*Madrid* 22-25 March 2015

# NEW TRENDS IN ANTICANCER DRUG DEVELOPMENT

SPANISH NATIONAL CANCER RESEARCH CENTRE

CNIO Frontiers Meetings

**CNIO FRONTIERS MEETINGS 2015**

*Organisers*

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CNIO, Madrid, Spain

**ALBERTO BARDELLI**

IRCC, Torino, Italy

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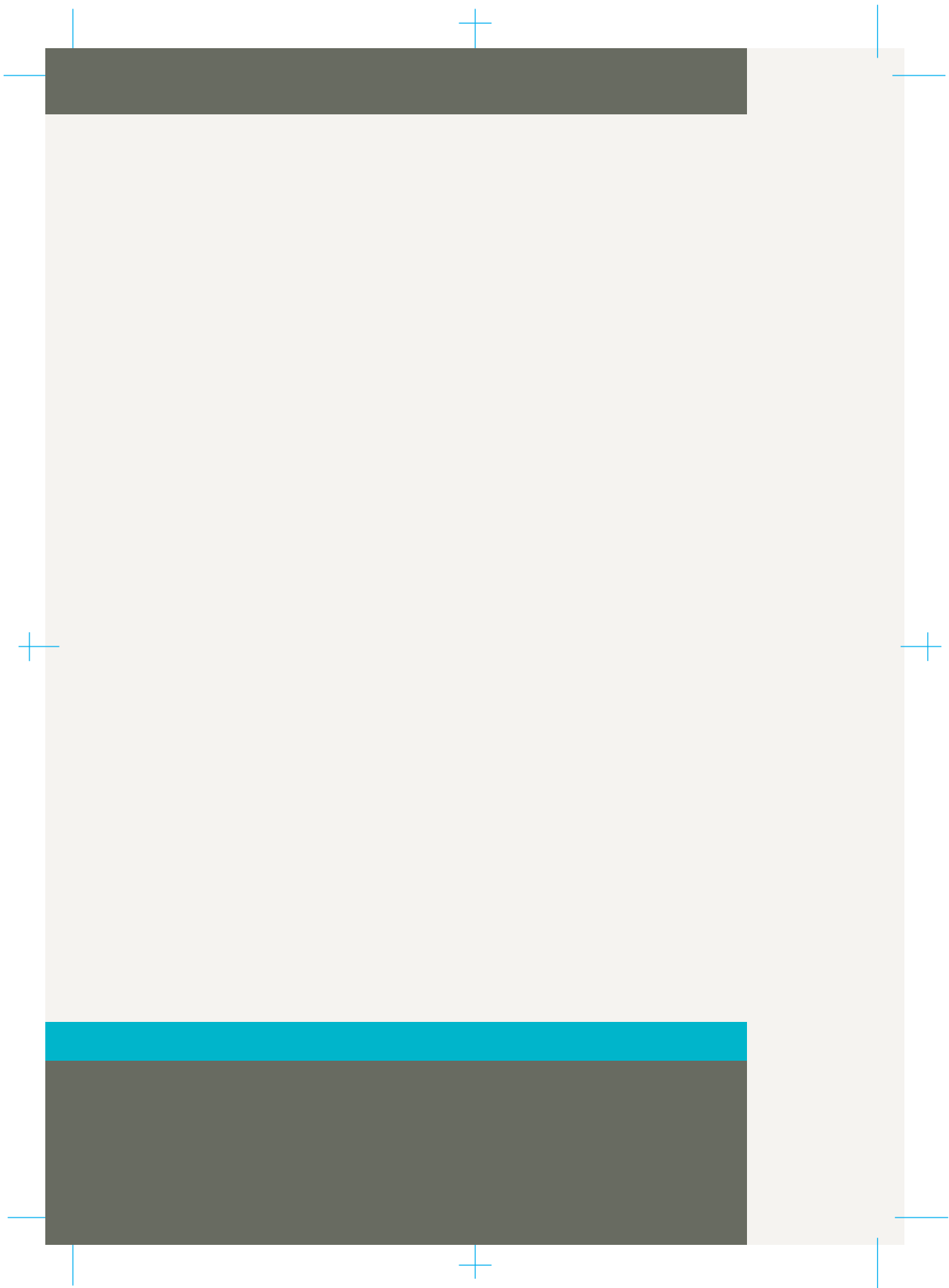Princess Margaret Cancer Centre Toronto, Canada

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Meetings

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CNIO FRONTIERS MEETINGS 2015

# SUMMARY

*Madrid* 22-25 March 2015
# NEW TRENDS IN ANTICANCER DRUG DEVELOPMENT

**Venue: Spanish National Cancer Research Centre (CNIO) Auditorium**

**Chairpersons:**
Manuel Hidalgo, CNIO, Madrid, Spain
Josep Tabernero, VHIO, Barcelona, Spain
Alberto Bardelli, University of Turin - Candiolo Cancer Institute IRCCS, Italy
Lillian Siu, Princess Margaret Cancer Centre, Toronto, Canada

**Rationale:**
During the last few years there has been continued progress in new anticancer drug development. New agents ranging from small molecules to engineered antibodies to immune modulators have been approved for cancer treatment. Furthermore, a large portfolio of new agents is currently at different stages of development. New cancer drug development has evolved methodologically from a one-size fits all approach to a personalize development mode. New drugs are targeted to specific new cancer abnormalities and clinical development is geared to selecting patients with these specific abnormalities. In addition to new clinical trial designs, there has been significant interest in strategies for non-invasive disease monitoring such as assessment of liquid biopsies or circulating tumor cells as well as in implementing preclinical models in the so called co-clinical trials approach. Since 2010 when we organized a CFM in Molecular Cancer Therapeutics there has been substantial new progress for a new meeting on the topic.

## Sunday March 22nd

**20:30-22:00**   **Welcome cocktail for Speakers & Participants**
Venue: Don Pio Hotel (Av. Pío XII, 25 - 28016 Madrid, Spain)
http://www.hoteldonpio.com/en

## Monday March 23rd

**08:45-09:00**    **Opening Remarks**
*Josep Tabernero, VHIO, Barcelona, Spain*
*Alberto Bardelli, University of Turin* - Candiolo Cancer Institute IRCCS, Italy

**S1**    **09:00-10:00**    **New Targets-Pathways in Clinical Development (1)**
*Chairperson: Manuel Hidalgo, CNIO, Madrid, Spain*

09:00-09:30    Leveraging circulating DNA studies to identify
mechanisms of resistance to CYP17A1 inhibition
*Gerhardt Attard, ICR, London, UK*

09:30-10:00    PI3K/mTOR Inhibitors
*Josep Tabernero, VHIO, Barcelona, Spain*

10:00-10:30    Ras-Raf-MEK Inhibitors
*Jordi Rodón, VHIO, Barcelona, Spain*

10:30-11:00    *Overcoming resistance to targeted therapies*
*Jeffrey Engelman, Massachusetts General Hospital Cancer Center, USA*

**11:00-11:30**    **Coffee Break & Group Picture**

11:30-12:00    Mechanistic basis of Palbociclib combinatorial activity in ER+ breast cancer
and non-breast indications
*David J. Shields, Pfizer Inc., NY, USA*

**KEY NOTE LECTURE**    **12:00-12:45**    **Key Note Lecture #1**
*Chairperson: Luis Paz-Ares, CNIO, Madrid, Spain*

**Targeted Therapies: Patient Selection and Mechanisms of Resistance**
Early Oncology Drug Development at Roche
*William Pao, Roche Pharma Research & Early Development, Basel, Switzerland*

**12:45-13:45**    **Lunch Break**

**S2**    **13:45-15:45**    **Innovative Approaches in Drug Development**
*Chairperson: Eduardo Díaz-Rubio, San Carlos University Hospital, Madrid, Spain*

13:45-14:15    Establishing dose, schedule and population(s): Novel trial approaches
*Jaap Verweij, Erasmus University Medical Center, Rotterdam, The Netherlands*

14:15-14:45    Precision medicine for cancer patients
*Alberto Bardelli, University of Turin-Candiolo Cancer Institute IRCCS, Italy*

14:45-15:15    Co-Clinical Trial Strategies:
An essential tool for the development of future anti-cancer therapies
*Mariano Barbacid, CNIO, Madrid, Spain*

15:15-15:45    Incorporating Novel Imaging Methods in Early Drug Development
*Elisabeth G. de Vries, University Medical Center, Groningen, The Netherlands*

**15:45-16:15**    **Coffee Break**

**16:15-17:00**    **Short Talks**

16:15-16:30    Combined inhibition of Ddr1 and Notch signaling is an effective
therapeutic  strategy to treat K-Ras-driven/p53-null lung adenocarcinomas
*Chiara Ambrogio, CNIO, Madrid, Spain*

16:30-16:45    Controlled release microspheres loaded with BMP7 suppress primary
tumors from human glioblastoma
*Pilar González-Gómez, ISCIII, Madrid, Spain*

16:45-17:00    Upregulation of MAPK negative feedback regulators and RET in mutant
ALK neuroblastoma: implications for targeted treatment
*Irina Lambertz, Ghent University, Belgium*

## Tuesday March 24th

KEY NOTE  LECTURE

**09:00-09:45**    **Key Note Lecture #2**
*Chairperson: Alfredo Carrato, Hospital Ramon y Cajal, Madrid, Spain*

**Harnessing the Immune System to Treat Cancer**
*Drew Pardoll, Johns Hopkins University, Baltimore, USA*

**S3**    **09:45-12:45**    **New Targets-Pathways in Clinical Development (2)**
*Chairperson: David Olmos, CNIO, Madrid, Spain*

09:45-10:15    Targeting DNA Damage Repair Pathways
*Hilary Calvert, UCL, London, UK*

10:15-10:45    Antibody-drug conjugates – a new wave of targeted cancer drugs
*Ingrid Sasson, Sanofi Oncology, Paris, France*

10:45-11:15    Targeting sheltering in cancer
*Maria A. Blasco, CNIO, Madrid, Spain*

**11:15-11:45**    **Coffee Break**

11:45-12:15    Targeting the Epigenome
*Manel Esteller, IDIBELL, Barcelona, Spain*

12:15-12:45    Stromal Disrupting Strategies
*Sunil R Hingorani, Fred Hutchinson Cancer Research Center, Seattle, USA*

12:45-13:15    Developmental and Cancer Stem Cell Pathway Inhibitors
*Timothy Hoey, OncoMed Pharmaceuticals, Redwood City, USA*

**13:15-14:15**    **Lunch Break**

**S4**    **14:15-16:15**    **Immunotherapy Approaches for Cancer Treatment**
*Chairperson: Jesús García-Donas, Sanchinarro Univ. Hospital, Madrid, Spain*

14:15-14:45    Check-point Inhibitors and Vaccine Combinations
*Mario Sznol, Yale University, New Heaven, USA*

14:45-15:15    From mechanisms to combinations in novel cancer immunotherapies
*Ignacio Melero, CIMA & Clinica Universidad de Navarra, Pamplona, Spain*

15:15-15:45    Targeting oncogene-induced replication stress for cancer therapy
*Oscar Fernández Capetillo, CNIO, Madrid, Spain*

15:45-16:15    Agonistic CD 40 Antibodies and Immune Therapy
*Ann L. White, University of Southampton, UK*

**16:15-16:45    Coffee Break**

**16:45-17:15    Short Talks**

16:45-17:00    The HBP1 tumor suppressor at multiple regulatory cross roads
in neuroblastoma
*Shana Claeys, University of Ghent, Belgium*

17:00-17:15    Characterization of the tumor suppressor function of the lysine-specific
methyltransferase KMT2D in follicular lymphoma
*Ana Ortega-Molina, Memorial Sloan-Kettering Cancer Center, NY, USA*

**20:30    Faculty dinner**  (Goizeko-Kabi Restaurant, Comandante Zorita street #37)
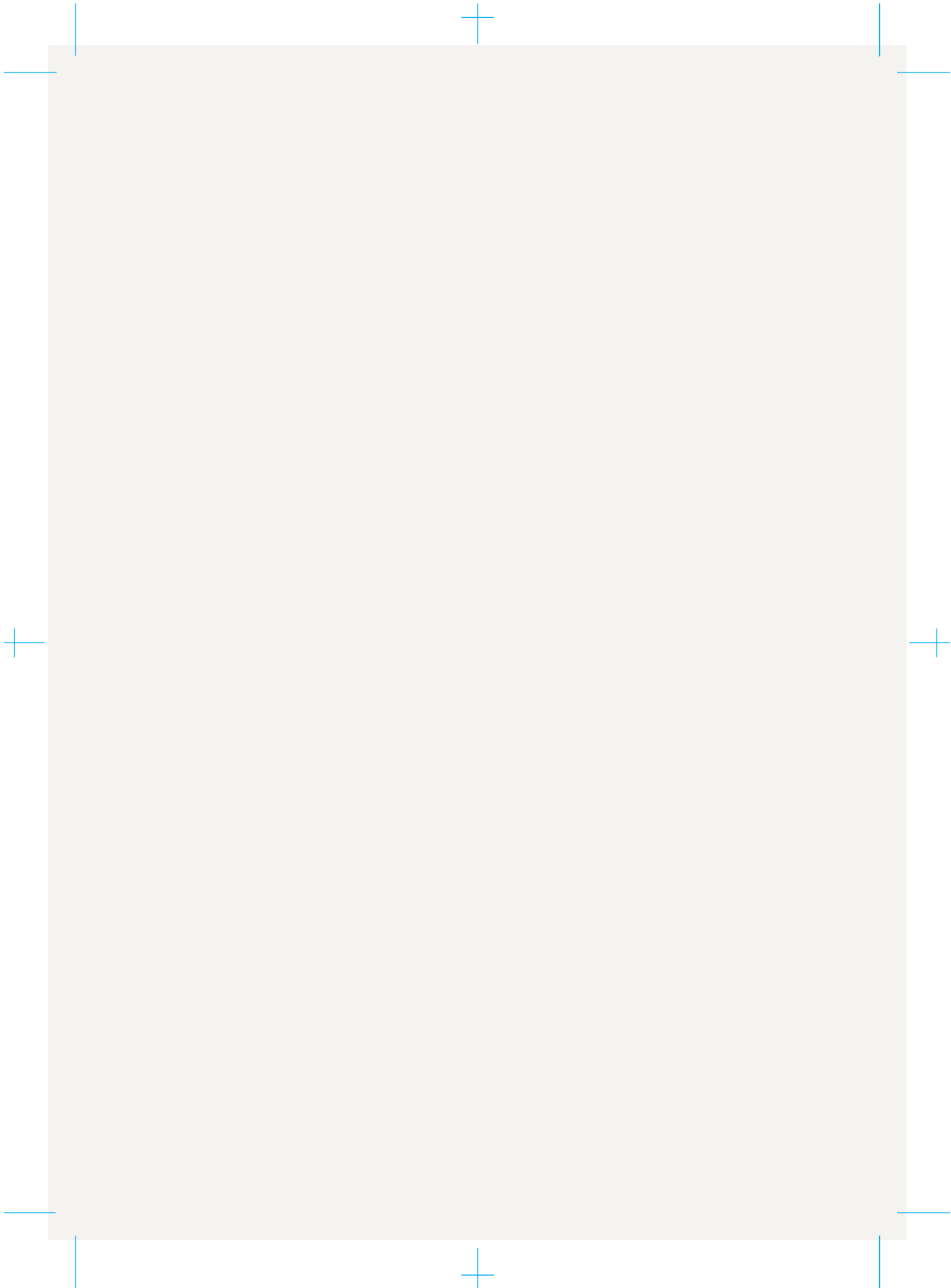http://kabi.goizeko-gaztelupe.com/

## Wednesday March 25th

09:00-09:45    **Key Note Lecture #3**
*Chairperson: Miguel A. Quintela, CNIO, Madrid, Spain*

**Exploiting Cancer Metabolic Vulnerabilities**
*Tak W. Mak, Princess Margaret Cancer Centre, University of Toronto, Canada*

**S5**  09:45-11:45    **Personalizing Cancer Treatment**
*Chairperson: Fatima Al-Shahrour, CNIO, Madrid, Spain*

09:45-10:15    Novel Applications of Cancer Genomics to Personalized Medicine
*Luis Diaz, Johns Hopkins University, Baltimore, USA*

10:15-10:45    Designing Clinical Trials for Personalized Medicine
*Lillian Siu, Princess Margaret Cancer Centre, Toronto, Canada*

10:45-11:15    Worldwide Initiatives in Personalized Medicine
*Christophe Le Tourneau, Curie Institute, Paris, France*

11:15-11:45    Integrating PDX Models in Personalized Medicine Studies
*Manuel Hidalgo, CNIO, Madrid, Spain*

11:45-12:00    **Closing Remarks**
*Manuel Hidalgo, CNIO, Madrid, Spain*
*Lillian Siu, Princess Margaret Cancer Center, Toronto, Canada*

KEY NOTE LECTURE

NEW TRENDS IN ANTICANCER DRUG DEVELOPMENT | PROGRAMME

**NEW TRENDS IN
ANTICANCER DRUG
DEVELOPMENT**

# KEYNOTE LECTURES

*Monday 23rd*

## WILLIAM PAO

Roche Pharma
Research & Early
Development
Basel, Switzerland

*Tuesday 24th*

## DREW PARDOLL

John Hopkins
University,
Baltimore, USA

*Wednesday 25th*

## TAK W. MAK

Campell Family Institue for
Breast Cancer Research,
Princes Margaret Cancer Ctr.,
Toronto, Canada

# Targeted Therapies: Patient Selection and Mechanisms of Resistance

**William Pao,**
Roche Pharma Research & Early Development,
Basel, Switzerland

Dr. Pao, Global Head of the Oncology Discovery and Translational Area for the Pharma Research and Early Development (pRED) unit headquartered in Basel, Switzerland, will discuss aspects on early oncology drug development at Roche.

NEW TRENDS IN ANTICANCER DRUG DEVELOPMENT | KEYNOTE LECTURE

# Harnessing the Immune System to Treat Cancer

**Drew Pardoll,**
Johns Hopkins University,
Baltimore, USA

NEW TRENDS IN ANTICANCER DRUG DEVELOPMENT | KEYNOTE LECTURE

## Exploiting Cancer Metabolic Vulnerabilities

**Tak W. Mak,**
Campbell Family Institute for Breast Cancer Research,
Princess Margaret Cancer Centre, University Health Network, University of Toronto,
Toronto, Canada

NEW TRENDS IN ANTICANCER DRUG DEVELOPMENT | KEYNOTE LECTURE

Tumour progression is driven by genetic aberrations that affect multiple oncogenes and tumour suppressor genes (TSGs). For the last three decades, the "Oncogene Revolution" prompted investigators to concentrate on the development of agents against oncogenes, with the goal of blocking cell growth and metastasis. It has now become clear that the cancer cell genome is too varied and the number of oncogenes too numerous for this strategy to work effectively for most tumours. For the last three decades, the "Oncogene Revolution" prompted investigators to concentrate on the development of agents against oncogenes, with the goal of blocking cell growth and metastasis. It has now become clear that the cancer cell genome is too varied and the number of oncogenes too numerous for this strategy to work effectively for most tumours. A relatively new and promising approach is to enhance the infiltration into the tumour microenvironment of leukocytes that can kill cancer cells. One other classes of target genes relevant in this context are those involved in cancer cell metabolic adaptation and the maintenance of aneuploidy. In this presentation, I discuss recent data from our group and other laboratories aimed at exploiting these strategies. For example, mutations have also been found in the isocitrate-dehydrogenase genes in solid cancers as well as lymphomas and leukemias. I will discuss recent data from our laboratory suggesting that these genetic aberrations alter signaling in tumour cells is intimately involved in mediating metabolic adaptation and the Warburg Effect.

**NEW TRENDS IN
ANTICANCER DRUG
DEVELOPMENT**

# SESSION I

## New Targets-Pathways in Clinical Development (1)

*Chairperson:* **Manuel Hidalgo,**
CNIO,
Madrid, Spain

# Leveraging circulating DNA studies to identify mechanisms of resistance to CYP17A1 inhibition

**Gerhardt Attard,**
ICR,
London, UK

CYP17A1 inhibition with abiraterone is an effective treatment for castration-resistance prostate cancer (CRPC), with significant improvements in survival, radiological progression free survival, pain, skeletal related events and other secondary end-points. However, resistance invariably develops. Due to mineralocorticoid excess, abiraterone is administered with glucocorticoids. Next-generation sequencing of circulating plasma DNA from CRPC offers an opportunity to monitor tumor genomic aberrations over the course of the disease and detect emergent changes that associate with resistance. Clones harboring resistance-conferring AR mutations emerge in approximately 20% of patients treated with abiraterone and exogenous corticosteroids. These mutations are activated by ligands that persist in abiraterone-treated patients, including by prednisolone or dexamethasone at clinically relevant doses and by progesterones, and confer a survival advantage. Often sub-clones with alternative genomic aberrations, including AR amplification, are also present suggesting multiple mechanisms co-exist that lead to re-activation of AR signaling. These data introduce a management paradigm requiring sequential monitoring of advanced prostate cancer patients with plasma and tumor biopsies to ensure early discontinuation of agents when they become potential disease drivers and identify therapeutic targets that will allow selection of the next best treatment.

# PI3K/mTOR inhibitors

**Josep Tabernero,**
Vall d'Hebron Institute of Oncology (VHIO),
Barcelona, Spain

The phosphatidylinositol 3-kinase (PI3K) pathway has an important role in cell metabolism, growth, migration, survival and angiogenesis. Inappropriate phosphoinositide 3-kinase (PI3K) signaling is one of the most frequent occurrences in human cancer and is critical for tumor progression. Various genetic mutations and amplifications have been described affecting key components of this pathway, with implications for tumorigenesis and also for resistance to targeted agents.

The frequent activation of the PI3K/AKT/mTOR pathway in cancer, and its crucial role in cell growth and survival, has made it a much desired target for pharmacologic intervention. Still, preclinical research has significantly advanced our understanding of the PI3K pathway and its complex downstream signaling, interactions and crosstalk. Following the regulatory approval of the rapamycin analogs everolimus and temsirolimus, recent years have seen an explosion in the number of phosphatidylinositol 3-kinase (PI3K) pathway inhibitors under clinical investigation. These include ATP-competitive, dual inhibitors of class I PI3K and mTORC1/2; 'pan-PI3K' inhibitors, which inhibit all 4 isoforms of class I PI3K ($\alpha$, $\beta$, $\delta$, $\gamma$); isoform-specific inhibitors of the various PI3K isoforms; allosteric and catalytic inhibitors of AKT; and ATP-competitive inhibitors of mTOR only (and thus mTORC1 and mTORC2).

With so many agents in development, clinicians are currently faced with a complex pathway plus a wide array of clinical trials investigating a multitude of inhibitors with different mechanisms of action, being used both as single agents, and in combination with other therapies. This presentation will give an overview of the pathway and current therapeutic strategies, and we will discuss key unresolved translational questions related to the clinical development of inhibitors of the PI3K/AKT/mTOR pathway.

## Ras-Raf MEK Inhibitors

**Jordi Rodón,**
VHIO,
Barcelona, Spain

NEW TRENDS IN ANTICANCER DRUG DEVELOPMENT | SESSION I

# Overcoming resistance to targeted therapies

**Jeffrey Engelman,**
Massachusetts General Hospital Cancer Center,
Boston, USA

# Mechanistic basis of Palbociclib combinatorial activity in ER+ breast cancer and non-breast indications

**David J. Shields,**
Pfizer Inc.,
New York, USA

Jing Yuan, Camino Menendez, John Chionis, Pedro Lopez, Chaoting Liu, Nathan V. Lee, Enhong Chen, Goldie Lui, Ping Wei, Tao Xie, Paul A. Rejto, Valeria R. Fantin, Peter Olson, Todd VanArsdale, Manuel Hidalgo, David J. Shields

Interaction with the D-type cyclins activates cyclin-dependent kinases 4 and 6 (CDK4/6), which in turn, phosphorylate the retinoblastoma protein (Rb), a critical checkpoint for G1/S cell cycle progression and commitment to cellular proliferation. The majority of human malignancies subvert these control mechanisms through a range of genetic and biochemical adaptations. Accordingly, tumors that depend on CDK4/6 activity for proliferation and survival may be particularly sensitive to inhibition of this pathway. Palbociclib (IbranceTM) is an orally administered, highly selective inhibitor of cyclin D-CDK4/6 kinase activities. Addition of palbociclib to letrozole significantly improved progression-free survival in a randomized phase 2 study of women with advanced estrogen receptor (ER)-positive, HER2-negative breast cancer. A phase 3 trial is currently underway. In the pre-clinical setting, palbociclib and estrogen antagonists combine for greater anti-proliferative activity in Rb+ breast cancer cell lines, increased hallmarks of cellular senescence and prolonged durability of response following drug removal. Dual inhibition of CDK4/6 and ER signaling demonstrated robust anti-tumor activity in xenograft studies. Combination of Palbociclib with other targeted therapeutics elicits improved activity in pre-clinical models of several non-breast indications and these effects also manifest through modulation of cellular proliferation, senescence and growth arrest. Data will be presented on the molecular basis of the improved responses to Palbociclib and disparate combination partners in ER+ breast cancer and other indications.

**NEW TRENDS IN
ANTICANCER DRUG
DEVELOPMENT**

# SESSION II

## Innovative Approaches in Drug Development

*Chairperson:* **Eduardo Díaz-Rubio,**
San Carlos University Hospital,
Madrid, Spain

## Establishing dose, schedule and population(s): Novel trial approaches

**Jaap Verweij,**
Erasmus MC Cancer Institute,
Rotterdam, The Netherlands

Early clinical trials in oncology are shifting from a time were toxicology (maximal tolerable dose or MTD) was driving close selection, to an activity- and pharmacodynamics driven dose selection. At the same time, there is a need to shorten the development period and take Go-NoGo decisions. This means that our trial designs will have to be adapted.

The preclinical assessment will have to ensure functionality of the assumed molecular target. And clinical pharmacodynamics have to be as robust as possible, in order to be able to assess activity long before randomized studies confirm such activity, and enable us to select the appropiate target populations for our early studies. Clinical examples will be discussed, also showing that from a molecular perspective the toxicology driven dose selection paradigm is no longer applicable.

Since drug development is a global effort, those early studies will also need to take into account genetically determined racial differences in tolerance and germline polymorphism explaining efficacy difference.

Several recent studies have shown suggested that, rather than endlessly expanding the last cohort of a phase I study, a randomized dose-expansion cohort could provide much more essential information and could increase certainty of being on the right track.

Finally, particularly for oral drugs, an early assessment of human bioavailability as well as an early assessment of food-effect on this bioavailability is essential for appropiate dose determination.

Several options of intergrated designs assessing all of the above mentioned critical elements will be discussed, focussing on efforts to incorporate as many topics as possible in a kind of all-in-one phase I study.

# Precision medicine for cancer patients

**Alberto Bardelli,**
University of Turin - Candiolo Cancer Institute IRCCS,
Candiolo (TO), Italy

It is now evident that colorectal cancers (CRC) indistinguishable by light microscopy are molecularly distinct diseases requiring unique therapeutic approaches. Tissue and liquid biopsies can be used to define CRC molecular subtypes and to monitor clonal evolution during therapy.

Using these approaches, CRC patients were found to respond selectively to targeted agents interfering with oncogenic nodes of the EGFR signaling pathway. Notably, the patient-specific responses can be recapitulated and paralleled in cellular and mouse clinical proxies (CRC-avatars). The inevitable development of acquired resistance to inhibitors of the EGFR signaling pathway presently limits further clinical advances. Strategies to prevent or overcome resistance are therefore essential to design the next generation of molecularly-driven clinical trials for CRC patients.

NEW TRENDS IN ANTICANCER DRUG DEVELOPMENT | SESSION II

## Co-clinical trials: An essential tool for the development of future anti-cancer therapies

**Mariano Barbacid,**
Experimental Oncology Group, Molecular Oncology Programme, CNIO,
Madrid, Spain

The deciphering of human cancer genomes has revealed that most tumors have mutations that deregulate multiple signaling pathways, suggesting that effective therapies will require to concomitantly inhibiting multiple targets. Identification of such therapeutic targets will require not only a deeper understanding of cancer biology but also the implementation of suitable pre-clinical models that faithfully recapitulate human neoplasias. Genetic and pharmacological inhibition of suspected therapeutic targets by carrying out co-clinical trials in such models should guide the way to develop clinical trials that will eventually define effective anti-cancer therapies. Our laboratory is focused on the identification of therapeutic targets for K-*Ras* driven tumors, mainly lung adenocarcinoma and pancreatic ductal adenocarcinoma, two cancers with some of the worse prognosis. To this end, we have developed genetically engineered mouse (GEM) models that closely recapitulate their natural history. In previous studies, we have introduce in these GEM strains either germ line or lox-Cre conditional knock out alleles encoding each of the downstream kinases of the Ras pathway (Raf/Mek/Erk) as well as the cell cycle Cdks. These studies have led us to validate the c-Raf and Cdk4 kinases as essential targets for tumor development (Puyol et al., Cancer Cell 2010; Blasco et al., Cancer Cell 2011). More importantly, these findings have already led to the development of phase II clinical trials for Cdk4/6 inhibitors such as Palbociclib and Abemaciclib in K-RAS mutant lung tumors. Now, we have established new GEM models in which tumor development can be temporally separated from target ablation. In addition, we have generated conditional knock-in strains that direct the expression of kinase dead isoforms instead of inducing protein ablation. This new generation of GEM strains will allow us to carry out co-clinical trials that should help us to identify effective targeted therapies against these tumors.

NEW TRENDS IN ANTICANCER DRUG DEVELOPMENT | SESSION II

# Incorporating Novel Imaging Methods in Early Drug Development

**Elisabeth G. de Vries,**
University Medical Center Groningen,
Groningen, The Netherlands

Drug development decisions could benefit from quantitative biomarkers to visualize the drug tissue distribution, to confirm effective whole-body target expression, engagement and modulation, and to evaluate heterogeneity across lesions and patients. Increasingly cancer patients are treated based on tumor characteristics. Typically characteristics are analyzed in tumor tissue, which is often archival tissue and may not reflect heterogeneity among lesions and within lesions. Molecular radionuclide imaging with positron emission tomography (PET) can potentially provide interesting support for these issues.

Visualization of the estrogen receptor (ER) with $^{18}$F-fluoroestradiol (FES) is feasible in breast and ovarian cancer patients. Heterogeneity of ER-expression occurs as both FES-positive and -negative lesions are present in 15-47% of patients with an ER-positive primary tumor. We performed a feasibility study to assess ER availability before and during treatment with the ER downregulator fulvestrant. Fulvestrant reduced tumor FES uptake incompletely on day 28 in 6 (38%) of the 16 patients, which was associated with early progression.

The androgen receptor (AR) can be imaged with $^{18}$F-fluoro-5α-dihydrotestosterone (FDHT) in prostate cancer patients. FDHT-PET showed that the AR antagonist enzalutamide, substantially reduce FDHT binding (Scher H et al. Lancet 2010). The AR is increasingly considered of interest in breast cancer and a trial with FDHT-PET in breast cancer is ongoing.

The numerous available antibodies can be radioactively labelled for PET imaging, a process called immunoPET. In metastatic breast cancer patients with HER2 overexpressing tumors quantifiable $^{89}$Zr-trastuzumab-PET tracer uptake in tumor lesions was seen. HSP90 chaperones have key client proteins that are involved in all hallmarks of breast cancer growth and progression. We evaluated the feasibility of using $^{89}$Zr-trastuzumab PET to determine in vivo degradation of HER2 caused by the novel HSP90 inhibitor NVP-AUY922. SUVmax change in individual tumor lesions on baseline versus 3 weeks $^{89}$Zr-trastuzumab PET was heterogeneous and related to size change on CT after 8 weeks treatment. NVP-AUY922 therefore showed proof-of-concept clinical response in HER2-amplified metastatic breast cancer.

With $^{89}$Zr-bevacizumab-PET, we visualized tracer uptake in primary breast cancers, and metastatic neuroendocrine tumors and renal cell cancers and showed how bevacizumab treatment reduced uptake of antibodies.

With $^{89}$Zr-antibody PET imaging it is potentially possible to study the distribution of an antibody to predict uptake of an antibody-drug conjugate with the same antibody and to determine target saturation by a certain therapeutic antibody dose. Antibodies can also be labeled with a near infrared fluorescent tracer such as IRDye800CW-trastuzmab. This allows optical imaging with intraoperative, endoscopic and hand held systems and precise drug localisation during microscopy.

Thus, new molecular imaging can identify characteristics of a specific tumor across the entire body over time, can provide new mechanistic and pharmacological insights and can contribute to distinguish patients most likely to benefit from a specific treatment and is therefore of interest to be used during drug development.

SHORT
TALK

# Combined inhibition of Ddr1 and Notch signaling is an effective therapeutic strategy to treat K-Ras-driven/p53-null lung adenocarcinomas

**Chiara Ambrogio[1],** Gonzalo Gómez-López[2], Mattia Falcone[1], Sanguine Byun[3], Hyung-Gu Kim[3], Nicola Crosetto[4], Rafael B. Blasco[1], Montserrat Sánchez-Céspedes[5], Xiaomei Ren[6], Zhen Wang[6], Ke Ding[6], Manuel Serrano[7], Sam Lee[3], David Santamaría[1], and Mariano Barbacid[1]

[1]Experimental Oncology, Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, Spain
[2]Bioinformatics Unit, Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, Spain
[3]Massachusetts General Hospital and Harvard Medical School, Boston, USA
[4]Science for Life Laboratory, Karolinska Institute, Stockholm, Sweden
[5]Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Spain
[6]State Key Laboratory of Respiratory Diseases, Chinese Academy of Sciences, Guangzhou, China
[7]Tumour Suppression Group, Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, Spain

Introduction

K-RAS is the driver oncogene in 30% of lung adenocarcinomas. Unlike patients bearing other driver mutations such as those in the EGF or ALK receptors, there are no selective therapies available for these tumors. In an attempt to identify targets whose activity might be imperative for all stages of tumor progression, we focused on the identification of genes involved in the earliest stages of tumor development.

Results and Discussion

We found that K-RasG12V-driven hyperplastic lesions display two independent transcriptional profiles. Whereas one of them is related to that of normal lung cells, the other resembles the profile of advanced human tumors. This aggressive signature is characterized by increased expression of the tyrosine kinase receptor Ddr1. Genetic analysis using Ddr1 knock-out mice revealed that it plays a key role in tumor initiation and progression in a p53-proficient background. Pharmacological inhibition of Ddr1 mimicked these genetic results. Moreover, concomitant inhibition of Ddr1 and Notch signaling, a downstream mediator of Ddr1 activity, induced significant antitumor effects even in aggressive K-RasG12V/p53-null tumors. Compared with standard chemotherapy, this targeted treatment had better therapeutic efficacy and lower toxic side effects. HES1 and DDR1 display a strong tendency to co-expression in human K-RAS driven adenocarcinomas. Furthermore, preliminary data indicate that activating mutations in DDR1 mediate chemoresistance suggesting that its pharmacological inhibition may be therapeutically relevant.

Conclusions
• The aggressive profile of K-RasG12V lung adenocarcinoma is determined early during tumor initiation.
• The Ddr1 tyrosine protein kinase receptor is required for tumor development.
• Combined pharmacological inhibition of Ddr1 and Notch signaling hampers the growth of K-RasG12V/p53-null lung adenocarcinomas and is more effective than standard chemotherapy.

# Controlled release microspheres loaded with BMP7 suppress primary tumors from human glioblastoma

SHORT
TALK

**González-Gómez Pilar[1],** Zahonero C[1], Crecente-Campo J[2], De la Fuente M[3], Hernández Laín A[4], Sánchez-Gómez P[1]*, Garcia-Fuentes M[2]*, Mira H[1]*.

[1]UFIEC, Instituto de Salud Carlos III, Majadahonda, Madrid, Spain.
[2]Center for Research in Molecular Medicine and Chronic Diseases (CIMUS),
Dep. Pharmacy and Pharmaceutical Technology, and Health Research Institute (IDIS),
Universidad de Santiago de Compostela, Santiago de Compostela, A Coruña, Spain.
[3]Nano-oncologicals Laboratory, Translational Medical Oncology,
Clinical University Hospital and Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, Spain
[4]Unidad Multidisciplinar de Neurooncología. Hospital Universitario 12 de Octubre, Madrid, Spain.

Tumor initiating cells (TICs) are believed to be the main drivers of glioblastoma (GBM) recurrence. Any potential treatment able to induce differentiation of GBM-TICs to a more benign phenotype or to a cell type more amenable to standard therapies is nowadays of great interest. Bone morphogenetic proteins (BMPs) are potent inducers of GBM-TIC differentiation that have been proposed as non-cytotoxic therapeutic compounds that may be of use in preventing the growth and recurrence of GBM. Our results show that BMP7 can stop the proliferation and block the self-renewal capacity of primary GBM-TIC cell lines that express the BMPR1B receptor. In order to further detail and characterize the mechanism of action and the in vivo therapeutic potential of this molecule, we have encapsulated BMP7 in poly (lactic-co-glycolic acid) microspheres in the form of a complex with heparin and Tetronic, a formulation that provides effective and controlled release for several weeks. Data from xenografts confirmed that tumor growth is markedly delayed in tumors treated with BMP7-loaded microspheres, which correlates with the activation of the BMP canonical pathway. Importantly, tumors treated with BMP7-loaded microspheres also showed downregulation of several markers related to the malignant stem cell-like phenotype: CD133+, Olig2 and GFAPδ, enhanced expression of cell cycle inhibitors and reduced expression of the proliferation marker PCNA. In summary, in this work we have validated the therapeutic potential of BMP7-loaded controlled release microspheres as a specific treatment against GBM-TICs. We envisage that this kind of selective therapy for tumor initiating cells could have a synergistic effect in combination with conventional cytoreductive therapy (chemo-, radiotherapy) or with immunotherapy.

NEW TRENDS IN ANTICANCER DRUG DEVELOPMENT | SHORT TALK

SHORT
TALK

# Upregulation of MAPK negative feedback regulators and RET in mutant ALK neuroblastoma: implications for targeted treatment

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Purpose: Activating ALK mutations are present in nearly 10% of primary neuroblastomas and mark patients for treatment with ALK inhibitors. However, recent studies have shown that multiple mechanisms drive resistance to molecular therapies targeting receptor tyrosine kinases. We anticipated that detailed mapping of the oncogenic ALK-driven signaling in neuroblastoma can aid to identify potential fragile nodes as additional targets for combination therapies.

Experimental design: To achieve this goal, transcriptome profiling was performed in neuroblastoma cell lines with the ALKF1174L or ALKR1275Q hotspot mutations, ALK amplification or wild-type ALK following pharmacological inhibition of ALK using four different compounds. Next, we performed cross-species genomic analyses to identify commonly transcriptionally perturbed genes in MYCN/ALKF1174L double transgenic versus MYCN transgenic mouse tumors as compared to the mutant ALKdriven transcriptome in human neuroblastomas.

Results: A 77-gene ALK signature was established and successfully validated in primary neuroblastoma samples, in a neuroblastoma cell line with ALKF1174L and ALKR1275Q regulable overexpression constructs and in other ALKomas. In addition to the previously established PI3K/AKT/mTOR, MAPK/ERK and MYC/MYCN signaling branches, we identified that mutant ALK drives a strong upregulation of MAPK negative feedback regulators, RET and RET-driven sympathetic neuronal markers of the cholinergic lineage.

Conclusions: We provide important novel insights into the transcriptional consequences and the complexity of mutant ALK signaling in this aggressive pediatric tumor. The negative feedback loop of MAPK pathway inhibitors may impact on novel ALK inhibition therapies while mutant ALK induced RET signaling can offer novel opportunities for testing ALK-RET oriented molecular combination therapies.

**NEW TRENDS IN
ANTICANCER DRUG
DEVELOPMENT**

# SESSION III

## New Targets-Pathways in Clinical Development (2)

*Chairperson:* **David Olmos,**
CNIO,
Madrid, Spain

# Targeting DNA Damage Repair Pathways

**Hilary Calvert,**
University College London (UCL),
London, UK

Many established anticancer drugs act by damaging DNA and active DNA repair pathways have been shown to be responsible for resistance to some of these agents. The development of DNA repair inhibitors was originally undertaken in order to potentiate these drugs and overcome resistance. So far the success of this approach has been limited because the bone marrow toxicity of the cytotoxic drug is also potentiated by the DNA repair inhibitor. Inhibitors of poly(ADP-ribose)polymerase (PARP) were originally developed with the idea that they could be used to potentiate monomethylating agents and topoisomerase I inhibitors and trials to assess their role in combination with chemotherapy are ongoing. However the elucidation of the role of mutations in the BRCA1 and BRCA2 genes in the 1990s and the observation that PARP inhibitors were highly active against cells without BRCA function led to the discovery of a synthetic lethal interaction. Cancer cells arising in BRCA carriers lack the ability to perform a type of double strand break repair (homologous recombination repair, HR). The PARP inhibitor blocks single strand break repair, on which the cancer cells are dependent, and is therefore selectively toxic to the tumour. The first PARP inhibitor to be licensed is olaparib which is approved for patients with BRCA related ovarian cancer. In addition to tumours that have a genetic loss HR, PARP inhibitors are also active against tumours with an acquired loss thus greatly increasing the number of patients who may benefit from treatment. There are also a number of other potentially exploitable synthetic lethal combinations in the DNA repair pathways that would require inhibitors of other DNA repair enzymes such as ATM and DNA-PK. Drugs are under development to act on these.

NEW TRENDS IN ANTICANCER DRUG DEVELOPMENT | SESSION III

## Antibody-Drug Conjugates:
## A new wave of targeted cancer drugs

**Ingrid Sassoon,**
Sanofi Oncology,
Paris, France

Biological therapies play an increasing role in cancer treatment, although the number of naked antibodies showing clinical efficacy as single agent remains limited. One way to enhance therapeutic potential of antibodies is to conjugate them to small molecule drugs. This combination is expected to bring together the benefits of highly potent drugs on the one hand and selective binders of specific tumor antigens on the other hand. However, designing an ADC is more complex than a simple meccano game, requiring thoughtful combination of cytotoxic, linker, and drugs in the context of a target and a defined cancer indication. Results and lessons learned from the first generation antibody-drug conjugate (ADC) will be presented together with current/future improvements of the technology.

NEW TRENDS IN ANTICANCER DRUG DEVELOPMENT | SESSION III

# Targeting Sheltering in Cancer

**Maria A. Blasco,**
CNIO Director, Telomeres and Telomerase Group, Molecular Oncology Programme CNIO,
Madrid, Spain

María García-Beccaria[1,*], Paula Martínez[1,*], Marinela Méndez-Pertuz[1,*], Sonia Martínez[2], Carmen Blanco-Aparicio[2], Marta Cañamero[3], Francisca Mulero[4], Chiara Ambrogio[5],
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Telomeres are considered anti-cancer targets, as telomere maintenance above a minimum length is necessary for cancer growth. Telomerase abrogation in cancer-prone mouse models, however, only decreased tumor growth after several mouse generations when telomeres reach a critically short length, and this effect was lost upon p53 mutation. Here, address whether induction of telomere uncapping by inhibition of the Trf1 shelterin protein can effectively block cancer growth independently of telomere length. We show that genetic Trf1 ablation impairs the growth of p53-null K-RasG12V-induced lung carcinomas and increases mouse survival independently of telomere length. This is accompanied by induction of telomeric DNA damage, apoptosis, decreased proliferation, and G2-arrest. Downregulation of Trf1 in established p53-deficient K-RasG12V lung cell lines also impairs tumor growth and metastasis in xenograft models. Importantly, long-term whole-body Trf1 deletion in adult mice did not impact on mouse survival and viability. Moreover, inhibition of TRF1 binding to telomeres by small molecules blocks the growth of already established lung carcinomas without affecting mouse survival or tissue function. Thus, induction of acute telomere uncapping emerges as a potential new therapeutic target for lung cancer.

# Targeting the Epigenome

**Manel Esteller,**
IDIBELL,
Barcelona, Spain

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, with an emphasys in neoplasia, but without forgetting the novel advances in other human disorders. For cancer, 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.

NEW TRENDS IN ANTICANCER DRUG DEVELOPMENT | SESSION III

# Stromal Disrupting Strategies

**Sunil R Hingorani**,
Fred Hutchinson Cancer Research Center,
Seattle, USA

Pancreatic ductal adenocarcinoma co-opts multiple cellular and extracellular mechanisms to create a complex cancer organ with an unusual proclivity for metastasis and resistance to therapy. Cell-autonomous events are essential for the initiation and maintenance of pancreatic ductal adenocarcinoma, but recent studies have implicated critical non-cell autonomous processes within the robust desmoplastic stroma that promote disease pathogenesis and resistance. Thus, non-malignant cells and associated factors are culprits in tumor growth, immunosuppression, and invasion. However, even this increasing awareness of non-cell autonomous contributions to disease progression is tempered by the conflicting roles stromal elements can play. A greater understanding of stromal complexity and complicity has been aided in part by studies in highly faithful genetically engineered mouse models of pancreatic ductal adenocarcinoma. Insights gleaned from such studies are spurring the development of therapies designed to re-engineer the pancreas cancer stroma and render it permissive to agents targeting cell-autonomous events or to reinstate immunosurveillance. Integrating conventional and immunological treatments in the context of stromal targeting may provide the key to a durable clinical impact on this formidable disease.

# Developmental and Cancer Stem Cell Pathway Inhibitors

**Timothy Hoey,**
OncoMed Pharmaceuticals,
Redwood City, USA

Cancer stem cells (or tumor initiating cells) mediate tumor progression, metastasis, and recurrence after therapy. Using our platform of patient-derived xenografts, comprised of approximately 200 tumors, we have developed first-in-class biologic agents that block key CSC pathways including Notch, Wnt and RSPO-LGR. We have developed six therapeutics currently in clinical testing - anti-DLL4 (demcizumab), anti-Notch2/3 (tarextumab), anti-Notch1, anti-FZD (vantictumab), and Fzd8-Fc (ipacfricept) and anti-DLL4/VEGF. In addition, we have developed a new therapeutic agent, anti-Rspo3. These agents inhibit tumor growth through multiple mechanisms including a reduction of CSC frequency. The presentation will focus on the activity of anti-Rpso3 in colon, lung and ovarian cancers. We have found that anti-Rpso3 reduces tumor growth as a single agent and in combination with chemotherapeutic agents. Anti-Rspo3 treatment inhibits expression of stem cell markers and reduces tumorigenicity in serial transplantation studies. We have observed a strong correlation between Rpso3 expression and sensitivity to treatment, enabling a biomarker-focused strategy for patient selection and clinical development. Anti-Rspo3 (OMP-131R10) will enter clinical testing in 2015.

NEW TRENDS IN ANTICANCER DRUG DEVELOPMENT | **NOTES**

**NEW TRENDS IN
ANTICANCER DRUG
DEVELOPMENT**

# SESSION IV

## Immunotherapy Approaches for Cancer Treatment

*Chairperson:* **Jesús García-Donas,**
Sanchinarro University Hospital,
Madrid, Spain

## Check-point Inhibitors and Vaccine Combinations

**Mario Sznol,**
Yale University,
New Heaven, USA

NEW TRENDS IN ANTICANCER DRUG DEVELOPMENT | SESSION IV

# From mechanisms to combinations in novel cancer immunotherapies

**Ignacio Melero**,
CIMA and University Clinic, University of Navarra,
Pamplona, Spain

CD137 (4-1BB) is a surface molecule that belongs to the TNFR family. It was originally identified as T-cell activation antigen but has been found over time on a variety of leukocyte types (NK cells, B cells, myeloid precursors, mast cells, dendritic cells) and on tumor endothelial cells. When ligated by its only cognate ligand (CD137L) or by agonist monoclonal antibodies it conveys activatory signals that are considered costimulation as they prevent apoptosis, enhance effector function and promote cell proliferation. Administration of agonist anti-CD137 mAb to mice bearing induces tumor rejections in a number of models. In animal continuously dosed periportal liver infiltrates of overactivated CD8 T cells cause a mild form of hepatitis and TNF-mediated alterations of hematopoiesis take place. Two human monoclonal antibodies are undergoing clinical trials with signs of antitumor effects in monotherapy and evidence for dose-dependent liver inflammation in a about 1/10 of patients.

The response to hypoxia as mediated by HIF1α is a driving factor for CD137 expression. Accordingly hypoxic endothelial cells in tumors become CD137 and tumor infiltrating lymphocytes express CD137 at bright levels. Upon treatment with anti-CD137 mAb the endothelium up-regulates adhesion molecules that promote T cell traffic to the tumor and activates TILs. More recently we have found that hypoxia also up-regulates CD137 expression on T cells and tumor cells. The predominant CD137 iso form expressed by cancer cells is soluble and able to block CD137l in neighbouring cells contributing as a tumor immune escape mechanism.

Upon ligation of CD137 at the lymphocyte surface TRAF2 and TRAF1 mediates signalling. Interestingly, the crosslinked CD137-mAb complex is internalized towards an endosomal compartment were the K63-ubiliquin ligase activity of TRAF2 is operational. Our data indicates that self K63-polyubiquitination of TRAF2 and other targets is an early signal event that leads to the activation of NF-kB and MAPK. Deubiquitinases regulate these early signaling events.

Anti-CD137 mAb treatment synergizes with adoptive T cell therapy and with antibodies eliciting NK-mediated anti-tumor ADCC. For adoptive therapy a clear contribution is exerted by endogenous CD8 T cells capable of expressing CD137. In our hands also potently synergizes with intratumoral injections of a semliki forest viral vector encoding IL-12.

In a spontaneous transgenic hepatocellular carcinoma mouse model driven by c-myc in which tumor cells coexpress ovalbuminin CD137 monotherapy was ineffective. However, its combination with anti-PD-L1+anti-OX40 mAbs extended survival and reached curative efficacy if adoptive transfer of anti-OVA T cells was added to the combination. None of the treatments as monotherapy impacted this difficult-to-treat model.

Many lines of evidence from various laboratories around the world indicate that CD137 immune stimulation is a powerful partner for combinatorial immunotherapy.

NEW TRENDS IN ANTICANCER DRUG DEVELOPMENT | SESSION IV

## Targeting oncogene-induced replication stress for cancer therapy

**Oscar Fernández-Capetillo,**
Genomic Instability Group, Spanish National Cancer Research Centre (CNIO),
Madrid, Spain

Our laboratory has focused much of its research in trying to understand how cells respond to "replicative stress" (RS), a type of DNA damage which arises unavoidably every time that a cell replicates its DNA, and which is mainly prevented by a RS-Response (RSR) coordinated by ATR and Chk1 kinases. Given that certain oncogenes can generate substantial amounts of RS, we hypothesized that cells carrying these oncogenes might be "addicted" to a proficient RSR. To explore these ideas, we have generated several cellular, animal and chemical tools for the study of ATR function in mammals. These incluce (1) a cell system in which ATR can be selectively activated at will[1]; (2) mice with a reduced[2] or increased[3] RSR, and (3) chemical inhibitors of ATR (developed together with the Experimental Therapeutics Programme at CNIO)[4]. Our early works suggested that ATR inhibitors would indeed be particularly deleterious for tumors with high levels of RS, such as Myc-induced lymphomas[5]. ATR inhibitors were further developed to improve their pharmacological properties. We now have compounds that are orally available and with good ADMET and PK/PD properties, and have identified tumors that preferentially benefit from these compounds. Our ideas and new results in this area will be presented.

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## Agonistic CD40 Antibodies and Immune Therapy

**Ann L. White**,
University of Southampton,
Southampton, UK

Recent clinical data have revealed the potential for cancer eradication by immune modulation, with monoclonal antibodies (mAb) designed to block inhibitory signals and stimulate immunity delivering durable responses. Agents that stimulate immunity by agonistic engagement of immune co-stimulatory receptors such as CD40 are also showing clinical promise, but have lagged behind the check-point blockers largely due to a lack of mechanistic understanding. In this talk I will review recent data examining the role of mAb isotype and Fcγ receptor interaction in dictating immunostimulatory and therapeutic activity of anti-CD40 mAb and discuss ways to optimise immunostimulatory agents through mAb engineering.

SHORT
TALK

# The HBP1 tumor suppressor at multiple regulatory cross roads in neuroblastoma

**Shana Claeys[1],** Irina Lambertz[1], Alan Van Goethem[1], Anneleen Beckers[1],
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Neuroblastoma (NB) is a devastating childhood tumor of the peripheral nervous system. Poor survival rates warrant development of more efficient and less toxic treatment. In search for opportunities for combination molecular therapy in ALK mutated NB, we established a 77-gene signature that recapitulates the transcriptional response upon ALK inhibition. Functional annotation analysis revealed predominantly MAPK/ERK, PI3K/AKT/mTOR, MYC/MYCN and neuronal differentiation signaling components. Amongst these, we identified HBP1, a transcriptional repressor and tumor suppressor gene. Based on a study describing HBP1 as a target of the PI3K/FOXO pathway and our observation of PI3K/AKT activation by ALK, we established an ALK-PI3K/AKT-FOXO3-HBP1 regulatory pathway in NB. In keeping with this, treatment with BEZ-235, an AKT/mTOR inhibitor, leads to loss of AKT and FOXO3 phosphorylation and subsequent HBP1 upregulation. Interestingly, we also found a functional connection between MYCN and HBP1 activity. Using MYCN and miR-17-92 inducible NB cell line models, we show that MYCN upregulated miR-17-92 targets the 3' HBP1 UTR leading to dampening of HBP1 mRNA levels. Low HBP1 levels were marked by poor survival and HBP1 and MYCN mRNA levels showed strong inverse correlation. Given this interconnection, we hypothesized that combination treatment directly targeting both proteins could offer novel opportunities for chemotherapy resistant tumors and/or boost single compound treatment targeting MYCN in MYCN amplified tumors. To test this, we analysed effects on mouse xenografts with EGCG (epigallocatechin gallate) as tool compound for upregulating HBP1 levels in combination with the BRD4 inhibitor JQ1, effective for MYCN-amplified NB. Tumor growth was significantly delayed in the combination-treated group. In conclusion, we identified HBP1 as a novel potent drugable target in MYCN amplified and ALK mutant NB. Further in vivo testing and phase I clinical trials is ongoing.

# Characterization of the tumor suppressor function of the lysine-specific methyltransferase KMT2D in follicular lymphoma

SHORT
TALK

**Ana Ortega-Molina**[1*], Isaac Boss[2,3*], Andres Canela[4], Heng Pan[2,3], Yanwen Jiang[2,3], Xin Gao[5], Deqing Hu[5], Hua-Tang Chen[4], Kai Ge[6], Ji-Eun Lee[6], Chunying Zhao[1], Rita Shaknovich[2], Ali Shilatifard[5], Andre Nussenzweig[4], Ari M. Melnick[2,3**], Hans-Guido Wendel[1**]

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*Equal contribution

Follicular lymphoma (FL) is a common and incurable form indolent B-cell lymphoma. Genomic studies have now catalogued many recurrent mutations in FL. Epigenetic regulators have emerged as the most common targets of somatic point mutations. For example, the histone methyltransferase KMT2D (MLL4/MLL2) is the most frequently mutated gene in FL with reported mutational frequencies of up to 84%. However, the transcriptional and biological consequences of KMT2D loss of function are currently unknown. Using a well-described murine model of FL, we showed that deficiency of KMT2D promotes the initiation of indolent FL in vivo. To explore the mechanism of KMT2D-mediated tumor suppression we used cross species comparisons of gene expression, histone H3K4 methylation marks and KMT2D genomic occupancy. These analyses converge on a relatively small group of conserved target genes. Strikingly, they include bona fide tumor suppressors and regulators of B-cell proliferation (e.g. TNFAIP3/A20, SOCS3, ARID1A, and TNFRSF14). Our results indicate that KMT2D restrains FL development through simultaneous effects on multiple key regulators of B-cell behavior.

NEW TRENDS IN ANTICANCER DRUG DEVELOPMENT | **SHORT TALK**

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*Madrid* 22-25 March 2015

## NEW TRENDS IN ANTICANCER DRUG DEVELOPMENT

# SESSION V

## Personalizing Cancer Treatment

*Chairperson:* **Fatima Al-Shahrour,**
CNIO,
Madrid, Spain

# Novel Applications of Cancer Genomics to Personalized Medicine

**Luis Diaz,**
Johns Hopkins University, Baltimore, USA

NEW TRENDS IN ANTICANCER DRUG DEVELOPMENT | SESSION V

## Designing Clinical Trials for Personalized Medicine

**Lillian L. Siu,**
Princess Margaret Cancer Centre,
Toronto, Canada

In the cancer genomics era, it seems likely that evaluating drug efficacy against tumors defined by a combination of histopathology and molecular genetic profiles will result in a greater therapeutic gain. Given that the definition of molecular subsets will stratify tumor types into smaller subgroups, and that the same or related genomic aberrations can exist in multiple tumor types, innovation and transformation in clinical trial designs are necessary to help address this paradigm shift in cancer treatment decisions. Current clinical trial designs are focused largely on tumor genotype variations between patients that predict for response to targeted treatments (interpatient heterogeneity). Clinical trial frameworks focusing on interpatient heterogeneity include histology-based trials to evaluate therapeutic targeting of different molecular aberrations harbored by patients with a single tumor type ("umbrella trials"); as well as those that are histology-agnostic, aberration-specific to encompass the assessment of the same or similar molecular changes across different tumor types ("basket trials"). N-of-one clinical trial designs have also emerged as possible ways to assess individual genotype-targeted agent matchings. Subpopulations of cancer cells with unique genomes in the same patient (intratumor heterogeneity) may exist across different geographic locations of a tumor (geographic or spatial heterogeneity) or evolve over time (clonal evolution). There are challenges to the development of predictive biomarkers in the context of intratumor heterogeneity as it is often impractical to sample multiple regions within a single tumor, multiple tumor lesions concurrently or over time. The application of circulating technologies (e.g. circulating DNA) may help assess the overall genomic landscape and enable dynamic monitoring, but these have yet to be validated in the clinical setting. The ability to detect and interrogate intratumor heterogeneity may ultimately impact on the eradication of resistant clones that are existent from the onset of malignancy or become dominate due to selective pressures over time. In this presentation, the benefits and challenges of genomics-based clinical trials are discussed, including a forecast into the next generation precision medicine-based clinical research.

# Worldwide Initiatives in Personalized Medicine

**Christophe Le Tourneau,**
Curie Institute,
Paris, France

Despite molecularly targeted agents modulate a specific deregulated pathway in the tumor or its microenvironment, these drugs have followed the same clinical development than cytotoxic agents and have been developed in selected tumor types and histologies. Now, some molecular alterations have been described across different tumor types, although with variable prevalence and functional impact. The latter raises the question of whether treatment decision should be mainly based on molecular biology, independently of tumor location and histology. This approach refers to what is commonly named personalized medicine and can today be addressed in clinical trials, since major advances in high throughput technologies allow depicting most druggable molecular alterations for an affordable cost in a timeframe that is compatible with clinical practice. Several studies have been initiated that aim at personalizing medicine in oncology. They include molecular screening programs, as well as personalized medicine trials that can be divided in two categories: 1) stratified clinical trials according to either molecular alterations or tumor types, and 2) algorithm-testing trials evaluating a treatment algorithm instead of drugs efficacy. Multiple challenges are associated with personalized medicine trials, but the main one remains our ability to predict drug efficacy based on molecular alterations. It is expected that taking into account several molecular alterations for the prediction of drug efficacy using systems biology approaches will improve patients' outcome. Bioinformatics research will be an important factor of future progression in this emerging field.

# Integrating PDX Models in Personalized Medicine Strategies

**Manuel Hidalgo,**
Clinical Research Programme, CNIO,
Madrid, Spain

Pancreatic cancer remains one of the most deadly cancers. Over the last few years, the genomic landscape of pancreatic cancer as well as precursor pancreatic cancer lesions have been deciphered in great depth. These studies show that PDA develops as the consequence of accumulation of mutations in key oncogenes and tumour suppressor genes. The disease, once established, is characterized by high complexity, heterogeneity and genomic instability. Despite this facts, some patients harbour actionable mutations which targeting has resulted in significant clinical benefit. Indeed, one of the most active areas of research in PDA is the development of strategies and approaches to personalize the treatment of patients. This is a complex field that can be tackle from many complementary angles. Our group has been interested in using patient derive xenogaft (PDX) models, aka Avatar mouse models, to guide cancer treatment. A piece of freshly collected tumour is implanted in immunodeficient mouse models, expanded, treated with different anticancer agents alone and in combination to select the most effective drug/regimen to treat the patient cancer. Our data show that the approach is highly predicted but, because of complexity and cost issues, not widely applicable to clinical practice at the present stage. To solve some of these limitations we are working on different aspects. One area is technological development to increase the take rate of tumours and to speed time to engraftment and expansion time. Currently, these figures are approximately 60-80 % and 5-7 months. Studies are in progress to optimize this aspect. Another key question is the selection of agents, both alone and in combination, to be tested in the model. In this regard, it is important to integrate biomarker assessment in the tumour to pre-select a series of treatment candidates that can then be tested in the PDX models. To this end, we have now integrated next generation sequencing and assessment of copy number variation in patient's tumour. These studies provide us with an unbiased overview of the tumour genomic landscape. From this data, using different bioinformatics and biological methods we extract the most relevant drug targets that are then bench tested against the patient Avatar mouse model to select the most effective treatment.

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**NEW TRENDS IN
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# SPEAKERS' BIOGRAPHIES

## Gerhardt Attard

Cancer Research UK (CRUK) Clinician Scientist and Consultant Medical Oncologist
The Institute Of Cancer Research and Royal Marsden NHS Foundation Trust, London, UK

Dr Attard graduated with a degree in Medicine from the University of Malta in 1999 and obtained a PhD in Medicine from the University of London in 2010. He was awarded a CRUK clinician scientist fellowship in 2012 and appointed to an honorary consultant position at the Royal Marsden in April 2013. His main research interest is the development of novel biomarker driven strategies for castration resistant prostate cancer. He is an author on more than 90 peer-reviewed manuscripts and has published several important papers on advanced prostate cancer. Dr Attard sits on a number of advisory boards and the editorial board of Annals of Oncology.

## Mariano Barbacid

Molecular Oncology Programme, Spanish Cancer Research Centre (CNIO), Madrid, Spain

Mariano Barbacid (Madrid, 1949) got his Ph.D. degree in Biochemistry from the University of Madrid in 1974 and trained as a postdoctoral at the National Cancer Institute in Bethesda, Maryland. From 1988 to 1998, Dr. Barbacid was Vice President, Oncology Drug Discovery at the Bristol Myers-Squibb Pharmaceutical Research Institute. In 1998, he returned to his native Madrid to create and direct the Spanish National Cancer Research Centre (CNIO). In June 2011 he stepped down as Director to concentrate on his own research.

In 2012, he was inducted to the National Academy of Sciences of the USA as a Foreign Member and in 2014 was elected Fellow of the AACR Academy. He has received several international awards and Honorary Doctoral Degrees

To date, Dr. Barbacid has authored 287 publications including over 230 original research articles and invited reviews in journals with impact factor. According to Google Scholar and Web of Science his publications have been cited more than 45,000 times. Currently, Dr. Barbacid's Hirsch "h" factor is 101.

## Alberto Bardelli

University of Torino, Dept. of Oncology
Director of the Laboratory of Molecular Oncology at the
Candiolo Cancer Institute-IRCCS,
Candiolo, Italy.

Associate Professor at University of Torino, Dept. of Oncology and Director of the Laboratory of Molecular Oncology at the Candiolo Cancer Institute-IRCCS, Candiolo - Italy.

Prof. Bardelli received a PhD in Biochemistry and Molecular Biology at UCL (London) in 1996. As a post doc at the Howard Hughes Medical Institute at the Johns Hopkins University (USA), in the group led by Bert Vogelstein, he has developed the first comprehensive mutational profile of kinases in CRCs.

Recently, Prof. Bardelli's work has defined mechanisms of acquired resistance to anti EGFR therapies in CRC patients thus providing insights into new therapies aimed at overcoming resistance. These studies involve an innovative methodology - named liquid biopsy - which allows the use of circulating tumor DNA to monitor patient's response using a blood draw.

In 2014 he has been listed in the Thomson Reuters List of Highly Cited Researchers (http://highlycited.com/). His H factor is 58.

## María A. Blasco

Director of the CNIO,
Telomeres and Telomerase Group, Molecular Oncology Programme,
Madrid, Spain

Maria A. Blasco obtained her PhD in 1993 at the *Centro de Biología Molecular "Severo Ochoa"* under the supervision of M. Salas. That same year, Blasco joined the Cold Spring Harbor Laboratory in New York (USA) as a Postdoctoral Fellow under the leadership of C. W. Greider.

In 1997 she returned to Spain to start her own research Group at the *Centro Nacional de Biotecnología* in Madrid. She joined the CNIO in 2003 as Director of the Molecular Oncology Programme and Leader of the Telomeres and Telomerase Group. In 2005 she was also appointed Vice-Director of Basic Research. Since June 2011, she is the CNIO Director.

Her research has focussed in demonstrating the importance of telomeres and telomerase in cancer as well as age-related diseases.

Blasco has received the following awards: Josef Steiner Cancer Research, *Rey Jaime I*, Körber European Science, *Fundación Lilly Preclinical Research*, as well as the *Santiago Ramón y Cajal* Research Award in Biology in 2010. Blasco has also been awarded the EMBO Gold Medal and has served on its Council since 2008. In 2014 received a *Doctorate* Honoris Causa from the Universidad Carlos III of Madrid, Spain.

## Hilary Calvert

Cancer Institute, University College London (UCL),
London, UK

Hilary Calvert is a Medical Oncologist who has spent much of his career researching new anticancer drugs. Initially he undertook the clinical development of carboplatin and also of folate-based inhibitors of thymidylate synthase. While working in the University of Newcastle he led the team that developed the first-in-class PARP inhibitor, rucaparib, in collaboration with Agouron Pharmaceuticals. He is currently Emeritus Professor of Cancer Therapeutics in the UCL Cancer Institute, University College, London.

## Luis Diaz

Johns Hopkins Kimmel Cancer Center,
Baltimore, USA

Dr. Luis Diaz is a leading authority in oncology, having pioneered several genomic diagnostic and therapeutic approaches for cancer. He is an attending physician at the Johns Hopkins Hospital where he specializes in the treatment of advanced pancreatic and colorectal cancers. He is a member of the Ludwig Center for Cancer Genetics and Therapeutics where he directs translational medicine and is the Director of the Swim Across America Lab. Dr. Diaz has undergraduate and medical degrees from the University of Michigan, and completed residency training at the Osler Medical Service at Johns Hopkins and medical oncology training at the Sidney Kimmel Cancer Center at Johns Hopkins.

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## Jeffrey A. Engelman

Massachusetts General Hospital Cancer Center,
Boston, USA

**Manel Esteller**

IDIBELL,
Barcelona, Spain

Manel Esteller (Sant Boi de Llobregat, Barcelona, Catalonia, Spain, 1968) graduated in Medicine from the Universidad de Barcelona in 1992, where he also obtained his Ph.D. degree specialising in molecular genetics of endometrial carcinoma, in 1996. He was an Invited Researcher at the School of Biological and Medical Sciences at the University of St. Andrews, (Scotland, UK) during which time his research interests focused on the molecular genetics of inherited breast cancer. From 1997 to 2001, 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, where his principal area of research were the alterations in DNA methylation, histone modifications and chromatin in human cancer. 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 and reviewer for many journals and funding agencies. Dr Esteller is also Associate Editor for Cancer Research, The Lancet Oncology, Carcinogenesis and The Journal of The National Cancer Institute, Editor-in-Chief of Epigenetics and President of the Epigenetics Society. His work has received, among other, the Best Young Cancer Researcher Award by the European School of Medical Oncology (1999), First Prize in Basic Research at the Johns Hopkins University and Medical Institution (1999), Best Young Investigator Award from the European Association for Cancer Research (2000), Carcinogenesis Award (2005), Beckman-Coulter Award (2006), Fondazione Piemontese per la Ricerca sul Cancro (FPRC) Award (2006), Swiss Bridge Award (2006), Innovation Award from the Commonwealth of Massachussets (2007), Human Frontier Science Program Award (2007), DEbiopharm-EPFL Award (2009), Dr. Josef Steiner Cancer Research Award (2009), Lilly Foundation Preclinical Biomedical Research Award (2009), World Health Summit Award (2010), National Award in Genetics (2011), the European Research Council Advanced Grant (2011), Dexeus International Award in Women Health (2012), "Rey Jaime I" Research Award (2013), Severo Ochoa Award in Biomedicine (2014) and National Award in Oncology Fundacion Echevarne (2014).

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## Oscar Fernández-Capetillo

Genomic Instability Group, Spanish National Cancer Research Centre, CNIO, Madrid, Spain

Oscar Fernandez-Capetillo (Bilbao, 1974) received his PhD in Biochemistry at the Univ of The Basque Country, working with E2F factors. He next did his postdoctoral research in the laboratory of Andre Nussenzweig at the NCI, working on the role of histone H2AX phosphorylation on DNA repair. Since 2005, he is a group leader at the CNIO, where he has focused on the study of replicative stress and ATR-CHK1 signaling. The group has developed chemical inhibitors of ATR and investigated their potential for cancer therapy. Oscar has been recently selected as one of the 40-under-40 investigators by the journal Cell.

### Elisabeth G. de Vries

University Medical Center,
Groningen, The Netherlands

Prof. Dr. E.G. Elisabeth de Vries, MD, PhD is Professor of Medical Oncology, and head of the Department of Medical Oncology at the University Medical Center Groningen, Groningen, the Netherlands. She is involved in patient care, teaching, and research. Her research is aiming at increasing the sensitivity of tumors to anticancer drugs, and she uses imaging techniques to support this.

Apart from laboratory studies, she performs and coordinates clinical trials. She has received numerous grants, including grants from the Dutch Cancer Society, EU, and is PI of CTMM (Center for Translational and Molecular Medicine) grant MAMMOTH, of ERC advanced grant OnQview. She is currently chairperson of the committee for the new RECIST 2.0 version on behalf of the EORTC.

She is a member of the Royal Academy of Arts and Sciences (KNAW) and fellow of the European Academy of Cancer Sciences. She received the European Society of Medical Oncology (ESMO) and was awarded a Royal Netherlands Academy of Sciences professorship.

## Manuel Hidalgo

Vicedirector of Translational Research
Clinical Research Programme Director
Head of Gastrointestinal Cancer Clinical Research Unit
Spanish National Cancer Research Centre (CNIO),
Madrid, Spain

Centro Integral Oncologico Clara Campal (CIOCC)
Director

University CEU San Pablo
Professor of Oncology

Manuel Hidalgo was born in Antequera, Malaga, in 1968. He received his MD from the Universidad de Navarra, Pamplona, in 1992 and his PhD from the Universidad Autonoma de Madrid in 1997.

Manuel specialised in Medical Oncology at the Hospital Universitario 12 de Octubre, Madrid, obtaining his license in 1996. He completed his training in drug development at the University of Texas Health Science Center, San Antonio (USA), where he briefly joined as Faculty. He then moved to Johns Hopkins University in 2001 as Co-Director of the Drug Development and GI Programmes.

He joined the CNIO in 2009 to lead the GI Cancer Clinical Research Unit. Manuel is a founding member of the pancreatic cancer research team - a clinical trials group focusing on novel therapeutics for pancreatic cancer. He has participated in the clinical development of more than 30 novel anticancer agents and led the early clinical trials with erlotinib and temsirolimus - two recently approved drugs.

Manuel´s work has contributed to the incorporation of molecular endpoints in early clinical trials. His group pioneered the utilisation of personalised xenograft models for drug screening, biomarker development and personalised cancer treatment.

He has published more than 220 papers in peer-reviewed journals and his work has been funded by the NCI, AACR, and ASCO.

Manuel received an AACR Clinical Research Fellowship and an ASCO Career Development Award for his work on the development of EGFR inhibitors. His most recent efforts focus on novel therapeutics for pancreatic cancer.

In 2011, he was named Vice Director of Translational Research at CNIO charged with the mission to foster translational research at CNIO and with a broader implication of the Center in cancer care.

## Sunil R. Hingorani

Associate Member, Fred Hutchinson Cancer Research Center,
Seattle, USA

Dr. Hingorani is a medical oncologist and cancer biologist specializing in pancreas cancer. He is Associate Member at Fred Hutchinson Cancer Research Center and Associate Professor in the Division of Medical Oncology at the University of Washington School of Medicine. His laboratory studies the molecular pathogenesis of pancreas cancer primarily through the use of genetically engineered mouse models. He is the Founding Director of the Pancreas Cancer Specialty Clinic at the Seattle Cancer Care Alliance, a multidisciplinary clinic, and also directs a comprehensive translational research program in pancreas cancer, the Center for Accelerated Translation in Pancreas Cancer.

### Timothy Hoey

OncoMed Pharmaceuticals,
Redwood City, USA

Dr. Timothy Hoey is Senior Vice President, Cancer Biology at OncoMed Pharmaceuticals. The Cancer Biology group is responsible for testing new drugs targeting cancer stem cells and translational research to discover biomarkers indicative of CSC frequency and patients most likely to respond to OncoMed therapeutic antibodies. Dr. Hoey previously served as Director, Biology Department at Amgen (San Francisco) and was responsible for characterization of oncogenes and development of drugs to target oncogene products. Prior to this he was Director, Biology Department at Tularik, responsible for Cancer and Immunology research.

Prior to joining Tularik, he performed post doctoral studies on the mechanisms of transcriptional regulation at U.C. Berkeley under Dr. Robert Tijian. Dr. Hoey received his Ph.D. from Columbia University, where he conducted research on regulation of gene expression and embryonic development with Dr. Michael Levine. Dr. Hoey is a co-inventor on several patents and has authored or co-authored over 60 scientific publications.

## Christophe Le Tourneau

Head of the Phase I Program
Department of Medical Oncology, Curie Institute,
Paris, France

Christophe Le Tourneau (MD,PhD) has been appointed as a senior Medical Oncologist at the Institut Curie in Paris in November 2009. He is heading the Phase I Program as well as the Head and Neck Clinic. He is also running the multicenter randomized personalized medicine SHIVA trial. Christophe Le Tourneau was certified in Medical Oncology in 2005 and got his PhD in Clinical Epidemiology in 2007. He then did a 2-year Clinical Research Fellowship at Princess Margaret Hospital in the Drug Development Program. His main interests are oncology phase I clinical trials with a special attention at the methodology to conduct these trials, as well as Head and Neck oncology.

## Tak W. Mak

Campbell Family Institute for Breast Cancer Research,
Princess Margaret Cancer Centre, University Health Network,
University of Toronto,
Toronto, Canada

Tak W. Mak is the Director of the Campbell Family Institute for Breast Cancer Research at the Princess Margaret Cancer Centre, and a University Professor in the Departments of Medical Biophysics and Immunology at the University of Toronto.

Dr. Mak's research interests center on immune cell recognition/regulation, molecular mechanisms underlying the survival and death of normal or malignant cells, as well as the role of inflammation in the progression of autoimmune disease and cancer. He is best known as the lead scientist of the group that first cloned the genes of the human T cell antigen receptor, a discovery that provided essential insights into the molecular basis of cellular immunity. In addition, Dr. Mak has devoted a large portion of his research to investigating the pathogenesis of cancer. In particular, he is interested in mechanisms of metabolic transformation in order to identify potential targets for novel cancer therapeutics.

Dr. Mak has published over 800 peer-reviewed research papers and holds many patents. His many accomplishments have been recognized by the scientific community through numerous prestigious awards and honours.
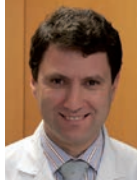
## Ignacio Melero

CIMA & Clinica Universidad de Navarra,
Pamplona, Spain

Ignacio Melero earned an MD degree from the University of Navarra School of Medicine (1988) and was trained as a resident in clinical immunology at Hospital de la Princesa (Universidad Autonoma de Madrid). He also attained a PhD degree working with Dr. Miguel Lopez-Botet pioneering the characterization of NK cell inhibitory receptors (KIRs) In 1994 he moved to Seattle (USA) where he worked on tumor immunology and immunotherapy, studying T cell ignorance of tumor antigens and the role of T-cell costimulation in mouse models of cancer. His studies of that time on CD137-mediated co-stimulation of curative antitumor immune responses have received much attention by the immunotherapy of cancer community and have resulted in therapeutic agents undergoing phase II clinical trials. Since 1998 he returned to Navarra University where he currently serves as a full professor of Immunology at the Clinica Universidad de Navarra and at the investigation centre CIMA. His current areas of research are focused on from bench to bed side translational research with cell, gene and monoclonal antibody-mediated strategies of immunotherapy for cancer.

## William Pao

Roche Pharma Research & Early Development,
Basel, Switzerland

Dr. William Pao is the Global Head of the Oncology Discovery and Translational Area (DTA) for Roche's Pharmaceutical Research & Early Development (pRED) unit, based in Basel, Switzerland. He obtained his MD and PhD degrees at Yale University, did his housestaff training in Internal Medicine at New York Presbyterian Hospital-Weill Cornell Campus, and completed his medical oncology and postdoctoral fellowship training at Memorial Sloan-Kettering Cancer Center (MSKCC). He joined the faculty at MSKCC and was eventually recruited to Vanderbilt, where he became Professor of Medicine, Director of the Division of Hematology/Oncology, and Director of Personalized Cancer Medicine at Vanderbilt-Ingram Cancer Center.

## Drew Pardoll

Johns Hopkins University,
Baltimore, USA

Dr. Pardoll is an Abeloff Professor of Oncology, Medicine, Pathology and Molecular Biology and Genetics at the Johns Hopkins University, School of Medicine. He is Director of the Cancer Immunology in the Sidney Kimmel Comprehensive Cancer Center. Dr. Pardoll attended Johns Hopkins University, where he earned his M.D., Ph.D., in 1982 and completed his Medical Residency and Oncology Fellowship in 1985. He then worked for three years at the National Institutes of Health as a Medical Staff Fellow. Dr. Pardoll joined the departments of oncology and medicine in 1988. Dr. Pardoll has published over 300 papers as well as over 20 book chapters on the subject of T cell immunology and cancer vaccines. He has served on the editorial board of the Journal of the National Cancer Institute and Cancer Cell, and has served as a member of scientific advisory boards for the Cancer Research Institute, the University of Pennsylvania Human Gene Therapy Gene Institute, Biologic Resources Branch of the National Cancer Institute, Harvard-Dana Farber Cancer Center, Cerus Corporation, Global Medical Products Corporation, Genencor Corporation, CellGenesys Corporation, Mojave Therapeutics, the American Association of Clinical Oncology and the American Association of Cancer Research. Dr. Pardoll has made a number of basic advances in Cellular Immunology, including the discovery of gamma - delta T cells, NKT cells and interferon-producing killer dendritic cells. Over the past two decades, Dr. Pardoll has studied molecular aspects of dendritic cell biology and immune regulation, particularly related to mechanisms by which cancer cells evade elimination by the immune system. He is an inventor of a number of immunotherapies, including GVAX cancer vaccines and Listeria monocytogenes based cancer vaccines. Dr. Pardoll's basic immunology discoveries include the identification of $\gamma\delta$-T cells, NKT cells and IKDC. He elucidated the role of Stat3 signaling in tumor immune evasion and in Th17 development, leading to the discovery that Stat3-driven Th17 responses promote carcinogenesis. Dr. Pardoll discovered one of the two ligands for the PD-1 inhibitory receptor and leads the Hopkins cancer immunology program that developed PD-1 pathway-targeted antibodies, demonstrating their clinical activity in multiple cancer types. His more than 300 articles cover cancer vaccines, gene therapies, cancer prevention technologies, recombinant immune modulatory agents for specific pathways that regulate immunity to cancer and infectious diseases.

## Jordi Rodón

VHIO,
Barcelona, Spain

Dr. Jordi Rodón did his specialization in Medical Oncology at the Catalan Institute of Oncology (Institut Català d'Oncologia). He has been Research fellow at the Advanced Drug Development Fellowship program at the Institute For Drug Development in San Antonio, Texas, and Senior Research fellow at the Investigational Cancer Therapeutics Department at MD Anderson Cancer Center in Houston, Texas. He joined the Medical Oncology Department in 2008 and has been principal investigator or co-investigator in more than 80 phase I trials. At VH, he coordinates the phase I program and the clinical research at UITM, where they focus on complex clinical trials with drugs in early development (phase I and early phase II trials) focused in novel targets. Their main interest is proof-of-concept and proof-of-mechanism trials with targeted therapies, especially target therapies focusing on cell signaling and cancer stem cells. These trials include First-in-human studies of targeted therapies, rational combinations of targeted therapies, biomarker-driven trials and trials in molecularly selected populations. In the last two years, they have collaborated with the Molecular Pathology and the Genomics labs to perform molecular analysis of the patients tumor in order to select the best possible treatment with the available experimental treatments, in a step towards Personalized Medicine.

## Ingrid Sassoon

Sanofi Oncology,
Vitry-sur-Seine, France

Ingrid Sassoon received her Biotechnology Engineer Degree in 1994 and her PhD in Cell Biology and Genetics from the Strasbourg University in 1998. She performed her PhD and post-doctorate in the group of Anthony Hyman at the European Molecular Biology Laboratory (EMBL, Germany). In 2000, she moved to the Oncology Department of Aventis in France working on the optimization of small molecules against cell cycle targets. In 2006, she joined the Oncology-Biologics group, leading several Antibody Drug Conjugates (ADC) projects from discovery to early clinical development, coordinating an internal initiative to develop new cytotoxics and linkers for ADC, and more recently, bringing her ADC expertise into the onco-immunology field.

## David J. Shields

Pfizer Inc.,
New York, USA

Dr. Shields is a Director in the Oncology Research Unit, Pfizer Inc. (New York). He has held Group Leader positions from Target Discovery to Precision Medicine, led Oncology Research combination strategy and directed pre-clinical translational support for assets such as Sutent, Inlyta and the recently approved, Ibrance (palbociclib). Prior to joining Pfizer, Dr. Shields earned a B.Sc (Hons) in Biomedical Sciences from University College Cork, Ireland, a Ph.D in Biochemistry from University of Alberta, Canada, conducted post-doctoral training at The Scripps Research Institute and University of California, San Diego, and was Assistant Project Scientist at Moores UCSD Cancer Center.

## Lillian L. Siu

Princess Margaret Cancer Centre,
Toronto, Canada

Dr. Lillian Siu (MD, FRCPC) is a senior staff medical oncologist at Princess Margaret Cancer Centre (PM) since 1998, and is Professor of Medicine at the University of Toronto since 2009. Dr. Siu is the Director of the Phase I Program at the PM. Dr. Siu currently serves on the Board of Directors for ASCO for a four-year term (2012-2016). She also serves as a member of the Nomination Committee for the AACR (2014-2016). She is the Principal Investigator of a phase I cooperative agreement UM1 award (2014-2019) sponsored by US NCI. In addition, Dr. Siu has been leading genomics initiatives in the area of precision medicine at the PM. She has published over 170 peer-reviewed manuscripts, and is currently an editor for *Cancer Discovery* and *Journal of Clinical Oncology*.

### Mario Sznol

Yale University,
New Heaven, USA

Dr. Mario Sznol graduated from Rice University and Baylor College of Medicine (BCM) in Houston, Texas. He trained in internal medicine at BCM and completed a medical oncology fellowship in the Department of Neoplastic Diseases, Mount Sinai Hospital, New York. He spent the next twelve years in the Biologics Evaluation Section (BES), Investigational Drug Branch (IDB), Cancer Therapy Evaluation Program of the National Cancer Institute, and was Head of the BES from 1994-1999. He attended in the Biological Response Modifiers Program, NCI, from 1988-1996 and on the Immunotherapy Service of the Surgery Branch, NCI, from 1997-1999.

From 1999-2004, Dr. Sznol was a Vice President and Executive Officer of Vion Pharmaceuticals in New Haven, CT. Dr. Sznol is currently a Professor of Internal Medicine at Yale University School of Medicine. Deputy Chief of the Section of Medical Oncology, Clinical/Translational Research Leader of the Melanoma Program, and co-Director of Yale SPORE in Skin Cancer.

## Josep Tabernero

Head Medical Oncology Department,
Vall d'Hebron University Hospital (VHIO),
Barcelona, Spain

Josep Tabernero holds MD and PhD degrees from the Universitat Autònoma de Barcelona, Spain. He is currently the Head of the Medical Oncology Department at the Vall d'Hebron University Hospital in Barcelona and the Director of the Vall d'Hebron Institute of Oncology. He is very actively involved in translational research and early drug development studies with pharmacodynamic endpoints with novel agents directed to the membrane receptors, like the EGFR-family and IGF-1R, the PI3K and ERK signalling pathways. One of the main objectives of the group is to identify new predictive markers of response to diverse treatments and to identify markers of primary resistance (de novo) and secondary treatment. At a preclinical level, the group he is leading is developing new xenograft models with explant tumors from patients ("xenopatients") in mice in order to mimic the patient's disease and study the 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). He has (co)authored approximately 300 peer-reviewed papers.

## Jaap Verweij

Erasmus MC: University Medical Center Rotterdam, Rotterdam, The Netherlands

Jaap Verweij, M.D., Ph.D is a Professor of Medical Oncology, Dean of the Faculty of Medicine of Erasmus University and Vice-Chairman of the Board of Erasmus Medical Center in Rotterdam, The Netherlands since April 2013. He served as chair of the Department of Medical Oncology, and chair of the Daniel den Hoed Cancer Center at the Erasmus University Medical Centre from 2008-2013. His main scientific interests are new drug development, including the performance of clinical phase I and early phase II trials, and the inclusion of pharmacokinetics and pharmacodynamics in these studies. He also has a major interest in the design aspects of early clinical studies. Besides his clinical activities he has been the chairman of the Early Clinical Studies Group of the European Organisation for Research and Treatment of Cancer (EORTC) from 1993-1996, chairman of the EORTC Soft Tissue and Bone Sarcoma Group from 1996-1999, chairman of the EORTC New Treatment Committee, the EORTC New Drug Advisory Committee, and Vice-President of EORTC. He has also been president of the Connective Tissue Oncology Society (CTOS), chairman of the RECIST working group, and chairman of the Scientific Council of the Dutch Cancer Foundation He has recently been editor of the European Journal of Cancer and is still associate editor of the Journal of Clinical Oncology. He currently serves as vice-chairman in the Board of Governors of the Dutch Cancer Foundation. In 2011 Jaap Verweij was appointed as member of the Royal Netherlands Academy of Arts and Sciences. He has authored or co-authored over 700 papers on various aspects, and has given numerous lectures on a variety of topics at international meetings.

## Ann L. White

University of Southampton,
Southampton, UK

Ann White is a Senior Research Fellow within the Cancer Sciences Unit, University of Southampton, UK. Her research is focused upon optimisation of anti-cancer therapeutic mAb through the manipulation of mAb structure. Ann received a PhD in Molecular and Cellular Biology from the MRC Clinical Research Centre, London in 1991. She then spent 10 years in the US researching lipoprotein metabolism, first in San Antonio, Texas, then at the University of Texas Southwestern Medical Center at Dallas. Ann joined Southampton University in 2005 and is part of a large antibody development programme funded primarily through the charity Cancer Research UK.

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NEW TRENDS IN ANTICANCER DRUG DEVELOPMENT | **NOTES**

*Madrid* 22-25 March 2015

**NEW TRENDS IN
ANTICANCER DRUG
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# POSTER SESSION

① 
# PGA-Based Combination Therapy for the Treatment of Breast Cancer

**Ana Armiñán[1],** Coralie Deladriere[1], Juan J. Arroyo[1], Esther Masia[1,2], A. Paul[3], María J. Vicent[1,2]

[1]Polymer Therapeutics Lab. Centro de Ivestigación Príncipe Felipe (CIPF), Valencia, Spain
[2]Screening Plataform. Centro de Ivestigación Príncipe Felipe (CIPF), Valencia, Spain
[3]Cardiff University, Chemistry Dpt., Cardiff, UK

Introduction

Polymer-drug conjugates are drug delivery technologies in which a bioactive agent is covalently bound to a polymeric carrier, normally via a biodegradable linker. The first generation of polymer conjugates already achieved clinical proof and more sophisticated second-generation polymer conjugates are already being developed1. The use of polymer-drug conjugates in combination therapy is seen as an important opportunity to enhance tumour response rates and to reduce the severe side-effects2. By conjugating two different drugs covalently to a single polymer chain, the simultaneous or controlled delivery of both drugs can be accomplished. The combination of endocrine therapy with chemotherapeutic agent by simultaneous binding to the polymer could bring significant advantage versus single treatments. We have previously reported the first conjugate of this type: an HPMA copolymer carrying the combination of endocrine therapy (the aromatase inhibitor aminoglutethimide (AGM)) and chemotherapy (Dox), HPMA copolymer-AGM-Dox conjugate3. In vivo proof of concept for the combination conjugate has already been achieved in an orthotopic 4T1 murine metastatic breast cancer model and its molecular mechanism of action studied4. In order to further improve this construct, we now propose the use of a biodegradable and multivalent carrier poly(L-glutamic acid) (PGA) being able to increase conjugate molecular weight enhancing therefore its tumour targeting by EPR effect.

Results And Discussion

A novel PGA-AGM-DOX conjugate family has been done synthesised via carbodiimide coupling reaction. Different polymer drug linkers have been explored looking at a possible structure-activity relationship. Conjugate identity by different techniques, (NMR, HPLC, etc) solution conformation by Small Angle Neutron Scattering (SANS), and drug release kinetics in presence of the lysosomal enzyme cathepsin B have been carried out in order to identify the design features required to achieve drug synergism. Biological evaluation of combination conjugates in comparison with the single counterparts has been also performed in 4T1 and MCF-7ca cell lines looking at drug synergism. The best conjugates were selected for in vivo evaluation in the 4T1 model and PGA-G-AGM10-Dox5 has been selected as the best candidate to move forward. Importantly, we have demonstrated with this PGA conjugate family that conjugate solution conformation is a key feature ruling biological performance, in vitro as well as in vivo.

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# Rational drug design and new allosteric compounds from structure-based virtual screening of Focal Adhesion Kinase

2

**Marta Camacho-Artacho[1],** Álvaro Cortés-Cabrera[2], Giorgio Saladino[3], Francesco L. Gervasio[3], Federico Gago[2], Daniel Lietha[1]

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[2]Department of Biomedical Sciences, School of Medicine and Health Sciences, University of Alcalá,
Alcalá de Henares, Madrid, Spain.
[3]Institute of Structural and Molecular Biology and Department of Chemistry, University College London, London WC1H 0AJ,
United Kingdom.

Focal adhesion kinase (FAK) is a non-receptor tyrosine kinase that plays an important as a mediator in cell migration, proliferation and survival. Since overexpression of this protein highly correlates with tumour invasiveness and poor prognosis, FAK is considered to be a suitable target for anticancer drug design [1, 2]. From the structural point of view, FAK consists of a catalytic kinase domain, a regulatory FERM domain and a carboxy-terminal focal adhesion targeting (FAT) domain [3]. To inhibit FAK signalling we devised two different structure-based virtual screening (VS) strategies: i) design of putative ligands with affinities for the orthosteric site in alternative conformations (e.g. DFG-out) and ii) identification of novel scaffolds with the ability to bind in five allosteric and transient pockets within the kinase and FERM domains. These pockets were identified after analyses of long timescale molecular dynamics (MD) trajectories (100 ms) carried out at DE Shaw Research. Over half a million commercially available fragment compounds [4] (Mw <= 250 Da, logP <= 3.5) were screened in silico. The complexes of FAK with the best scoring VS hit compounds were subjected to unbiased MD simulations to evaluate their stability. Our approach, combining VS of fragment libraries with MD simulations is aimed at increasing the likelihood of identifying putative hits with the ability to interact with shallow allosteric pockets. Such compounds should provide new chemical scaffolds for further development into suitable candidate molecules for selective FAK inhibition.

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NEW TRENDS IN ANTICANCER DRUG DEVELOPMENT | POSTER SESSION

NEW TRENDS IN ANTICANCER DRUG DEVELOPMENT | POSTER SESSION

(3) ### Targeting acquired resistance to targeted therapies in cutaneous melanoma

**Elisabetta Fratta,** Francesca Colizzi, Maurizio Polano, Aurora Rizzo, Riccardo Dolcetti and Luca Sigalotti

Cancer Bioimmunotherapy Unit, Centro di Riferimento Oncologico, Istituto di Ricovero e Cura a Carattere Scientifico, Aviano

Activating BRAF mutations are effectively targeted by specific inhibitors, such as vemurafenib, which have shown important clinical responses in advanced cutaneous melanoma (CM). However, their clinical effectiveness is impaired by the emergence of an early drug resistance. This behaviour prompts for the identification of resistance mechanisms, which could allow defining new therapeutic options. Sequential adaptation to increasing concentrations of vemurafenib was used to raise drug-resistant isogenic cell cultures from a panel of BRAF-typed, vemurafenib sensitive, cell lines generated from CM metastatic lesions. Gene expression profiling, RNAsequencing, quantitative RT-PCR, receptor tyrosine kinase (RTK) arrays, western blotting and MTT vitality assays were used to compare vemurafenib resistant (VR) cells to their parental sensitive cells in the presence or absence of different small molecule inhibitors. VR cultures were generated from 8 metastatic CM cell lines. Gene expression profiling showed a significant upregulation of RTK mRNAs following resistance acquisition. Quantitative RT-PCR confirmed upregulation of AXL and its ligand GAS6, EGFR and/or PDGFRβ in 6 out of 8 VR cell cultures, with frequent co-expression of multiple RTK. Accordingly, increased phosphorilation of AXL, EGFR and PDGFRβ was observed in lysates from VR. Small-molecule-mediated inhibition of AXL and PDGFRβ, partially restored the sensitivity of VR cells to vemurafenib, while no effect was observed upon inhibition of EGFR, despite significant reduction of its phosphorylation following treatment. The data: i) further support the role of RTK activation in contributing to the acquired resistance to BRAF-targeted therapies; ii) identify for the first time AXL as an important player; iii) suggest for a common mechanism leading to the concomitant upregulation of different RTKs; and iv) may suggest the use of combined targeted therapeutics to overcome the acquired resistance to BRAF inhibition.

# Drug discovery targeting cancer stem cells

4

**Angel Garcia Martin**

StemTek Therapeutics, Parque Tecnológico de Bizkaia, Derio, Vizcaya, Spain

StemTek Therapeutics is a start-up biotechnolgy company dedicated to accelerating drug discovery in cancer using cutting edge technology, worldclass science and a stem cell centric point of view for cancer therapy. Our mission is to help design novel treatments for cancer targeting cancer stem cells.

NEW TRENDS IN ANTICANCER DRUG DEVELOPMENT | POSTER SESSION

NEW TRENDS IN ANTICANCER DRUG DEVELOPMENT | POSTER SESSION

## 5 Cell-penetrating peptides based on the interaction between connexin43 and c-Src as a therapy for human glioblastoma stem cells

**Myriam Jaraíz-Rodríguez,** Marta Domínguez-Prieto, José M Medina, Arantxa Tabernero

Instituto de Neurociencias de Castilla y León (INCYL) - Universidad de Salamanca, Spain

Central Nervous System (CNS) is composed by different types of cells: neurons and glial cells. Astrocytes are the most numerous glial cells and they are widely communicated by gap junctions. The main gap junction channel-forming protein in astrocytes is the connexin43 (Cx43). This protein is downregulated when astrocytes acquire a malignant phenotype and originate brain tumours called gliomas. Cx43 has been described to exert a tumour suppressor effect through the interaction with the oncoprotein c-Src, as our previous work has shown in gliomas. Interestingly, Cx43 is downregulated in glioma stem cells (GSCs), a subpopulation of cells thought to be responsible for tumor initiation, relapse, and therapeutic resistance in gliomas. Restoring Cx43 levels reverses GSCs phenotype and consequently reduces their tumorigenicity. On this basis, we have designed several cellpenetrating peptides (CPPs) containing different regions of Cx43 involved in c-Src interaction and we have investigated their role in GSC proliferation and migration.

Human G166 GSCs, patient-derived GSCs, C6 rat glioma cells, neurons and astrocytes cultures were treated with CPPs. Cell growth was analyzed by MTT. Migration was studied using wound-healing assays, Time-Lapse live-cell Imaging and Immunocytochemistry.

Our results show that CPPs are internalized and reduce the rate of cell growth. Interestingly, the effects of CPPs are stronger in GSCs compared to other types of cells. TAT sequence did not significantly change the rate of growth. Although several studies show that Cx43 increases cell migration, our findings indicate that the region of Cx43 that interacts with c-Src does not exert this effect. In fact, the CPPs used in this study reduced the rate of GSC migration and locomotion.

In conclusion, our results indicate that c-Src plays an essential role in the effects of Cx43 on GSCs proliferation and migration and suggest these CPPs as promising therapies.

## Studying hematopoietic stem cells via CK1 alpha ablation ⑥

**Waleed Minzel,** Guy Brachya & Yinon Ben-Neriah

The Lautenberg center for immunology and cancer research, Hebrew University, Jerusalem, Isreal

Bone marrow transplantation is used for the treatment of leukemia, certain other forms of cancer and for restoring hematopoietic deficiency. It often requires depletion of the entire pool or residual hematopoietic stem cells (HSCs) for vacating the stem cell niches. Here we examined the effect of CK1α deletion on HSCs and found that CK1α is indispensable for proper function of HSCs. Interestingly, CK1α deletion led to HSCs depletion in a p53 dependent manner. Following CK1α deletion the bone marrow can be easily reconstituted with wild type bone marrow and the engrafted mice live normally many month. Inoculation of HSC transduced with a BCR-ABL carrying retrovirus to healthy WT mice induces chronic myeloid leukemia (CML) which evolves to blast crisis, constituting a good model for studying leukemia initiating cells (LICs). LICs are believed to be essential for maintaining and sustaining the disease. We determined the therapeutic potential of deleting CK1α in LICs during the blast crisis and found that CK1α ablation or inhibition prevents CML progression in mice, suggesting that targeting CKIα might be of great potential for treating CML including blast crisis, for which there is yet no effective therapy.

**7** ### A cell competition-based high-throughput screen for anti-cancer drugs using an isogeneic BCR-ABL cell model

**Tadele Dagim[1],** Piechaczyk Laure, Ayuda Pilar, Enserink JM

[1]Department of Molecular Biology, Institute of Microbiology, Oslo University Hospital, Oslo, Norway.

Chronic myeloid leukemia is caused by the BCR-Abl fusion gene, also known as the Philadelphia chromosome. The BCR-Abl oncogene is also found in certain forms of aggressive Acute Lymphoid Leukemia (ALL). During disease development, there is intense competition between healthy cells and leukemia cells for a niche in the bone marrow. This element of competition is usually not taken into account in conventional high-throughput screens for anticancer drug discovery. To address this limitation, we developed a cell competition-based assay using CML as a model. Clonal GFP-expressing Ba/F3 cells expressing BCR-ABL were co-cultured with isogeneic RFP-expressing wild-type cells in an equal proportion. The cocultures were then exposed to a drug library for 72 hrs and the ratio of GFP/RFP cells was measured by high-throughput flow cytometry. We screened a library of 17,962 small molecules to identify compounds that selectively affect BCR-ABL expressing cells. Among the identified compounds that specifically inhibited BCR-ABL-expressing cells but not wild-type cells were phosphodiesterase (PDE) inhibitors and the topoisomerase II inhibitor sobuzoxane. Interestingly, sobuzoxane is approved for clinical use in Japan for the treatment of leukemia and lymphoma. On the other hand, we identified several compounds that conferred a competitive advantage to BCR-ABL cells, including a JAK2 inhibitor. Whereas JAK2 activity is normally required for survival and proliferation of wild type cells, this requirement thought to be bypassed by BCR-ABL (Nat Chem Biol., 8(3):285-93; Leukemia, 28(9):1918-22). Indeed, we found that inhibition of BCR-ABL restored sensitivity of BCR-ABL expressing cells to the JAK2 inhibitor. Our results demonstrate that competition assay emulates competition that occurs in vivo making it an attractive, physiologically relevant model with a potential for broad applicability in anti-cancer drug screening.

# Essential oil of Pistacia lentiscus variation chia as a potential antiinflammatory agent

**Tiptiri-Kourpeti Angeliki,** Spyridopoulou Katerina, Theofanidou Theodora, Fitsiou Eleni, Galanis Alexis, Pappa Aglaia, Chlichlia Katerina

Dept. Molecular Biology and Genetics, Democritus University of Thrace, University Campus-Dragana, Alexandroupolis, Greece

Phytochemicals derived from medicinal plants are nowadays extensively studied for their anti-cancer and anti-inflammatory properties. The essential oil from Chios mastic gum is produced by the resin of the Pistacia lentiscus var. chia plant and demonstrates numerous biomedical and pharmacological properties, including anti-microbial, anti-oxidant and anti-tumor activities. Since inflammation facilitates cancer development and tumor growth, we examined the anti-inflammatory properties in an in vitro system using the human monocytic cell line THP-1. Cell viability studies estimated a biosafe concentration of mastic oil less than 0.01% v/v. THP-1 cells stimulated for 48 hours with PMA differentiated to adherent macrophages. Afterwards, cells were treated for 24 hours with LPS in the presence or absence of mastic oil and pro- or anti-inflammatory cytokines were determined a) at transcriptional level by RT-PCR and b) at translational level, in cell culture supernatants by ELISA. Both IL-6 and IL-8 levels were significantly decreased in THP-1 cells treated with 0.005% v/v mastic oil. Moreover, administration of 0.01% v/v mastic oil for 24 hours prior to LPS completely abrogated expression and production of the pro-inflammatory cytokine TNFalpha. Thus, mastic essential oil promotes an anti-inflammatory transition in LPS-stimulated PMA-activated THP-1 cells, suggesting its role as a promising novel anti-inflammatory agent. Bioactive constituents present in mastic oil warrant further investigation for their anti-inflammatory and anticarcinogenic properties.

**NEW TRENDS IN ANTICANCER DRUG DEVELOPMENT | POSTER SESSION**

(9) # Mastic essential oil inhibits growth and induces apoptotic cell death in murine colon carcinoma cells

**Spyridopoulou Katerina[1],** Tiptiri-Kourpeti Angeliki[1], Tompoulidou Evgenia[1],
Fitsiou Eleni[1], Vasileiadis Stavros[1], Evangeli Lampri[2], Anna Goussia[2], Vasiliki Malamou-Mitsi[2],
Galanis Alexis[1], Pappa Aglaia[1], Chlichlia Katerina[1]

[1]Dept. Molecular Biology and Genetics, Democritus University of Thrace, University Campus-Dragana, Alexandroupolis, Greece
[2]Department of Pathology, Medical School, University of Ioannina, Ioannina, Greece

Plant extracts have been the backbone of pharmaceutical innovation since the dawn of medicine. Nowadays, there is an increasing awareness on nutraceuticals as therapeutic agents against cancer and various diseases. In this context, we investigated the anti-cancer properties of mastic oil, an essential oil that has been traditionally used as food additive and flavoring agent. Mastic oil is extracted from the resin of the plant Pistacia lentiscus var. chia, a plant that has been cultivated for its aromatic resin mostly in the southern part of Chios island in Greece. Significant anti-proliferative effects were observed in vitro against two colon cancer cell lines, HT29 (human) and CT26 (murine), accompanied by apoptotic cell death. This effect was in part caspase-dependent, since treatment with the general caspase inhibitor z-VAD-fmk abrogated, to some extent, the growth-inhibitory effect of mastic oil on CT26 colon carcinoma cells. In addition, flow cytometric analysis on cell cycle progression showed that mastic oil induced a G1-phase arrest on CT26 cells. A proof of principle study was conducted using an established experimental model of colon cancer, where a dramatic reduction of approximately 80% in tumor volume was observed. Thus, mastic oil is not only cytotoxic but also cytostatic to murine colon carcinoma cells and when administered orally, induced a dramatic reduction in tumor growth in a mouse colon cancer model. Mastic oil's anticancer properties may be ascribed mainly to alpha-pinene, while there might be an underlying synergistic effect among its major constituents. Further research is required in order to identify the underlying biological and molecular mechanisms.

*Madrid* 22-25 March 2015

**NEW TRENDS IN
ANTICANCER DRUG
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# Previous CNIO Frontiers Meetings and CNIO Cancer Conferences

# 2013

### CHROMOSOME INSTABILITY AND ANEUPLOIDY IN CANCER

27/05/2013 - 29/05/2013

**Organisers:** Robert Benezra, Ana Losada,
Marcos Malumbres, René Medema

# 2012

### ALLOSTERIC REGULATION OF CELL SIGNALLING

17/09/2012 - 19/09/2012

**Organisers:** Francesco Gervasio, Ermanno Gherardi,
Daniel Lietha, Giulio Superti-Furga

# 2011

### RECAPTURING PLURIPOTENCY:
### LINKS BETWEEN CELLULAR REPROGRAMMING AND CANCER

07/11/2011 - 09/11/2011

**Organisers:** Maria A. Blasco, Konrad Hochedlinger,
Manuel Serrano, Inder Verma

### CANCEROMATICS II :
### MULTILEVEL INTERPRETATION OF CANCER GENOME

28/03/2011 - 30/03/2011

**Organisers:** Søren Brunak, Stephen Chanock,
Núria Malats, Chris Sander, Alfonso Valencia

### BREAST CANCER

07/02/2011 - 09/02/2011

**Organisers:** Joaquín Arribas, José Baselga,
Miguel Ángel Piris, Lajos Pusztai and Jorge Reis-Filho

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# 2010

## CANCER PHARMACOGENETICS: PERSONALIZING MEDICINE

22/11/2010 - 24/11/2010

**Organisers:** Javier Benítez, William E. Evans,
Miguel Martín and Magnus Ingelman-Sundberg

## MOLECULAR CANCER THERAPEUTICS

08/03/2010 - 10/03/2010

**Organisers:** Gail Eckhardt, Roy S. Herbst
and Manuel Hidalgo

# 2009

## THE ENERGY OF CANCER

02/11/2009 - 04/11/2009

**Organisers:** Toren Finkel, David M. Sabatini,
Manuel Serrano and David A. Sinclair

## CANCER-OM-ATICS : MULTILEVEL INTERPRETATION OF CANCER GENOME DATA

06/07/2009 - 08/07/2009

**Organisers:** Søren Brunak, Núria Malats,
Chris Sander and Alfonso Valencia

## STEM CELLS AND CANCER

23/02/2009 - 25/02/2009

**Organisers:** Elaine Fuchs, Maria A. Blasco,
Eduard Batlle and Mirna Pérez-Moreno

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# 2008

### SIGNALLING UPSTREAM OF mTOR

03/11/2008 - 05/11/2008

**Organisers:** Dario R. Alessi, Tomi P. Mäkelä
and Montserrat Sánchez-Céspedes

### STRUCTURE AND MECHANISMS
### OF ESSENTIAL COMPLEXES FOR CELL SURVIVAL

23/06/2008 - 25/06/2008

**Organisers:** Niko Grigorieff, Eva Nogales
and Jose María Valpuesta

### DEVELOPMENT AND CANCER

04/02/2008 - 06/02/2008

**Organisers:** Konrad Basler, Ginés Morata,
Eduardo Moreno and Miguel Torres

# 2007

### LINKS BETWEEN CANCER, REPLICATION
### STRESS AND GENOMIC INTEGRITY

05/11/2007 - 07/11/2007

**Organisers:** Oskar Fernández-Capetillo, Jiri
Lukas, Juan Méndez and André Nussenzweig

### MYC AND THE TRANSCRIPTIONAL CONTROL
### OF PROLIFERATION AND ONCOGENESIS

11/06/2007 - 13/06/2007

**Organisers:** Robert N. Eisenman,
Martin Eilers and Javier León

### MOLECULAR MECHANISMS IN LYMPHOID NEOPLASM

19/02/2007 - 21/02/2007

**Organisers:** Elias Campo, Riccardo Dalla-Favera,
Elaine S. Jaffe and Miguel Angel Piris

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# 2006

### TELOMERES AND TELOMERASE-CNIO / JOSEF STEINER CANCER CONFERENCE

13/11/2006 - 15/11/2006

**Organisers:** Maria A. Blasco and Jerry Shay

### MEDICINAL CHEMISTRY IN ONCOLOGY

02/10/2006 - 04/10/2006

**Organisers:** Fernando Albericio, James R. Bischoff, Carlos García-Echeverria and Andrew Mortlock

### INFLAMMATION AND CANCER

22/05/2006 - 24/05/2006

**Organisers:** Curtis Harris, Raymand Dubois, Jorge Moscat and Manuel Serrano

### PTEN AND THE AKT ROUTE

08/05/2006 - 10/05/2006

**Organisers:** Ana Carrera, Pier Paolo Pandolfi and Peter Vogt

# 2005

### CANCER AND AGING

07/11/2005 - 09/11/2005

**Organisers:** Maria A. Blasco, Kathy Collins, Jan Hoeijmakers and Manuel Serrano

### MAP KINASES AND CANCER

30/05/2005 - 01/06/2005

**Organisers:** Philip Cohen, Roger Davis, Worcester, Chris Marshall and Ángel Nebreda

### ANIMAL TUMOUR MODELS AND FUNCTIONAL GENOMICS

07/03/2005 - 09/03/2005

**Organisers:** Allan Balmain, Mariano Barbacid, Anton Berns and Tyler Jacks

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# 2004

### CADHERINS, CATENINS AND CANCER

29/11/2004 - 01/12/2004

**Organisers:** Amparo Cano, Hans Clevers, José Palacios and Franz Van Roy

### STRUCTURAL BIOLOGY OF CANCER TARGETS

27/09/2004 - 29/09/2004

**Organisers:** Ernest Laue, Guillermo Montoya and Alfred Wittinghofer

# 2003

### APOPTOSIS AND CANCER

01/12/2003 - 03/12/2003

**Organisers:** Gabriel Nuñez, Marisol Soengas and Scott Lowe

### SMALL GTPases IN HUMAN CARCINOGENESIS

16/06/2003 - 18/06/2003

**Organisers:** Juan Carlos Lacal, Channing Der and Shuh Narumiya

### TARGETED SEARCH FOR ANTICANCER DRUGS

17/03/2003 - 19/03/2003

**Organisers:** Amancio Carnero and David H. Beach

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# 2002

## MECHANISMS OF INVASION AND METASTASIS

18/11/2002 - 20/11/2002

**Organisers:** Joan Massagué and Richard Hynes

## THE CELL CYCLE AND CANCER

30/09/2002 - 02/10/2002

**Organisers:** Marcos Malumbres,
Charles Sherr and Jiri Bartek

## CANCER EPIGENETICS : DNA METHYLATION AND CHROMATIN

29/05/2002 - 31/05/2002

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Nature Reviews Cancer, London, UK

**Victoria Aranda**
Nature Medicine, New York, US

**Xiaohong Helena Yang**
Cancer Cell, Cambridge, US

**Hector Peinado**
CNIO, Madrid, Spain

*Confirmed Speakers*

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Mount Sinai Medical Center,
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## 2014

FRIDAY 19 SEP
**Rafael Rosell**
Catalan Institute of Oncology, Germans Trias i Pujol Hospital, Barcelona, Spain

FRIDAY 26 SEP
**Alberto Bardelli**
Institute for Cancer Research of Candiolo-IRCCS, Torino, Italy

FRIDAY 3 OCT
**Samir Hanash**
The University of Texas MD Anderson Cancer Center, Houston, USA

FRIDAY 17 OCT
**Félix Goñi**
University of the Basque Country, CSIC-UPV/EHU, Vizcaya, Spain

FRIDAY 24 OCT
**Iain Cheeseman**
Whitehead Institute for Biomedical Research, Cambridge, USA

FRIDAY 31 OCT
**Hendrik Stunnenberg**
Radboud University Nijmegen Medical Centre, The Netherlands

TUESDAY 4 NOV
**Jean-Pierre Changeux**
Collège de France, Institut Pasteur, Paris, France

FRIDAY 7 NOV
**Shahragim Tajbakhsh**
Pasteur Institute, Paris, France

FRIDAY 14 NOV
**Rosalind Eeles**
The Institute of Cancer Research & Royal Marsden NHS Trust, London, UK

FRIDAY 21 NOV
**Bruce Stillman**
Cold Spring Harbor Laboratory (CSHL), NY, USA

FRIDAY 28 NOV
**Anja Groth**
Biotech Research and Innovation Centre, University of Copenhagen, Denmark

FRIDAY 5 DEC
**François Burgat**
The National Center for Scientific Research; Institute for Research and Study on the Arab and Muslim Worlds (IREMAM), Aix en Provence, France

FRIDAY 12 DEC
**Enrique Dans**
IE Business School, Madrid, Spain

FRIDAY 19 DEC
**Joan Margarit**
Poet, Barcelona, Spain

## 2015

FRIDAY 16 JAN
**Mª José García Borge**
ISOLDE-CERN, Geneva, Switzerland

FRIDAY 23 JAN
**Ignacio Cirac**
Max-Planck Institute, Munich, Germany

FRIDAY 6 FEB
**Margaret C. Frame**
Edinburgh Cancer Research Centre, College of Medicine and Veterinary Medicine, University of Edinburg, UK

FRIDAY 13 FEB
**Ely Tanaka**
Center for Regenerative Therapies TU Dresden, Germany

FRIDAY 20 FEB
**Mª Elena Torres-Padilla**
Institute of Genetics and Molecular and Cellular Biology, (IGBMC), Strasbourg, France

FRIDAY 6 MAR
**William Kaelin**
Howard Hughes Medical Institute, Dana-Farber Cancer Institute, Boston, USA

FRIDAY 20 MAR
**Thijn Brummelkamp**
Netherlands Cancer Institute, Amsterdam, The Netherlands

FRIDAY 17 APR
**Héctor Gómez**
University of La Coruña, Spain

FRIDAY 24 APR
**Stephen West**
London Research Institute, Cancer Research, South Mimms, UK

FRIDAY 8 MAY
**Manolis Pasparakis**
Institute for Genetics, University of Cologne, Germany

FRIDAY 22 MAY
**Luigi Fontana**
Washington University School of Medicine, St. Louis, USA

FRIDAY 29 MAY
**James Berger**
Walter and Ruth Schubert Family Chair in Biochemistry and Molecular Biology, University of California, Berkeley, USA

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