CANCER THERAPEUTIC RESISTANCE

PROGRESS AND PERSPECTIVES

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April, 7th and 8th, 2016

WELCOME

Dear friends and colleagues,

On behalf of the **Catalan Institute of Oncology (ICO)** and the **Vall d'Hebron Institute of Oncology (VHIO)**, it is our great pleasure to welcome you to the **B-Debate Conference** on **"Cancer Therapeutic Resistance: Progress and Perspectives"**.

As part of the celebration of the **20th anniversary of the ICO**, this conference represents a joint effort of two major research institutes in the area with the aim of providing a high-impact scientific forum to present and discuss the latest advances in research against "Cancer Therapeutic Resistance".

Resistance to therapy is the principal cause of failure to cure of cancer patients. This fundamental clinical problem affects, to a different extent, any type of cancer and therapy. Thus, despite major advances in understanding of the molecular basis of cancer obtained during recent years, there are very few examples of clinical translation of therapeutic strategies against resistance. The conference will be focused on how to promote, improve and translate to the clinic successful research against resistance. To accomplish this objective, the program includes open presentations by world-leaders in the field and debates aiming at providing valuable recommendations for different decision-levels.

Thank you for attending our conference and contributing your knowledge, ideas and enthusiasm.

Miguel Angel Pujana (ICO) and **Joaquín Arribas (VHIO)**
Scientific Leaders of the conference

PROGRAM

Thursday, April, 7th, 2016

9:00 **Welcome**
Jordi Portabella, Director, Area of Research and Knowledge, la Caixa Foundation
Albert Barberà, CEO, Biocat
Josep Maria Vilà i Cortasa, President, Catalan Institute of Oncology (ICO)
Josep Tabernero, Director, Vall d'Hebron Institute of Oncology (VHIO)

9:15 **SESSION 1. IMMUNOLOGY AND CANCER THERAPY**
Chair: **Miquel Àngel Pujana** (ICO, IDIBELL)

Chemoimmunotherapy- a New Approach to treat Refractory Prostate and Liver Cancers
Michael Karin, University of California, San Diego, USA

Targeting the Heterogeneity of Cancer with Individualized Neo-epitope Vaccines – Preclinical and Clinical insight
Sebastian Kreiter, Translational Oncology University Medical Center (TRON), Mainz, Germany

Viroimmunotherapy for Cancer Treatment
Ramon Alemany, ProCURE, Catalan Institute of Oncology (ICO, IDIBELL), Barcelona, Spain

Cellular Senescence and Immune Infiltration in HER2-positive Breast Cancers
Joaquin Arribas, Vall d'Hebron Institute of Oncology (VHIO), ICREA, Barcelona, Spain

11:35 **Coffee Break**

12:05 **SESSION 2: GENETICS, EPIGENETICS AND MECHANISMS**
Chair: **Oriol Casanovas** (ProCURE, ICO, IDIBELL)

Cancer Pharmacoepigenetics: Genes and Drugs
Manel Esteller, Bellvitge Biomedical Research Institute (IDIBELL), ICREA, Barcelona, L'Hospitalet de Llobregat, Spain

Searching for New Strategies to treat T-Acute Lymphoblastic Leukemia
Anna Bigas, Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain

Epigenetic Control of Gene Regulatory Programs in Metastatic Prostate Cancer
Alvaro Aytes, ProCURE, Catalan Institute of Oncology (ICO, IDIBELL), Barcelona, Spain

13:30 **Lunch**

14:30 **ROUND TABLE: From Precision Medicine to more Effective Treatments. Dealing with Resistance to Anti-cancer Therapies**
Chair: **Josep Corbella**, Health and Science Journalist at La Vanguardia

Joaquin Arribas, Director of Preclinical Research at Vall d'Hebron Institute of Oncology, ICREA
Gabriel Capellà, Research and Innovation Program at Department of Health, Generalitat de Catalunya
Jesus Fernández Crespo, Director General of National Institute of Health Carlos III
Nieves Mijimolle, Member of the board of trustees of the Spanish Association Against Cancer (FCaecc)
Alberto Villanueva, Leader of the Chemoresistance Group at Catalan Institute of Oncology
Francesc Mitjans, Member of the board of trustees at CataloniaBio

16:30 **Coffee Break**

17:00 **SESSION 3: MOLECULAR CLASSIFICATION AND THERAPEUTIC TARGETING**
Chair: **Josep Tabernero** (VHIO)

Dissecting Colorectal Cancer in Multiple Subtype
Rodrigo Dienstmann, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

Co-Activation of STAT3 and Src-Notch Pathways in EGFR Mutant Lung Cancer
Rafael Rosell, Catalan Institute of Oncology (ICO, IGTP), Barcelona, Spain

Identification and Therapeutic Targeting of Poor Prognosis Subtypes in Colorectal Cancer
Eduard Batlle, Institute for Research in Biomedicine (IRB), ICREA, Barcelona, Spain

Microenvironment-mediated Chemotherapy Resistance in Colorectal Cancer
David G Molleví, Catalan Institute of Oncology (ICO, IDIBELL), Barcelona, Spain

19:00 **Welcome Cocktail and CosmoCaixa visit**

PROGRAM

Friday, April, 8th, 2016

9:30 **SESSION 4: CANCER OMICS AND THERAPEUTICS**
Chair: **Héctor G. Palmer** (VHIO)

Genomic Analysis of Therapy Response and Resistance
Elaine Mardis, McDonnell Genome Institute, Washington University, USA

Integrated Systematic Genomic approaches to define Cancer Networks
William Hahn, Broad Institute, Dana-Farber Integrative Cancer Biology Program, Cambridge, USA

10:50 **Coffee break**

11:20 **Patient-derived Tumor Explants as a Robust Pharmacogenomic Platform for Pre-clinic Drug Testing**
Carlos Caldas, University of Cambridge, UK

New Molecular Landscape in CRC. New Therapeutic Landscape?
Ramon Salazar, Catalan Institute of Oncology (ICO, IDIBELL), Barcelona, Spain

Diagnostic and Therapeutic Implications of unconventional Protein secretion in Cancer
Josep Villanueva, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

13:15 **Lunch**

14:15 **SESSION 5: MOLECULAR SIGNALING AND MODELS**
Chair: **Josep Villanueva** (VHIO)

A Vulnerability of BRAF Resistant Melanoma with Potential Clinical Utility
René Bernards, Netherlands Cancer Institute (NKI), Amsterdam, Netherlands

Targeting the MAPK Pathway in K-RAS Mutant Tumors. Challenges and Opportunities
Mariano Barbacid, Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, Spain

Restoration of DNA Homologous Recombination (HR) Functionality as a major Mechanism of PARP inhibitor Resistance in HR-deficient Breast Cancer
Violeta Serra, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

Otrho-xenograft Models and Personalized Medicine
Alberto Villanueva, ProCURE, Catalan Institute of Oncology (ICO, IDIBELL), Barcelona, Spain

16:45 **Coffee break**

17:15 **SESSION 6: STEM CELLS AND MALIGNIZATION**
Chair: **David Garcia** (ProCURE, ICO, IDIBELL)

A Stem Cell-like Program in Therapeutic Resistance
Miguel Angel Pujana, ProCURE, Catalan Institute of Oncology (ICO, IDIBELL), Barcelona, Spain

The Role of Cancer Stem Cells in the Inhibition of mTOR signaling in HCC
George Thomas, Bellvitge Biomedical Research Institute, IDIBELL, L'Hospitalet de Llobregat, Spain

New Pre-clinical Models to study Target-directed Drugs in advanced Colorectal Cancer
Hector G. Palmer, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

Deciphering Resistance to Anti-angiogenic Therapies for Prediction of Response and New Treatments
Oriol Casanovas, ProCURE, Catalan Institute of Oncology (ICO, IDIBELL), Barcelona, Spain

19:15 **Closing and Conclusions**

SCIENTIFIC COMMITTEE

Miquel Àngel Pujana, Independent Group Leader and Director of the Program Against Cancer Therapeutic Resistance (ProCURE) at the **Catalan Institute of Oncology (ICO, IDIBELL)**, Barcelona, Spain.

Scientific Co-Leader of the event

BSc in Biology and PhD in Human Genetics (Prof. Xavier Estivill) at the Cancer Research Institute, L'Hospitalet del Llobregat (Barcelona). Postdoctoral studies at the Center for Cancer Systems Biology, Dana-Farber Cancer Institute, Harvard Medical School (Prof. Marc Vidal). His research focuses on comprehensively understand breast cancer development and progression through the integration and modeling of different biological data levels. He currently applies systems-biology approaches and uses in vivo xenograft models to decipher resistance to endocrine and other targeted therapies, and to evaluate novel strategies to overcome resistance. He is member of the Spanish National Research Network on Breast Cancer and of the international Consortium of Investigators of BRCA1/2 modifiers.

Joaquin Arribas, Director of the Preclinical Research Program at **Vall d'Hebron Research Institute (VHIO)**, ICREA Research Professor, Barcelona, Spain.

Scientific Co-Leader of the event

Joaquín Arribas completed his undergraduate studies in biochemistry at the Universidad Autónoma de Madrid in 1987. At the same university he subsequently worked on the regulation of the catalytic activities of the proteasome and received his PhD in Biology in 1991. Sponsored by a fellowship from the Spanish Ministry of Education and Science, he joined the Memorial Sloan-Kettering Cancer Center, New York (USA), as a Postdoctoral Fellow to work with J. Massagué (1992-1996) on the proteolytic processing of transmembrane growth factors. In 1997 he joined the oncology department at Hospital Vall d'Hebron in Barcelona as a Staff Scientist, since them he has lead the research group on Growth Factors. Since 2010 he has served as Director of VHIO´s Preclinical Research Program. His research has been recognized through an EMBO Young Investigator Programme (YIP) Award and the Beckman Coulter Award for the Best Young Spanish Investigator in Biochemistry and Molecular Biology

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Alberto Villanueva, Responsible of the Group of Chemoresistance, Program Against Cancer Therapeutic Resistance (ProCURE) at the **Catalan Institute of Oncology (ICO, IDIBELL)**, Co-founder of a the spin-off Xenopat, Barcelona, Spain.

Alberto Villanueva graduated in Biology from the Universitat de Barcelona, where he also obtained his Ph.D. degree in 1997 investigating molecular aspects of pancreatic cancer in the Hospital de Sant Pau in the laboratory of Gabriel Capella. Dr. Villanueva was a Postdoctoral Fellow at Memorial Sloan-Kettering Cancer Center (MSKCC) in New York (USA) in the Laboratory of Signal Transduction where he studied the role of several kinases (jnk and abl) in response to several stresses (drugs, irradiation, etc.) in the model organisms C.elegans. From January 2002 to the end of 2007 it was an Ramon y Cajal investigator at Catalan Institut of Oncology (ICO). Since 2008, Dr Villanueva became the Responsible of Group of Chemoresistance in the Program Against Cancer Therapeutic Resistance (ProCURE) of the ICO/IDIBELL. He is an expert in the generation of Personal Derived Orthototpic Xenograft (PDOX), named Orthoxenografts® and its use for: (i) the study of the mechanisms of acquisition of resistance to standard chemotherapeutic drugs (i.e., cisplatin, 5-fluorouracil and oxaliplatin); (ii) the development of new drugs and treatments, and (iii) the development of strategies of personalized medicine in real-time. Dr Villanueva is also co-founder of a spin-off named Xenopat (www.xenopat.com).

INVITED SPEAKERS

Thursday, April, 7th, 2016

Miquel Àngel Pujana, Independent Group Leader and Director of the Program Against Cancer Therapeutic Resistance (ProCURE) at the **Catalan Institute of Oncology (ICO, IDIBELL)**, Barcelona, Spain.

Chair of the SESSION 1: IMMUNOLOGY AND CANCER THERAPY

(See his CV at the Scientific Committee Section)

Michael Karin, Distinguished Professor of Pharmacology Ben and Wanda Hildyard Chair for Mitochondrial and Metabolic Diseases American Cancer Society Research Professor at the **University of California**, San Diego, USA.

Dr. Karin was born in Tel Aviv, Israel and received the Bachelor of Science degree in 1975 from Tel Aviv University, with a major in Biology. In 1975 he arrived in the US and in 1979 received a Ph.D. degree in Molecular Biology from the University of California, Los Angeles. He followed his graduate studies with postdoctoral fellowships at the Fox Chase Institute for Cancer Research, working in the laboratory of Dr. Beatrice Mintz, and the laboratory of Dr. John Baxter at the University of California, San Francisco. Dr. Karin joined the faculty at the University of California, San Diego in 1986, where currently he is a Distinguished Professor of Pharmacology. He has received the Oppenheimer Award for Excellence in Research from the Endocrine Society in 1990, an American Cancer Society Research Professorship in 1999, the C.E.R.I.E.S. Research Award for Physiology or Biology of the Skin in 2000, the Harvey Prize in Human Health in 2011, the Brupbacher Prize in Cancer Research in 2013 and the William B. Coley Award for Distinguished Research in Basic and Tumor Immunology in 2013. Dr. Karin was elected to the National Academy of Sciences in 2005, as a Foreign Associate of EMBO in 2007, and to the Institute of Medicine in 2011. Dr. Karin also serves on several advisory boards and was cofounder of Signal Pharmaceuticals (currently Celgene). Karin has spent his entire academic career investigating stress and inflammation signaling covering the entire gamut of research approaches from basic biochemistry through molecular cell biology to animal pathophysiology. After discovering how environmental stress caused by either infection, inflammation or exposure to toxic substances leads to activation of AP-1, NF- B and other transcription factors, his lab began to examine the role of the key signaling pathways controlling these transcription factors in the pathogenesis of cancer, degenerative and metabolic diseases. The Karin group has identified some of the fundamental mechanisms through which inflammation and obesity promote tumor development and progression and contribute to type II diabetes. They had established the mechanisms through which members of the IL-6 cytokine family contribute to the development of colorectal and liver cancer through activation of STAT3 and other transcription factors. They had also established the complex and cell type specific mechanisms through which NF- B activation via I B kinases (IKK) controls development and progression of colon, liver and prostate cancers. They were amongst the first to demonstrate that not only innate immune cells, such as macrophages, but also adaptive immune cells, including T regulatory cells and B lymphocytes, also contribute to tumorigenesis and its progression. Through this work, Dr. Karin has contributed to the founding of the Inflammation and Cancer field.

Chemoimmunotherapy - a new approach to treatment refractory prostate and liver cancers

In the last two years, we have seen amazing progress in the development and implementation of cancer immunotherapies, in particular immune checkpoint inhibitors. Although such drugs have shown remarkable responses in melanoma, non-small cell lung cancer and renal cell carcinoma, many other cancers, including liver and prostate cancers, have proven refractory to immunotherapy. Treatment refractoriness has been attributed to the absence of CD8+ T cells within the tumors or insufficient production of tumor antigens. Regardless of the exact cause we found that treatment refractory prostate and liver cancers can be rendered responsive to checkpoint blockade upon treatment with immunogenic chemotherapeutics. These are drugs such as oxaliplatin or cyclophosphamid that are capable of inducing immunogenic cell death (ICD). Although the exact mechanism of ICD is the matter of intense investigation, it is clear that ICD inducers lead to the release of tumor antigens along with the damage associated molecular patterns (DAMP). Which stimulate dendritic cells (DC) maturation, antigen update and successful antigen presentation to T cells that have been recruited into the ICD-treated tumor. Once CD8+ cytotoxic T cells (CTC) recognize tumor antigens have been activated they kill the remainder of the tumor and cause its rejection. We found that the success of this approach is compromised by presence within the tumor of immunosuppressive IgA-producing plasmocytes that also express IL-10 AND PD-L1. Once the immunosuppressive cells have been removed or their PD-L1 has been neutralized, oxaliplatin treatment led to very effective rejection of prostate cancer in mice. Most recently, we have adopted this procedure for the treatment of the most common and aggressive form of primary liver cancer - hepatocellular carcinoma.

Sebastian Kreiter, Director of the Immune Therapy Development Center (TRON) - Translational Oncology University Medical Center at the **Johannes Gutenberg University**, Mainz, Germany.

Sebastian Kreiter (M.D.) graduated in Medicine from the Johannes Gutenberg University in Mainz (Germany). Clinical training in hematology and oncology led him to translational science in the field of immunotherapies. Currently he is Director of the Immune Therapy Development Center at TRON - Translational Oncology at the Johannes Gutenberg University in Mainz and Vice President Immunotherapy of BioNTech RNA Pharmaceuticals. Early efforts focused on preclinical development of in-vitro transcribed mRNA cancer vaccination, which is currently under clinical testing. More recently, he took part in the pioneering development of actively personalized cancer vaccination where jointly with Ugur Sahin he worked out the scientific and technical PoC for an mRNA based mutanome vaccine in murine model systems together with team members.

Targeting the Heterogeneity of Cancer with Individualized Neo-epitope Vaccines – Preclinical and Clinical insight

Mutated antigens in cancer cells are an important source of targets for cancer immunotherapy. Nonsynonymous single nucleotide variants (SNVs) which constitute the majority of relevant cancer mutations change the amino acid translated by the respective codon potentially generating a neo-epitope. In the recent years multiple data published provided evidence for a central role of mutated neo-epitopes in the primary immune response against cancer as well as for the efficacy of immunotherapies. Various findings by Rosenberg and colleagues indicate a major contribution of neo-epitope specific T cells to long term survival of ACT-treated patients. Independently different groups observed a correlation between the mutation load in cancer patients and the response rate of check-point inhibitors. Moreover, a temporary expansion of mutation-specific T cells upon anti-PD-1 treatment was observed. Our group was able to show preclinically in 2012 for the first time that NGS-based identification of mutated neo-epitopes allows the generation of a therapeutic vaccine. Recently, we found in different murine tumor models frequent immunogenicity of mutations and predominance of MCH-class II restricted responses. mRNA vaccination against these mutations resulted in potent tumor control (Nature, 2015, 520). Based on these findings we initiated a “fist in concept” clinical phase-I trial in 2014 treating melanoma patients with an actively individualized polytopic mRNA vaccine. In my presentation I will give insight into the concept of actively individualized neo-epitope vaccines, our preclinical data as well as the promising data from the clinical trial.

Ramon Alemany, Research Group Leader of the Cencer Virotherapy at the **Catalan Institute of Oncology (ICO, IDIBELL)**, Barcelona, Spain.

Graduated in Biology (1989) and PhD in Genetics (1994) from the University of Barcelona. Postodoc (1994-95) in MD Anderson Cancer Center working on gene therapy with adenovirus vectors under the supervision of Dr. Jack Roth. Scientist at Baxter Healthcare (1995-99) to develop oncolytic adenoviruses and hemophilia A gutless adenoviruses. Research Associate (1999-2001) at the University of Alabama at Birmingham to modify the capsid of oncolytic Adenoviruses under the supervision of Dr. David Curiel. Author of more than 100 papers on adenoviruses applied to cancer, 17 patents, founder of VCN-Biosciences, and currently President of the Spanish Society of Gene and Cell Therapy.

Viroimmunotherapy for cancer treatment

Oncolytic viruses replicate selectively in tumor cells. Besides the tumor debulking mechanism of oncolysis, it has been proposed a mechanism of action based on immunotherapy. The evidence for such mechanism will be presented and the main challenges to induce immune responses against tumor antigens using oncolytic viruses.

Joaquin Arribas, Director of the Preclinical Research Program at **Vall d’Hebron Research Institute (VHIO)**, ICREA Research Professor, Barcelona, Spain.

Scientific Co-Leader of the event

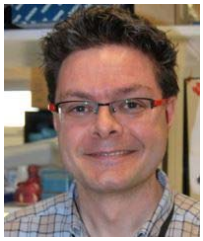
(See his CV at the Scientific Committee Section)

Cellular Senescence and Immune Infiltration in HER2-positive Breast Cancers

Breast cancer is a heterogeneous disease. Approximately 20% of breast cancers express excessive levels of HER2 (also known as ErbB2 or neu), a receptor tyrosine kinase that belongs to the family of the Epidermal Growth Factor Receptor (EGFR). These tumors, known as HER2-positive breast cancers, are also heterogeneous; one third of them express a heterogenous collection of carboxy-terminal fragments of HER2 collectively known as p95HER2. Using a variety of breast cancer models driven by HER2 and/or p95HER2, we have recently focused in the following areas of research:

- Individual characterization of different p95HER2 fragments in vitro and in vivo. As a consequence we have shown that some of these fragments are far more oncogenic than full-length HER2.
- Development of specific antibodies against p95HER2 currently used in diagnosis. We are are also developing these antibodies for breast cancer therapy.
- The role of cellular senescence induced by oncogenes during breast cancer progression and treatment.
- Development of preclinical models to study breast cancer immunology.

In summary, using p95HER2 and HER2-driven oncogenesis, we have characterized different aspects of the biology of breast cancers and, in addition, we have developed novel diagnostic and therapeutic tools to fight this deadly disease.



Oriol Casanovas, Staff Researcher and ERC-Fellow at Head of Tumor Angiogenesis Group at ProCURE Program Against Cancer Therapeutic Resistance, **Catalan Institute of Oncology (ICO, IDIBELL**), Barcelona, Spain.

Chair of the SESSION 2: GENETICS, EPIGENETICS AND MECHANISMS

Dr. Oriol Casanovas is an internationally renowned laboratory researcher with ample knowledge and expertise in basic and translational research of mouse models of cancer and tumor angiogenesis. His research at ICO-IDIBELL in Barcelona has always been focused on determining the consequences of adaptation and resistance to anti-angiogenic therapies against cancer. His scientific achievements have been published in highly prestigious journals specialized in the field of cancer research, and for their particular impact, his papers have frequently been published with "preview" articles and associated to several highlights or commentary articles in the most prominent scientific journals. Accumulated IF: 1805 (Scopus), H-Index Score: 13 (Scopus).

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 four 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.

Cancer Pharmacoepigenetics: Genes and Drugs

For the last twenty-five years an increasing amount of evidence has shown the relevance of epigenetics in cell biology and tissue physiology, being DNA methylation aberrations in cancer the flag-ship for the recognition of its disturbance in human diseases. From the candidate gene approaches, new powerful technologies such as comprehensive DNA methylation microarrays and whole genome bisulfite sequencing has recently emerged that have reinforced the notion of epigenetic disruption in the crossroad of many sickness. From the poster-boy cases of MGMT and GSTP1 hypermethylation in the prediction of alkylating drug response and prostate cancer detection, respectively, to the personalized treatment of leukemia with small molecules targeted to fusion proteins involving histone modifiers such as DOT1L and MLL, the field has walked a long path. The current talk will focus in the epigenetic profiling, basically at the level of DNA methylation and histone modifications, that is starting to provide clinical value in the diagnosis, prognosis and prediction of response to drug therapies in neoplasia. We have already a wide view of the undergoing DNA methylation events that expand beyond classical promoter CpG islands of tumor suppressor genes and we have a growing list of mutated chromatin remodeler genes that contributes to the tumorigenesis process. It is time to apply this knowledge in practical clinical situations like the diagnosis of cancers of unknown primary, the screening of malignancies in high-risk populations or a biomarker selection of the patients that should receive treatment with epigenetic drugs.

Anna Bigas, Leader os the Stem Cells and Cancer Research Group, Research Cancer Program, at **Hospital del Mar Medical Research Institute** (IMIM), Barcelona, Spain.

Anna Bigas graduated in Biology from University of Barcelona where also obtained her PhD in Cell Biology in 1993. She was a postdoctoral fellow in the Fred Hutchinson Cancer Research Center (Seattle, USA) where identified a role of Notch in regulating hematopoietic differentiation, which has been a highly influential contribution to the field of hematopoiesis. Since starting her independent research group in IDIBELL (Barcelona, Spain) in 1998, she has sought to decipher the molecular mechanisms that regulate stem cell commitment, maintenance, differentiation and oncogenic transformation, mainly focussed in the hematopoietic system. From 2009, she holds a Group Leader position at the Institut Hospital del Mar d'Investigacions Mèdiques (IMIM).

Searching for new strategies to treat T-Acute Lymphoblastic Leukemia

Notch activation is instrumental in the development of most T-cell acute lymphoblastic leukemia (T-ALL) cases, however although many Notch inhibitors are available, the ones tested have shown undesirable effects. On the other hand, Notch mutations alone are not sufficient to recapitulate the full human disease in animal models and probably in patients, thus it is important to identify collaborators in the transformation capacity of this pathway. I will present our recent work in T-ALL with the aim to search for new collaborators of Notch in transformation of hematopoietic cells. Taking advantage of animal models, we have characterised the cells of leukemic origin and identified their dependence on the Wnt/β-catenin pathway. We have taken genetic and pharmacological approaches to demonstrate the importance of this signalling pathway and the possibility of therapeutic targeting.

Álvaro Aytes, Principal Investigator of the Prostate Cancer Lab at the **Catalan Institute of Oncology (ICO, IDIBELL)**, Barcelona, Spain.

Álvaro leads the Program for Translational Research in Prostate Cancer. Previously, he received his PhD in cell biology and pathology from the University of Barcelona in 2008 and performed postdoctoral training at Columbia University Medical Center under the mentoring of Drs. Cory Abate-Shen and Andrea Califano. Dr. Aytes laboratory focuses on prostate cancer biology exploiting genetically-engineered mouse models of prostate cancer and reverse engineering of cellular networks to uncover causal mechanisms of cancer progression and resistance to cancer therapeutics. Dr. Aytes is particularly interested in elucidating mechanisms of metastatic castration-resistant prostate cancer, for which new therapeutic targets and drug combinations are a pressing clinical need. To pursue their research, they are funded by the European Association of Urology Research Foundation and the Instituto de Salut Carlos III (Spain).

Epigenetic Control of Gene Regulatory Programs in metastatic Prostate Cancer

Gene regulatory networks from human cancer and mouse models provide a platform for cross-species analysis and identification of cancer drivers and determinants of drug activity and resistance. We have previously applied this framework to identify non-oncogenic addictions that drive prostate cancer aggressiveness by, at least in part, regulating the PI3k and MAPk pathways activation. Using drug-response transcriptomes from a variety of genetically-engineered backgrounds in vivo we have defined a gene signature that predicts drug activity against this particular regulatory module. In addition, we generated a conditional and inducible mouse model of prostate cancer based on the Nkx3.1-mediated cre recombination in the prostate epithelium of the Pten tumor suppressor and activation of a mutant Kras oncogene. This mice display a fully penetrant metastatic phenotype that can be lineage traced using a YFP reporter. We've used this mouse model to obtain transcriptomes from metastatic and primary tumors and we´ve compared this transcriptomes to those of equivalent prostate cancer patients. Strikingly, the most enriched GO category for the master regulators of metastasis in both species is that of epigenetic regulator. In fact, a classifier of epigenetic master regulators clearly identifies metastatic from primary tumors using independent human datasets and can be used as a prognostic biomarker for overall survival. Functional studies on the top candidates demonstrate their role in metastatic growth and the mutational landscape of these candidates provide further evidence of their relevance in advanced prostate cancer.

ROUND TABLE SPEAKERS

FROM PRECISION MEDICINE TO MORE EFFECTIVE TREATMENTS. DEALING WITH RESISTANCE TO ANTI-CANCER THERAPIES

Josep Corbella Domènech, Health and Science Journalist, **La Vanguardia,** Barcelona, Spain.

Chair of the ROUND TABLE

Josep Corbella (Barcelona, 1966) has been working as a science journalist in the daily newspaper La Vanguardia since 1990. Previously he worked in the newspaper *Diari de Barcelona* and in the magazine *Carrer Gran*. He has been a regular contributor to the radio station RAC1 since its founding in 2012, where he has kept a weekly science section in the program Versió RAC1 since 2012. He has coauthored several books, including *Sapiens* (with archeologist Eudald Carbonell in 2000), *La ciencia de la salud* (with cardiologist Valentín Fuster in 2006, translated in the US as The Heart Manual) and *La cocina de la salud* (with cardiologist Valentín Fuster and chef Ferran Adrià).

Gabriel Capellá, Research and Innovation Program at Department of Health, **Generalitat de Catalunya,** Barcelona, Spain.

Gabriel Capellá obtained his MD degree by the University of Barcelona in 1983. He trained as a general and digestive surgeon at the Hospital de Sant Pau, Barcelona. His interest in translational cancer research lead him to a postdoctoral stay with Dr. Manuel Perucho the years 1989 and 1990. Back to Spain he spent 8 years at the Gastrointestinal Research Laboratory at the Hospital de Sant Pau where he focused his research in the molecular basis of pancreatic and colorectal cancer. Since 1998 he works at the Instituto Catalán de Oncología where he has been Director of the Translational Research Laboratory until 2011. Since 2010 he is serving as Director of the Hereditary Cancer Program. His main interest is the study of the genetic basis of gastrointestinal cancer focusing in novel technologies for the clinical management of patient at risk of developing GI Cancer. He is coauthor of more than 220 publications in international peer-reviewed journals. Since 2013 he serves as Vice-Director for Research and Innovation, Health Department, Catalan Government. He is co-founder of VCN Biosciences an spin-off aimed at developing new cancer therapies based on oncolytic adenoviruses.

Jesús Fernández Crespo, Director General of the **National Institute of Health Carlos III (ISCIII),** Madrid, Spain.

Graduate in Medicine and Surgery by the" Universidad Autónoma de Madrid" in 1986. Doctor of medicine from the same University in 1992. Fellow in residency training program in the specialty of Allergy at the "Ciudad Sanitaria La Paz" in Madrid. In 1992 he obtained a scholarship award of the UCB Institute of Allergy which involved a stay at the Arkansas Children's Hospital (USA), prolonged to 1993 thanks to a Mobility Award granted by the Spanish Ministry of Health and Consumer Affairs. He has combined his clinical activity in several hospitals as a specialist in allergy with a comprehensive training in the Management of Clinical Units and Health Organizations. From 2005 to 2010 he was Director of the Research Foundation of the "Hospital Universitario 12 de Octubre" in Madrid, participating actively in the creation and accreditation of the Health Research Institute in 2010. From 2010 to 2013 he was the Director of this Institute. As a researcher, he has participated in 8 research projects, 94 publications in both national and international journals, and 39 papers in scientific congresses. He has been director of 1 PhD thesis and teaches in several PhD and Graduate programmes and summer courses since 1996. He is president of the Board of Directors of the Research Institute "Escuela Nacional de Sanidad UNED (IMI-ENS)". Member of the Spanish National Cell Line Bank, the Research Centre for Neurological Diseases (FCIEN), and the Research and Training Committees of the "Hospital Universitario 12 de Octubre". Member of the Scientific Committees of the National Cancer Research Centre (CNIO) and the National Cardiovascular Research Centre (CNIC). He held several managing positions at the ISCIII from 2013 to 2015. On March 6, 2015 he was appointed Director General of Institute of Health Carlos III.

Nieves Mijimolle, Member of the board of trustees of the **Scientific Foundation of the Spanish Association Against** Cancer (FCaecc), Madrid, Spain.

Nieves Mijimolle holds a BSc in Pharmacy from the University Complutense of Madrid and a PhD from University Autonoma of Madrid. She is currently member of the board of trustees of the Scientific Foundation of the Spanish Association Against Cancer (FCaecc) and technical director and co-holder of pharmaceutical and orthopedics office. She has been involved in translational research in cancer, where she has developed number of studies and published highly cited papers under the supervision of Dr. Mariano Barbacid at the Spanish National Cancer Centre (CNIO). Since then she has focused her work in orthopedics and optic, where she is developing a significant research in the field. In addition, Dr. Mijimolle is in the board of the Pharmaceutical Association and member of the charity "Mundi Pharmaceutics". She has been awarded with the Abilio Rodriguez Paredes for her degree in pharmacy.

Alberto Villanueva, Responsible of the Group of Chemoresistance, Program Against Cancer Therapeutic Resistance (ProCURE) at the **Catalan Institute of Oncology (ICO, IDIBELL)**, Co-founder of a the spin-off Xenopat, Barcelona, Spain.

(See his CV at the Scientific Committee Section)

Francesc Mitjans, Member of the board of trustees at **CataloniaBio,** Coordinator of the Biomed Division at **Leitat**, Barcelona, Spain.

Francesc is Doctor Biology for the University of Barcelona and has a MBA for EUNCET. He worked at Merck in between 1991 and 2008, as Group Leader and Department Head. From 2008 he is the Director of the Biomed Division at Leitat. He has published several articles and participated in several IP. He currently works with pre-clinical research – oncology, focusing the efforts to new therapies and new diagnosis tools for cancer, management of the activities of the division (14 staff team): internal drug discovery program, third-party research, and collaborations in the fields of therapy and diagnosis.

INVITED SPEAKERS

Thursday, April, 7th, 2016

Josep Tabernero, Head of the Medical Oncology Department at the **Vall d'Hebron University Hospital** in Barcelona and Director of the Vall d'Hebron, Barcelona, Spain.

Chair of the SESSION 3: MOLECULAR CLASSIFICATION AND THERAPEUTIC TARGETING

Josep Tabernero heads the Medical Oncology Department at the Vall d'Hebron University Hospital in Barcelona and is Director of the Vall d'Hebron Institute of Oncology. He holds MD and PhD degrees from the Universitat Autònoma de Barcelona, Spain. Dr. Tabernero is very actively involved in translational research and pharmacodynamic phase I studies with molecular targeted therapies. He is especially devoted to Phase I and II pharmacodynamic endpoints studies with novel agents that target membrane receptors, including the HER and FGFR families, the PI3K and ERK signaling pathways, as well as downstream cytoplasmic and intra-nucleus effectors such as Mdm2/p53 and aurora kinase. On the hypothesis that each tumor has an independent genetic identity, his research the group very actively participates in the development of molecular therapies that target specific oncoprotein, with the purpose of developing personalized therapies (e.g. against EGFR, HER2, FGFR, BRAF, MEK, PI3K, Akt, mTOR or IGF1-R, etc.) for patients displaying genetic lesions or pathway dysregulation. One of the main objectives of the group is to identify new predictive markers of response to diverse treatments as well as markers of primary resistance (de novo) and secondary treatment. At the preclinical level, his research group is developing new xenograft models with explant tumors from patients ("xenopatients") in mice in order to mimic the patient's disease and study tumor development in optimized research models. It also leads a program devoted to the study of circulating biomarkers (detection and genotyping of circulating free DNA).

Dr. Tabernero has (co)authored approximately 350 peer-reviewed paper. He is the President-Elect of the European Society for Medical Oncology (ESMO) 2018-2019, and an active member of the American Association for Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO). He participates on different Editorial Boards, including the Journal of Clinical Oncology, Clinical Cancer Research, Cancer Discovery, Clinical Colorectal Cancer and Annals of Oncology and he is/has been on the Educational and Scientific Committees of the ESMO, ECCO, ASCO, AACR, AACR/NCI/EORTC, ASCO Gastrointestinal, and WCGIC meetings.

Rodrigo Dienstmann, Medical Oncologist, leader of Oncology Data Science (ODysSey) Group at **Vall d´Hebron Institute of Oncology,** Researcher of Computational Oncology Group at Sage Bionetworks, Barcelona, Spain.

Dr. Dienstmann is a medical oncologist with expertise in clinical and translational research. After graduating in Brazil, he moved to Spain for training in phase 1 development of cancer drugs. He helped develop a molecular prescreening strategy to match genomic profile of each patient's tumor to targeted agents, the central dogma of precision oncology. During his post-graduation at the Massachusetts General Hospital, he provided standardized decision support with structured reports of the next-generation sequencing tests performed at the clinical lab. By designing the framework for variant annotation, prioritization and interpretation, together with a comprehensive gene-drug knowledge database of predictive genomic biomarkers in solid tumors, he had a central role in the process of clinical implementation of these tests. He then assisted the Sage Bionetworks Computational Oncology team in the development of novel predictive and prognostic models using cancer genomics data and was deeply involved in the Colorectal Cancer Subtyping Consortium, which resulted in the identification and clinical-molecular characterization of the intrinsic disease subtypes. He is now Principal Investigator of the Oncology Data Science Group of Vall d'Hebron Institute of Oncology, integrating clinical and translational researcher with genomics for precision cancer therapy and coordinating the clinical-molecular databases of matched targeted agents and immunotherapies.

Dissecting Colorectal Cancer in Multiple Subtypes

Colorectal cancer (CRC) is a frequently lethal disease with heterogeneous outcomes and drug responses. In an attempt to identify biologically homogeneous subtypes of CRC, multiple independent groups recently reported on gene expression–based subtyping. To provide a robust and unified classification, we formed an international consortium dedicated to large-scale data sharing and analytics across expert groups. We show marked interconnectivity between the six classification systems coalescing into four consensus molecular subtypes (CMS) with distinguishing features: CMS1 (MSI Immune), hypermutated, hypermethylated, microsatellite unstable, enrichment for BRAF mutations, with strong immune infiltration and activation; CMS2 (Canonical), epithelial, chromosomally unstable, microsatellite stable, with marked WNT and MYC signalling activation and upregulation of EGFR and IRS2; CMS3 (Metabolic), epithelial, less frequent copy number

alterations, intermediate levels of gene hypermethylation, enrichment for KRAS mutations with evident metabolic dysregulation; and CMS4 (Mesenchymal), chromosomally unstable, microsatellite stable, prominent transforming growth factor β activation and angiogenesis, stromal invasion and immunosuppressive microenvironment. The four CMS groups to be the most robust and reproducible classification system currently available for CRC and the basis for future clinical stratification.

Rafael Rosell, Director of the Cancer Biology & Precision Medicine Program at the **Catalan Institute of Oncology (ICO, IGTP)**, Germans Trias i Pujol Health Sciences Institute and Hospital, Barcelona, Spain.

Dr. Rafael Rosell is also a Chief Medical Officer and President of the Dr Rosell Oncology Institute, Quirón Dexeus University Hospital (Barcelona). Dr. Rosell's contributions to translational oncology, with particular emphasis on the field of EGFR mutated non-small-cell lung cancer have earned him international recognition. The main contributions have been the demonstration in 1994 of improved survival of neoadjuvant chemotherapy in NSCLC stage IIIAN2 (Rosell et al. NEJM, January 20, 1994). The discovery of treatable genomic alterations such as mutations of EGFR gene in 2004 was the reason that lead Dr. Rosell to conduct a Spanish trial focused in the detection of EGFR mutated lung cancer that targets therapy with selective EGFR inhibitors (Rosell et al. NEJM 2009). This contribution marks a before and an after in clinical practice. After that, he has contributed to various aspects of tumor resistance such as lung cancer with EGFR mutations and identification of the coexistence of EGFR mutation T790M, which he published for the first time in 2011 and later in 2014. He has also collaborated in various international researches with the discovery of important signaling pathways as NFKB (Bivona et al Nature 2011.), AXL (Zhang et al Nature Genetics, 2012;. Elkabets et al Cancer Cell 2015.), YAP (Li et al. Nature Genetics 2015). Also the interpretation of new mechanisms of resistance in various types of tumors such as melanoma BRAF mutations and colon cancer KRAS mutations (Rosell. NEJM 2013). He conducted the first study of erlotinib treatment in patients with lung cancer with EGFR mutations in Europe (EURTAC trial. Rosell et al. Lancet Oncology 2012). This study helped to the approval by the FDA in April 2014 of Tarceva for the treatment of lung cancer with EGFR mutations. He also contributed usefully in the implementation of liquid biopsy, with the analysis of EGFR mutations and other genes in circulating DNA (Karachaliou et al. JAMA Oncology 2015).

Co-Activation of STAT3 and Src-Notch Pathways in EGFR Mutant Lung Cancer

Although EGFR tyrosine kinase inhibitors (TKIs) collapse a network of downstream signaling in EGFR mutant NSCLC, simultaneously promote lateral rescue pathways, like STAT3 and Src-YAP, that render targeting ineffective. Herein we demonstrate that EGFR TKIs cannot abrogate STAT3 and Src in EGFR mutant NSCLC, providing a rationale for combining EGFR TKIs with STAT3 (e.g. TPCA-1) and Src (e.g. saracatinib) inhibitors. The prognostic and predictive impact of STAT3 and YAP was investigated in clinical tumor samples. Cell viability and colony formation assays, western blotting and quantitative-real time PCR were performed in cell lines and clinical tumor samples. A PC-9 xenograft model was constructed for in vivo experiments. STAT3 phosphorylation on the tyrosine residue 705 (pSTAT3 Y705) was increased in a time- and dose-dependent manner with gefitinib alone in PC-9 cells (EGFR exon 19 deletion). pSTAT3 Y705 was diminished with the combination of gefitinib+TPCA-1. Gefitinib+TPCA-1 did not inhibit YAP activation through Src family kinase phosphorylation on Y357. Gefitinib+saracatinib inhibited pYAP Y357 but not pSTAT3 Y705. The triple combination of gefitinib+TPCA-1+saracatinib abrogated both pSTAT3 Y705 and pYAP Y357. Fewer colonies were formed with the triple combination compared to gefitinib alone or double combinations in PC-9 cells. The triple combination was highly synergistic in PC-9 and H1975 (L858R+ T790M EGFR mutation) cells. In a PC-9 xenograft model, the triple combination led to a greater effect than gefitinib alone or the double combinations. In 64 EGFR mutant NSCLC patients (p) treated with first line EGFR TKIs, high STAT3 or YAP mRNA expression was significantly correlated with shorter median progression-free survival (mPFS) [9.6 months (m) vs 18.4m (P<0.001) and 9.6m vs 23.4m (P=0.005), respectively]. Furthermore, mPFS was 25.7m for p with low both STAT3 and YAP vs 9.4m for p with high both STAT3 and YAP mRNA expression (P=0.004).
Single EGFR TKI treatment can no longer be considered adequate for p with EGFR mutant NSCLC and a clinical trial co-targeting EGFR, STAT3 and Src is warranted.

Eduard Batlle, Coordinator of the Oncology Programme at the **Institute for Research in Biomedicine (IRB)**, Barcelona, Spain.

Eduard Batlle graduated in Biology from the University of Barcelona in 1993. During his PhD in the laboratory of Antonio García de Herreros, he became Associate Professor in Biochemistry-Life Sciences at the University Pompeu Fabra, Barcelona. In 2000, Eduard moved to the laboratory of Hans Clevers at the Netherlands Institute for Developmental Biology, Utrecht, NL for his postdoctoral training, after spending a short 8 months stay in the laboratory of Miguel Beato at the Institut für Molekularbiologie und Tumorforschung in Marburg, Germany. His postdoctoral research gave rise to the first link between stem cell biology and colorectal cancer. In 2004, Eduard became Senior Research Professor at ICREA and was recruited to the Institute for Research in Biomedicine, where he has been working since. Batlle's research activity is focused on the mechanisms of that drive colorectal cancer initiation and progression. Amongst other findings, Eduard batlle originally discovered the transcription factor snail as suppressor of E-cadherin in tumour cells and the role of EphB receptors in Cancer. Current research in his lab

is centered on the role of stem cells in cancer. In addition, his recent work on the influence of the tumor microenvironment on metastasis formation represents the basis for translational projects aiming to improve diagnosis and treatment of CRC patients. His track record has deserved numerous awards and recognitions.

Identification and Therapeutic Targeting of Poor Prognosis Subtypes in Colorectal Cancer

Colorectal cancer (CRC) represents the second leading cause of death by cancer. About 40%–50% of all patients with CRC will present with metastasis either at the time of diagnosis or as recurrent disease upon intended curative therapy. Metastasis is the leading cause of death by CRC. In the absence of genetic alterations that explicate these processes, it remains a major challenge to predict which patients will develop metastatic disease or to design targeted therapies. We have discovered that metastasis depends on a gene program expressed by the tumor microenvironment upon TGF-beta stimulation. TGF-beta instructs the secretion of prosurvival factors by stromal cells during the colonization phase of metastasis. This dependency can be exploited to improve diagnosis and treatment of patients with advanced colorectal cancer. On one hand, blockade of this crosstalk between tumour cells and their microenvironment through the use of chemical inhibitors prevents metastasis formation in experimental models of colon cancer. In addition, low stromal TGF-beta signaling is a robust predictor of disease-free survival after therapy, which improves on the current AJCC staging system. Recent molecular signatures based on global gene expression that predict poor prognosis are also characterized by the presence of TGF-beta activated fibroblasts. Our work thus defines a unifying criteria to identify accurately poor prognosis CRC patients through a unique biological process: stromal activation by TGF-beta.

David Garcia Molleví, Group Leader, Microenvironment and Resistance Group, Program Against Cancer Therapeutic Resistance at the **Catalan Institute of Oncology (ICO, IDIBELL),** Barcelona, Spain.

David G. Molleví graduated in Biology from the Universitat Autònoma de Barcelona (1996). After learning microsurgical techniques at the Thomas Starzl Transplantation Institute, University of Pittsburgh Medical Center, he did his PhD at the Department of Surgery Universitat de Barcelona and Liver Transplantation Unit Hospital Universitari de Bellvitge, specializing in liver (orthotopic) and heart (heterotopic) hamster-to-rat xenotransplantation model (1997-2001). Dr. Molleví carried out his postdoctoral studies at The Catalan Institute of Oncology, where he studied the prognostic value of TP53 mutations in liver metastases from colorectal carcinoma. Since April 2008 he started his career as independent junior researcher focusing his research on the study of tumor microenvironment, particularly, carcinoma-associated fibroblasts and their involvement in the prognosis of colorectal cancer, and developing new mice models for the study of cancer based on xenograft implantation. His current research is devoted to the role of carcinoma-associated fibroblasts in the development of chemoresistance in colorectal and pancreatic cancer and the study of new stromal targets for sensitizing cells to chemotherapy in both types of cancer.

Microenvironment-mediated Chemotherapy resistance in Colorectal Cancer

Research into therapies against specific targets or signaling pathways is one of the pillars of current cancer research, although most tumours are still treated with conventional cytotoxic therapies. Depending on the type of cancer and the stage of disease, these conventional drugs are used with different success, whereat drug-resistance remains the main obstacle for success of cytotoxic therapies. Most research on drug resistance has focused on acquired resistance of malignant cells, which is basically limited to the reduction of an initial tumour burden, thus failing to eradicate a sufficient number of cancer cells that would prevent clinical recurrence. Despite the extensive use of chemotherapy, the specific mechanisms that cause tumour regression after treatment are poorly known. In an ideal case a successful treatment leads to death of malignant cells, of surrounding CAFs and of endothelial cells as well. However, it is not entirely clear whether the death of malignant cells is the first event of the fall or if is the final consequence of tumour regression. Accordingly, this is one of the great unknowns to be discovered.

Resistance to cancer treatment can be basically divided into two categories: de novo and acquired. Functionally, the de novo drug resistance can be subdivided into two groups: soluble-factor-mediated resistance (induced by cytokines, chemokines and growth factors secreted by carcinoma-associated fibroblasts) and cell-adhesion-mediated drug resistance, which requires the direct contact between tumour integrins and stroma cells or extracellular matrix (ECM) components. Thus, the microenvironment plays a central role in the induction of resistance, and particularly in the development of acquired resistance, because the stroma is able to protect tumour cells from therapy until they evolve acquired-resistance phenotypes.

INVITED SPEAKERS

Thursday, April, 8th, 2016

Héctor G. Palmer, Head of the Stem Cells and Cancer Group at the **Vall d´Hebron Institute of Oncology (VHIO),** Barcelona, Spain.

Chair of the SESSION 4: CANCER OMICS AND THERAPEUTICS

Héctor G. Palmer obtained his PhD in Biochemistry and Molecular Biology from the Universidad Autónoma de Madrid in 2001 for his work at the Instituto de Investigaciones Biomedicas (IIB, CSIC-UAM, Madrid) under the supervision of A. Muñoz. At this time his studies focused on the anti-tumoral capacity of vitamin D analogues on human colon cancer cells. From 2001 - 2003 he continued his work at the Instituto de Investigaciones Biomedicas in Madrid as a Postdoctoral Fellow studying the crosstalk between vitamin D receptor and the transcriptional repressor Snail in colon cancer. In 2003 Palmer was awarded a Marie Curie Intra European Fellowship and in 2004 he joined the London Research Institute-Cancer Research UK (LRI-CRUK) as a Postdoctoral Fellow under the leadership of F. M. Watt where he described the vitamin D receptor as a novel transcriptional effector of the Wnt pathway that controls stem cells fate in adult epidermis. He also discovered that the central role of the Wnt signalling in tumor initiation depends on VDR function, opening a new avenue for the use of Vitamin D-based drugs to prevent the development of cancer. In 2008 Héctor returned to Spain to join the Vall d'Hebron Institute of Oncology (VHIO) as Principal Investigator where he leads the Stem Cells & Cancer Group focusing on the relevance of cancer stem cells in tumor self-renewal, drug-resistance, relapse and metastasis.

Elaine Mardis, Ph.D. Robert E. and Louise F. Dunn Distinguished Professor of Medicine, Professor of Genetics and Molecular Microbiology, Co-director at McDonnell Genome Institute at **Washington University School of Medicine,** St Louis, USA**.**

Elaine Mardis graduated Phi Beta Kappa from the University of Oklahoma with a B.S. degree in zoology. She holds a Ph.D. in Chemistry and Biochemistry(1989). Dr. Mardis was a senior research scientist for four years at BioRad Laboratories in Hercules, CA. Dr. Mardis served as Director of Technology Development at the (then) Washington University Genome Sequencing Center, helping create methods and automation pipelines for sequencing the Human Genome. Dr. Mardis co-led the teams that first used next-generation sequencing to characterize the whole genome of an AML patient (Nature 2008), first sequenced and compared a primary tumor to its metastasis and xenograft, and first reported whole genome sequencing of samples from a breast cancer clinical trial. Beyond cancer genomics discoveries, Dr. Mardis is leading efforts to facilitate the translation of basic science discoveries about human genetic diseases into the clinical setting, especially focused on the use of next-generation sequencing. Dr. Mardis was elected to the AACR Board of Directors in 2015. She serves as an associate editor of Molecular Cancer Research, Disease Models and Mechanisms and Annals of Oncology, and acts as a reviewer for Nature, the New England Journal, Cell and Science. Mardis is the Editor-in-Chief of Molecular Case Studies. She serves on the scientific advisory boards of Qiagen Ingenuity, DNA Nexus, and ZS Genetics, and is a member of the Supervisory Board of Qiagen N.V. Dr. Mardis received the 2010 Scripps Translational Research award for her work on cancer genomics, and was named a Distinguished Alumni of the University of Oklahoma College of Arts and Sciences in 2011. Discover Magazine featured her work in cancer genomics as one of their top 100 science stories of 2013. In 2014 and 2015, she was one of the most highly cited researchers in the world, according to Thompson-Reuters. She will receive the Morton K. Schwartz award from the American Association of Clinical Chemistry for Significant Contributions in Cancer Research Diagnostics in 2016.

Genomic Analysis of Therapy Response and Resistance

Assays that utilize massively parallel sequencing approaches to evaluate tumor tissue or blood for evidence of genomic harbingers of therapy response and resistance are becoming increasingly used in studies of clinical samples. There are various types of approaches that can be used, including active monitoring of patients either during or at the end of their therapeutic regimen, by comparison to a baseline sample. The sensitive and quantitative nature of these assays can pinpoint patients with therapy resistance, by virtue of unaltered prevalence of mutations relative to the baseline, or patients with an incomplete response such as minimal residual disease (MRD). Knowledge of the response status is important, as are any putative genetic indications toward potential targeted therapy that can be interpreted from the disease genotype. Therapeutic response monitoring is also possible during the course of treatment and can indicate those non-responding patients that might benefit from another therapy. Finally, post-mortem genomic analyses of therapy resistant disease can be obtained from banked metastatic lesions to inform on the genomic nature of therapy resistance. These studies can be

incredibly informative toward future monitoring paradigms, therapeutic combinations or new drug design efforts to combat acquired resistance.

William Hahn, William C. Hahn, M.D., Ph.D, Professor in the Department of Medical Oncology and an Institute Member of the **Broad Institute** of MIT, Harvard University, USA.

Dr. William C. Hahn is a medical oncologist and Professor in the Department of Medical Oncology and an Institute Member of the Broad Institute of MIT and Harvard. He co-directs the Center for Cancer Genome Discovery, is the Chief of the Division of Molecular and Cellular Oncology and is the Chair of the Executive Committee for Research at the Dana-Farber Cancer Institute. Dr. Hahn has made numerous seminal discoveries that have informed our current molecular understanding of cancer and which have defined new conceptual paradigms and formed the foundation of new translational studies. Using genome scale tools and approaches, his laboratory is focused on the discovery of new targets and combination therapies for pancreatic, colon, breast and prostate cancer. Dr. Hahn has served as the President of the American Society for Clinical Investigation and has been elected to the Association of American Physicians. Dr. Hahn has been the recipient of many honors and awards including the Wilson S. Stone Award from M.D. Anderson Cancer Center for outstanding research in cancer (2000), a Howard Temin Award from the National Cancer Institute (2001), the Ho-Am Prize in Medicine (2010) and the Richard and Hinda Rosenthal Award from AACR (2015).

Integrated Systematic Genomic approaches to define Cancer Networks

Recent advances in genomics now make it possible to consider enumerating all of the genetic lesions in specific cancers. These approaches will yield critical information regarding the identification, number, and types of alterations found in human tumors and are increasingly being applied prospectively to patient samples in the clinic. At the same time, complementary approach to decipher the molecular basis of malignant transformation depends upon the application of genome scale tools to annotate the function of genes involved in cancer initiation and progression. Over the past several years, we have developed genome scale RNAi, CRISPR and open reading frame expression libraries that permit a systematic evaluation of genes involved in cancer initiation and maintenance. Using these libraries, we have now performed screens in a panel of human cancer cell lines to systematically identify cancer vulnerabilities. By combining these functional approaches with information derived from mapping the structural abnormalities present in cancer genomes, we have identified several new oncogenes that contribute to cancer development. The ability to systematically manipulate gene expression at genome scale now provides opportunities to investigate the function of genes involved in cancer initiation and maintenance, which will provide a framework for therapeutic strategies.

Carlos Caldas, Professor of Cancer Medicine, **University of Cambridge** and Senior Group Leader, Cancer Research UK Cambridge Research Institute, United Kingdom, UK.

Professor Caldas holds the Chair of Cancer Medicine at the University of Cambridge since 2002. He heads the Breast Cancer Functional Genomics Laboratory at the Cancer Research UK Cambridge Institute. He is an Honorary Consultant Medical Oncologist at Addenbrooke's Hospital, Lead of the Cambridge Experimental Cancer Medicine Centre, and Director of the Cambridge Breast Cancer Research Unit. He is Fellow of the American College of Physicians, the Royal College of Physicians, the Royal College of Pathologists and the Royal Society of Biology. He was elected a Fellow of the Academy of the Medical Sciences in 2004 and a Fellow of the European Academy of Cancer Sciences in 2010. He was selected as an NIHR Senior Investigator in 2012. He was elected as an EMBO Member in May 2015.

His research focus is in the functional genomics of breast cancer and its biological and clinical implications. He has published over 300 papers. His laboratory recently completed the analysis of the largest genomic and transcriptomic study of breast cancers and redefined the molecular taxonomy of the disease, revealing novel subtypes and their respective drivers [Curtis et al, Nature 2012, Dawson et al, EMBO J 2013], and subsequently robustly validated this new breast cancer molecular taxonomy [Ali et al, Genome Biology 2014]. They also completed miRNA profiling of 1,300 of the same tumors and this is uncovering a new role for miRNAs as modulators of the immune response in a subset of breast cancers [Dvinge et al, Nature 2013]. His group also co-lead seminal studies that define the clonal heterogeneity of triple negative breast cancers [Shah et al, Nature 2012] and the patterns of whole-genome ER binding in primary tumors, which reveal new biology [Ross-Ines, Nature 2012]. Finally his group has co-lead studies that established ctDNA as a monitoring biomarker [Dawson et al, NEJM 2013] and a liquid biopsy to unravel therapy resistance [Murtaza et al, Nature 2013; Murtaza el al, Nature Communications 2015]. More recently his laboratory has been developing the use of patient-derived tumor explants as a model system for breast cancer [Eirew et al, Nature 2015].

Patient-derived Tumor Explants as a Robust Pharmacogenomic Platform for Pre-clinic Drug Testing

We have generated a large collection (n >80) of breast cancer patient-derived tumour xenografts (PDTX) that preserve trough passaging the morphological, molecular and clonal architecture characteristics of the originating tumour. An integrated platform for ex vivo high-throughput drug screens combining in vivo maintenance of PDTXs with short-term

cultures of PDTX-derived cells (PDTC) has been optimized. This PDTX-PDTC living biobank represents a powerful resource for pre-clinical pharmacogenomic studies, paving the way towards personalized treatment.

Ramon Salazar, Head of Medical Oncology Department at **Catalan Institute of Oncology (ICO, IDIBELL),** L'Hospitalet de Llobregat, Barcelona, Spain.

Ramon Salazar, MD, PhD is head of the medical oncology department at the Catalan Institute of Oncology, located at L'Hospitalet de Llobregat in Barcelona, Spain. He also leads the early clinical research, colorectal, and neuroendocrine tumor units at the hospital. Dr. Salazar received his medical degree and his PhD from the Hospital Santa Creu i Sant Pau in Barcelona. He then was a research fellow at the Beatson Oncology Centre in Glasgow, Scotland and completed additional training in the Neuroendocrine Oncology Unit of the University of Uppsala in Uppsala, Sweden. Dr. Salazar has authored or co-authored more than 120 peer-reviewed articles, book chapters, monographs, and online pieces. He serves on the board of the Spanish Cooperative Group for Gastrointestinal Tumour Therapy, EORTC GI group steering committee and on the scientific Ad Board committee of the European Neuroendocrine Tumor Society. He is also an active member of the European Society for Medical Oncology where he participates in various educational committees.

New Molecular Landscape in CRC. New Therapeutic Landscape?

The new colorectal cancer consensus molecular subtype classification is based on intrinsic gene expression clustering. This will allow us to refine subgroups of CRC with prognostic and predictive implications. For example, activation of a gene expression signature of epithelial-mesenchymal transition has been associated with activated cellular dependence on TGFB signaling, which confers poor prognostic and lack of clinical benefit to standard chemotherapies and targeted therapies but may warrant a clinical trial of chemotherapy in combination with anti-TGBB mAbs. Other molecular profiles beyond the well-known RAS genes (KRAS/NRAS - exons 2, 3 or 4) mutational status can potentially guide treatment decisions in the near future. MSI is a good prognostic biomarker in stage II and confers poor prognosis in stage IV. Other prognostic gene signatures have been developed to refine risk in stage II. BRAF is also a strong poor prognostic marker but only in stage IV. There is growing evidence that both MSI and BRAF tumors are differentially sensitive to immune checkpoint inhibitors and BRAF-EGFR inhibitor combinations, respectively. Other genetic events in additional nodes of the MAPK-PI3K pathways that bypass EGFR signaling may also confer resistance to cetuximab or panitumumab, cetuximab binding site mutations or PIK3CA mutations, ERBB2 or MET amplifications. Non-genetic mechanisms are also thought to be involved in resistance, including compensatory activation of receptor tyrosine kinases HER3 and MET, together with high expression of the ligands amphiregulin, transforming growth factor α, heregulin and hepatocyte growth factor in the tumor microenvironment. Some of these primary or secondary resistance driving molecular events can potentially be picked up by analysis of tumor circulating DNA in the blood with new ultrasensitive technology in what is now known as liquid biopsies, and this can ultimately guide treatment decisions, since new treatment options are arising for some of these molecular alterations.
In this talk, I will discuss how this new molecular information can be translated into clinically relevant risk stratification of the disease and new drug development of companion diagnostics, with optimization of patient selection in upfront and subsequent evolutionary stages of this heterogeneous disease.

Josep Villanueva, Group leader of Tumor Biomarkers Laboratory at **Vall d'Hebron Institute of Oncology (VHIO),** Barcelona, Spain.

Chair of the SESSION 5: MOLECULAR SIGNALING AND MODELS

Josep Villanueva obtained his PhD in Biochemistry and Molecular Biology from the Universitat Autónoma de Barcelona in the year 2000. For his post-doctoral studies, he joined the laboratory of Paul Tempst at Memorial Sloan-Kettering Cancer Center (MSKCC), New York (USA), where he participated in a new clinical proteomics program aimed at identifying serum cancer biomarkers. In 2006 he was promoted as Senior Staff Scientist at MSKCC. He then initiated a long-term project focused on developing novel methodology for the high-throughput proteomics profiling of tumor cell-secreted inventories (the 'secretome') with a clear emphasis on biomarker and drug target discovery. He returned to Barcelona three years later as an independent researcher and was appointed as Principal Investigator of VHIO´s Tumor Biomarkers Group. His research focuses on the discovery of new tumor-specific biomarkers and therapeutic targets using proteomic methodologies to improve cancer diagnostics and anti-cancer therapies.

Diagnostic and Therapeutic Implications of unconventional Protein secretion in Cancer

Secreted proteins such as growth factors, proteases and extracellular matrix proteins play key roles during tumor initiation and progression. Our group is methodologically focused on the proteomic analysis of the cancer secretome. Our main goal is to characterize the mechanisms adopted by cancer cells to communicate amongst themselves as well as with their microenvironment during tumorigenesis, and exploit this to advance biomarker and drug target discovery. Most secreted proteins contain a signal peptide that direct their sorting to the extracellular space through the endoplasmic reticulum (ER)–Golgi secretory pathway. One of the most striking observations when secretome profiles are carefully produced and

analyzed is that they contain hundreds of theoretical intracellular proteins. Recent reports showing intracellular proteins with alternative extracellular functions, suggest that new protein functions associated with alternative subcellular localizations could be relevant in tumorigenesis. Our recent efforts in the context of therapeutics and tumor invasion have led us to hypothesize that the characterization of unconventional protein secretion could lead to novel therapies against cancer.

René Bernards, Professor of Molecular Carcinogenesis, **Center for Biomedical Genetic and Cancer Genomics**, The Netherlands Cancer Institute, Amsterdam, Netherlands.

René Bernards studied adenovirus transformation for his PhD research from 1980 to 1984 with Alex van der Eb in Leiden. He joined the laboratory of Robert Weinberg at the Whitehead Institute in Cambridge, USA for his postdoctoral training, were he worked on the isolation of the retinoblastoma tumor suppressor gene. He was appointed assistant professor at the Massachusetts General Hospital Cancer Center in 1988. In 1992 he joined the Netherlands Cancer Institute. In 1994 he was also appointed part time professor of molecular carcinogenesis at Utrecht University, The Netherlands.
His scientific accomplishments include the development of MammaPrint, the first clinically-used gene expression profile for personalized treatment of breast cancer. To bring this discovery to the clinic he co-founded “Agendia”, a genomics-based diagnostic company that started offering the first microarray-based diagnostic test for the clinical management of breast cancer in 2004. His laboratory also developed the first shRNA vector for gene silencing in mammalian cells and used this vector to create the first genome-scale library of shRNA vectors. His laboratory has used this vector collection to identify biomarkers of response to cancer drugs and to identify particularly powerful drug combinations for the treatment of cancer, based on the concept of synthetic lethality. His work has identified the powerful effects of combining a BRAF inhibitor with an EGFR inhibitor in BRAF mutant colon cancer. There are currently five clinical trials ongoing that test the efficacy of the combination therapies suggested by his genetic screens.
He received several awards for his research, including the Pezcoller Foundation-FECS Recognition for Contribution to Oncology, the Ernst W. Bertner Award for Cancer Research from the M.D. Anderson Cancer Center, the ESMO Lifetime Achievement Award in Translational Research in Breast Cancer, the Spinoza award from the Netherlands Organization for Scientific Research and the Queen Wilhelmina Research Prize from the Dutch Cancer Society. He is also a member of the Royal Netherlands Academy of Arts and Sciences and received the Academy Professor Prize from this organization in 2013.

A Vulnerability of BRAF Resistant Melanoma with Potential Clinical Utility

Cancer remains difficult to treat, even with the new generation of targeted cancer drugs. By far the most formidable obstacle is the rapid emergence of therapy resistance. Indeed, many of the new cancer drugs elicit powerful initial responses, leading to dramatic effects on progression free survival, but far less long-term benefit is seen in terms of overall survival. One major difference between conventional chemotherapies and targeted therapies with respect to development of resistance is that resistance to targeted therapies follows a more predictable path. For instance, resistance of BRAF(V600E) mutant melanomas to drugs that target the BRAF and/or MEK kinases is almost always caused by reactivation of signalling through this pathway in the presence of drug. Drug withdrawal in such patients often does not lead to a flare up of disease but rather to a transient pause in tumor growth, known as the “drug holiday effect”. This effect can be explained, at least in part, by hyper-activation of MAPK pathway signalling following drug withdrawal, leading to a cellular state that has hallmarks of oncogene-induced senescence4. Downregulation of this hyper-active MAPK signalling during the drug holiday results in a regained drug sensitivity upon rechallenge with BRAF inhibitor.

We argued that any drug that can maintain high levels of MAPK signalling in melanoma cells with an acquired resistance to BRAF and/or MEK inhibitors would potentially be able to maintain a state of prolonged proliferation arrest upon BRAF inhibitor withdrawal. Such a state of persistent proliferation arrest with hallmarks of oncogene-induced senescence is also seen in melanocytic naevi (moles) that carry a BRAF(V600E) mutation5.
In my presentation, I will show that drugs can be identified that maintain high levels of MAPK pathway signalling in BRAF inhibitor resistant melanomas upon cessation of BRAF inhibitor treatment. These drugs are only active in melanoma cells that have acquired resistance to BRAF inhibitors and not in parental melanoma cells, because they require MAPK hyper-activation that is induced by the gained resistance to BRAF inhibitors to be effective. In general, second line treatment of tumors that have acquired resistance to first line therapy is less effective. The unique aspect of the second line therapy identified here is that it exploits a vulnerability that is only gained upon acquisition of resistance to BRAFi therapy. The proposed therapy also takes advantage of the fact that acquisition of resistance to BRAFi follows a predictable path in the clinic making their responses to second line also more predictable.

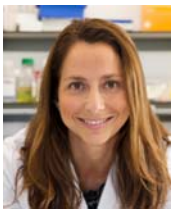
Mariano Barbacid, AXA-CNIO Professor of Molecular Oncology at **Spanish National Cancer Research Center**, Madrid, Spain.

Mariano Barbacid got his Ph.D. in Madrid (1974) and trained as a postdoctoral fellow at the US National Cancer Institute. In 1978 he started his own research group to study the molecular events responsible for the development of human tumors. His work led in the spring of 1982 to the isolation of the first human oncogene (H-Ras) and to the identification of the first mutation associated with the development of human cancer. In 1988, he joined Bristol Myers-Squibb where he became Vice

President, Oncology Drug Discovery. In 1998, he returned to Madrid to create and direct the Spanish National Cancer Research Center (CNIO). In 2011 he stepped down as Director to concentrate on his own research projects that currently focus on the identification and functional validation of therapeutic targets in K-RAS driven lung and pancreatic tumors. In 2012, he was inducted to the US National Academy of Sciences US as a Foreign Member (2012), In 2014, he was elected Fellow of the AACR Academy. He holds Honorary Degrees from the University Menendez y Pelayo (1995), University of Cantabria (2011) and University of Barcelona (2014). His work has been recognized by several awards including the Steiner Prize (Bern, 1988), Ipsen Prize (Paris, 1994), Brupbaher Cancer Prize (Zurich, 2005), the Medal of Honor of the International Agency for Cancer Research (Lyon, 2007) and an Endowed Chair from the AXA Research Fund (Paris, 2011). He has also received several Spanish Awards. To date, Dr. Barbacid has authored a total of 290 publications, including 234 research articles in journals with impact factor. His current "h" factor is 105.

Targeting the MAPK Pathway in K-RAS Mutant Tumors. Challenges and Opportunities

K-RAS oncogenes have been implicated in about one fifth of all human cancers. To identify effective therapeutic strategies, we have developed genetically engineered mouse (GEM) models that closely recapitulate their natural history. We are using these mice to validate targets of potential therapeutic value with the ultimate goal to translate these findings to the clinic. We have generated a new generation of GEM models in which expression of the resident K-Ras oncogene, as well as ablation of the p53 tumor suppressor is mediated by the frt-FLp recombinase system, a strategy that allows temporal separation of tumor development from target ablation. In addition, we have generated lox-Cre based conditional knock-in strains that upon recombination direct the expression of kinase dead isoforms instead of inducing protein ablation. These strains should serve as better models to mimic drug intervention in the clinic. Finally, we are now combining ablation (or inactivation) of these targets in order to identify combinations that might eradicate advanced tumors. We hope that these studies will serve to guide the design of future clinical trails to treat patients carrying K-RAS mutant tumors.



Violeta Serra, Principal Investigator of Experimental Therapeutics Group at **Vall d'Hebron Institute of Oncology (VHIO)**, Barcelona, Spain.

Violeta Serra obtained her PhD in 2001 in the field of cellular aging and telomeres from Newcastle University (UK). She gained a Marie Curie Postdoctoral Fellowship, to study cancer chemotherapy resistance at the Humboldt University, Berlin (Germany). In 2004, she joined the Spanish National Cancer Research Center (CNIO, Madrid), where she pursued her interest in understanding the role of intracellular kinases as potential drug targets in cancer. In 2006, she joined José Baselga's group at the Vall d'Hebron Institute of Oncology (VHIO) to explore the mode of action and mechanisms of resistance to PI3K-pathway inhibitors. Her work has been pivotal in defining adaptive responses to these agents in breast cancer cells. Since 2014 she has led VHIO´s Experimental Therapeutics Group, and continues to expand her research into targeted therapies in triple negative breast cancers -- specifically PARP inhibitors. To establish herself as an independent Principal Investigator, Violeta was awarded with two ISCII Project Grants and a Career Catalyst Research Grant from the Susan G. Komen Foundation. Violeta is member of the American Association of Cancer Research (AACR), serves on the Editorial Board of Clinical Cancer Research, and is also ad-hoc reviewer for Cancer Research, Clinical Cancer Research, Molecular Cancer Therapeutics, and Breast Cancer Research.

Restoration of DNA homologous recombination functionality as major mechanism of PARP inhibitor resistance in germline BRCA Breast Cancer

PARP1/2 inhibitors (PARPi) are active anti-cancer agents in germline BRCA1 or BRCA2 mutation carriers (gBRCA) with advanced breast or ovarian cancer. However, not all BRCA-tumors respond to PARP blockade, and eventually all develop acquired resistance. Little is known about clinically relevant mechanisms of PARPi resistance in BRCA-breast cancer. In our laboratory, we sought to identify mechanisms of primary and acquired resistance to these agents and provide clinically relevant response biomarkers. After screening a panel of 12 patient-derived tumor xenografts (PDX) from germline BRCA1/2 tumors we have observed that functional DNA repair by homologous recombination (HR) is associated with primary- and acquired-resistance. This finding is now confirmed in human tumor specimens. In my talk I will focus on the specific biological mechanisms that gBRCA tumor cells exploit to restore HR and likely enable PARPi-resistance in the clinic.

Alberto Villanueva, Responsible of the Group of Chemoresistance, Program Against Cancer Therapeutic Resistance (ProCURE) at the **Catalan Institute of Oncology (ICO, IDIBELL),** Co-founder of a the spin-off Xenopat, Barcelona, Spain.

See his CV at the Scientiffic Committee section

Otrhoxenograft tumor models and personalized medicine in real-time

Developing strategies to personalize cancer treatment based in the mice generation of orthoxenografts, means patient-derived orthotopic xenografts, is a complex process that begins just with tumor resection or tumor-biopsy is taken from

primary or metastasis. Once the implanted tumor has grown, important considerations have to been taken in consideration: (i) the time needed to realize in mice treatment-response assay and the therapeutic window for patient treatment (ii) the existence of solid evidences about the correlation among specific genetic alterations identified in the tumor and their correlation with drug responses, and finally (iii) can we treat the patients with the best drug identified in mice?. Here we show several cases of personalized medicine in different tumor-types realized in real-time in advanced/bad prognostic patients based on the generation of their own orthoxenograft and what is the correlation with the clinical course of patients.

David Garcia Molleví, Group Leader, Microenvironment and Resistance Group, Program Against Cancer Therapeutic Resistance at the **Catalan Institute of Oncology (ICO, IDIBELL),** Barcelona, Spain.

Chair of the SESSION 6: STEM CELLS AND MALIGNIZATION

See his CV at the session 3

George Thomas, Director of the Department of Cancer Metabolism at **IDIBELL** and Professor of **University of Barcelona (UB),** Barcelona, Spain.

George Thomas graduated with a BS degree from the University of California San Diego in 1969 and obtained his PhD. in 1975 with Dr. Harry Noller at the University of California Santa Cruz, on the structure and function of ribosomes. He then received one of the first EMBO Long-Term Fellowships awarded to Americans to begin his seminal studies in the mTOR/S6K1 signaling pathway at the Friedrich Miescher Institute in Basel, Switzerland. During the next thirty years he advanced from Fellow, to Junior and then Senior Group leader, finally being appointed Head of the Department of Growth Control in 2003. In 2005 he was recruited to the Genome Research Institute, a joint venture between Procter & Gamble and the University of Cincinnati, where he held the John and Gladys Chair in Cancer Biology and was appointed Scientific Director in 2006. In 2011 he moved his Laboratory to the IDIBELL/ICO in Barcelona, where he is the Director of the Department of Cancer Metabolism and Professor of University of Barcelona. He is acknowledged by his peers as an innovative leader in the field of signal transduction and growth control based on his pivotal studies on the discoveries and regulation of S6K1. His discovery that S6K1 is activated by phosphorylation gave credence to the purely conceptual notion of kinase signaling cascades. He then went on to demonstrate that S6K1 plays critical regulatory role in cell growth, energy balance and stem cell biology, cellular processes underlying many pathological states. These studies eventually changed our understanding of signal transduction and disease processes, forming the basis for clinical investigation of novel anti-cancer agents that act on the mTOR/S6K1 pathway.

The Role of Tumor Initiating Cells in the Inhibition of mTOR in HCC

Despite the recent success of sorafenib in hepatocellular carcinoma (HCC), prognosis remains poor for advanced disease patients. In HCC the mammalian Target of Rapamycin (mTOR) was thought to be an attractive target, as it is hyperactivated in 80% of cases. However, the FDA-approved mTOR-allosteric inhibitor everolimus (RAD001) has failed in two clinical trials as a single agent in HCC, probably due to incomplete mTOR Complex 1 (mTORC1) inhibition. Likewise, we showed that RAD001 had minimal effects on HCC cell proliferation or tumor regression, but when combined with BEZ235, a PI3K/mTOR-ATP site competitive inhibitor, synergistically blocked the growth of HCC cells and caused tumor regression in a mouse model approximating human HCC with bad prognosis and in orthotopic xenograft of Huh7, human HCC cell line. We also found that RAD001/BEZ235 induced the upregulation of autophagy, a tumor suppressor in liver, particularly a dramatic stimulation of mitophagy. Despite this observation, it is argued that a small population of human tumor initiating cells (TICs) is protected from mTOR inhibitors. In contrast, the biguanides, phenformin and metformin, potent inhibitors of mTORC1, are reported to selectively suppress the proliferation of TICs. These effects are argued to be through inhibition of OXPHOS, blocking ATP production, activating AMPK, and inducing autophagy. Given the ability of biguanides to inhibit mTORC1 and to selectively inhibit the proliferation of TICs, we set out to determine their effect on tumor progression, energy usage and autophagy. Unexpectedly, the benefits of biguanides in suppressing tumor progression are autophagy independent, but consistent with mitochondrial damage.

Héctor G. Palmer, Head of the Stem Cells and Cancer Group at the **Vall d´Hebron Institute of Oncology (VHIO),** Barcelona, Spain.

See his CV at session 4.

New Pre-clinical Models to study Target-directed Drugs in advanced Colorectal Cancer

We have established a network to derive tumour cells from CRC patients directly post surgery. This has involved committed coordination between oncologists, pathologisst, surgeons and our translational research laboratory. This network has resulted in successfully derived PDX models from more than 100 CRC patients (primary and liver metastasis) and is currently expanding to include more tumor types and small biopsies of patients in clinical trials. The growing collection of PDXs includes all pathological, clinical, genetic and biological data for each CRC patient. Based on this multidisciplinary approach our group has been able to develop different research projects with robust and rapid translation to cancer patients.

One first example of such a project was investigating the role of beta-catenin and FOXO3a transcription factors in CRC (Tenbaum et al. Nat. Med. 2012). We described the capacity of nuclear beta-catenin to promote metastasis in coordination with FOXO3a and to confer resistance to PI3K and AKT inhibitory drugs. These findings have become relevant to understand the enhanced resistance of CRC patients to this family of drugs. Indeed, many cancer patients are being treated with these inhibitors in phase I clinical trials worldwide and or results helped to explain the negative results on response observed in the clinic.

Oriol Casanovas, Staff Researcher and ERC-Fellow at Head of Tumor Angiogenesis Group at ProCURE Program Against Cancer Therapeutic Resistance, **Catalan Institute of Oncology (ICO, IDIBELL**), Barcelona, Spain.

See his CV at session 2.

Deciphering Resistance to Anti-angiogenic Therapies for Prediction of Response and New Treatments.

Several anti-angiogenic drugs are clinically used in a variety of tumor types to block angiogenesis, impair tumor growth, progression and dissemination. Nevertheless, as in most systemic therapies, resistance to anti-angiogenic treatments emerges over time with tumor regrowth and disease progression. Indeed, several clinical trials report a lack of long-lasting effects of anti-angiogenic agents as consequence of tumor adaptation to the therapy. Several molecular mechanism have been described that give raise to acquired resistance to antiangiogenics, including a promotion of the tumor invasive/metastatic behavior. While several strategies have been postulated to fight resistance, a key question still needs to be answered: How can we predict which patients will be intrinsically resistant, responsive or will acquire resistance?
Focused on deciphering the mechanisms of resistance to antiangiogenics, we have developed an extensive panel of patient-derived mouse models of Renal Cell Carcinoma based on the orthotopic implantation of primary renal tumor biopsies. In these advanced models we can observe initial anti-tumor effects of anti-angiogenic drugs followed by emergence of resistance to therapy in the long-term treatments (with tumor re-growth) due to tumor adaptation. Molecular analysis has led us to unravel new biological mechanisms of resistance but also to develop several predictive factors that could be useful for the discrimination of resistant patients and the responsive patients.
In this talk, we will present the mechanisms of resistance to anti-angiogenic therapies and the initial development of biomarkers to predict resistance to antiangiogenic therapies as a key advancement in the upcoming personalized cancer therapy era.

PRACTICAL INFORMATION

Venue: CosmoCaixa Barcelona

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Conferences
Agora room on -2 floor

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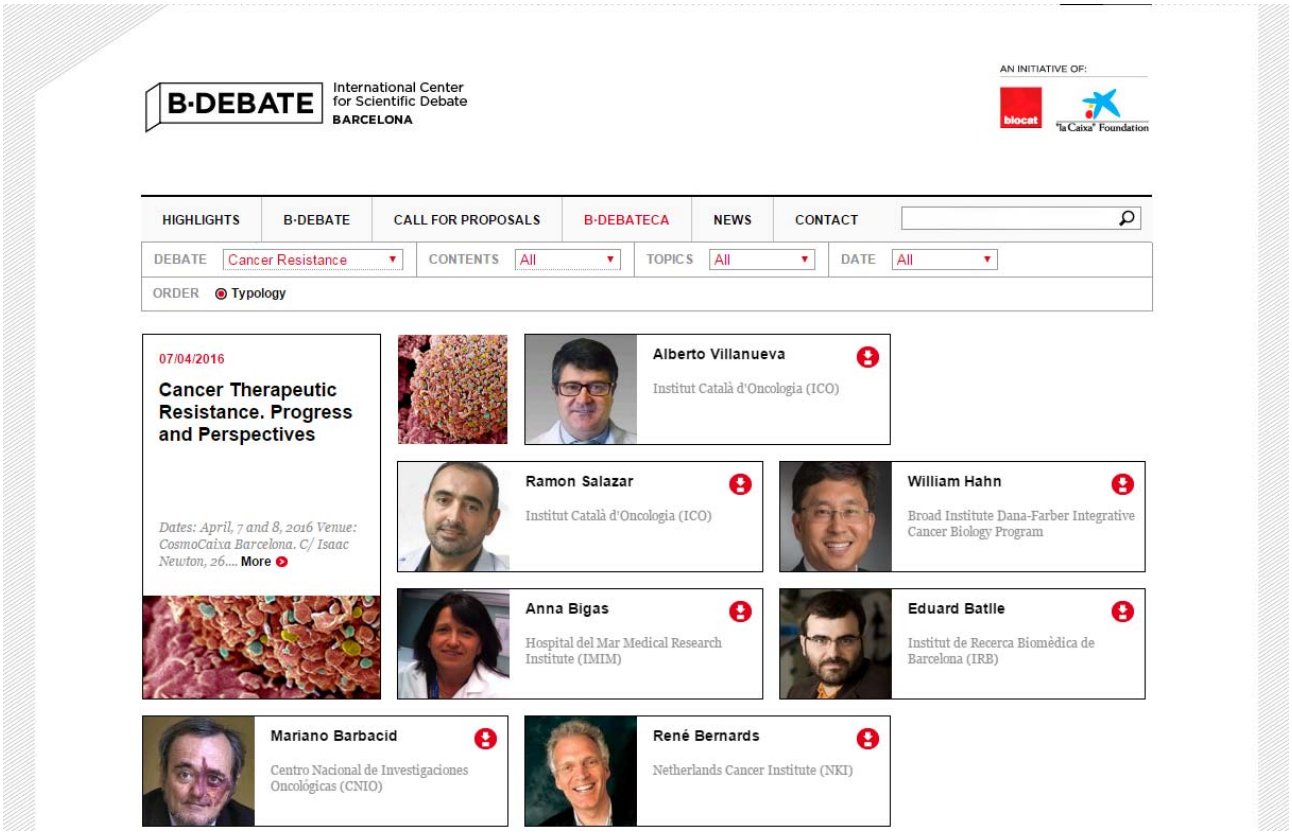
OUTCOMES

B·Debateca

On the website of **B·Debate**, you will find all the information related with the celebration of the meeting that includes reports, conclusions, scientific documents, interviews with the experts, speaker's CVs, videos, images, press documentation and other related materials. We invite you to visit the section **B·Debateca** on **www.bdebate.org**

Contents of the meeting "CANCER THERAPEUTIC RESISTANCE: PROGRESS AND PERSPECTIVES"



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B·Debate International Center for Scientific Debate Barcelona is a **Biocat** initiative with support from **"la Caixa" Foundation**. It drives first-rate international scientific debates, to foster dialogue, collaboration and open exchange of knowledge with prestigious national and international experts, to approach complex challenges of high social interest in life sciences. B·Debate sees debate as a powerful, effective way to generate knowledge and strives to help position Barcelona as a benchmark in generating knowledge a nd Catalonia as a country of scientific excellence.

B·Debate sees debate as a powerful, effective way to generate new knowledge. The debates are top-notch international scientific meetings featuring a selection of experts of renowned international prestige and scientists that work in Barcelona and Catalonia, moderated by scientific leaders. Since 2009 B·Debate has invited about 1200 recognized speakers and over 7.000 attendees. B·Debate seeks out answers to the challenges and needs of society in the field of life sciences, taking into account the complex, ever-changing conditions of this global world.

The debates foster the integration of different disciplines of science and deal with such diverse topics as ageing, new therapeutic approaches to various diseases, innovative technology to improve knowledge of the human genome, food resources, new tools to integrate knowledge management, clinical genomics, neurosciences, climate change, and new energy sources, among others. The knowledge and results obtained through these events is spread throughout both the scientific community and general society through the various B·Debate channels and instruments.

More info: **www.bdebate.org**

The **Catalan Institute of Oncology** (ICO,) is a public health center working exclusively in the field of cancer. Its approach to the disease is comprehensive, combining care, prevention, research and specialized training in one organization. Through an extensive network of hospitals, the ICO constitutes the referral center for more than 50% of the adult population of Catalonia. Thus, ICO's Mission is "to work to reduce the impact of cancer in Catalonia" and, based on benchmark scientific ranks, the ICO is at the forefront of biomedical research in Spain and placed 28th worldwide. The present year is the 20th anniversary of the ICO and it has launched a new "research program against cancer therapeutic resistance" (**ProcURE**). The Mission of ProCURE is to make a significant contribution to "reducing the impact of cancer" through a global, multi-disciplinary approach to the questions of why resistance to current (and future) cancer treatments develops and how it can be impaired. Thus, nine research groups work coordinately with clinicians and additional ICO Programs to accomplish the Mission. Collectively, ProCURE is committed to foster improvement in precise and effective cancer therapy.

More info: **http://ico.gencat.cat/en**

Established in 2006, the **Vall d´Hebron Institute of Oncology** (VHIO) is a leading comprehensive cancer center of excellence where its scientists and research physicians adopt a purely translational research model, working together as multidisciplinary teams to both accelerate and advance personalized and targeted therapies against cancer. Undertaking one of Spain´s most dynamic cancer research programs, VHIO is dedicated to delivering on the promise of ´precision´ medicine in oncology – turning cancer discovery into more effective treatments and better practice for the care of our patients.

Organized into four main programs: Preclinical, Translational, Clinical, and Core Technologies, VHIO´s team of some 200 researchers and physician scientists focus on understanding the fundamental biology of human cancer, from cellular and molecular biology and genetics through to therapeutics.

Its optimal organizational structure, coupled with its privileged location within the campus of the Vall d´Hebron University Hospital – affording direct access to patients as well as the entire spectrum of oncology professionals who care for them, allows VHIO to tackle the many unresolved questions in ultimately outsmarting the multifaceted, heterogeneous and complex disease that is cancer.

More info: www.vhio.net

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The Company of Biologists is a not-for-profit publishing organisation dedicated to supporting and inspiring the biological community. The Company publishes five specialist peer-reviewed journals: Development, Journal of Cell Science, Journal of Experimental Biology, Disease Models & Mechanisms and Biology Open. It offers further support to the biological community by facilitating scientific meetings, providing travel grants for researchers and supporting research societies.

More info: **www.biologists.com**

The Spanish Cooperative Cancer Network (RTICC) is one of 17 health networks of RETICS program, funded by the ISCIII, focused in cancer research, formed through association to the Instituto de Salud Carlos III of a range of multidisciplinary research groups in cancer research, which seek to conduct cooperative research projects of general interest, as a strategy to shorten the gap between the production of new knowledge and of transferring and actually applying this knowledge to medical practice.

The RTICC is composed of 73 research groups, with more than 1.200 researchers, distributed in 49 institutions, hospitals, universities and research centers from 13 autonomous communities, structured in seven specific programs (i) Molecular mechanisms: molecular characterization of tumors, cancer genomics and biomarkers, (ii) Epidemiology and Prevention of cancer, (iii) Hematological tumors, (iv) Breast cancer, (v) Colon and Gastrointestinal cancer, (vi) Lung and Upper Respiratory tract, (vii) Other Solid and pediatric tumors and a transversal program "Training and Coordination" that will support all organizational activities, training and dissemination set.

More info: **www.rticc.org**

COLLABORATORS

CosmoCaixa offers interactive, enjoyable science and an open door for anyone who is eager to learn and understand and who never stops wondering why things are the way they are. **CosmoCaixa Barcelona** boasts the Geological Wall and the Amazon Flooded Forest, which features more than 100 plant and animal species that convince visitors they have been transported from the Mediterranean to the very heart of the tropical jungle. In addition to its permanent facilities and its open areas, CosmoCaixa offers a scientific and educational programme that includes exhibitions, workshops, conferences, courses and debates involving experts from all over the world.

More info: **http://obrasocial.lacaixa.es**

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