cells, the study of the interactions between epigenetic modifications and non-coding RNAs, and the development of new epigenetic drugs for cancer therapy. Author of more than three hundred original peer-reviewed manuscripts in biomedical sciences, he is also a Member of numerous international scientific societies, Editorial Boards, reviewer for many journals and funding agencies and recipient of prestigious awards.

Albert Jordan, Research Scientist and Group Leader of Chromatin regulation of human and viral gene expression group at **Molecular Biology Institute of Barcelona (IBMB) - CSIC**, Barcelona, Spain.

After graduating in Biology at the Autonomous University of Barcelona (UAB) Albert Jordan went on to do his Ph.D. (1992-95) in the laboratory of Drs. Jordi Barbé and Isidre Gibert at the Dept. Genetics and Microbiology, UAB, where he was a lecturer afterwards (1996-98). In the meantime he spent five consecutive summer periods in Dr. Peter Reichard's laboratory at the Karolinska Institute, Stockholm. He then moved to San Francisco to undertake his postdoctoral work in the group of Dr. Eric Verdin at the Gladstone Institutes (1999-2001), where he became interested in the role of chromatin in human and viral gene expression control. In 2002 he got a Ramon y Cajal appointment to join the group of Dr. Miguel Beato at CRG where he became staff scientist afterwards. Finally, in 2008 he got a permanent CSIC position to start a new group at IBMB, Dept. Molecular Genomics. He was Department director between 2011-13. In parallel, Dr. Jordan was appointed coordinator of the Molecular Biology section of the Catalan Society of Biology (SCB) in 2009, and Sections Coordinator and member of the Directive Committee of SCB in 2012. Dr. Jordan has been awarded several grants, directed 6 Ph.D. theses and published 32 papers.

INVITED SPEAKERS

Thursday, October 13th, 2016

Session 1: Epigenetic Control of Cell States

Luciano di Croce, Group leader and ICREA Research Professor, **Centre for Genomic Regulation (CRG)**, Barcelona, Spain.

See his CV at the Scientific Committee section.

Gene regulation dynamics in stem cell and cancer

Polycomb group of proteins are transcriptional repressors and play essential roles in regulating genes required for differentiation and embryonic development. Moreover, alteration in the expression of Polycomb group proteins have long been linked to the occurrence of different types of human diseases. Mechanistically, Polycomb proteins form at least two distinct complexes: the Polycomb-repressive complexes 1 and 2 (PRC1 and PRC2). It is especially critical for stem cells that their potential to self-renewal and to differentiate is tightly controlled and properly orchestrated. Misregulation of the levels of Polycomb protein often leads to either a block or an unscheduled activation of developmental pathways, and thus to an alteration in the cell cycle control. The consequences of this misregulation have been linked to the establishment of cancer stem cells, which can produce tumors through the combination of an increase in self-renewal with a lack of complete cellular differentiation. I will discuss how Polycomb proteins impact on cancer, and their role in stem cell biology.

Chair of the SESSION 1

Richard A. Young, Professor of Biology, **Whitehead Institute and MIT**, Cambridge, USA.

Richard Young studies gene regulatory circuitry in health and disease. His research accomplishments range from the development of genome-wide analysis technologies to discovery of the core regulatory circuitry of human embryonic stem cells. Dr. Young received his Ph.D. in Molecular Biophysics and Biochemistry at Yale University, conducted postdoctoral research at Stanford University and joined Whitehead Institute and MIT in 1984. He has served as an advisor to the National Institutes of Health, the World Health Organization, the Vatican and numerous scientific societies and journals. Dr. Young has founded and advised companies in the biotechnology and pharmaceutical industry and is currently a member of the Board of Directors of Syros Pharmaceuticals and Marauder Therapeutics. His honors include Membership in the National Academy of Sciences, the Chiron Corporation Biotechnology Research Award, Yale's Wilbur Cross Medal, and in 2006 Scientific American recognized him as one of the top 50 leaders in science, technology and business.

Cancer: the view from chromosome neighborhoods

The control of cell identity is orchestrated by transcriptional and chromatin regulators in the context of specific chromosome structures. Genes and their regulatory elements typically occur together within specific DNA loop structures called insulated neighborhoods, which have emerged as structural and functional units of gene control. Insulated neighborhoods are chromatin loops that contain genes and their regulatory elements and are formed by the interaction of CTCF proteins bound to two distal DNA sites called loop anchors. In this context, I will discuss how mutations in cancer cells create super-enhancers and alter loop anchor sites in oncogene-containing insulated neighborhoods, and how these contribute to the dysregulation of gene expression that is inherent to the cancer state.

Sandra Peiró, Head of the Chromatin Dynamics Group, **Hospital del Mar Medical Research Institute (IMIM)**, Barcelona, Spain.

Sandra Peiró Sales obtained his Honours Degree in Biochemistry at Universitat de Barcelona (UB)in 1995. She then obtained his PhD in 2001 in Biochemistry at the Faculty of Medicine in UB. In 2001 she started her first postdoc in the laboratory of Prof. Francisco X Real and Pilar Navarro at the UPF. Then she did a second postdoc in the laboratory of Prof. Antonio García de Herreros (IMIM) where she became interested in epigenetics and gene. She established is own research at IMIM in 2008 as a Junior researcher. She is a Group Leader at IMIM since 2014.

Chromatin during epithelial to mesenchymal transition

Histone tail modifications are key in regulating many cellular processes. Oxidation of H3 on lysine 4 (H3K4ox) is carried out by lysyl oxidase–like 2 protein (LOXL2) and is associated with transcriptional repression. The LOXL2 enzyme is overexpressed in many tumour types, in which its expression correlates with poor prognoses. Using an H3K4ox-specific antibody, we determined that the H3K4ox modification is enriched in triple-negative (TN) breast cancer cells, correlating with high LOXL2 levels in these cells. Additionally, it is found primarily in heterochromatin in these cells, as shown by ChIP-seq. We now show that this modification controls heterochromatin compaction and inhibits the DNA damage response (DDR), which is interesting in light of recent work showing that the mutational rate in cancer cells is higher in heterochromatin than in euchromatin. A LOXL2 knockdown resulted in a reduction in H3K4ox levels and a change in chromatin conformation towards a more “open” state. Under these conditions, DNA lesions are exposed, DDR is activated, and TN cells die in few days. Treating TN breast cancer cells with a LOXL2 inhibitor also sensitizes the cells. Together, these results reveal a role for oxidized H3 in DDR, providing a new mechanism by which this modified H3 affects chromatin compaction and opening a therapeutic window for treating TN breast tumours.

Session 2: Stem Cells and Cancer

Michaela Frye, Principal Investigator, Genetics Cambridge, **University of Cambridge**, Cambridge, UK.

Michaela Frye completed her PhD in Frankfurt/Main in Germany in 2000 studying the role of epithelial defensins in Cystic Fibrosis. In 2001 she joined the lab of Fiona Watt as a Postdoctoral Fellow at the CR-UK London Research Institute, where she developed her fascination for the question how stem cells in the skin are regulated. Michaela received a CR-UK Career Development Fellowship in 2007 when she started as a group leader at the WT-MRC Stem Cell Institute. She has renewed this fellowship in 2012 and is now a CR-UK Senior Fellow.

RNA modifications in the stress responses and cancer

Many of the over 100 types of chemical RNA modifications are evolutionary highly conserved and functionally indispensable for protein synthesis because they regulate translational accuracy and enhanced activity. Here, I discuss the importance of RNA methylation on global and specific protein translations rates in skin stem cells in homeostasis, cancer and in response to chemotherapeutic drug treatments. Quiescent skin stem cells lack RNA methyltransferases and consequently synthesize less protein than their immediate progenitors in vivo, even when forced to proliferate in a tumor model. Surprisingly, this translation inhibition renders epithelial tumor-initiating cells hypersensitive to chemotherapeutic drugs. Thus, stem cells must revoke translation inhibition pathways to regenerate tumor after drug treatment.

Chair of the SESSION 2

Salvador Aznar Benitah, Principal Investigator and ICREA Research Professor at the **Institute for Research in Biomedicine in Barcelona (IRB Barcelona)**, Barcelona, Spain.

(See his CV at the Scientific Committee Section)

Epigenetic mechanisms governing stem cell function in homeostasis and cancer

Metastasis is the leading cause of cancer-related deaths. However, the identity of the cells that promote metastasis is unknown, hampering our ability to develop therapies to prevent or inhibit the spread of tumor cells to distant sites. We have identified the cells uniquely responsible for the formation of metastasis in different types of human tumors. These cells have intriguing characteristics: i) they form primary lesions as efficiently as their tumor-initiating counterparts, but are exclusive in their ability to generate metastases; ii) they are characterized by a unique lipid metabolic signature; iii) they are exquisitely sensitive to the levels of fat in circulation, and consequently, they relate the predisposition of metastasis directly to the content of dietary fat; iv) they are highly sensitive to inhibition of this metabolism, which almost completely abolishes their metastatic potential in preclinical models. Altogether, our results indicate that the metastatic process is particularly sensitive to dietary lipids. I will discuss these results regarding the impact of our diet on metastasis, and the potential use of these findings for therapeutic purposes.

Giacomo Donati, Principal Investigator, Department of life sciences and System Biology, **University of Turin & Human Genetics Foundation (HuGeF)**, Turin, Italy.

2004-2008 PhD in Genetic and Biomolecular Sciences. University of Milan, Department of Biomolecular Sciences and Biotechnology (Italy). Roberto Mantovani Laboratory. Research field: Relationship between the transcription factor NF-Y and histones post-translational modifications in inducible systems.
2009-2016 Post-doc at Cancer Research UK Cambridge Research Institute and at Centre for Stem Cells and Regenerative Medicine, King's College London in Fiona Watt Laboratory. Research field: Niche crosstalk and stem cell fate in skin homeostasis, regeneration and cancer.
Present – Principal Investigator at Department of Life Sciences and System Biology, University of Turin & Human Genetics Foundation (HuGeF), Italy.

Understanding epidermal cell plasticity

Tissue repair is a tightly regulated process that re-establishes the integrity of the injured site. In mammals, it displays limited regenerative potential in adult life but it can have an important role in the pathogenesis of tumors. Therefore investigating cell plasticity during tissue repair is important for regenerative medicine purposes, but also to understand pre-neoplastic events and, possibly, new tumor evolution mechanisms. In the adult epithelia, compartmentalized stem cells produce new cells of diverse, and spatially distinct lineages to maintain only the homeostasis of specific epithelial niches. These homeostatic restrictions are lost after tissue damage where epithelial stem cells exhibit striking plasticity to contribute to the repair of any injured niches. The analysis of transcriptomic data from epidermis under homeostatic and lineage perturbation conditions revealed new transcriptional mechanisms of lineage selection and a new epidermal lineage. The comparison of multiple follicular lineages during wound healing, through lineage tracing experiments, revealed unexpected distinct repair strategies.

Session 3: Regulation of RNA functions in Cancer

Juan Valcárcel, Group leader, Gene Regulation, Stem Cells and Cancer Program, **Centre for Genomic Regulation (CRG)**, Barcelona, Spain.

Juan Valcárcel obtained his PhD from work on influenza virus splicing regulation carried out in the lab of Juan Ortín at the Center of Molecular Biology Severo Ochoa in Madrid. After a postdoc with Michael Green at the University of Massachusetts, working on mechanisms of splice site recognition and regulation, he established his group at the European Molecular Biology Laboratory (EMBL) in Heidelberg in 1996. In 2002 the group moved to the newly created Center for Genomic Regulation (CRG) of Barcelona, where he is currently ICREA Research Professor, Fundación Botín Investigator and associated Professor of the University Pompeu Fabra. Elected EMBO member in 2004, he was deputy Coordinator of the European Alternative Splicing Network of Excellence, and head of the RNAREG Consolider consortium (which coordinated work of RNA biologists and molecular oncologists in Spain). He is member of the Editorial Board of the Journals RNA, Molecular and Cellular Biology and Molecular Cell and of the Board of Reviewing Editors of eLife, as well as of the Wellcome Trust Interviewing Panel. He will serve as President of the RNA Society in 2017-2018. Work in his group focuses on molecular mechanisms and networks of alternative splicing regulation in cancer and pluripotent cells.

Networks of alternative splicing regulation in cancer

Removal of introns from mRNA precursors (pre-mRNA splicing) is an essential step for the correct expression of eukaryotic genes, and requires one of the most complex molecular machineries of eukaryotic cells, the spliceosome, composed of 5 snRNAs and over 200 protein components. Alternative splicing of mRNA precursors regulates the vast majority of human genes by generating different mRNAs that encode proteins with distinct, sometimes antagonistic functions. Alterations in alternative splicing can impact every hallmark of cancer and can be caused by cancer-associated mutations in splicing regulatory sequences or in splicing factors. In my talk, I will describe our recent efforts to systematically reveal splicing regulatory circuits altered in cancer cells and the potential use of this knowledge to design anti-cancer therapies.

These include methods for saturation mutagenesis of alternative exons, genome-wide identification of regulatory factors, and reconstruction of splicing regulatory networks via profiling of alternative splicing after systematic knock down of spliceosomal components. Our results reveal highly dense regulatory content of alternative exon sequences and extensive regulatory potential of core splicing factors. They also reveal detailed molecular mechanisms of versatile splicing modulation by anti-tumor drugs and by modified antisense oligonucleotides, as well as the impact of signaling pathways important for cancer cell proliferation.

Chair of the SESSION 3

Davide Ruggero, Professor in Helen Diller Family Comprehensive Cancer Center, **University of California, San Francisco**, San Francisco, CA, USA.

Dr. Ruggero is a Professor at the University of California, San Francisco in the Helen Diller Cancer Center and Departments of Urology and Cellular and Molecular Pharmacology. He received his Ph.D. from University of Rome in 1994 and carried out his postdoctoral work at Memorial Sloan Kettering Cancer Center in New York. Dr. Ruggero held his first position as independent scientist at Fox Chase Cancer Center in Philadelphia, PA in 2004 and joined the University of California, San Francisco in 2007 as an Assistant Professor. He was promoted to Associate Professor in 2010 and received an accelerated promotion to full Professor in 2014. Dr. Ruggero's laboratory has been a pioneer in understanding the molecular mechanisms by which impairments in accurate control of RNA modification, mRNA translation, cell growth, and overall cellular protein synthesis rates lead to cancer and human disease. His lab's findings have been instrumental in the design of a new generation of compounds that modulate the cellular proteome at the post-genomic level and act as cancer therapeutic agents.

Translating the Cancer Genome One Codon at a Time and its Therapeutic Implications

Our research is centered on understanding the molecular mechanisms by which impairments in accurate control of mRNA translation, cell growth, and protein synthesis lead to cancer and human disease. We have uncovered that a common denominator of multiple oncogenic pathways is their ability to directly control the core translation machinery of a cell, resulting in rewiring of the mRNA translation program in cancer cells. We have shown that this process reflects an adaptation and addiction of cancer cells to aberrant protein synthesis that fuels their growth and survival. I will discuss our most recent findings delineating the in vivo requirements for a distinct threshold of the major cap-binding protein, eIF4E, in normal organismal development compared to that required for translating the cancer genome. We show that cancer cells require increased eIF4E activity for their survival as distinct subsets of mRNAs that regulate the cancer cell oxidative

response are marked by the presence of a novel eIF4E-dependent cis-acting translational control motif present in their 5'UTRs. I will also discuss the generation of the first comprehensive systems-level analysis of the 'cancer translatome' during each phase of cancer development in vivo that highlights a dichotomy in transcriptional vs. translational control of gene expression guiding key, select steps in cancer development and evolution. These studies have uncovered a previously unappreciated translation program guiding tumor cell evasion of immune checkpoints. The immediate impact of our research has been the design of a new generation of compounds to target the aberrant translation machinery in cancer cells, which are currently in clinical trials, and may reflect a new frontier in cancer therapy.

Raúl Méndez, ICREA Research Professor and Group Leader at Molecular Medicine at **the Institute for Research in Biomedicine (IRB Barcelona)**, Barcelona, Spain.

(See his CV at the Scientific Committee Section)

RNA-binding proteins in cancer

The Cytoplasmic Polyadenylation Element Binding (CPEB)-family of RNA-binding proteins regulates pre-mRNA processing and translation of CPE-containing mRNAs in early embryonic development and synaptic activity. However, the specific functions of each CPEB in the adult organism are poorly understood. We show that CPEB is required to suppress high fat diet- and aging-induced endoplasmic reticulum (ER) stress, and its subsequent hepatic steatosis. Stress-activated expression of CPEB in the liver is controlled through a double layer of regulation. First, Cpeb is transcriptionally regulated by the circadian clock and then, its mRNA translation is regulated by the Unfolded Protein Response (UPR) through the upstream Open Reading Frames (uORFs) present in its 5' UTR. Thus, CPEB is synthesized only upon ER-stress but the amplitude of the induction is circadian. In turn, CPEB activates a second wave of UPR-translation required to maintain ER and mitochondrial homeostasis. Our results suggest that combined transcriptional and translational regulation of CPEB generates a "circadian sensor", which coordinates the UPR sensitivity with periods of high liver ER folding activity preventing Non-alcoholic fatty liver disease (NAFLD). The impact of thes CPEB4 stress-mediated response in tumor development will be discussed.

Adrian Krainer, Professor, Gene Regulation & Cell Proliferation, **Cold Spring Harbor Laboratory (CSHL)**, New York, USA.

Dr. Adrian R. Krainer is the St Giles Foundation Professor of Molecular Genetics, and Program Chair in Cancer & Molecular Biology at Cold Spring Harbor Laboratory, in Long Island, NY. He is a founder and member of the board of directors of Stoke Therapeutics, and consults for and collaborates with Ionis Pharmaceuticals. He has served on the scientific advisory boards of: the Swiss National Center of Competence in Research on RNA & Disease; the European Alternative Splicing Network of Excellence (EURASNET); the Pasteur Institute in Montevideo, Uruguay; Reactome; CureSMA; FightSMA; H3 Biomedicine; MetaStat; Envisagenics BioAnalytics; and on the board of directors of the Broad Hollow Science Park.
Dr. Krainer is a Pew Scholar in the Biomedical Sciences, a MERIT-award recipient from the National Institute of General Medical Sciences, a member of the American Academy of Arts & Sciences and of the UK's Royal Society of Medicine, a recipient of the Colleen Giblin Memorial Award for research on pediatric neurological diseases, and he previously served as President of the RNA Society. He has published ~200 research articles and reviews, and is an inventor in 11 patents.

Oncogenic splicing factors in breast-cancer pathogenesis

Splicing factor SRSF1 is upregulated in human breast tumors, and its overexpression promotes transformation of mammary cells. Using RNA-seq, we identified SRSF1-regulated alternative-splicing targets in organotypic three-dimensional MCF-10A cell cultures, which undergo acinar morphogenesis and mimic a context relevant to breast cancer. We identified and validated hundreds of endogenous SRSF1-regulated alternative-splicing events, and determined the overlap with presumptive SRSF1-regulated events deregulated in human breast tumors. Overexpressing one such isoform, exon-9-included CASC4, increased acinar size and proliferation, and decreased apoptosis, partially recapitulating SRSF1's oncogenic effects. We then used the same experimental approach in a comparative analysis of several other SR-protein paralogs and the SR-like protein Tra2β, which are likewise deregulated in breast cancer. These factors had differential effects in various in vitro and in vivo oncogenic assays, correlating with changes in alternative splicing of their downstream targets. In particular, we found that Tra2β regulates cell migration and invasion, and plays a role in metastatic growth in vivo. One of our goals is to uncover oncogenic alternative-splicing events that represent potential targets for therapeutics development, e.g., using splice-switching antisense oligonucleotides.

Friday, October 14th, 2016

Session 4: Oncogenic and Non-oncogenic Addictions in Cancer

Laura Soucek, ICREA Research Professor and Principal Investigator of Mouse Models of Cancer Therapies Laboratory, **Vall d'Hebron Institute of Oncology (VHIO)**, Barcelona, Spain.

Laura Soucek is ICREA Research Professor, Associate Professor at the Universidad Autonoma de Barcelona and head of the Mouse Models of Cancer Therapies Group at the Vall d'Hebron Institute of Oncology (VHIO), in Barcelona, Spain. Her main research focus is the Myc oncoprotein, whose deregulation is implicated in almost all human cancer types. Her seminal studies demonstrated that Myc inhibition has a remarkable therapeutic index in different mouse models of cancer, while only causing mild and reversible side effects in normal tissues, suggesting that Myc inhibition could be a viable and effective strategy against most, if not all, types of cancer. Dr. Soucek has published in some of the most prestigious international journals including Nature, Nature Genetics, Nature Medicine and Nature Communications. She received prestigious awards and grants, including recognitions by AACR, Worldwide Cancer Research and the European Research Council (ERC). In December 2014 she founded a spin-off company called Peptomyc, which aims at treating cancer with anti-Myc peptides, and in 2016 she assumed the position of Chief-Executive-Officer of the company.

Chair of the SESSION 4

Andreas Trumpp, Full Professor and Head of the Division "Stem Cells and Cancer" at the, **DKFZ Heidelberg**, Germany and Managing Director of **Heidelberg Institute for Stem Cell Technology and Experimental Medicine (HI-STEM)**, Heidelberg, Germany.

Andreas Trumpp is full professor and head of the Department for "Stem Cells and Cancer" at the DKFZ in Heidelberg (Germany) and also the founding director of the Heidelberg Institute for Stem Cell Technology and Experimental Medicine (HI---STEM gGmbH). He studied biology at the University of Freiburg (Germany) and received his PhD from the EMBL in Heidelberg (Germany). In 1994, he started his postdoctoral research in the laboratories of Dr. J. Michael Bishop and Dr. Gail R. Martin at the University of California at San Francisco. In 2000 he became head of the Genetics and Stem Cell Laboratory at the Swiss Institute for Experimental Cancer Research (ISREC) in Lausanne and subsequently professor of molecular oncology and stem cell biology at the École Polytechnique Fédérale de Lausanne (EPFL) before moving to Heidelberg in 2008.

Myc functions in stem cells and cancer

Stem cells are essential for maintaining and repairing regenerative tissues. Moreover, genetic alterations of stem cells and their progeny can lead to the generation of "cancer stem cells" (CSCs) that drive tumorigenesis and metastasis. One of our main goals is to elucidate the molecular and cellular basis of hematopoietic stem cell (HSC) and embryonic stem cell (ESC) self-renewal. We have shown that the most potent HSCs are in a state of deep dormancy. In response to bacterial (LPS) or viral infections (Interferons) or chemotherapy mediated cell loss, dormant HSCs become activated to produce new stem cells and progenitors (Wilson et al., Cell 2008; Essers et al., Nature 2009). Using genome-wide transcriptomics, proteomics and methylome analysis, we have established the molecular landscape of HSCs and immediate progenitors to understand the molecular basis of self-renewal and multipotency, as well as the interactions between stem cells and their niche (Cabezas et al., Cell Stem Cell 2014). Using single cell RNAseq and single cell functional assays we uncover the molecular mechanisms driving dormancy. Moreover, we have recently shown that the oncogene MYC can regulate the dormancy of pluripotent cells present within pre-implantation embryos during the state of diapause (Scognamilglio et al., Cell 2016). We assume that MYC may be the key regulator controlling entry and exit from dormancy in normal stem cells as well as in cancer and metastasis stem cells.
Pancreatic ductal adenocarcinoma (PDAC) is clinically still treated as a single disease. Here we present PDX models and cell lines derived thereof representing all three PDAC subtypes: quasi-mesenchymal, classical and exocrine-like. These subtypes show significant differences in overall survival and drug sensitivity, with the exocrine-like subtype being resistant to tyrosine kinase inhibitors and paclitaxel. Cytochrome P450 3A5 (CYP3A5) metabolizes these compounds in exocrine-like tumors, and pharmacological or shRNA-mediated CYP3A5 inhibition sensitizes tumor cells to these drugs (Noll et al., Nature Medicine 2016). Our findings designate CYP3A5 as predictor of therapy response and as a tumor cell-autonomous detoxification mechanism that must be overcome to prevent drug resistance.

Johannes Zuber, Group Leader (PI), **Research Institute of Molecular Pathology (IMP)**, Vienna, Austria.

Dr Zuber is a group leader at the Research Institute of Molecular Pathology (IMP) in Vienna, Austria. He studied medicine and received a doctorate in molecular cancer research at Charité Medical School in Berlin in 2001. Following a four-year clinical residency in hematology and oncology, he joined Scott Lowe's lab at Cold Spring Harbor Laboratory (CSHL) as a postdoc in 2005, where he later was appointed as a Clinical Research Fellow. In 2011, he founded his own lab at the IMP in Vienna, where he develops and applies innovative functional-genetic approaches for identifying and probing candidate therapeutic targets in leukemia and other cancers. He received an ERC Starting Grant in 2015, has been selected as an EMBO Young Investigator (YIP) in 2015, and has been awarded with the German Cancer Prize 2016.

Exploring and exploiting aberrant cell fate programs in leukemia

The ability to evade differentiation hierarchies and indefinitely self-renew is a hallmark of leukemia. While genetic studies and first "differentiation therapies" testify to the great therapeutic potential of inhibiting drivers of aberrant self-renewal, this phenomenon remains poorly understood on the mechanistic level. To explore key factors and candidate targets involved in this process, our lab pursues three complementary approaches: [1] To systematically probe factors involved in maintaining aberrant chromatin states, we have constructed a miR-E based shRNA library targeting known and predicted chromatin regulators (650 genes, 5500 shRNAmirs) and are employing it in comparative genetic screens in leukemia models of defined genetic and tissue context. [2] To explore self-renewal associated transcriptional networks in an unbiased way, we have generated Tet-off conditional AML models involving five common drivers of aberrant cell fates (so-called "type-II mutations"), which can be withdrawn in established AML. Through identifying a shared "type-II" effector signature and functionally probing it using focused shRNAmir screening, we have discovered common factors involved in maintaining aberrant self-renewal in diverse AML subtypes. [3] Taking advantage of well-known cellular hierarchies in hematopoietic differentiation, we have established FACS-based screening strategies for identifying triggers of differentiation, which in contrast to multiplexed "drop-out screens" provides a positive-selection setup that is compatible with bulk-cloned shRNAmir and sgRNA libraries at genome scale. Collectively, through integrating results from these systematic functional studies, we have identified and validated factors that are required for maintaining aberrant self-renewal and may provide new entry points for the development of targeted therapeutics.

Cayetano Gonzalez, ICREA Research Professor, **IRB Barcelona** and **BIST**, Barcelona, Spain.

After completing a PhD at the Centre for Molecular Biology in Madrid, Cayetano González moved to the UK, first at Imperial College and later as a CRC Joint Principal Investigator at Dundee. In 1994, he took his first independent position, as a Group Leader at EMBL (Heidelberg, Germany). After the customary nine-year period at EMBL, he moved to CNIO (Madrid). In 2004 he moved to his present post at the Institute for Research in Biomedicine (IRB-Barcelona) where he leads the Cell Division Group.

The contribution of genomic instability to malignant growth in Drosophila

I will summarize data derived from Drosophila tumour models on how genome instability and unscheduled gene expression impinge on tumour initiation and malignant growth. Most of the malignant tumours that can be experimentally induced in flies are larval brain tumors caused by loss-of-function of any of several genes that control the asymmetric division of neural precursors. There is also a different type of fly cancer model, which derives from the neuroepithelium. In the latter, genes that are normally expressed in germline cells become aberrantly activated. In the human oncology literature, these genes are referred to as cancer-testis, or cancer-germline genes. Direct proof of the functional relevance of such genes in human malignancy is still lacking, but research on the fly models is unveiling unsuspected functions of these genes that may have direct therapeutic implications. Another key aspect of human malignant growth that Drosophila tumour models recapitulate well is genome instability. Through ongoing experiments on this front we are currently addressing the cause-effect relation between genome instability and malignant growth and how the former can be used to inhibit the latter.

Session 5: Modeling cancer therapeutics

Laura Soucek, ICREA Research Professor and Principal Investigator of Mouse Models of Cancer Therapies Laboratory, **Vall d'Hebron Institute of Oncology (VHIO)**, Barcelona, Spain.

(See his CV at the Session 4)

New first-in-class anti-Myc therapeutics

Deregulated Myc is associated with most human cancers suggesting that its inhibition would be a useful therapeutic strategy. Indeed, we have shown that Myc inhibition displays extraordinary therapeutic benefit in various transgenic mouse models of cancer (i.e. skin, lung, pancreatic cancer and glioma), without eliciting resistance to therapy, and causes only mild, well-tolerated and reversible side effects in normal tissues [1-3]. For these studies we employed a dominant negative inhibitor of Myc, called Omomyc, which is an effective inhibitor of Myc transactivation function both in vitro and in vivo. Omomyc has so far been utilized exclusively as a transgene and served as a successful proof of principle. Here we present our current results based on the direct use of Omomyc itself as a peptide displaying unexpected and efficient cell-penetrating activity (OmomycCPP). When tested in vitro, OmomycCPP causes growth arrest and/or death of several cancer cell lines. In vivo, upon intranasal administration, it rapidly biodistributes to the lung and brain, as well as to other tissues of the animals, and - like its transgenic counterpart before – has a notable therapeutic impact on KRasG12D-driven Non-small Cell Lung Cancer (NSCLSC) and Glioblastoma (GB).
In summary, our results show that OmomycCPP represents a novel and viable pharmacological strategy to inhibit Myc in vivo, a strategy that has the potential to be translated rapidly to the clinic.

Chair of the SESSION 5

Oscar Fernandez-Capetillo, Group Leader, **Spanish Natonal Cancer Research Centre**, Madrid, Spain.

The Fernandez-Capetillo laboratory at the Spanish National Cancer Research Centre works in the field of DNA replication stress (RS) and its links to cancer and ageing. They were first to show that RS can promote aging in mammals, through a humanized allele that led to the first viable mouse model of the ATR kinase (the main responder to RS). Later on, using mice carrying extra alleles of RS-suppressing genes (SUPER-mice), they have been able to rescue RS-driven ageing. Regarding cancer, they provided genetic proof-of-concept to the idea that targeting ATR might be beneficial for certain tumors. Furthermore, through the use of a cell-system previously generated by the group where ATR can be activated at will, they developed inhibitors of the ATR kinase. In addition to sharing these compounds for researchers in the field, the drugs were licensed to the pharmaceutical company Merck, which is working on bringing them to the clinic. In addition to this line of work on ATR, the group has also explored other fields related to gene maintenance such as the role of nucleotide metabolism, the impact of DNA damage during the generation of induced pluripotent stem cells, or performing genomewide CRISPR screens to identify mechanisms of resistance to cancer therapies. Since 2015, Oscar is also a Professor of "Cancer Therapy" at the Karolinska Institute in Sweden.

A p53-dependent checkpoint limits the viability of mammalian haploid cells.

The recent development of mammalian haploid cell lines has facilitated forward genetic screenings both in mouse and human cells. A known limitation of haploid mammalian cultures is the rapid reduction in the percentage of haploid cells, which are replaced by diploid cells. This phenomenon, thought to be a consequence of diploidization, demands constant sorting to maintain haploid lines. Here we show that diploidization is a rare event, so that single cell sorting significantly increases the stability of haploid cell cultures. Rather than diploidization, the loss of haploidy is associated to frequent mis-segregation events in haploid cells that trigger a p53-dependent cytotoxic response. Consistently, p53-deletion stabilizes haploidy in human HAP1 cells, and facilitates the generation and maintenance of haploid primary mouse stem cell lines. We propose that similar to aneuploidy or tetraploidy, haploidy triggers a p53-dependent checkpoint that limits the expansion of mammalian haploid cells.

Eduard Batlle, ICREA Research Professor and Head of the Oncology Program , **Institute for Research in Biomedicine in Barcelona (IRB Barcelona)**, Barcelona, Spain.

(See his CV at the Scientific Committee Section)

A stromal gene program drives metastasis in colorectal cancer

About 40-50% of Colorectal Cancer (CRC) patients with locally advanced disease show resistance to therapy and develop recurrent cancer over the course of their treatment. Current CRC staging based on histopathology and imaging has a limited ability to predict prognosis. A major advance has been the elaboration of molecular classifications based on global gene expression profiles, which have defined CRC subtypes displaying resistance to therapy and poor prognosis. We have recently evaluated these molecular classification systems and discovered that their predictive power arises from genes expressed by stromal cells rather than by epithelial tumor cells. Our functional dissection of CRC progression shows that metastasis relies on a tumor cell non-autonomous program driven by TGF-beta in the microenvironment. Virtually all poor prognosis CRC subtypes upregulate this stromal gene program, which confers a survival advantage to metastatic stem cells during organ colonization. Here I will discuss our latest data about the dichotomy of TGF-beta signaling in epithelial versus stromal cells during CRC progression and the use of patient derived tumor organoids and mouse models to test the efficacy of anti-TGF-beta therapies for CRC treatment.

Session 6: Mining genomics to understand cancer

Oscar Fernandez-Capetillo, Group Leader, **Spanish Natonal Cancer Research Centre**, Madrid, Spain.

(See his CV at the Session 5)

Chair of the SESSION 6

Ben Lehner, EMBL & AXA Professor, EMBL-CRG Systems Biology, **Centre for Genomic Regulation**, Barcelona, Spain.

Ben Lehner received his BA and PhD from the University of Cambridge, UK and was a postdoctoral fellow at the Wellcome Trust Sanger Institute. Since 2006 he has been a group leader at the EMBL-CRG Systems Biology Program in Barcelona and is currently ICREA and AXA Professor. His lab uses model organisms and data to understand how genetic and non-genetic variation influences complex traits across individuals. Amongst other prizes, Ben was awarded the EMBO Gold Medal (2016), the Bettencourt Prize (2016) and the Eppendorf Award (2013).

Long-lasting trans-generational epigenetic memory of environmental change

Since Darwin and Lamarck, biologists have speculated about the possibility of the inheritance of acquired traits. In our work on the causes of inter-individual variation we chanced upon an example of a >10 generation epigenetic memory of environmental change in C. elegans. We have been using this as a model system to understand how information about the environment can be transmitted for many generations without establishing permanent epigenetic states. I will present this work and I will also show how impaired DNA replication during development can lead to genome-wide epigenetic reprogramming.

Carlos López-Otín, Professor of Biochemistry and Molecular Biology, **Universidad de Oviedo**, Ovideo, Spain.

Carlos López-Otín is Professor of Biochemistry and Molecular Biology at the University of Oviedo (Spain) where he combines his teaching responsibilities with research on Cancer and Aging Biology, as well as on the functional analysis of genomes. His group has discovered more than 60 novel human genes encoding proteases associated with cancer and has described their functional role in cancer and in other pathological processes. Lopez-Otin's group has also identified the genetic determinants of several diseases, including the discovery of two novel premature aging syndromes, the Nestor-Guillermo Progeria Syndrome (NGPS) and the Atypical Neonatal Progeria Syndrome (ANPS), and the finding of new genes causing hereditary sudden death, microcytic anemia, bone abnormalities and familial melanoma. He has contributed to the first integrative analysis of the hallmarks of aging and proposed different strategies for the metabolic control of longevity. Since 2009, Carlos Lopez-Otin co-directs the Spanish contribution to the International Cancer Genome Consortium (ICGC-CLL), which has unveiled the complete tumor genome sequence of hundreds of patients with chronic lymphocytic leukemia. The work by Carlos López-Otín is collected in more than 350 publications, which have been cited more than 35.000 times, with a Hirsch index of h=92

The genomic landscape of chronic lymphocytic leukemia: functional role of coding and non-coding mutations

Chronic lymphocytic leukemia (CLL), the most frequent leukemia in adults, is amongst the first human neoplasias whose study has benefited from the recent introduction of high-throughput sequencing technologies of outstanding efficiency. The aim of the CLL-ICGC Spanish Consortium is to generate a catalogue of genetic, epigenetic and transcriptomic alterations relevant to the pathogenesis and clinical evolution of this heterogeneous disease. We have recently completed a comprehensive evaluation of the genomic landscape of about 500 CLL cases. These studies have allowed us the identification of a series of oncogenes and tumor suppressors, such as NOTCH1, SF3B1, POT1, XPO1 and MYD88, which are recurrently mutated in CLL. We have also identified recurrent mutations in non-coding regions, including the 3'UTR of NOTCH1, which cause aberrant splicing events and more aggressive disease. In addition, mutations in an enhancer located on 9p13 result in reduced expression of the B-cell-specific transcription factor PAX5. Functional analysis of these mutated genes together with clinical studies in a large number of CLL patients have led us to define specific genes and molecular pathways that drive the development and progression of this disease. This study has provided an integrated portrait of the CLL genomic landscape and suggested clinical interventions which may improve the management of this frequent neoplasia.

John Edgar Dick, Senior Scientist, Canada Research Chair in Stem Cell Biology, **Princess Margaret Cancer Centre, University Health Network**, Toronto, Canada.

John Dick is a Senior Scientist at the Princess Margaret Cancer Centre and the McEwen Centre for Regenerative Medicine of the University Health Network and Professor of Molecular Genetics at the University of Toronto. Dr. Dick is also Director of the Cancer Stem Cell Program at the Ontario Institute for Cancer Research. Dr. Dick's research has revolutionized the study of normal and leukemic human stem cells. Two of his most important achievements were developing a system for transplanting normal and malignant human hematopoietic cells into immune-deficient mice to identify and characterize both normal and leukemic human stem cells. His work has culminated in the isolation of human HSC as single cell resolution and a new model for early hematopoietic development. His lab established that only a small proportion of human leukemic cells were capable of initiating human leukemia within the immune-deficient mice, providing direct evidence for the cancer stem cell hypothesis. Dr. Dick's seminal contributions to the fields of molecular hematology, stem cell biology and oncology have been recognized by numerous prestigious awards including election as a Fellow of The American Association for Cancer Research Academy (2016)and a Fellow of the Royal Society of London, UK (2014).

Linking stemness properties to therapy failure and disease recurrence

The functional heterogeneity of individual tumor cells can be due to genetic diversity and/or because the tumor is organized as a cellular hierarchy with some tumor cells possessing stemness programs (defining them as cancer stem cells-CSC). Three lines of evidence show that genetic and hierarchy models are highly integrated. Gene signatures specific to AML leukemia stem cells (LSC) have revealed a common stemness program that is highly predictive of patient response to therapy and overall survival. Thus, determinants of stemness influence clinical outcome of AML across a spectrum of mutations indicating that many genetic abnormalities coalesce around stem cell properties. Secondly, combined genetic and functional tumor-initiation studies point to the link between clonal evolution and CSC. LSC originate genetically diverse subclones that are related through a complex branching evolutionary process. Thus clonal evolution occurs within cells that are capable of long term clonal propagation. Finally, our studies have shown that it is possible to backtrack the genetic steps that the leukemia took within otherwise normal stem and progenitor cells prior to diagnosis; these ancestral

cells can actually still be found in the blood cells that are still present in the leukemia blood sample taken at diagnosis. These pre-leukemic stem cells (pre-L HSC) with only single mutations represent the cell of origin. Now, by genetic tracking of pre-L HSC, LSC and bulk leukemia blast cells we have gained insight into the origin of relapse. In some patients, ultrarare LSC already present at diagnosis prior to any chemotherapy are already chemoresistant and have the capacity for regeneration. In other cases, relapse comes from a minor population of the commited leukemia cell population that have acquired stemness properties. Overall we have gained unprecedented insight into the complex evolutionary processes that underlie leukemic progression and the role that stemness plays in disease recurrence.

POSTERS

1 Diana Gómez, Neus Serrat, Joan Manils, Josep Maria de Anta, Sònia-Vanina Forcales, and Concepció Soler. **Analysis of epigenetic regulation of TREX2 promoter in squamous cell carcinomas**

2 Oscar Reina. **ChroGPS 2, visualizing, analyzing and comparing epigenomes**

3 César S. Huertas and Laura M. Lechuga. **Decoding the epigenome for cancer diagnosis with advanced label-free nanodevices**

4 Mariona Terradas, Marta Martín, Joan Repullès Huarte and Anna Genescà. **Distinct sets of lncRNAs are differentially modulated after exposure to high and low doses of X-rays**

5 Lorenzo Rinaldi, Alexandra Avgustinova, Debayan Datta, Guiomar Solanas, Luciano Di Croce, and Salvador Aznar Benitah. **Dnmt3a associates with promoters and enhancers to protect epidermal stem cells from cancer**

6 Mauvezin C, Almacellas E, Tauler A. **E2F1 role in lysosomal exocytosis and cancer invasion**

7 Tianlu Li, Antonio Garcia-Gomez, Javier Rodriguez-Ubreva, Mercedes Garayoa and Esteban Ballestar. **Epigenetic regulation of osteoclastogenesis in Multiple Myeloma**

8 Marc Masanas, Aroa Soriano, Ariadna Boloix, Núria Masiá, Laia París, Carlos Jiménez, Josep Roma, Josep Sánchez de Toledo, Soledad Gallego, Anna Santamaria, Miguel F. Segura. **Functional high-trhoughput screening reveals miR-323a-5p and miR-342-5p as tumor-suppressive microRNAs in neuroblastoma**

9 Gabrijela Dumbovic, Johanna Samuelsson, Cristian Polo, Cristina Moreta, Andreu Alibés, Tatiana Ruiz-Larroya, Pepita Giménez-Bonafé, Sergio Alonso, Sonia-V Forcales, and Manuel Perucho. **Helicase lymphoid specific (HELLS) contributes to the maintenance of methylation of SST1 pericentromeric repeats that are frequently demethylated in colon cancer and associate with genomic damage**

10 L.Marruecos, A.Bigas and L.Espinosa. **Histone marks at the base of PS-IκBα function**

11 J.P. Unfried, V. Segura, C. Prior, L. Boix, J. Bruix, B. Sangro & P. Fortes. **Long non-coding RNAs induced in hepatocellular carcinoma are involved in proliferation of HCC cell lines**

12 Soledad Gómez, Giancarlo Castellano, Gemma Mayol, Mariona Suñol, Ana Queiros, Marina Bibikova, Kristopher L Nazor, Jeanne F Loring, Isadora Lemos, Eva Rodríguez, Carmen de Torres, Jaume Mora, José I Martín-Subero and Cinzia Lavarino. **Non-CpG DNA methylation in neuroblastoma affects genes related to cell differentiation and embryonic development.**

13 Serena Orlando, Edurne Gallastegui, Gabriel Abril, Laura Sin, Carla Domuro, Jonatan Martinez, Rosa Aligué, María Jesús Pujol and Oriol Bachs. **p27Kip1 and p21Cip1 collaborate in the regulation of transcription by recruiting cyclin-Cdk complexes on the promoters of target genes**

14 Carlos Jiménez, Luz Jubierre, Aroa Soriano, Josep Roma, Josep Sánchez de Toledo, Soledad Gallego, Luciano Di Croce, Miguel F. Segura. **Targeting ZRF1 as a new epigenetic therapy strategy for neuroblastoma**

15 Joan Gibert, Neus Martínez-Bosch, Elena Ortiz-Zapater, Gonzalo Fernández-Miranda, Héctor Anta, Mireia Moreno, Raúl Méndez and Pilar Navarro. **The dual role of the RNA binding protein CPEB1 in pancreatic cancer progression**

16 Luciano di Croce. **Unveiling Polycomb Functions in Stem Cells and Cancer**

PRACTICAL INFORMATION

Venue: CosmoCaixa Barcelona

CosmoCaixa Barcelona
C/ Isaac Newton, 26
08022 Barcelona, Spain

Contact persons during the event

Meritxell Gavaldà
Office of Communications and External Relations **Institute for Research in Biomedicine (IRB Barcelona)**, Barcelona
meritxell.gavalda@irbbarcelona.org | Phone: :+34 618302463
www.irbbarcelona.org

Marta Soler
Head of Research and Scientific Debate, Biocat
msoler@biocat.cat | Phone: +34 662315500 | +34 93 310 33 57
www.bdebate.org | www.biocat.cat

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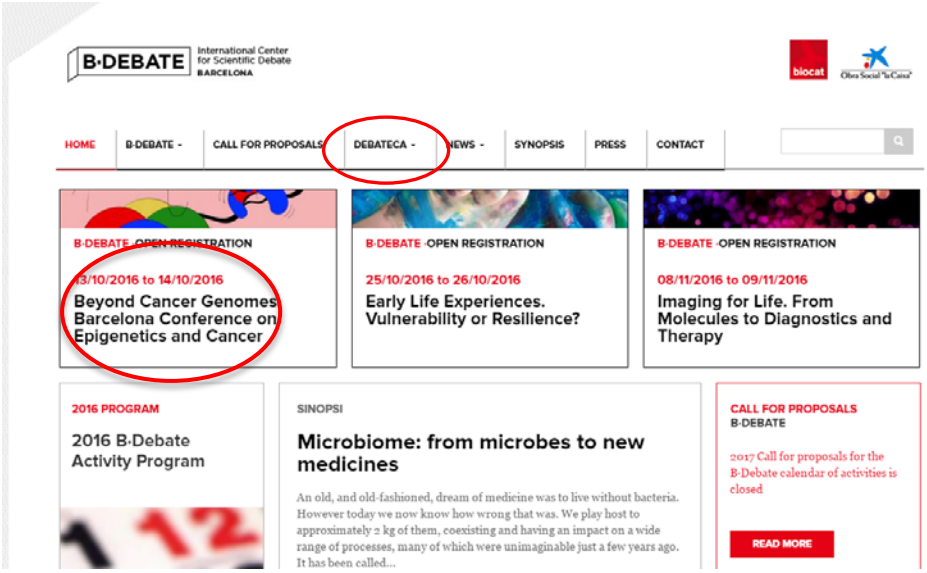
Contents of the meeting "Beyond Cancer Genomes. Barcelona Conference on Epigenetics and Cancer"



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More info: www.irbbarcelona.org

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More info: **www.ibmb.csic.es**

The **Institute of Predictive and Personalized Medicine of Cancer (IMPPC)** is a later addition to the successful group of CERCA institutes. The institute focuses on cancer and specializes in epigenetics and other related areas. The long-term goal is to mine epigenomic and genomic information to improve cancer risk prediction.

More info: **www.imppc.org**

The Cancer Epigenetics and Biology Programme (**PEBC**) is the latest research programme incorporated at the Bellvitge Biomedical Research Institute (**IDIBELL**) and represents the largest epigenetics department in southern Europe, with over 120 scientists, and the latest investment of the national government for cutting edge biomedical research.

More info: **www.pebc.cat**

The Centre for Genomic Regulation (CRG) is an international biomedical research institute of excellence, founded in December 2000 whose mission is to discover and advance knowledge for the benefit of society, public health and economic prosperity. The CRG believes that the medicine of the future depends on the groundbreaking science of today. This requires an interdisciplinary scientific team focused on understanding the complexity of life from the genome to the cell to a whole organism and its interaction with the environment, offering an integrated view of genetic diseases. Research at the CRG falls into four main areas: gene regulation, stem cells and cancer; cell and developmental biology; bioinformatics and genomics; and systems biology.

More info: **www.crg.eu**

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Cambridge Epigenetix (CEGX) is a biosciences company that aims to be the world leading provider of high quality, easy to use epigenetic tools that will improve human health. Our starting point is TrueMethyl™ oxidative bisulfite sequencing (oxBS-Seq), a novel technology that pioneers quantitative, single-base resolution sequencing of the modified bases hydroxymethylcytosine (5hmC) and methylcytosine (5mC). TrueMethyl enables analysis of the DNA methylome with unprecedented accuracy and opens new avenues for basic research, pharmaceutical discovery and diagnostics.
CEGX is funded by Syncona Partners, GV (Google Ventures), and Sequoia Capital, and our management team comprises industry leaders with epigenetics expertise.

More info: www.cambridge-epigenetix.com

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