



# Cancer Epigenetics and Biology Symposium

and presentation of the  
PEBC research program

28-29 May 2009  
Barcelona



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Bellvitge Hospital Auditorium  
Barcelona



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# Presentation by the Government of Catalonia's Minister of Health, Marina Geli

It is an honour for me to present the first edition of the Cancer Epigenetics and Biology Symposium, which focuses on a rapidly expanding area of research that is leading to new approaches to treating the oncological diseases so widespread in our society. In this research field the goal is to develop personalised therapies that are less aggressive and more effective than conventional treatments.

Initiatives like this one open up new opportunities in terms of both improving people's health and boosting economic and social development. Today more than ever, we must act on the basis of a clear commitment to knowledge. Only by investing in education, innovation and research will we be able to compete effectively and ensure the well-being of our societies. That's why the Government of Catalonia is strongly committed to developing a knowledge society – a goal we pursue by implementing policies that support research centres and fostering the creation of a business fabric based on new enterprises that exploit health-related technologies.

I hope this symposium provides an opportunity to share results and experiences that will facilitate further progress in this exciting area of research. I would also like to take advantage of this occasion to welcome you all to Catalonia.



**Marina Geli i Fàbrega**  
Minister of Health

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## Foreword by Emilià Pola, IDIBELL General Director

The Bellvitge Biomedical Research Institute – IDIBELL is an emerging research institution where medicine meets with research for a better understanding of patients needs and diseases of all sorts. With a dedicated team of more than 500 researchers, IDIBELL has a commitment to address relevant clinical problems to bring about significant improvements in health and quality of life. Our research is based on the activity of the two partner hospitals (Bellvitge University Hospital and Catalan Institute of Oncology) and consequently has a very wide scope, ranging from epidemiology to infectious diseases, organ transplantation and immunology, human genetics, neurology, metabolic diseases and cancer in its very diverse forms.

The Cancer Epigenetics and Biology Program (PEBC) is the most recent addition to our scientific activity, and helps to keep IDIBELL at the forefront of global biomedical research. The emerging discipline of epigenetics is ushering in a new paradigm that significantly expands our understanding of genes and their interaction with the environment, shedding new light on many biological and medical challenges.

It is for me a pleasure and a privilege to host the symposium and to welcome you all to this exciting opportunity to discuss and to participate in one of the hottest and most rapidly developing fields of modern biology and medicine.



**Emilià Pola**  
General Director IDIBELL

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## Welcome address by Manel Esteller, PEBC Director

It was a great pleasure to announce the launching in 2008 of a new research program supported by the Department de Salut de la Generalitat de Catalunya within the IDIBELL devoted to biomedical sciences, the "Cancer Epigenetics and Biology Program" (PEBC) that I have the honour to direct.

Current research projects developed at the PEBC include, but are not restricted to, cancer epigenetics, chromatin and stem cell biology, aging, cell cycle and transformation, imprinting and the identification of cancer genes. The PEBC is located in the outskirts of Barcelona (Catalonia, Spain) within walking distance of metro station and ten minutes driving from the airport. It is located in a biomedical and scientific campus that includes two Hospitals (Hospital de Bellvitge and Hospital Duran i Reynals), the School of Medicine of the University of Barcelona, The Bellvitge Institute for Biomedical Research (IDIBELL) and an area of biotech development (Biopol).



Barcelona has recently made an enormous effort in biomedical research and the PEBC is the last new addition to this trend. The foundational goals of the PEBC are the development of high-quality basic research with a potential application for the benefit of the cancer patient in a scientific environment of international excellence. The current "Cancer Epigenetics and Biology Symposium" brings together the world class experts in the different pathways leading to human tumors and all of us will benefit from their superb and original investigations.

I look forward to hearing from you, I extend my invitation to visit our place and our beautiful city, I wish you a pleasant exploration of the PEBC web site (<http://www.pebc.cat/>) and a wonderful enjoyment of the scientific meeting.

My best wishes,

**Manel Esteller**  
M.D., PhD. PEBC Director

# Sessions of Symposium

## May 28<sup>th</sup>

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09:00-09:45 Congress welcome and introduction remarks:  
Marina Geli, Consellera, Departament de Salut, Generalitat de Catalunya  
Xavier Corbella, Director, Bellvitge University Hospital  
Jordi Alberch, Vice Dean of Research, University of Barcelona  
Emilià Pola, General Director, Bellvitge Biomedical Research Institute (IDIBELL)  
Manel Esteller, Director, Cancer Epigenetics and Biology Program (PEBC)

### Cancer Models

09:45-10:30 Mariano Barbacid  
**Mouse Tumor Models and Target Validation**  
10:30-11:15 Pier Paolo Pandolfi  
**Targeting the cancer initiating cell for therapy**  
11:15-11:45 *Coffee Break*

### Cancer Pathways

11:45-12:30 Alan Ashworth  
**Synthetic Lethal Approaches to the Development of New Therapies Targeting DNA Repair Deficiencies in Cancer**  
12:30-13:15 Rene Bernards  
**Finding mechanisms and biomarkers of drug resistance in cancer**  
13:15-15:00 *Lunch Break*

### Epigenetic Pathways

15:00-15:45 Tony Kouzarides  
**Chromatin modifying enzymes: their function and role in cancer**  
15:45-16:30 Mina Bissell  
**Extracellular matrix and tissue architecture regulate epigenetics of tissue specificity and breast cancer**  
16:30-17:15 Thea Tlsty  
**Re-programming the Epigenome in Carcinogenesis**  
17:15-17:45 *Coffee Break*

### Cancer Epigenetics

- 17:45-18:30 Peter Jones  
**Reversing Cancer Epigenomic Alterations**
- 18:30-19:15 Andy Feinberg  
**The Epigenetic Progenitor Model of Cancer**
- 19:15-20:00 Manel Esteller  
**Human Cancer Epigenetics**

## May 29<sup>th</sup>

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### Stem Cells

- 09:00-09:45 Peter Andrews  
**Population Dynamics of Human ES Cell Cultures: Self-Renewal, Adaptation and Cancer**
- 09:45-10:30 Maarten van Lohuizen  
**Role of Polycomb Repressors in Cancer and Development**

### Cancer Genetics

- 10:30-11:00 *Coffee Break*
- 11:00-11:45 Michael Stratton  
**Patterns of somatic mutation in human cancer genomes**

### DNA Replication and Repair

- 11:45-12:30 Geneviève Almouzni  
**Chromatin assembly factors and the challenges of DNA replication and repair**

### Non-coding RNAs

- 12:30-13:15 Frank Slack  
**MicroRNAs in cancer and aging**

- 13:15 **Closing remarks: Manel Esteller**

- 13:30 *Lunch and departure*

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# Cancer Epigenetics and Biology Symposium

## 28-29 May 2009, Barcelona

Chairman: Manel Esteller, PEBC Director

### Genevieve Almouzni

CNRS/Institut Curie, Paris, France  
*"Chromatin assembly factors and the challenges of DNA replication and repair"*

### Peter Andrews

University of Sheffield, Sheffield, U.K.  
*"Population dynamics of human ES cell cultures: self-renewal, adaptation and cancer"*

### Alan Ashworth

The Breakthrough Breast Cancer Research Centre, London, U.K.  
*"Synthetic lethal approaches to the development of new therapies targeting DNA repair deficiencies in cancer"*

### Mariano Barbacid

Spanish National Cancer Research Centre (CNIO), Madrid, Spain  
*"Mouse tumor models and target validation"*

### Rene Bernards

NKI-AVL, Amsterdam, The Netherlands  
*"Finding mechanisms and biomarkers of drug resistance in cancer"*

### Mina Bissell

Lawrence Berkeley National Laboratory, Berkeley, USA  
*"Extracellular matrix and tissue architecture regulate epigenetics of tissue specificity and breast cancer"*

### Manel Esteller

Cancer Epigenetics and Biology Program (PEBC),  
IDIBELL-ICREA, Barcelona, Spain  
*"Human cancer epigenetics"*

### Andrew Feinberg

Johns Hopkins University School of Medicine, Baltimore MD, USA  
*"The epigenetic progenitor model of cancer"*

### Peter Jones

USC/Norris Comprehensive Cancer Center, Los Angeles, USA  
*"Reversing cancer epigenomic alterations"*

### Tony Kouzarides

The Gurdon Institute, Cambridge, U.K.  
*"Chromatin modifying enzymes: their function and role in cancer"*

### Pier Paolo Pandolfi

Harvard University, Boston MA, USA  
*"Targeting the cancer initiating cell for therapy"*

### Frank Slack

Yale University, New Haven CT, USA  
*"MicroRNAs in cancer and aging"*

### Michael Stratton

Wellcome Trust Sanger Institute, Hinxton, Cambridge, U.K.  
*"Patterns of somatic mutation in human cancer genomes"*

### Thea Tlsty

UCSF, Helen Diller Family Comprehensive Cancer Center,  
San Francisco, USA  
*"Re-programming the epigenome in carcinogenesis"*

### Maarten van Lohuizen

NKI-AVL, Amsterdam, The Netherlands  
*"Role of polycomb repressors in cancer and development"*

Venue: Bellvitge's Hospital Auditorium

Web page: [www.idibell.org](http://www.idibell.org)  
Secretariat: [alegrand@idibell.org](mailto:alegrand@idibell.org)

# Cancer Epigenetics and Biology Symposium venue

## How to get to the Auditorium of the Bellvitge Hospital



Bellvitge University Hospital is located in Granvia de l'Hospitalet de Llobregat Avenue, in Bellvitge area, in a green area close to Castelldefels motorway.

Barcelona University Bellvitge Campus is only a few meters away and on the other side of the motorway you can find our PEBC laboratories [www.pebc.cat](http://www.pebc.cat) in the Duran i Reynals Hospital.

We recommend you use public transportation to visit us.



### How to reach us in metro

**Line 1 (Red):** Stop at Hospital de Bellvitge and at the exit you will see the main Hospital building



### How to reach us in bus

- 46** Barcelona (Pl. Espanya) - Aeroport
- 65** Barcelona (Pl. Espanya) - El Prat de Llobregat
- 79** Barcelona (Pl. Espanya) - L'Hospitalet de Llobregat (Bellvitge)
- L10** El Prat de Llobregat (St. Cosme) - Sant Just Desvern
- L70** Barcelona (Pl. Espanya) - Sant Boi (C.Cooperativa)
- L72** Barcelona (Pl. Espanya) - Sant Boi (C.Cooperativa)
- L80** Barcelona (Pl. Espanya) - Gavà (Av. Joan Carles I)
- L81** Barcelona (Pl. Espanya) - Gavà (Av. Joan Carles I)
- L86** Barcelona (Pl. Espanya) - Viladecans (Av. Can Palmer)
- L87** Barcelona (Pl. Espanya) - Viladecans (Av. Can Palmer)
- L94** Barcelona (Pl. Catalunya) - Castelldefels (Les Botigues)
- L95** Barcelona (Pl. Catalunya) - Castelldefels (Carles Riba)
- L'H1** L'Hospitalet de Llobregat
- L'H2** L'Hospitalet de Llobregat
- N16 Nocturn** Barcelona (Pl. Catalunya) - Castelldefels (Carles Riba)
- N17 Nocturn** Barcelona (Pl. Catalunya) - Aeroport



# Speakers Biography and Abstract

## Geneviève Almouzni

Geneviève Almouzni, PhD, is chair of the Unit "Nuclear dynamics and genome plasticity - UMR218 CNRS /Institut Curie, in the Research section in Paris, France. She obtained her PhD in 1988 from the university Pierre and Marie Curie, Paris. She carried out her postdoctoral research at NIH, Bethesda, USA and contributed to the characterization of the importance of chromatin for transcriptional regulation using *Xenopus* as a model system for developmental approaches. In 1994, she was appointed as a junior group leader, to develop her independent research on chromatin dynamics at the Curie Institute and then expanding her interest to various aspects of DNA metabolism including DNA repair and replication and also the use of a variety of experimental systems. She has a long standing experience in studying chromatin (over 18 years). Her work contributed to many aspects of chromatin analysis from the development of *in vitro* systems, to the identification of the role of key histone chaperones. She also developed approaches using single molecules and analysis of nuclear architecture. Taken together this has given rise to series of publications in journal of wide audience (over 100 peer-reviewed papers, and one patent). Her current interest is to understand the basic principles underlying the 3D organization of the cell nucleus and their interrelationships with genome stability. These studies are pursued in the context of development and cell cycle, in normal and pathological situations such as the one encountered during tumorigenesis. She serves as a member of several scientific advisory boards and the board of EMBO Journal EMBO Reports, Journal of Cell Science, Chromosoma, Genes & Development, Cell, Current Opinion in Cell Biology and Nature Reviews Molecular Cell Biology (Highlights advisor). She has developed collaborations at the European level and promoted research in the field of Epigenetics while serving as a co-coordinator in the epigenome Network of Excellence. She is an EMBO Member (2000) and Faculty 1000, and received the silver medal from the CNRS and the Prize "Cino et Simone del Duca" from the Institut de France (2006).



Institut Curie, CNRS  
Paris, France

### Chromatin assembly factors and the challenges of DNA replication and repair

Inheritance and maintenance of the DNA sequence and its organization into chromatin are central for eukaryotic life. To orchestrate DNA-replication and -repair processes in the context of chromatin is a challenge.

Factors have been isolated from cell extracts that stimulate early steps in chromatin assembly *in vitro*. One such factor, chromatin assembly factor-1 (CAF-1), facilitates nucleosome formation coupled to DNA synthesis. It is thought to participate in a marking system at the crossroads of DNA replication and repair to monitor genome integrity and to define particular epigenetic states. We have now identified a chromatin assembly pathway independent of DNA synthesis involving the HIRA protein. Notably, CAF-1 is part of the histone H3 complex, H3.1 complex (replicative form) and HIRA of the H3.3 complex (replacement form) (Tagami et al, 2004, Nakatani et al, 2004). In addition, another histone chaperone, Asf1, has to be integrated in a network of interactions leading to nucleosome deposition. A major goal in our laboratory is now to better integrate the function of these factors *in vivo* during development and also in connection with replication, repair and control of histone pools. We will discuss our recent findings on this topics and the interrelationships with other assembly factors.

### Selected Publications

- Groth A., Rocha W., Verreault A. & Almouzni G. (2007) *Chromatin challenges during DNA replication and repair*. *Cell*, 128, 721-733.
- Groth A., Corpet A., Cook A., Roche D., Bartek J., Lukas J. & Almouzni G. *Regulation of replication fork progression through histone supply/demand*. *Science* (2007).
- Loyola A. & Almouzni G. (2007) *Marking histone H3 variants make your choice or let's play the game*. *Trends in Biochem. Sc.*, 32, 425-433.
- De Koning L., Corpet A., Haber J.E. & Almouzni G. (2007) *Histone chaperones: An escort network regulating histone traffic*. *Nature Struct. & Mol. Biol.*, 14, 997-1007.
- Quivy J.P., Gérard A., Cook A.J.L., Roche D., Moné M. & Almouzni G. (2008) *A functional HP1-CAF-1 interaction module necessary to replicate and propagate pericentric heterochromatin impacts on S-phase progression in mouse cells*. *Nature Struct. & Mol. Biol.*, 15, 972-979.

## Peter W Andrews

Peter Andrews, PhD, obtained a BSc in Biochemistry from the University of Leeds in 1971, and a D. Phil. in Genetics from the University of Oxford in 1975. Following postdoctoral research at the Institut Pasteur in Paris and the Sloan Kettering Institute in New York, he was a research scientist on the staff of the Wistar Institute of Anatomy and Biology in Philadelphia from 1978 to 1992. In 1992 he was appointed to the Arthur Jackson Chair of Biomedical Research in the University of Sheffield, where he is currently co-director of the Centre for Stem Cell Biology. His research focuses on the biology of pluripotent human stem cells. Among his current activities he co-ordinates the International stem Cell Initiative, which is focused upon characterising standard markers and culture conditions for human ES cells. He is also the co-ordinator of ESTOOLS, a European Integrated Project of 21 partners under the sixth framework program.



The Centre for Stem Cell Biology  
and Department of Biomedical Science,  
The University of Sheffield, UK

### Population Dynamics of Human ES Cell Cultures: Self-Renewal, Adaptation and Cancer

A key feature of pluripotent stem cells is their ability to proliferate indefinitely while maintaining an ability to differentiate into all somatic cell types. Such proliferation is known as 'self-renewal'. However, these cells may also differentiate spontaneously, or in response to specific cues. When they divide, stem cells must choose between self renewal and commitment to differentiation. Further, if they commit to differentiate they must choose between different lineages. An understanding of the molecular mechanisms that control these decision processes underlies any potential use of human embryonic stem (ES) cells, or iPS cells, whether in regenerative medicine or in other areas such as drug discovery, toxicology or disease modeling.

Some degree of spontaneous differentiation is common in cultures of human ES cells. This can confuse studies of human ES cell behavior if assays are based on assessment

of the population as a whole, without taking account of the consequent heterogeneity of such cultures. Further, a propensity for differentiation provides a basis for selective pressures that may lead to the appearance of variant ES cells that exhibit an increased probability of self renewal over differentiation, or cell death through apoptosis. Indeed human ES cell lines do tend to accumulate non-random genetic changes on prolonged culture. These genetic changes include amplifications of chromosomes 12, 17 and X similar to those seen in embryonal carcinoma (EC) cells, the stem cells of teratocarcinomas and the malignant counterparts of ES cells. Thus the progressive culture adaptation of human ES cells in culture provides a unique model that may be pertinent to the progression of stem cell based cancers.

Accumulating evidence suggests that the 'stem cell compartment' in both ES and other stem cells, including cancer stem cells, may be composed of distinct substates. Another aspect of culture adaptation of human ES cells is that it alters the population dynamics of ES cultures, particularly affecting the behavior of substates within the stem cell compartment. Understanding the nature of these substates and their interactions may provide insights into the mechanisms that control self renewal, commitment to differentiation and lineage selection of ES and, ultimately iPS cells. Inevitably these same mechanisms may also play a role in cancer progression.

### Selected Publications

- Andrews, P.W. (2002). *From teratocarcinomas to embryonic stem cells*. *Phil. Trans. R. Soc. Lond. B* 357, 405-417.
- Baker, D.E.C., Harrison, N.J., Maltby, E., Smith, K., Moore, H.D., Shaw, P.J., Heath, P.R., Holden, H., Andrews, P.W., (2007) *Adaptation to culture of human embryonic stem cells and oncogenesis in vivo*. *Nature Biotechnology* 25: 207 – 215.
- Draper J.S. Smith, K., Gokhale, P.J., Moore, H.D., Maltby, E., Johnson, J., Meisner, L., Zwaka, T.P., Thomson, J.A., Andrews, P.W. (2004) *Karyotypic evolution of human Embryonic Stem (ES) cells in culture: recurrent gain of chromosomes 17 (17q) and 12*. *Nat. Biotech.* 22: 53-54
- Enver T, Soneji S, Joshi C, Iborra F, Orntoft T, Thykjaer T, Maltby E, Smith K, Abu Dawd R, Matin M, Gokhale P, Draper JS, Andrews, P.W. (2005) *Cellular differentiation hierarchies in normal and culture adapted human embryonic stem cells*. *Human Mol Genet.* 14: 1-12.

## Alan Ashworth

Professor Alan Ashworth FRS, is Professor of Molecular Biology and Director of The Breakthrough Breast Cancer Research Centre at The Institute of Cancer Research, London. The Centre contains around 120 scientists and researchers working on aspects of breast cancer ranging from basic molecular and cellular biology through to translational research and clinical trials.



Ashworth contributed to the discovery of the BRCA2 gene in 1995 and ten years later, Prof. Ashworth's team identified the synthetic lethal relationship between BRCA mutations and PARP inhibitors. The exquisite sensitivity of BRCA1 or BRCA2 mutant cells to PARP inhibitors forms the rationale behind clinical trials that are now assessing the potential of these agents. Ashworth's other research interests are wide ranging and include high-throughput genomic and functional approaches to the study of cancer.

Ashworth is an elected member of EMBO and the Academy of Medical Sciences. In 2008, he was elected a Fellow of the Royal Society for his contributions to mammalian genetics and the developments of new therapeutic approaches for cancer.

Breakthrough Breast Cancer Research Centre  
The Institute of Cancer Research  
London, UK

### Synthetic Lethal Approaches to the Development of New Therapies Targeting DNA Repair Deficiencies in Cancer

Many tumours harbour defects in their ability to maintain genomic integrity. This contributes to the mutational burden and likely fosters pathogenesis. We have been exploring therapeutic strategies to exploit these defects. We have used a synthetic lethal approach to target the defect in DNA repair by homologous recombination in tumours with a BRCA1 or BRCA2 mutation. This strategy using PARP inhibitors is showing considerable promise in the clinic. Here, I will describe the approach as well recent work defining determinants of sensitivity and resistance to PARP inhibitors. The application of the synthetic lethal approach to other cancer types will also be discussed.

#### Selected publications

- Turner N, Tutt A, Ashworth, A (2004) *Hallmarks of 'BRCAness' in sporadic cancers. Nat Rev Cancer* 4: 814-819
- Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, Santarosa M, Dillon KJ, Hickson I, Knights C, Martin NM, Jackson SP, Smith GC, Ashworth, A (2005) *Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature* 434: 917-921
- lorns, E., Lord, C.J., Turner, N. and Ashworth, A (2007) *Utilizing RNA interference to enhance cancer drug development. Nat Rev Drug Disc*, 6, 556-568.
- Edwards, S., Brough, R., Lord, C.J., Natrajan, R., Vatcheva, R., Levine, D.A., Boyd, J., Reis-Filho, J.S. and Ashworth, A. (2007) *Resistance to Therapy caused by Intragenic Deletion in BRCA2. Nature*, 451 (7182): 1111-5
- Ashworth A (2008) *A synthetic lethal therapeutic approach: poly(ADP) ribose polymerase inhibitors for the treatment of cancers deficient in DNA double-strand break repair. J Clin Oncol*, 26: 3785-3790

## Mariano Barbacid

Mariano Barbacid, PhD, was born in Madrid, Spain in 1949. He got his Ph.D. degree in Biochemistry from the Universidad Complutense of Madrid in 1974. From 1974-1978 he trained as a postdoctoral fellow in retroviral oncogenes in the group of Stuart A. Aaronson at the National Cancer Institute in Bethesda, Maryland. In 1978 he started his own group to work on the molecular biology of human tumours. His work led to the isolation of the first human cancer gene (oncogene) in the spring of 1982. Subsequently, he demonstrated that this oncogene was a mutant allele of the H-Ras proto-oncogene and owed its oncogenic properties to a single somatic mutation in its coding sequences. These seminal findings, also made independently by the groups of Robert Weinberg (MIT) and Michael Wigler (CSHL), have played a key role in establishing the molecular bases of human cancer.



In 1984, Barbacid moved to Frederick Maryland as Head of the Developmental Oncology Section and in 1988, Barbacid joined the Bristol Myers-Squibb Pharmaceutical Research Institute in Princeton, New Jersey where he became Vice President, Oncology Drug Discovery in 1995.

In 1998, he returned to his native Madrid to create the CNIO that currently houses 450 investigators allocated in twenty five research groups (see Commentary in *Cell*, 129: 641-644, 2007). Since his return to Spain, Barbacid is concentrating on the study of the role of cell cycle regulators in vivo and on the design of new animal models of cancer using gene-targeting technologies.

Other contributions of special scientific relevance include the identification of Ras oncogenes as targets of chemical carcinogens (1984-85), the discovery of the Trk family of tyrosine protein kinase receptors (1985-88) and the subsequent demonstration that they are the signalling receptors for the NGF family of neurotrophic factors (1991). More recently (2003-07), the Barbacid lab has demonstrated that mammalian Cdks are not essential for driving the specific phases of the cell cycle but to sustain proliferation of specialized cell types. These observations have led to a new model for the mammalian cell cycle.

The relevance of his work has been recognised by several awards, including the Young Investigator Award of the American Association of Cancer Research (USA, 1986), Steiner Prize (Switzerland, 1988), Ipsen Prize in Neurobiology (France, 1994), the Brupbacher Cancer Research Prize (Switzerland, 2005) and the Medal of Honour of the International Agency for Cancer Research (WHO) (Lyon 2007). In addition, Barbacid has received several Spanish Awards and a Doctorate Honoris causa by the Universidad Internacional Menendez y Pelayo (1995). He is a Member of EMBO since 1996.

Barbacid has 239 publications, including 170 original articles and 24 invited reviews in journals with impact factor (average IF 12.1) as well as 45 book chapters and proceedings of various symposia. He has an overall Hirsch "h" factor of 84.

Director,  
Centro Nacional de Investigaciones Oncológicas (CNIO)  
Madrid, Spain

### Mouse Tumor Models and Target Validation

To date, more than 500 genes have been found mutated in human cancer, thus providing a wealth of therapeutic targets. Unfortunately, only a handful of these mutated genes encode druggable products. Moreover, even in those the cases in which the mutated protein can be pharmacologically inhibited (protein kinases, growth factors, receptors, etc.), the degree of therapeutic efficacy observed upon pharmacological inhibition has been rather modest, with the exception of Gleevec and possibly Herceptin. A plausible explanation for these observations has been recently provided by efforts aimed at sequencing cancer genomes. Advanced and metastatic tumors, those most likely in need of pharmacological intervention, carry mutations in multiple pathways, thus suggesting that successfully cancer therapies will require combinations of drugs capable of blocking two or possibly more distinct pathways. To achieve this

goal, it will be necessary to expand the repertoire of druggable targets beyond those actually mutated in the tumor by including other targets within the same pathways, providing that their inhibition will have similar consequences.

An illustrative example of such tumors are those carrying mutations in the K-Ras oncogene. These tumors account for about one third of all human malignancies, including those with rather poor outcomes such as pancreatic adenocarcinoma (PDA), colorectal carcinoma (CRC) and non-small cell lung carcinoma (NSCLC). Unfortunately, the K-Ras oncoprotein is not druggable since this molecule owes its tumorigenic properties to mutations that eliminate its intrinsic enzymatic activity (a GTPase). Hence, there are no available strategies to block K-Ras oncogenic signaling. On the hand, Ras signaling pathways are loaded with druggable kinases some of which (B-Raf, PI3K, Akt) have also been found mutated in other human tumors. Thus, it could be argued that blocking one of these downstream kinases should have significant therapeutic effect. Unfortunately, early clinical results, at least with B-Raf inhibitors, have not been too encouraging.

In order to understand the molecular bases of tumor intervention in vivo and to devise better strategies to block oncogenic signaling, we and others have developed mouse tumor models in which an endogenous K-Ras oncogene can be activated by genetic means in adult animals leading to the development of tumors that faithfully resemble those observed in human patients. These mice can be subsequently endowed with germ line, or better, conditional mutations whose activation ablates the putative therapeutic targets. These mice can be used to evaluate the relative contribution of these targets to tumor development by eliminating them, either alone or in combination, at various times during tumor progression. I will present our most recent results following these basic strategies to evaluate the therapeutic effect of ablating the Raf, Mek and Erk kinases as well as the cell cycle Cdks (Cdk2, Cdk4 and Cdk6) in K-Ras induced NSCLCs.

## René Bernards

René Bernards received his PhD in 1984 from the University of Leiden. He joined the laboratory of Robert Weinberg at the Whitehead Institute in Cambridge, USA for his postdoctoral training. Here, he studied the function of both oncogenes and tumor suppressor genes. He continued this work when he joined the Massachusetts General Hospital Cancer Center as an assistant professor in 1988. In 1992 he was appointed senior staff scientist at the Netherlands Cancer Institute. In 1994 he was appointed part time professor of molecular carcinogenesis at Utrecht University, The Netherlands. In the last six years, his laboratory has focused on the development of new tools to carry out genome-wide genetic screens to identify novel genes that act in cancer-relevant pathways. In July of 2003 he co-founded "Agendia", a genomics-based diagnostic company that started offering the first microarray-based diagnostic test for the clinical management of breast cancer in 2004. He received several awards for his research, including the Pezcoller Foundation-FECS Recognition for Contribution to Oncology, the Ernst W. Bertner Award for Cancer Research from the M.D. Anderson Cancer Center, the ESMO Lifetime Achievement Award in Translational Research in Breast Cancer and the Spinoza award from the Netherlands Organization for Scientific Research. He is a member of the Royal Netherlands Academy of Arts and Sciences.



Division of Molecular Carcinogenesis,  
The Netherlands Cancer Institute,  
Amsterdam, The Netherlands

### Finding mechanisms and biomarkers of drug resistance in cancer

Unresponsiveness to therapy remains a significant problem in the treatment of cancer, also with the new classes of targeted therapeutics. In my laboratory, we use functional genetic approaches to identify biomarkers that can be used to predict responsiveness to clinically-relevant cancer therapeutics. We focus on the clinically-relevant targeted cancer drugs such as trastuzumab (Herceptin), PI3K inhibitors, mTOR inhibitors, Histone Deacetylase inhibitors and retinoic acid. These drugs target specific molecules or pathways that are often activated in cancer. Nevertheless, it remains poorly explained why a significant number of tumors do not respond to the therapy. We aim to elucidate the molecular pathways that contribute to unresponsiveness to targeted cancer therapeutics using a functional genetic approach. This will yield biomarkers that can be used to predict how individual patients will respond to specific drugs. Furthermore, this work may allow the development of drugs that act in synergy with the established drug in the treatment of cancer.

To identify biomarkers that control tumor cell responsiveness to cancer therapeutics, we use both genome-wide gain-of-function genetic screens (with cDNA expression libraries) and genome wide loss-of-function genetic screens (with RNA interference libraries) in cancer cells that are sensitive to the drug-of-interest. We search for genes whose over-expression or whose down-regulation in cultured cancer cells confers resistance to the drug-of-interest. Once we have identified such genes, we ask if their expression is correlated with clinical resistance to the drug-of-interest using tumor samples of cancer patients treated with the drug in question, whose response to therapy is documented. Examples of loss-of-function genetic screens to identify mechanisms of resistance to different cancer drugs will be presented.

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## Mina Bissell

Mina Bissell, PhD, is a pioneer in the area of the role of extracellular matrix (ECM) and microenvironment in regulation of tissue-specific function with special emphasis in breast cancer, where she has changed some established paradigms. She earned an A.B. with honors in chemistry from Harvard/Radcliffe College and a Ph.D. in bacterial



genetics from Harvard University. She joined the Lawrence Berkeley National Laboratory in 1972, became Director of Cell & Molecular Biology in 1988, and was appointed Director of all of Life Sciences in 1992. Upon stepping down as the Life Sciences Division Director, she was named Distinguished Scientist. She is also the OBER/DOE Distinguished Scientist Fellow in Life Sciences.

Dr. Bissell has authored more than 300 publications, is member of 5 international scientific boards, and is on the editorial board of a dozen scientific journals, including Science magazine. She has given more than 90 'named and distinguished' lectures. Her awards include the Lawrence Award and medal, the Mellon Award from the University of Pittsburgh, the Eli Lilly/Clowes Award from AACR, the first "Innovator Award" of the US DOD for breast cancer research, the Brinker Award from Komen Foundation, the Discovery Health Channel Medical Honor and medal, the H. Lee Moffitt Cancer Center Ted Couch Lectureship and Award, the Pezcoller Foundation–AACR International Award for Cancer Research, the 2008 Excellence in Science Award from FASEB. She has been awarded the 2008 Mina J. Bissell Award by the University of Porto and the 2008 American Cancer Society's Medal of Honor for Basic Research Award.

Dr. Bissell was elected as a Fellow of AAAS, the Institute of Medicine of the National Academies, the American Academy of Arts and Sciences, and the American Philosophical Society. She served as President of the American Society of Cell Biology and the International Society of Differentiation. She has received honorary doctorates from Pierre & Marie Curie University in Paris and the University of Copenhagen.

Distinguished Scientist, Life Sciences Division  
Faculty, Comparative Biochemistry, UC Berkeley  
Ernest Orlando Lawrence Berkeley National Laboratory  
Berkeley, California, USA

## Extracellular matrix and tissue architecture regulate epigenetics of tissue specificity and breast cancer

The ability of epithelial cells to organize into polarized three dimensional (3D) structures correlates closely with their normal or malignant status. In a versatile model of morphogenesis, we have shown in past studies that inhibiting a number of key signaling pathways in human breast cancer cells grown in laminin-rich ECM gels leads to 'reversion' of the malignant phenotype. The resulting growth-arrested polarized structures resemble normal 'acini,' and the reversion model has helped us to understand how polarity of the normal gland structures may be disrupted as breast cancer progresses. We now have used two additional models to study signaling integration in single mammary cells and also mammary organoids, where we have modeled mammary invasion into the stromal collagen during branching morphogenesis to learn how tumor cells usurp these pathways to invade. We provide additional proof for our contention that all signaling pathways must directly or indirectly communicate to maintain homeostasis. We show how biochemical and mechanical signaling from the ECM, the ECM receptors and MMPs interconnect with cell and tissue architecture in reciprocal and reiterating loops to maintain tissue specificity.

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## Manel Esteller

**Manel Esteller** (Sant Boi de Llobregat, Barcelona, Catalonia, Spain, 1968) graduated in Medicine with Honours from the Universidad de Barcelona in 1992, where he also obtained his PhD. 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 of the Bellvitge Biomedical Research Institute (IDIBELL) in L'Hospitalet, Barcelona and leader of the Cancer Epigenetics Group. 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 two 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 and Carcinogenesis, Editor-in-Chief of Epigenetics and Advisor of the Human Epigenome Project, Associate Member of the Epigenome Network of Excellence and President of the Epigenetics Society. His numerous awards include: Best Young Cancer Researcher Award bestowed 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), Young Investigator Award from the American Association for Cancer Research-AFLAC (2001), Carcinogenesis Award (2005), Beckman-Coulter Award (2006), Francisco Cobos Biomedical Research Award (2006), Fondazione Piemontese per la Ricerca sul Cancro (FPRC) Award (2006), Swiss Bridge Award (2006). National Research Award in Oncology "Maria Julia Castillo" (2007), "Dr Josep Trueta" Award by the Academy of Medical Sciences of Catalonia (2007), Innovation Award from the Commonwealth of Massachusetts (2007), Human Frontier Science Program Award (2007), "Dr. Jacint Vilardell" Foundation Award (2008), Prize "Conde de Cartagena" by the Spanish Royal Academy of Medicine (2009), Award in Preclinical Biomedical Research by the Lilly Foundation (2009) and Josef Steiner Cancer Research Award (2009).

Dr Manel Esteller is the Director of the Cancer Epigenetics and Biology Program of the Bellvitge Institute for Biomedical Research (IDIBELL), Leader of the Cancer Epigenetics Group, Professor of Genetics in the School of Medicine of the University of Barcelona, and an ICREA Research Professor.

Cancer Epigenetics and Biology Program,  
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## Human Cancer Epigenetics

An altered pattern of epigenetic modifications is central to many common human diseases, including cancer. Many studies have explored the mosaic patterns of DNA methylation and histone modifications in cancer cells on a gene-by-gene basis, among them the seminal finding of transcriptional silencing of tumor suppressor genes by CpG island promoter hypermethylation. Epigenetic gene inactivation in transformed cells involves many "belts of silencing". We are in the process of completing the molecular dissection of the entire epigenetic machinery involved in methylation-associated silencing, such as DNA methyltransferases, methyl-CpG binding domain proteins, histone deacetylases, histone methyltransferases, histone demethylases and Polycomb proteins. The first indications are also starting to emerge about how the combination of cellular selection and targeted pathways leads to abnormal DNA methylation. In addition to classical tumor-suppressor and DNA repair genes, epigenetic gene silencing includes genes involved in premature aging and microRNAs with growth inhibitory functions. Recent technological advances are now enabling cancer epigenetics to be studied genome-wide. It is time to "upgrade" cancer epigenetics research and put together an ambitious plan to tackle the many unanswered questions in this field using genomics approaches to unravel the epigenome.

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## Andrew Feinberg

Andrew Feinberg, PhD, studied mathematics and humanities at Yale in the Directed Studies honors program, and he received his B.A. (1973) and M.D. (1976) from the accelerated medical program at Johns Hopkins University, as well as an M.P.H. from Johns Hopkins (1981). He performed a postdoctoral fellowship in developmental biology at UCSD, clinical training in medicine and medical genetics at University of Pennsylvania and genetics research and clinical training at Johns Hopkins. Dr. Feinberg performed seminal work linking altered DNA methylation to human cancer, loss of imprinting (LOI) in cancer, and the molecular basis of Beckwith-Wiedemann syndrome. He also identified the first common variant (genetic or epigenetic) for cancer risk, LOI of IGF2 in colorectal cancer. He is King Fahd Professor of Medicine, Molecular Biology & Genetics and Oncology, and he holds an Adjunct Professorship at the Karolinska Institute in Sweden. Dr. Feinberg is Director of the Center for Epigenetics, an NHGRI-designated Center of Excellence in Genome Sciences. As part of the center, he has organized a highly innovative program to bring gifted minority high school students into genetics and genomics. Dr. Feinberg also has invented a number of widely used molecular tools, including random priming. His honors include election to the American Society for Clinical Investigation, the Association of American Physicians, and the Institute of Medicine of the National Academy of Sciences, as well as membership on the ISI most cited authors list, a MERIT Award of the National Cancer Institute, a Doctor of Philosophy (Hon. Caus.) from Uppsala University, and the President's Diversity Recognition Award of Johns Hopkins University.



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### The Epigenetic Progenitor Model of Cancer

In over 20 years since the discovery of altered DNA methylation in cancer, many epigenetic alterations have been found in human cancer, including global and specific gene hypomethylation, hypermethylation, altered chromatin marks, and loss of genomic imprinting. Cancer epigenetics has been limited by questions of cause and effect, since epigenetic changes can arise secondary to the cancer process and its associated widespread changes in gene expression. To address the issue of causal mechanism, we have focused most recently on cancer-predisposing epigenetic alterations. We have linked loss of imprinting (LOI) of the autocrine growth factor gene IGF2 to cancer risk, suggesting an epigenetic progenitor model of cancer, in which epigenetically altered stem cells precede gatekeeper mutations in cancer, which differs from the classical clonal mutational model. Recent work suggests a model of chemoprevention targeted at epigenetically altered stem cells. We are identifying additional mechanisms that trigger epigenetic reprogramming of stem cells in cancer. Finally, we have developed a novel approach to discovering site-specific epigenetic alterations throughout the genome and are applying this approach to the cancer genome. This work shows both hypomethylation and hypermethylation of CpG islands and nearby sequences we term CpG island shores. Methylation changes in cancer are at sites that vary normally in tissue differentiation, consistent with the epigenetic progenitor model of cancer.

## Peter A. Jones

Peter A. Jones, PhD, DSc, Director of the University of Southern California/Norris Comprehensive Cancer Center and Distinguished Professor of Urology and Biochemistry & Molecular Biology, at the Keck School of Medicine University of Southern California, is known for his studies on the molecular biology of cancer and of basic mechanisms of DNA methylation and its role in cancer and differentiation. His laboratory discovered the effects of 5-azacytidine on DNA methylation and linked this process to the activation of silenced genes.



Dr. Jones was born in South Africa, raised and attended school in Rhodesia (now Zimbabwe), and received his Doctor of Philosophy Degree from the University of London in 1973. He joined the USC in 1977, attaining the rank of Professor in 1985, and became Director of the Cancer Center in 1993. In 1983 he won the USC Associates Award for Creativity in Research and Scholarship. He is the author of more than 250 journal publications and book chapters, and serves on several national and international committees, panels, and editorial boards. He is the past President of the American Association for Cancer Research. He has received a variety of honors, including the Outstanding Investigator Grant from the National Cancer Institute.

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### Reversing Cancer Epigenomic Alterations

Epigenetic reprogramming is commonly observed in cancer and involves multiple mechanisms including DNA methylation and polycomb repressor complexes (PRCs). We examined patterns of gene expression, DNA methylation and polycomb marks which differentiate prostate cancer from normal prostate epithelial cells. Three major changes in the epigenome distinguish the two cell types. Several genes containing CpG islands which are silenced by PRCs in normal cells, acquire DNA methylation silencing and lose their PRC marks (epigenetic switching). Because these genes are normally silent, the switch does not cause de novo repression but might significantly reduce epigenetic plasticity. Two other groups of genes are silenced either by de novo DNA methylation or de novo PRC occupancy. More recently, we have examined the fine structure of the start sites of these genes and have implicated the presence of nucleosomes at the transcription start sites as being fundamental to silencing. Interestingly, DNA demethylation drugs such as 5-aza-CdR rapidly reverse all of these changes when reactivating genes. An integrated analysis of the epigenome and its response to drug therapy should allow for the better design of drugs which target epigenetic silencing mechanisms in cancer.

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## Tony Kouzarides

Tony Kouzarides is the Royal Society Napier Professor at the University of Cambridge and Deputy Director of Gurdon Institute. His laboratory at the Gurdon Institute investigates the function of chromatin modifications and their role in cancer.



Tony did his PhD at the University of Cambridge on the cancer inducing potential of human cytomegalovirus. He continued this work at the MRC Laboratory of Molecular Biology in Cambridge as a post-doctoral scientist. He then went to New York to extend his postdoctoral work at New York University Medical Center where he characterised the leucine zipper dimerisation domain of the c-Fos oncoprotein. He returned to Cambridge to lead a research group and has been at the Gurdon Institute since 1991.

He was elected member of the European Molecular Biology organization in 1998 and the British Academy of Medical Sciences in 2001. He is a member of the Science Strategy Advisory Group for Cancer Research UK foundation and on the scientific advisory board for the Marie Curie Institute (UK), the Institute of Molecular Biology and Biotechnology (Greece), the Centre for Genomic Research (Spain) and the Cancer Epigenetics and Biology Program (Spain).

He is a founder of Chroma Therapeutics, a cancer drug discovery company which has as its focus enzymes that modify chromatin. He is also a founder and director of Abcam Ltd, an antibody reagents company.

Tony is invited to give over 25 talks a year around the world and has over 130 publications in research journals. He has been awarded the Wellcome Trust medal for research in biochemistry related to medicine (UK), the Tenovus Medal (UK), the Bodossaki Foundation prize in Biology (Greece) and the Bijvoet Medal (Holland).

Gurdon Institute,  
University of Cambridge, UK

### Chromatin modifying enzymes: their function and role in cancer

Modifications of chromatin play an important role in the regulation of many biological processes, including transcription, DNA repair and replication. There are at least eight different classes of enzymes that modify histone and generate covalent and non-covalent changes to key residues within histones. Many lines of evidence now point to such enzymes as being implicated in a variety of cancers. The development of anti-cancer drugs that act on this class of enzyme is high following the approval of a deacetylases inhibitor in the treatment of cutaneous T cell leukaemia.

Our lab is interested in characterising the function of chromatin modifying enzymes and understanding the function of different modifications in the process of transcription. We are involved in characterising the methylation of lysines and arginines, the conversion of arginines to citrulline, the phosphorylation of serines and tyrosines and the isomerisation of prolines. We are also analysing the clipping of histone H3 tail by an endopeptidase, a process which regulates gene expression in budding yeast. Finally, we have a drive to identify novel modifications of chromatin with the premise that the newly identified pathways may also be implicated in cancer.

## Pier Paolo Pandolfi

Pier Paolo Pandolfi received his MD in 1989 and his PhD in 1996 from the University of Perugia, Italy, after having studied Philosophy at the University of Rome, Italy. He received post-graduate training at the National Institute for Medical Research and the University of London in the UK. He became an Assistant Member of the Molecular



Biology Program and the Department of Human Genetics at Memorial-Sloan-Kettering Cancer Center in 1994. Dr. Pandolfi grew through the ranks to become a Member in the Cancer Biology and Genetics Program at the Sloan Kettering Institute; Professor of Molecular Biology and Human Genetics at the Weill Graduate School of Medical Sciences at Cornell University; Professor, Molecular Biology in Pathology and Laboratory Medicine, Weill Medical College at Cornell University; and Head of the Molecular and Developmental Biology Laboratories at MSKCC. Dr. Pandolfi was also the incumbent of the Albert C. Foster Endowed Chair for Cancer Research at Memorial Sloan-Kettering Cancer Center.

Dr. Pandolfi presently holds the Reisman Endowed Chair of Medicine, and is Professor of Pathology at Harvard Medical School. He serves as the Director of Research, Beth Israel Deaconess Cancer Center; Director, Cancer Genetics Program; and Chief, Division of Genetics in the Department of Medicine, Beth Israel Deaconess Medical Center, and is a Member of the Department of Pathology, Beth Israel Deaconess Medical Center.

Dr. Pandolfi has been the recipient of numerous awards including the LLSA Scholar Award (1997), the Irma T. Hirschl Trust Award (1999), the Alexandra J. Kefalides Prize for Leukemia Research (1999), the Hamdan Award for Medical Research Excellence (2000), the Lombroso Prize for Cancer Research of the Weizmann Institute of Science (2001), the Leukemia and Lymphoma Society's Stohlman Scholar Award (2001); the William and Linda Steere Foundation Award (2004) and the prize for Scientific Excellence in Medicine from the American-Italian Cancer Foundation (2005). He also has recently been awarded the NIH MERIT Award for superior competence and outstanding productivity in research and the Fondazione Cortese International Award.

In 2006 Dr. Pandolfi was elected as a member of the American Society for Clinical Investigation (ASCI) and the American Association of Physicians (AAP), and in 2007 as Member of the European Molecular Biology Organization (EMBO).

The research carried out in Dr. Pandolfi's laboratory has been seminal to elucidating the molecular mechanisms and the genetics underlying the pathogenesis of leukemias, lymphomas and solid tumors as well as in modeling these cancers in the mouse. Dr. Pandolfi and colleagues have characterized the function of the fusion oncoproteins and the genes involved in the chromosomal translocations of acute promyelocytic leukemia (APL), as well as of major tumor suppressors such as PTEN and p53, and novel proto-oncogenes such as POKEMON. The elucidation of the molecular basis underlying APL pathogenesis has led to the development of novel and effective therapeutic strategies. As a result of these efforts, APL is now considered a curable disease. Additional novel therapeutic concepts have emerged from this work and are currently being tested in clinical trials.

Cancer Genetics Program, Beth Israel Deaconess Cancer Center, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA

### Targeting the cancer initiating cell for therapy

Failure to eradicate the cancer-initiating cell (CIC) and, specifically, the quiescent CIC population is at the core of disease relapse upon conventional and targeted therapies. We will discuss here how the elucidation of a novel PTEN/PI3K signaling regulatory network for the control of stem cell-ness has allowed us to propose and experimentally test novel concepts for CIC eradication of immediate therapeutic applicability.

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## Frank Slack

Frank Slack received his B.Sc from the University of Cape Town in South Africa, before completing his PhD in molecular biology at Tufts University School of Medicine. He started work on microRNAs as a postdoctoral fellow in Gary Ruvkun's laboratory at Harvard Medical School, where he co-discovered the second known microRNA, let-7. He is currently an Associate Professor in the Department of Molecular, Cellular and Developmental Biology at Yale University. The Slack laboratory studies the roles of microRNAs and their targets in development, disease and aging.



Department of Molecular, Cellular  
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New Haven, USA

### MicroRNAs in cancer

MicroRNAs are small non-coding RNAs that regulate gene expression to control important aspects of development and metabolism such as cell differentiation, apoptosis and lifespan. let-7 encodes a microRNA implicated in human cancer. Specifically, human let-7 is poorly expressed or deleted in lung cancer, and over-expression of let-7 in lung cancer cells inhibits their growth, demonstrating a role for let-7 as a tumor suppressor in lung tissue. let-7 is expressed in the developing mammalian lung and regulates the expression of important oncogenes implicated in lung cancer, suggesting a mechanism for let-7's involvement in cancer. We are focused on the role of let-7 and other oncomirs in regulating proto-oncogene expression during development and cancer, and on using miRNAs to suppress tumorigenesis.

NIH, CT DPH

## Michael R Stratton

Michael Stratton is Deputy Director of the Wellcome Trust Sanger Institute, where he is Head of the Cancer Genome Project, and is Professor of Cancer Genetics at the Institute of Cancer Research. He qualified in medicine at Oxford University and Guys Hospital, trained as a histopathologist at the Hammersmith and Maudsley Hospitals and obtained a PhD in the molecular biology of cancer at the Institute of Cancer Research. His research interests have been in the genetics of cancer. He led the group that mapped and identified the high risk breast cancer susceptibility gene, BRCA2. More recently he has found moderate risk breast cancer susceptibility genes such as CHEK2, ATM, BRIP and PALB2 as well as genes for skin, testis, colorectal, thyroid, and childhood cancers. At the Cancer Genome Project he conducts high throughput, systematic genome-wide searches for somatic mutations in human cancer in order to identify new cancer genes, to understand processes of mutagenesis in human cancers and to reveal the role of genome structure in determining abnormalities of cancer genomes. These studies have led to the discovery of activating somatic mutations in the BRAF and ERBB2 genes in melanoma and lung cancer respectively and have described basic patterns of somatic mutation in cancer genomes. He was elected a Fellow of the Royal Society in 2008.



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### Patterns of somatic mutation in human cancer genomes

All cancers are believed to be due to somatically acquired abnormalities in DNA. There are three major classes of somatic mutation in human cancer genomes; point mutations (including base substitutions and small insertions/deletions), rearrangements and copy number changes. Our understanding of the basic patterns and variation in pattern of these mutation types between cancers is improving as

mutational screens of cancer genomes become more extensive and are conducted at higher resolution. These large scale systematic screens are yielding new cancer genes. They are also revealing traces of the mutational processes, including exposures and DNA repair defects, that have been operative during the development of individual cancers and are providing insights into the mutability of the genome itself. In this presentation recent mutational screens will be described that have provided information relating to each of these areas.

### Selected publications

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## Thea Tlsty

Thea Tlsty, PhD, is a Professor in the Department of Pathology, Director of the Program in Cell Cycling and Signaling in the UCSF Comprehensive Cancer Center and Director of the Center for Translational Research in the Molecular Genetics of Cancer at the University of California, San Francisco, School of Medicine, San Francisco, CA. She received a Ph.D. in Molecular Biology from Washington University. Dr. Tlsty trained with Dr. Robert Schimke at Stanford University as a Postdoctoral Fellow and Senior Research Associate in the Department of Biological Sciences before she was recruited to the University of North Carolina as Assistant Professor of Pathology and Member of the UNC Lineberger Comprehensive Cancer Center. In 1994 she joined the faculty at UCSF.



Dr. Tlsty studies genetic, epigenetic and functional changes involved in the earliest steps of epithelial cancers and how interactions between stromal components and epithelial cells collaborate to moderate carcinogenesis. Her research studies of human epithelial cells from healthy individuals are providing novel insights into how early molecular events affect genomic integrity and fuel carcinogenesis. Prior work from her laboratory has shown that surrounding stroma can dramatically influence tumorigenesis. She investigates how these changes are initiated and moderated, as well as their consequences for clinical disease. These insights are applied in risk assessment, early detection, and prognostic studies. Areas of particular interest include human breast carcinogenesis and the role of tumor suppressor genes in regulating premalignant phenotypes. Her studies use molecular, biochemical and cellular analyses to evaluate primary human cells, develop recombinant models of cell-cell interactions and apply novel information to intact human tissue.

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CA, USA

### Re-programming the Epigenome in Carcinogenesis

The active acquisition of epigenetic changes is a poorly understood but important process in development, differentiation, and disease. Our work has shown that repression of the p16/pRb pathway in human epithelial cells, a condition common to stem cells and many tumor cells, induces dynamic epigenetic remodeling resulting in the targeted methylation of a selected group of CpG islands. We hypothesized that cells in this epigenetically plastic state could be programmed by the microenvironment to acquire epigenetic changes associated with tumorigenesis. Here, we describe an *in vitro* model system where epigenetically plastic cells were placed in an environment that induced epithelial to mesenchymal transition (EMT) and led to a program of acquired *de novo* DNA methylation at targeted sites. In this model, we found that repression of E-cadherin transcription preceded the subsequent acquisition of methylated CpG sites. Furthermore, the induction of EMT was accompanied by *de novo* methylation of several other gene promoters, including those of the estrogen receptor and Twist. These data demonstrate that signals from the microenvironment can induce phenotypic and gene expression changes associated with targeted *de novo* epigenetic alterations important in tumor progression, and that these alterations occur through a deterministic, rather than stochastic, mechanism. Given the dynamic epigenetic reprogramming that occurs in these cells, DNA methylation profiles observed in human tumors may reflect the history of environmental exposures during the genesis of a tumor.

## Maarten van Lohuizen

Maarten van Lohuizen studied Biology at the University of Amsterdam and received his PhD in 1992 (cum laude, supervisors Dr. A. Berns and Prof dr. P. Borst) from the same University. During his thesis work, he demonstrated the power of using retroviruses in genetic screens to identify cooperating oncogenes in cancer-predisposed mice.



After staying on for one year as a postdoc, he joined the group of Prof. Dr. Ira Herskowitz, University of California at San Francisco, USA, for his postdoctoral training. Here, he was involved in analysis of a novel cell cycle checkpoint mechanism and in studying regulation of the Yeast MAP-kinase signaling pathway. In 1995 he returned to The Netherlands Cancer Institute as an assistant professor in the division of Molecular Carcinogenesis, to take up studying his old favorite: mechanisms of epigenetic silencing by mammalian Polycomb-group protein complexes and their role in cancer, when deregulated. After his tenure in 2000, he joined the division of Molecular Genetics in 2001, of which he was appointed head of division in 2002. In addition, in 2001 he became a part time professor on the subject of regulation of Cell Cycle control and Oncogenesis at Utrecht University Medical School and was appointed as a member of the Centre for Biomedical Genetics in 2003 and as EMBO member in 2004. In 2007 he became part time professor at the University of Amsterdam Medical School (AMC) with the profile: Biology and epigenetic regulation of normal and cancer stem cells.

His group has made important contributions on the functional analysis of epigenetic gene silencing mechanisms by Polycomb-group protein complexes, which play crucial roles in controlling development and cell fate and when deregulated, contribute to cancer formation. Recently, his group has also developed high-throughput genome-wide genetic screens in cell-based assays and in cancer-prone mice (in collaboration with Prof. Dr. A. Berns and Prof. Dr. A. Bradley, The Sanger Center, UK) to identify new genes that contribute to cancer and classify them in functional groups/signaling pathways. By using the DamID technique, his group has recently comprehensively mapped all Polycomb target genes in the Drosophila genome (in collaboration with the group of Bas van Steensel). In addition,

his group has recently demonstrated a crucial role for Bmi1/Pc-G protein complexes in maintaining hemapoeitic, neuronal, breast epithelial and embryonal stem cell fate and has implicated the Sonic Hedgehog (Shh) morphogen as a regulator of Bmi1 expression in neuronal precursor cells. Unraveling the role of Bmi1/Pc-G in stem cell fate versus differentiation decisions and the consequence of this for cancer (stem) cell biology is currently a major focus of his group.

The Netherlands Cancer Institute,  
Amsterdam, The Netherlands


### **Polycomb repressors controlling stem cell fate: Implications for cancer and development.**

Repressive Polycomb-group (Pc-G) protein complexes and the counteracting Trithorax-group (Trx-G) of nucleosome remodeling factors are involved in the dynamic maintenance of proper gene expression patterns during development, acting at the level of chromatin structure. As such, they are important controllers of cell fate. When deregulated, these master switches of gene expression are strongly implicated in formation of a diverse set of cancers. An example is the Pc-G gene Bmi1 which is overexpressed in medulloblastoma, Non small cell lung cancer, hepatocellular carcinoma and breast cancer and Glioma and is causally implicated in leukemia. We and others have recently implicated Bmi1/Pc-G as a critical regulator of stem cell fate in hemapoeitic stem cells, neural stem cells, mammary epithelial precursor cells and ES cells. In addition, we have shown that Bmi1 is regulated by the Shh pathway and that the Ink4a/ARF tumor suppressors are critical Bmi1 target genes in stem cells and in cancer formation. However our recent work on brain cancer (Glioma) points to important ink4a/ARF-independent Bmi1 targets involved in adhesion and motility. Comprehensive profiling of Polycomb target genes in Drosophila revealed its crucial conserved role in repressing lineage differentiation pathways and morphogens, including Wg, Hh, Delta and Notch. Furthermore, we have characterized in detail an essential E3-ubiquitin ligase activity in the

PRC1 Polycomb complex that consists of a functional Ring1B-Bmi1 heterodimer. This E3 ligase activity is required for maintenance of Polycomb repression in normal- and cancer stem cells and hence offers potential novel ways to target cancer stem cells or tumor re-initiating cells in which the activity of this E3 ligase is hyperactivated. This is further substantiated by a novel way by which the activity of the Ring1B.Bmi1 E3 ligase is controlled. The implications of these findings for stem cell biology, development and cancer will be discussed.

### **Selected Publications**

- Jacobs et al. (1999) Nature 397, 164-8
- Jacobs et al. (2000) Nat Genet. 26, 291-99
- Lund et al. (2002) Nat Genet. 32, 160-5
- Voncken et al. (2003) Proc Natl Acad Sci USA 100, 2468-73
- Leung et al. (2004) Nature 428, 337-41
- Bruggeman et al. (2005) Genes Dev. 19, 1438-43
- Tolhuis et al. (2006) Nat Genet. 38, 694-9
- Bruggeman et al. (2007) Cancer Cell 12, 328-41
- Uren et al. (2008) Cell 133, 727-41
- Pietersen et al. (2008) Curr Biol. 18, 1094-9

A stained glass window with various geometric and floral patterns in colors like green, yellow, blue, and red, set against a white background. The window is partially obscured by a blue overlay.

Presentation of the  
Cancer Epigenetics  
and Biology Program  
(PEBC)

# PEBC Research Groups with their Leader Biographies, Scientific Interests and Illustrative Publications

## Dr Manel Esteller, MD, PhD Cancer Epigenetics Group

■ **Manel Esteller** (Sant Boi de Llobregat, Barcelona, Catalonia, Spain, 1968) graduated in Medicine with Honours 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 of the Bellvitge Biomedical Research Institute (IDIBELL) in L'Hospitalet, Barcelona and leader of the Cancer Epigenetics Group. 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 two 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 and Carcinogenesis, Editor-in-Chief of Epigenetics and Advisor of the Human Epigenome Project, Associate Member of the Epigenome Network of Excellence and President of the Epigenetics Society. His numerous awards include: Best Young Cancer Researcher Award bestowed 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), Young Investigator Award from the American Association for Cancer Research-AFLAC (2001), Carcinogenesis Award (2005), Beckman-Coulter Award (2006), Francisco Cobos Biomedical Research Award (2006), Fondazione Piemontese per la Ricerca sul Cancro (FPRC) Award (2006), Swiss Bridge Award (2006). National Research Award in Oncology "Maria Julia Castillo" (2007), "Dr Josep Trueta" Award by the Academy of Medical Sciences of Catalonia (2007), Innovation Award from the Commonwealth of Massachusetts (2007), Human Frontier Science Program Award (2007), "Dr. Jacint Vilardell" Foundation Award (2008), Prize "Conde de Cartagena" by the Spanish Royal National Academy of Medicine (2009), Award in Preclinical Biomedical Research by the Lilly Foundation (2009) and Josef Steiner Cancer Research Award (2009).

Dr Manel Esteller is the Director of the Cancer Epigenetics and Biology Program of the Bellvitge Institute for Biomedical Research (IDIBELL), Leader of the Cancer Epigenetics Group, Professor of Genetics in the School of Medicine of the University of Barcelona, and an ICREA Research Professor.

#### Associate Researchers

Agustin Fernandez, Dori Huertas, Ramon Sendra, Sonia Guil, Iñaki Martin-Subero

#### Postdoctoral researchers

Jurgen Veeck, Anna Portela, Veronica Davalos, Maria Berdasco

#### PhD Students

Amaia Lujambo, Sonia Melo, Marta Kulis, Javier Carmona, Jose Sanchez, Laia Simo, Rocio Gonzalez

#### Technicians

Fernando Setien, Marta Soler, Miguel Lopez, Catia Moutinho, Jordi Carrere

#### Research Interests

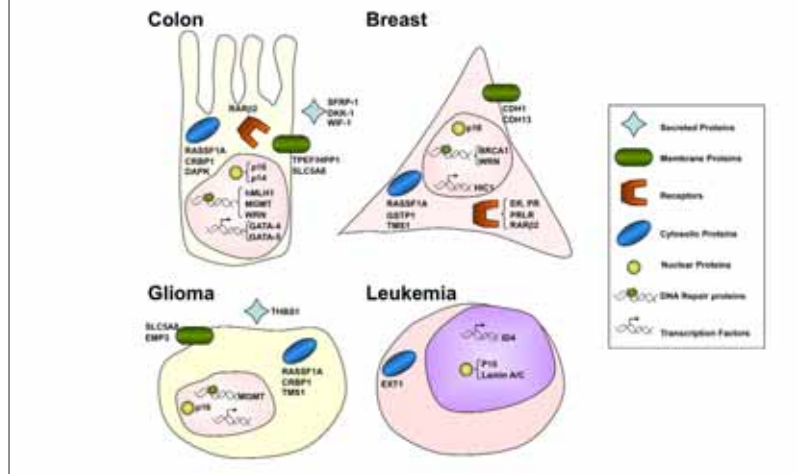
Our main interests are:

-Definition of the Epigenome of Cancer Cells: Profile of DNA methylation and histone modifications in tumor suppressor genes and repetitive sequences in cancer. Global and gene-specific definition of aberrant epigenetic changes and functional consequences in transcription regulation, DNA repair and chromosome instability (Esteller, *N Engl J Med*, 2008; Ballestar and Esteller, *Cell*, 2008).

-Study of the Epigenetics Machinery and Mechanisms: Role and function of DNA methyltransferases (enzymes that maintain DNA methylation), specificity of methyl-CpG binding domain proteins (the nuclear factors that recognize DNA methylation), analysis of biological properties of histone deacetylases and methyltransferases (enzymes that modify histones). An illustrative example is the regulation of DNMT3b by RNA binding proteins (Lopez de Silanes et al., *NAR*, 2009).

-Study of Mutations in the Epigenetic Machinery: The mechanisms underlying the disruption of the epigenetic landscape in transformed cells are unknown. It is possible that the enzymes that epigenetically modify DNA and histone are themselves targets of genetic disruption. Mutational analysis of "epigenetic modifier genes". Proof-of principle was provided by HDAC2 (Ropero et al., *Nature Genetics*, 2006).

#### CpG Island Promoter Hypermethylation of Tumor Suppressor Genes: Pathways and Cell Types



- Testing of Epigenetic Drugs: Study of the biological effects in cell lines and mouse models of different small epigenetic drugs directed against DNA methyltransferases, histone deacetylases and other enzymes of the epigenetic machinery (Lara et al., *Oncogene* 2008; Zubia et al., *Oncogene* 2009). Analysis of their use as anticancer drugs.

Overview of research:

Cancer is an epigenetic disease characterized by the breakdown of the DNA methylation and histone modification patterns. The stability of our genome and correct gene expression are maintained in large measure thanks to a perfectly pre-established pattern of DNA methylation and histone modifications. In cancer, this ideal scenario is destroyed by the occurrence of an interesting phenomenon whereby the regulatory regions (CpG islands) of certain tumor suppressor genes become hypermethylated, inactivating the gene as a consequence, whilst a wave of hypomethylation occurs in the genome. We have developed procedures (Chip-on-CHIP, MeDIP...) for massive genomic screening to find new hypermethylated genes in cancer cells and characterize their histone codes. Both DNA methylation and histone modifications control the activity of a third component of the epigenetic landscape, non-coding RNAs, particularly microRNAs that are also disrupted in human cancer.

Recent research achievements:

-Construction of epigenomic maps in health and disease: An altered pattern of epigenetic modifications is central to many common human diseases, including

cancer. We have previously explored the mosaic patterns of DNA methylation and histone modification in cancer cells on a gene-by-gene basis; among our results has been the seminal finding of transcriptional silencing of tumour-suppressor genes by CpG-island-promoter hypermethylation. However, recent technological advances are now allowing cancer epigenetics to be studied genome-wide - an approach that we have taken to provide both biological insight and new avenues for translational research. This 'upgrade' of cancer epigenetics research represent the backbone for the future obtention of the first complete epigenomes that include DNA methylomes and histone modification maps (Esteller, *Nat Rev Genet*, 2007; Esteller, *N Engl J Med* 2008; Esteller, *The Lancet* 2008; and Ballestar and Esteller, *Cell*, 2008). One of the first completed DNA methylome projects has been the full elucidation of the DNA methylation sequence of the double strand DNA viruses involved in human cancer (*Genome Res*, 2009).

-Contribution of the DNA-methylation mediated silencing of microRNAs to human metastasis. In the last few years, microRNAs have started a revolution in molecular biology and emerged as key players in the metastasis process. For these reasons, it is extremely important to understand the physiological and disease-associated mechanisms underlying the regulation of these small, single-stranded RNAs. Thus, it was merely a matter of time before microRNAs, metastasis and epigenetics coincided (Lujambio et al., *Cell Cycle* 2009). The mechanisms underlying microRNA (miRNA) disruption in human disease are poorly understood. In cancer cells, the transcriptional silencing of miRNAs with tumor suppressor function by CpG island promoter hypermethylation has emerged as a novel hallmark. We wondered if the same epigenetic disruption can contribute to human metastasis. We have observed that DNA hypermethylation of 5'-CpG islands of genomic sequences coding for miRNAs is associated with tumoral dissemination (Lujambio et al., *Proc Natl Acad Sci USA*, 2008). The main targets are miR-148a, miR-34bc and the miR-9 family which undergoes transcriptional inactivation by CpG island hypermethylation in human tumors with lymph node metastasis. Interestingly, we functionally link the epigenetic loss of these miRNAs with the activation of EZH2, CDK6, C-MYC and E2F3, bona fide oncogenic and tumor-enhancing factors. Most importantly, we have shown that miRNA disruption in cancer cells can also occur at other level: in a subset of colon, stomach and endometrial tumors, the production of mature miRNAs is perturbed by the presence of mutations in TRBP, a key gene of the miRNA processing machinery and the natural partner of DICER1 (Melo et al., *Nature Genetics* 2009).

## Selected Publications

- Melo SA, Ropero S, Moutinho C, Aaltonen LA, Yamamoto H, Calin GA, Rossi S, Fernandez AF, Carneiro F, Oliveira C, Ferreira B, Liu CG, Villanueva A, Capella G, Schwartz Jr S, Shiekhattar R, **Esteller M**. A *TARBP2* mutation in human cancer impairs microRNA processing and *DICER1* function. *Nature Genetics*, 41, 365-70, 2009
- Fernandez AF, Rosales C, Lopez-Nieva P, Graña O, Ballestar E, Ropero S, Espada J, Melo SA, Lujambio A, Fraga MF, Pino I, Javierre B, Carmona FJ, Acquadro F, Steenbergen RDM, Snijders PJF, Chris J. Meijer, Pascal Pineau, Anne Dejean, Lloveras B, Capella G, Quer J, Buti M, Esteban JI, Allende H, Rodriguez-Frias F, Castellsague X, Minarovits J, Ponce J, Capello D, Gaidano G, Cigudosa JC, Gomez-Lopez G, Pisano DG, Valencia A, Piris MA, Bosch FX, Cahir-McFarland E, Kieff E, **Esteller M**. The dynamic DNA methylomes of double-stranded DNA viruses associated with human cancer. *Genome Research*, 19, 438-51, 2009.
- Ballestar E, **Esteller M**. *SnapShot: the human DNA methylome in health and disease*. *Cell*, 135, 1144-1144.e1, 2008.
- Lujambio A, Calin GA, Villanueva A, Ropero S, Sánchez-Céspedes M, Blanco D, Montuenga LM, Rossi S, Nicoloso MS, Faller WJ, Gallagher WM, Eccles SA, Croce CM, **Esteller M**. A microRNA DNA methylation signature for human cancer metastasis. *Proc Natl Acad Sci USA*, 105, 13556-61, 2008.
- Esteller M**. *Epigenetics of Cancer*. *New England Journal of Medicine*, 358, 1148-59, 2008.
- Esteller M**. *Cancer epigenomics: DNA methylomes and histone modification maps*. *Nature Reviews Genetics*, 8, 286-98, 2007.
- Agrelo R, Cheng WS, Setien F, Ropero S, Espada J, Fraga MF, Herranz M, Paz MF, Sanchez-Céspedes M, Artiga MJ, Guerrero D, Castells A, von Kobbe C, Bohr VA, **Esteller M**. Epigenetic inactivation of the premature aging *Werner syndrome gene* in human cancer. *Proc Natl Acad Sci USA*. 102, 103, 8822-7, 2006.
- Ropero S, Fraga MF, Ballestar E, Hamelin R, Yamamoto H, Boix-Chornet M, Caballero R, Alaminos M, Setien F, Paz MF, Herranz M, Palacios J, Arango D, Orntoft TF, Aaltonen LA, Schwartz Jr S., **Esteller M**. A truncating mutation of *HDAC2* in human cancers confers resistance to histone deacetylase inhibition. *Nature Genetics*, 38, 566-9, 2006.
- Fraga MF, Ballestar E, Paz MF, Ropero S, Setien F, Ballestar ML, Heine-Suner D, Cigudosa JC, Urioste M, Benitez J, Boix-Chornet M, Sanchez-Aguilera A, Ling C, Carlsson E, Poulsen P, Vaag A, Stephan Z, Spector TD, Wu YZ, Plass C, **Esteller M**. Epigenetic differences arise during the lifetime of monozygotic twins. *Proc Natl Acad Sci USA*. 102, 10604-10609, 2005.
- Fraga MF, Ballestar E, Villar-Garea A, Boix-Chornet M, Espada J, Schotta G, Bonaldi T, Haydon C, Ropero S, Petrie K, Iyer NG, Pérez-Rosado A, Calvo E, Lopez JA, Cano A, Calasanz MJ, Colomer D, Piris MA, Ahn N, Imhof A, Caldas C, Jenuwein T, **Esteller M**. Loss of acetylated lysine 16 and trimethylated lysine 20 of histone H4 is a common hallmark of human cancer. *Nature Genetics*, 37, 391-400, 2005.

## Dr Montse Sanchez-Cespedes

### Genes and Cancer Group

- **Montse Sanchez-Cespedes** was born in Badalona (Barcelona) in 1968. She graduated in Biology and specialized in Genetics and Molecular Biology from the Universitat de Barcelona and carried out her Ph.D. work at the Molecular Biology of Cancer Laboratory, the Hospital "Germans Trias i Pujol" in Badalona. From 1997 to 2001 she was a Postdoctoral Fellow at the Johns Hopkins University School of Medicine (Baltimore-USA). She focused on the identification of novel genetic and molecular alterations in cancer. More specifically she looked for recurrent chromosomal abnormalities in lung tumours and genetically analysed candidate tumour suppressor genes in these regions. From October 2001 to 2004 she led the lung cancer biological research at the CNIO and from 2004 to September 2008 she was the Group Leader of the Lung Cancer Group at the same institution.

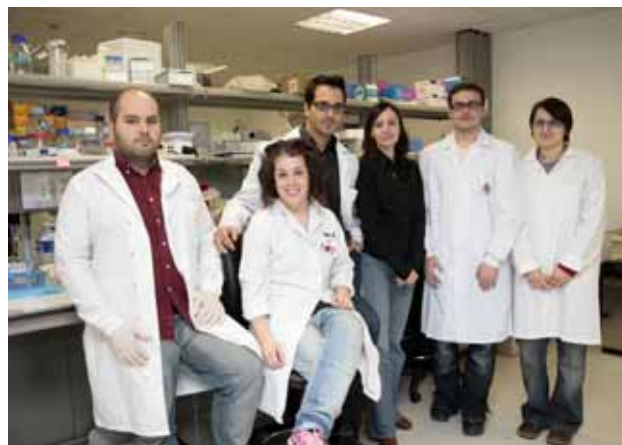
She is member of international scientific societies and reviewer for many journals and funding agencies. Her list of over 60 original publications and reviews in international and peer-reviewed journals of prestige serves as a testament of the experience she has already accumulated in the field of cancer research. Her current research is devoted to the identification of genes that are genetically altered in tumors and to the functional analysis of their implication in cancer development.

The complete genetic characterization of tumours is important not only to understand tumour biology, but also to the development of new drugs and to the selection of patients that may benefit of a given targeted cancer therapy. The promise of using proteins encoded by mutant cancer genes as molecular targets for the development of novel therapies drives endeavours to identify novel mutated cancer genes as well as to create catalogues of somatic mutations in cancer.

Our current projects in the laboratory are focused in the following directions:

- i) to identify novel genes altered in cancer;
- ii) to understand their contribution to cancer development and
- iii) to investigate correlations with clinical and pathological characteristics.

Genome-wide screenings allow the identification of the chromosomal regions that are frequently deleted in cancer and that may contain tumor suppressor genes. In lung cancer, one of the most frequently deleted chromosomal arms

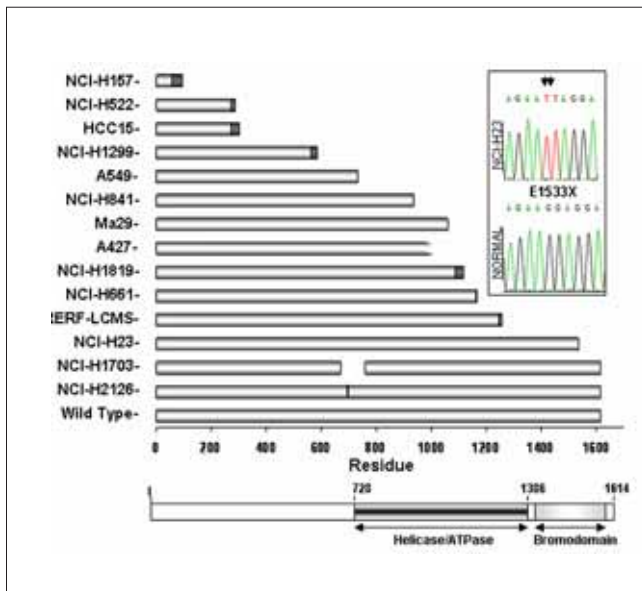


**Postdoctoral researchers:** Eva Pros, Salvador Rodriguez-Nieto

**PhD Students:** Ester Bonastre, Sandra Castillo, Rossana G Restani, Octavio Romero

**Technician:** Albert Coll

is 19p. During the past years we unveiled that LKB1, the Peutz-Jeghers syndrome (PJS) gene, was also mutated/inactivated in lung cancer. This exciting observation led us to devote intense efforts to fully understand how LKB1 inactivation contributes to carcinogenesis. To date we have provided important data on the mutational profile of LKB1 in lung cancer and on its association with various molecular and clinic-pathological characteristics. We also provided further insights in the relationship between LKB1 alterations in lung cancer and impaired AMPK activity and mTOR inhibition upon energetic stress. BRG1 is another gene that allocates on chromosome 19p and encodes and



protein belonging to the SWI/SNF chromatin-remodeling complex, involved in the regulation of gene expression by disrupting histone-DNA contacts. We recently identified inactivating mutations at BRG1 in a significant number of lung cancer cells, indicating that BRG1 is another bona fide tumor suppressor important in lung and, possibly, other types of cancer (Figure 1). Thus, in addition to LKB1, our ongoing work also deals with the understanding of how a deficient SWI/SNF chromatin-remodeling complex impinges on tumor development. Finally, there are additional open projects in the lab that, through the use of high resolution-wide genome scanning platforms have identified chromosomal regions carrying high levels of gene amplification and, therefore, interesting oncogene candidates.

## Selected publications

- The SRY-HMG BOX gene, SOX4, is a target of gene amplification on chromosome 6p in lung cancer* PP. Medina, SD Castillo, S. Blanco, M. Sanz-García, C.Largo, S.Alvarez, J. Yokota, JC. Cigudosa, PA. Lazo, M. Sanchez-Cespedes. *Hum. Mol Gen* (2009).
- A Gene-Alteration Profile Of Human Lung Cancer Cell Lines.* Blanco R, Iwakaw R, Tang M, Angulo B, Pio R, Montuenga LM Minna JD, Yokota J, Sanchez-Cespedes M. *Human Mut* (2009).
- LKB1 and BRG1, tales of two tumor suppressors on chromosome 19p.* Rodriguez-Nieto S, Sanchez-Cespedes M. *Carcinogenesis* (2009).
- Expression signatures in lung cancer shows a profile for EGFR-mutant tumors and identifies selective PIK3CA overexpression by gene amplification.* Angulo B, Suarez-Gauthier A, Lopez-Rios F, Medina PP, Conde E, Tang M, Soler G, Lopez-Encuentra A, Cigudosa JC, Sanchez-Cespedes M. *J Pathol*, 214:347-56 (2008).
- Frequent BRG1/SMARCA4-inactivating mutations in human lung cancer cell lines.* Medina PP, Romero OA, Kohno T, Montuenga LM, Pio R, Yokota J and Sanchez-Cespedes M. *Human Mut* 29:617-22 (2008).
- Dysfunctional AMPK activity, signalling through mTOR and survival in response to energetic stress in LKB1-deficient lung cancer.* Carretero J, Medina PP, Blanco R, Smit L, Tang M, Roncador G, Maestre L, Conde E, Lopez-Rios F, Clevers HC and M Sanchez-Cespedes. *Oncogene*. 26:1616-25 (2007).
- Specific pattern of LKB1 and phospho Acetyl-Coa Carboxylase protein immunostaining in human normal tissues and lung carcinomas.* E.Conde, A.Suarez, E.García-García, F.Lopez-Rios, A.Lopez-Encuentra, R.García-Lujan, M. Morente, L.Sanchez-Verde, M.Sanchez-Cespedes. *Human Pathol* 14:347-56 (2007).
- A role for LKB1 gene in human cancer beyond the Peutz-Jeghers syndrome.* Sanchez-Cespedes M. *Oncogene* 2007;26:7825-32.
- Oncogenic activity of Cdc6 through repression of the INK4/ARF locus.* Gonzalez S, Klatt P, Delgado SG, Conde E, Sanchez-Cespedes M, Mendez J, Antequera F, Serrano M. *Nature*; 440:702-6 (2006).
- DNA-repair gene polymorphisms predict favorable clinical outcome among patients with advanced squamous cell carcinoma of the head and neck (SCCHN) treated with cisplatin-based induction chemotherapy.* M.Quintela-Fandino, R Hitt, PP Medina, S.Gamarra, L.Manso, H.Cortes-Funes, M.Sanchez-Cespedes. *J Clin Oncol*. 24:4333-9 (2006).

## Dr Alejandro Vaquero

### Chromatin Biology Group

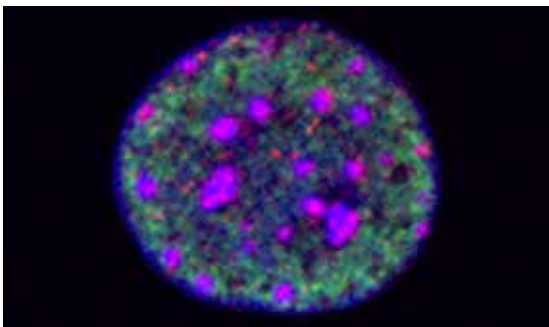
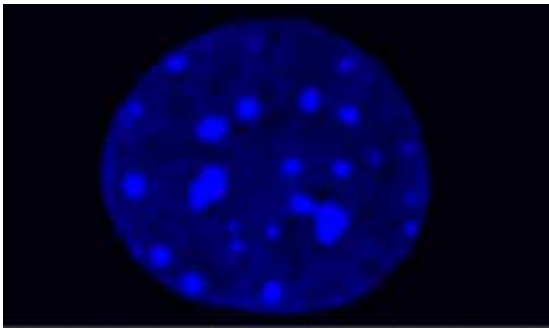
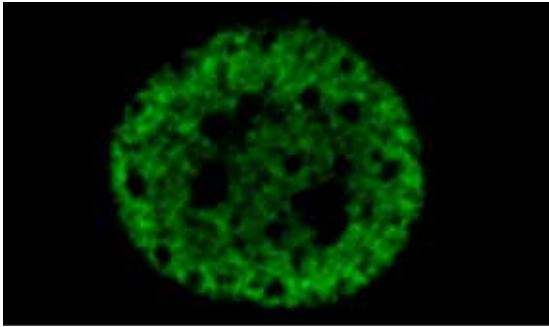
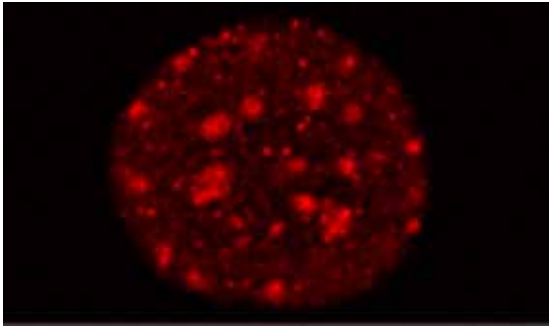
- **Alejandro Vaquero** (Barcelona, Spain, 1971) is senior group leader of the Chromatin Biology Laboratory at PEBC-IDI-BELL and ICREA researcher. He graduated in Biochemistry in 1994 from the University of Barcelona (UB), and received his PhD “Cum Laude” from the same University in 2000. From 2000 to 2005 he performed his postdoctoral studies in the laboratory of Dr Danny Reinberg (HHMI, Piscataway, NJ, USA), where he studied the role of Sirtuins, a group of NAD<sup>+</sup>-dependent deacetylases homologues of the yeast silencing factor Sir2, on chromatin function. In 2001, he became Howard Hughes Research associate, position he held until the end of 2005, when he returned to Spain as an I3P Researcher (CSIC) in the Institut de Biologia Molecular de Barcelona (IBMB-CSIC, Barcelona, Spain) where he was appointed Icrea Researcher in Dec 2006. In January 2008, he joined the Cancer Epigenetics and Biology Program (Barcelona, Spain).

#### Research Interests

The main goal of our laboratory is to understand the mechanisms that rule Chromatin dynamics and in particular how these post-translational modifications interplay with the rest of chromatin machinery to keep a healthy and efficient Chromatin organization. As a consequence of that, we are also interested in the functional implications of these mechanisms in cancer and aging. For that purpose, our lab uses a combination of Biochemistry, Molecular and Cell Biology approaches to gain insight into Chromatin Biology. In particular, our studies focus in a group of proteins, the Sir2 family or Sirtuins, that are homologues of the yeast silencing factor Sir2, a NAD<sup>+</sup>-dependent deacetylase involved in many aspects of chromatin regulation such as epigenetic silencing, DNA repair and replication, DNA recombination, etc... Two features make particularly interesting the Sir2 family: First, the requirement of the metabolic redox cofactor NAD<sup>+</sup> for the enzymatic activity of the family, allows their members to act as sensors of cell metabolism. Second, members of this family show a close link with the regulation of a specific modification, acetylation of lysine 16 in histone H4 (H4K16Ac), involved in many functions from Chromatin structure, gene expression and cancer to many epigenetic processes through evolution.



**Postdoctoral researchers:** Laia Bosch  
**PhD Students:** Helena Raurell, Paloma Martinez, Irene Santos, Max Becker  
**Technician:** Anna Marazuela



### Selected publications

- Vaquero, A. *The conserved role of Sirtuins in chromatin regulation.* *Int J Dev Biol.* In press. (2009)
- Vaquero, A., Scher, M., Erdjument Bromage, H., Tempst, P., Serrano, L., Reinberg, D. *SirT1 Regulates the Histone Methyl-transferase Suv39h1 During Heterochromatin Formation.* *Nature* 450: 440-444 (2007)
- Vaquero, A., Sternglanz, R., Reinberg, D. *NAD<sup>+</sup>-Dependent Deacetylation of H4 Lysine 16 by Class III HDACs.* *Oncogene* 26: 5505-5520 (2007)
- Trojer, P. \*, Li, G.-H. \*, Sims III, R.J. \*, Vaquero, A., Kalakonda, N., Bocconi, P., Lee, D.-H., Erdjument Bromage, H., Tempst, P., Nimer, S., Wang, Y.-H., Reinberg, D. *L3MBTL1, a histone methylation dependent chromatin lock.* *Cell.* 129: 915-928 (2007)
- Scher, M., Vaquero, A., Reinberg, D. *SirT3 is a Nuclear NAD<sup>+</sup>-Dependent Histone Deacetylase that Translocates to the Mitochondria Upon Cellular Stress.* *Genes & Dev.* 21(8): 920-928 (2007)
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Mouse embryonic fibroblast (MEF) during S-phase stained with BrdU (replication foci), H4K16Ac, DAPI, respectively. Lowest image is a merge of previous three.

## Dr Esteban Ballestar

### Chromatin and Disease Group

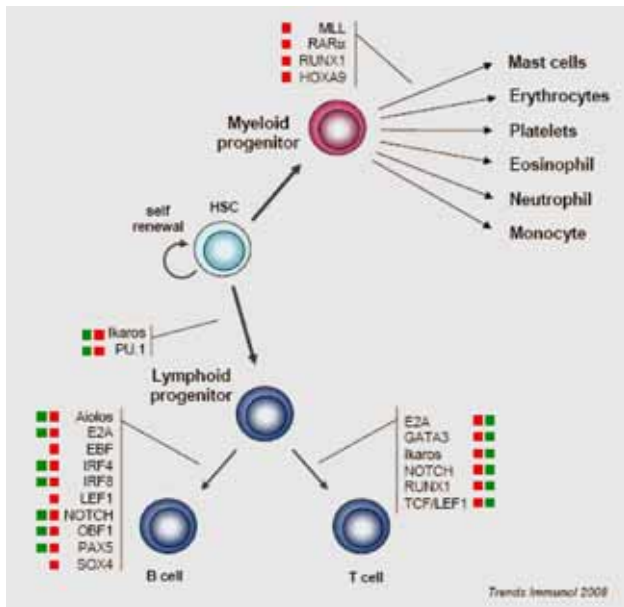
■ **Esteban Ballestar** (Valencia, Spain, 1969) graduated in Biology with First Class Honours from the Universitat de València in 1992, where he also obtained his Ph.D. degree under the supervision of Prof. Luis Franco, specialising in chromatin and histone modifications, in 1997. During this period, Ballestar identified and characterized a novel histone modification. From 1997 to 2000, Ballestar was a Postdoctoral Fellow at the Laboratory of Molecular Embryology led by Dr Alan Wolffe at the National Institutes of Health, (Bethesda, MD, USA) where he investigated associations between elements of the chromatin machinery and methylated DNA. There, Dr Ballestar contributed to demonstrate that methyl-CpG binding domain (MBD) proteins –a family of nuclear factors that associate with methylated DNA- establish mechanistic links between DNA methylation, chromatin remodelling and the histone modification machinery to silence genes. In addition, his work with MBD proteins demonstrated the ability of these proteins to associate with specific genes and their implications in epigenetic deregulation in Rett syndrome. From 2001 to 2008, Esteban Ballestar has worked at the CNIO Cancer Epigenetics Laboratory, in association with Dr Manel Esteller, where his principal area of research has been the study of the implication of chromatin factors in epigenetic alterations in human cancer. He has demonstrated the role of MBDs in the epigenetic deregulation in cancer and Rett syndrome. Also at the CNIO, he has contributed in seminal publications regarding specific alterations in the histone modification profile associated with hypomethylation in cancer and the age-dependent accumulation of epigenetic changes. Since 2002, Ballestar has coordinated together with Esteller a graduate course in Cancer Epigenetics within the Molecular Biology Program of the Universidad Autonoma de Madrid. Since 2004, Ballestar has been awarded with various grants to develop an independent research line on epigenetics and chromatin alterations in disease at the CNIO. As group leader of the Chromatin and Disease Group of the Cancer Epigenetics and Biology Program of the The Bellvitge Institute for Biomedical Research (IDIBELL) in Barcelona, his current research is devoted to the establishment of different mechanisms of epigenetic deregulation in the context of the hematopoietic system in both autoimmune diseases and hematological malignancies.

Author of more than fifty five peer-reviewed manuscripts in biomedical sciences, he is also a member of numerous international scientific societies and reviewer for many journals and national and international funding agencies.



**Postdoctoral researchers:** Javier Rodriguez-Ubreva  
**PhD Students:** Henar Hernando, Biola Javierre, Lorenzo de la Rica, Virginia Rodriguez, Lena Verdaguer  
**Technicians:** Laura Ciudad, Marina Corominas

years. Key breakthroughs include the identification of a code of histone modifications associated with specific functions, the finding of mechanistic links between DNA methylation and histone modifications or the recognition that epigenetic modifications and chromatin organization not only define cell identity but also constitutes a dynamic readout of environment. But most importantly, the identification of alterations in chromatin structure and epigenetic regulation in diseases including cancer, autoimmune disease, and a variety of syndromes, have added a clinical dimension to studies in chromatin and epigenetics, since these alterations are potentially reversible.



The study of lymphocyte differentiation and activation allows us to understand not only mechanisms of epigenetic regulation and chromatin organization but also how the abnormal control of these pathways can lead to abnormal behaviour in haematopoietic malignancies or other diseases such as autoimmune disorders. Appropriate cell fate decisions and maintenance of homeostasis are key in maintaining the normal behaviour of haematopoietic and immune system. Lymphocyte differentiation and activation involve many different transcription factors, including Runx1, PAX5, GATA3, all Ikaros and Notch family members or polycomb group proteins, that associate with the epigenetic machinery. In general, subsequent and specific expression of these transcription factors is associated with differentiation. Additionally, microRNAs (miRNAs), an important group of transcriptional regulators that affect the translation and/or the stability of protein-coding transcripts, have also been involved in lymphocyte differentiation. These processes are orchestrated in response to discrete intracellular signaling pathways, including phosphorylation cascades that culminate in the activation of mitogen-activated protein kinases (MAPKs). Connections between signaling cascades and epigenetic modifications have particular relevance for cells that participate in immune and inflammatory response.

In this context, there are fundamental questions that remain to be answered including the mechanisms of epigenetic regulation of transcription factors and miRNAs and their functional consequences in lymphocyte differentiation. In addition, the mechanisms by which signaling pathways result in epigenetic regulation are unknown. The consequences of misregulation of these processes have been proposed to participate in haematopoietic disorders, including

leukemias, lymphomas on one hand, or autoimmune disease, on the other; however the detailed mechanisms are also unknown. Our group is focused on the epigenetic alterations the haematopoietic system and their connections with upstream signaling pathways.

The three main lines of research are:

- Chromatin Deregulation Processes involved in Haematopoietic Malignancies
- Epigenetic Mechanisms involved in T cell Activation processes
- Epigenetic Deregulation in Autoimmune Disease

### Selected publications

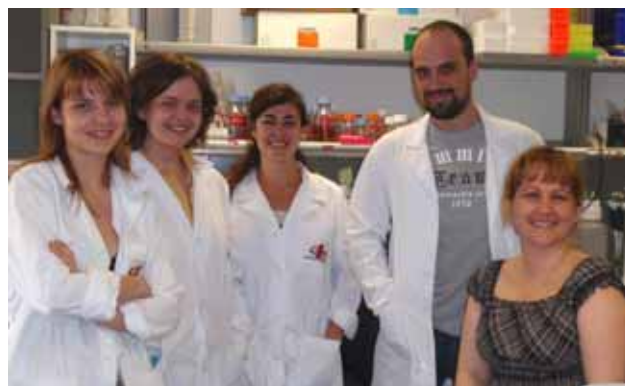
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## Dr Ethel Queralt

### Cell Cycle Group

■ Ethelvina Queralt (Benavites, Valencia, Spain, 1975) graduated in Biochemistry from the Universitat de Valencia in 1998, where she also obtained her PhD degree in Biochemistry specialising in Cell Cycle, in 2003. During her PhD studies she acquired knowledge in molecular biology and genetics using yeast as a model organism. She was interested in the study of the regulation of the G1/S transition in the cell cycle. Ethel Queralt presented her thesis work in several national and international meeting and she had got the Innogenetics Diagnostics prize (for PhD degree) in the XXVII Conference of SEBBM (Lleida September 2004). From 2003 to 2007, Queralt was a Postdoctoral Fellow at the London Research Institute, Cancer Research UK where she studied others aspects of the cell cycle as genome stability and chromosome segregation. For her postdoctoral position she chose an internationally leading institution to carry out a cutting edge project in Dr. Frank Uhlmann's laboratory. Dr. Uhlmann is an internationally recognised expert in the field of chromosome segregation. He has made key contributions to the current knowledge of genome inheritance during mitotic cell division.

During the postdoctoral work, Ethel Queralt studied the regulation of mitotic exit and cytokinesis in the model eukaryote *Saccharomyces cerevisiae*. Aneuploidy, i. e. missing or supernumerous chromosomes, is a near-ubiquitous feature of human cancer and is thought to promote tumour development. The regulation of mitosis is of particular importance in maintaining chromosome stability: Failure in cytokinesis initially leads to cells containing both sets of sister chromatids, and it is from these cells that most aneuploid tumour cells likely originate. Despite its importance, very little is known about mitotic exit regulation in any organism. Through her investigations, Ethel had made seminal contributions to our current understanding of the process in budding yeast. She published her postdoctoral work in leading international cell biology journals and presented her work in many international meeting. From 2007 to 2008, Queralt was in the Dra. Susana Rodriguez-Navarro's laboratory, Instituto de Investigación Príncipe Felipe as a Ramon y Cajal researcher. Dra. Rodriguez-Navarro has made very important contributions to the current knowledge of the coupling between mRNA export and transcription in budding yeast. Since March 2008, Dr Queralt is leader of the Cell Cycle Group at the Cancer Epigenetics and Biology Program of the Bellvitge Institute for Biomedical Research (IDIBELL) in Barcelona. Her current research is focused in the mechanisms that ensure faithful chromosome maintenance during



**Technician:** Nuria Russinol Coll

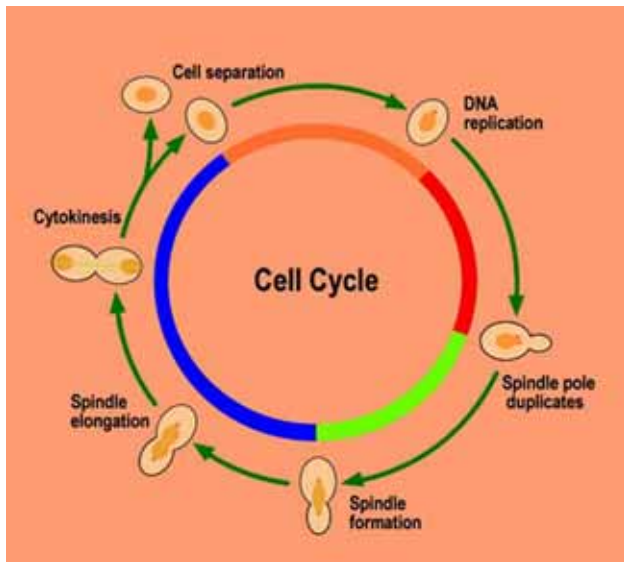
**PhD Students:** Inés Calabria Torres, Barbara Baró Sastre and Jose Antonio Rodriguez Rodriguez

healthy cell growth, in particular the molecular framework that is responsible for the initiation of mitosis.

#### Research interests

##### The *Saccharomyces cerevisiae* CELL CYCLE

The cell cycle is a series of order events that take place in eukaryotics cells in order to grow and divide in two new cells. Basically, cells have to complete four different events during the cell cycle: grow (G1 and G2 phases), replicate the DNA (S phase), segregate the chromosome (M phase) and divide (cytokinesis). How eukaryotes, including human, inherit their nuclear genome is a fundamental question in biology. It also has direct clinical implications as chromosome missegregation is a leading cause for miscarriages and birth defects, and is tightly linked to malignant tumour progression. The cell cyle in budding yeast is very similar to the cell cycle in humans and is regulated by the same proteins that are conserved through evolution.



Mitosis is an intricately coordinated set of events that ensures the accurate inheritance of genetic information from one cell generation to the next. Entry into mitosis occurs when the Cdk-cyclinB complex reach a peak of kinase activity. In metaphase the chromosomes are condensed, aligned in the metaphase plaque and attached to the mitotic spindle. Proper attachment of the chromosomes will lead to the activation of the anaphase-promoting complex (APC) by its co-activator Cdc20. APCCdc20 is an ubiquitin ligase that ubiquitinates securin, an inhibitor of the protease separase. Thereby, securin is degraded by the proteasome and separase is activated. Sister chromatid separation at anaphase onset is triggered when the Scc1 subunit of cohesin is cleaved by separase to destroy the cohesin complex. At this time, APCCdc20 also targets the cyclin Clb2 for degradation promoting the reduction of Cdk activity. However, cyclin destruction by APCCdc20 is not sufficient to completely remove all Cdk activity in order to exit from mitosis. For this reason, the activation of the mitotic phosphatase Cdc14 becomes essential. Cdc14 phosphatase directly counteracts the Cdk activity by dephosphorylating the Cdk targets. On the other hand, Cdc14 also contributes to the downregulation of the Cdk activity by dephosphorylating a second co-activator of APC, Cdh1, that complete destruction of all mitotic cyclins, and the Cdk inhibitor Sic1. In metaphase, Cdc14 is kept inactive in the nucleolus by binding to the nucleolar protein Net1 (also called Cfi1). During anaphase, Cdk-dependent phosphorylation of Net1 release active Cdc14. Phosphorylated Net1 shows reduced affinity for Cdc14 and loose its ability to inhibit Cdc14 in vitro. Two different regulatory pathways are essential for the Cdc14 release from the nucleolus. During early anaphase the FEAR pathway (Cdcfourteen early anaphase release) initiates the Cdc14 release and is kept active later in anaphase by a G protein signalling cascade, the mitotic exit network (MEN). A number of proteins including, Cdk, Slk19, Spo12,

Fob1 and separase have been implicated in this early anaphase Cdc14 release. Several mutants in the FEAR show a delay in the Cdc14 release from the nucleolus. Nevertheless, an essential role in Cdc14 activation and mitotic exit for separase has been recently described (Queralt et al., 2006). The FEAR dependent Cdc14 release requires Net1 phosphorylation at Cdk consensus sites. PP2ACdc55 phosphatase keeps Net1 under-phosphorylated in metaphase (Queralt et al., 2006). Separase-dependent PP2ACdc55 downregulation initiates the Cdk-dependent Net1 phosphorylation specifically in anaphase, when mitotic kinase activity starts to decline. The mechanistic basis for separase-dependent PP2ACdc55 downregulation remains to be elucidated. Later in anaphase, when the Cdk activity is low, the MEN kinases maintain Net1 phosphorylated and Cdc14 release also contributes to the downregulation of the Cdk activity by dephosphorylating a second co-activator of APC, Cdh1, that complete destruction of all mitotic cyclins, and the Cdk inhibitor Sic1.

#### Selected publications

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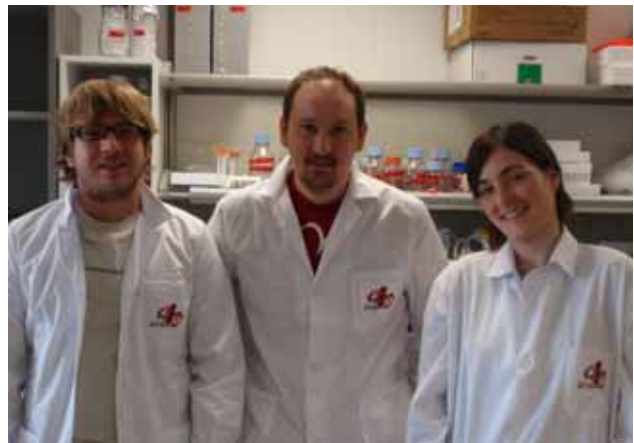
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## Dr Dave Monk

### Genomic Imprinting and Cancer Group

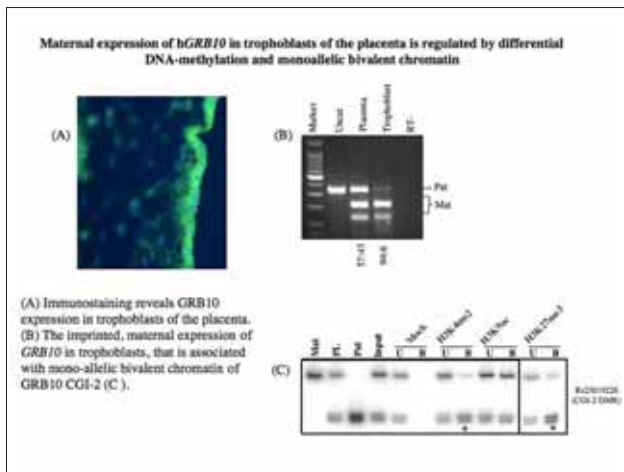
■ **David Monk** (London, United Kingdom, 1975) graduated from Anglia Ruskin University, Cambridge with a B.Sc (Hons) in Biomedical science before undertaking an M.Sc in Human Reproductive Biology at Imperial College London. In 2001 he wrote his PhD thesis on the genetic aetiology of Silver-Russell syndrome, a project mentored by Professors Michael Preece and Gudrun Moore at Queen Charlotte's and Chelsea Hospital (QCCH), Imperial College London. From 2001-2004 he was a Postdoctoral Researcher funded by the MRC to screen for novel imprinted genes using DNA methylation based technologies. This position was a multi-site collaborative project, which saw him spend time in the laboratories of Professor Moore, now at the Institute of Reproductive and Developmental Biology (IRDB) Imperial College London, Dr Gavin Kelsey at The Babraham Institute Cambridge, and with Professor Jo Peters at MRC Harwell. From 2005-2007, Dr Monk was a March of Dimes funded Postdoctoral Research Fellow at the IRDB, undertaking research into the epigenetic regulation of placental imprinting in the human, and the involvement of imprinted gene expression in human fetal growth. During this time he was awarded an EMBO short-term fellowship to spend time in the laboratory of Dr Robert Feil in CNRS, Montpellier France. In 2007, he was appointed as Lecturer in Molecular Epigenetics and Paediatric Oncology at the Institute of Child Health, University College London. Since the summer of 2008, Dr Monk is the Principal Investigator of the Genomic Imprinting and Cancer group within the Cancer Epigenetics and Biology Program of the Catalan Institute of Oncology (ICO) in Barcelona. His current research interests include: Aberrant epigenetic modifications and imprinting in MLL translocation leukaemias; Altered DNA methylation and imprinting profiles in cancers; and defining epigenetic signatures for loss-of-imprinting that occur in cancer and imprinting disorders.

Epigenetics is the term used in biology to refer to chromatin structure and DNA modifications that are stable over rounds of cell division but do not involve changes in the DNA sequence. Epigenetics play a pivotal role in cellular differentiation, allowing cells to stably maintain different characteristics despite containing the same genomic DNA. Epigenetic processes are also involved in gene silencing, X chromosome inactivation, reprogramming and are thought to be one of the major limitations to cloning. One of the main interests of this group is Genomic Imprinting. Imprinted genes are expressed from only one parental allele, the other is silenced by epigenetic modifications, classically involving



**PhD Students:** Amy Guilamet Adkins, Alejandro Martin Trujillo

**Visiting Student:** Alberto Garcia Lopez



DNA methylation and asymmetric chromatin structure. Imprinted genes are typically involved in embryonic growth and development. Abnormal imprinted gene expression is one of the most frequent aberrations in carcinogenesis.

Our research aims to understand the controlling mechanisms involved in genomic imprinting, and how genetic and epigenetic variation in imprinted genes is associated with cancer susceptibility and development. We currently have projects assessing the hierarchical chromatin organisation at imprinting control regions in leukaemias and solid tumours, assessing how aberrant histone modifications relate to DNA-methylation profiles. These projects use state-of-the-art technologies, including 5-mC HPLC, ChIP-seq and custom DNA-methylation arrays. In addition, using the same molecular techniques, we are assessing the epigenetic profiles of babies born following assisted reproductive techniques to try and understand the epigenetic mechanisms involved in ART associated loss-of-imprinting.

## Selected publications

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## Dr Puri Muñoz

### Aging and Cancer Group

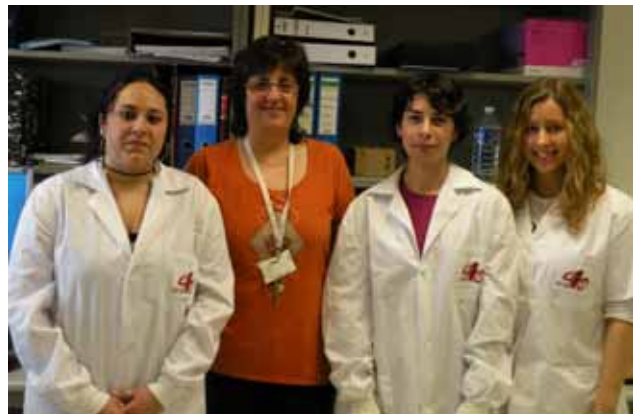
- Purificación Muñoz Moruno was born in L'Hospitalet de Llobregat, Barcelona in 1965. She graduated in Biology from the Universidad de Barcelona in 1988, where she also obtained her Ph.D. in Biology under the supervision of Dr. Antonio Zorzano Olarte. During her Ph.D. training she focused her studies on the characterization of the translocation of insulin-induced glucose transporters in skeletal muscle.

In order to investigate different aspects of DNA repair and cell cycle control, she joined the laboratories of Dr. Jean Marie Blanchard and Dr. Jacques Piette at the Institut de Génétique Moleculaire de Montpellier (France) as a postdoctoral fellow in May 1995. In 1999, she returned to Barcelona to join Dr. José Luis Rosa's laboratory in the Medical School of Barcelona from Universidad de Barcelona where her research work contributed to the analysis of p532 role in intracellular vesicular trafficking and cellular proliferation.

In 2002 she obtained a Research Contract from the "Ramón y Cajal" Program and joined the laboratory of Dra. Maria A. Blasco at CNIO (Madrid). There, her research interests focused on the role of DNA repair and homologous recombination proteins in telomere function and chromosomal stability. She also generated different mouse models to evaluate the role of telomere binding proteins in telomere function and genome stability. Her studies revealed a genetic interaction between telomeres and the nucleotide excision repair machinery, which underlies susceptibility to cancer and aging. Her scientific achievements have given rise to several publications in high impact international journals. Since June 2007, Dra. Muñoz is leader of the Aging and Cancer Group of the Cancer Epigenetic and Biology Program of Bellvitge Institute for Biomedical Research (IDIBELL) in Barcelona. Her current research is focused on studying genetic and epigenetic changes in adult stem cells during aging and cancer.

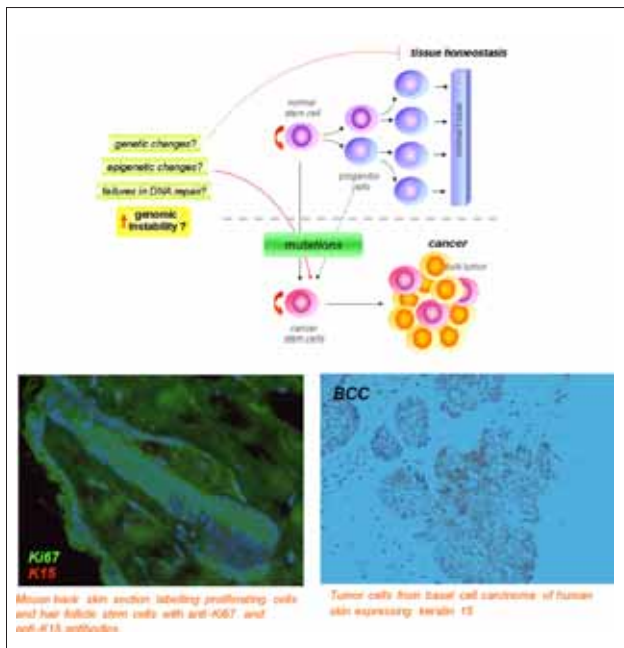
#### Research interests

The function of epidermal stem cells is essential for the maintenance of skin homeostasis. In contrast to keratinocytes of the epidermis that are continuously renewed, the stem cells are present in the skin during all the life of the organism. The continuous exposure of the epidermal stem cells to genotoxic agents during long periods of time makes these cells susceptible to accumulate mutations and DNA lesions, which in turn could compromise their function



**PhD Students:** Diana Riba Artés, Maria Victoria da Silva Diz  
**Technician:** Maria Urpi Castany

regenerating the skin. The incidence of skin tumors (non melanomas) in human increases with age and several studies indicate that these tumors could be generated from epidermal stem/progenitors cells. Our studies are focused on characterizing genetic and epigenetic changes in epidermal stem cells in aging and genetic identifying alterations responsible of loss of stem cell function and transformation of these cells in tumor initiating cells. Tumor initiating cells are a subpopulation of tumor cells that has been identified in some solid tumors as being responsible for tumor growth and distal metastasis. They show also more resistance to anti-tumoral treatments, suggesting that this tumor cell population can play a relevant role in relapsing tumor growth after chemotherapy. We will use different mouse models to isolate adult stem/progenitors cells and tumor initiating cells from normal skin and skin carcinomas. We are also interested in investigating the involvement of this population of tumor cells in the response to chemotherapy in human colorectal carcinomas.



## Lines of Research

1. Characterization of genetic and epigenetic changes in epidermal stem cells during aging.  
Despite their relevant role in tissue homeostasis, very little is known about the ability of adult stem cells to repair DNA lesions and signal through the DNA damage response (DDR) pathway or if these pathways are altered during normal aging. We are interested in analyzing if during aging epidermal stem cells accumulate DNA lesions and if these lesions result from failures in DDR and chromatin remodeling processes involved in DNA repair.
2. Isolation and characterization of tumor initiating cells from skin carcinomas.  
We aim to isolate and characterize tumor initiating cells from human and mouse skin carcinomas in order to identify genes responsible of the acquisition of their specific characteristics as well as to evaluate the impact of genomic instability during tumor growth. These studies offer the possibility to find new potential targets to suppress specifically the growth of these tumoral cells during cancer development.
3. Study of role of tumor initiating cells in the response to chemotherapy in human colorectal carcinoma.  
The aim of this project is to identify genes and mechanisms involved in chemotherapy resistance and genera-

tion of distant metastasis in colon cancer that could be used as predictive markers of chemotherapy response. Different immunodeficient mouse models, harboring human colorectal carcinomas grafts, have been generated. They allow us to immortalize colorectal carcinomas and to evaluate the role of tumor initiating cells in tumor progression and in response to chemotherapeutic treatments. This characterization will allow us to identify molecular markers with predictive value in response to treatment that could be useful in the selection of the more personalized anti-tumor treatment and with better clinical response.

## Selected publications

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## Dr Eva Gonzalez-Suarez

### Transformation and Metastasis Group

- Eva Gonzalez Suarez (Oviedo, Asturias, Spain, 1975) got her bachelor degree in Chemistry and her master degree in Biochemistry in the Universidad de Oviedo. Her college graduation work (1998) consisted in the study of the effects of melatonin in the apoptosis induced by glucocorticoids in thymocytes.

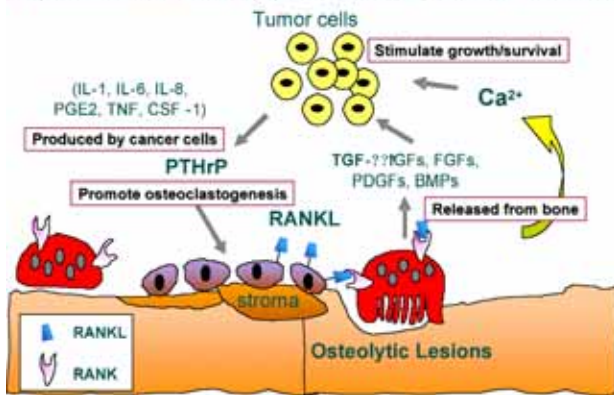
She is a PhD in Molecular Biology and Extraordinary Award by the Universidad Autónoma de Madrid (2003). Dra. Eva Gonzalez Suarez scientific career has been focused in the cancer field. Her doctoral work at the laboratory of Dr. María Blasco, in the department of Immunology and Oncology at the CNB, in Madrid aimed to elucidate the role of telomerase in tumorigenesis and aging. The results of this work can be summarized in two main discoveries: 1) in the absence of telomerase, when telomeres are strikingly short, tumors are abolished or dramatically reduced (González-Suárez et al., Nat Genetics, 2000 and Can Res, 2003) and 2) telomerase overexpression, even in the presence of long telomeres, results in a higher incidence of spontaneous and induced tumors (González-Suárez et al. EMBO J, 2001, Mol Cel Biol, 2002) but extends maximum longevity due to a lower incidence of senile lesions (González-Suárez et al., Oncogene, 2005). She received several awards for this work including Young Investigator 2003 “Severo Ochoa” Award, Best Doctorate Thesis 2003 and Juan Abelló Pascual II Award 2003.

From 2003 until 2007 Dr Eva Gonzalez worked as a post-doctoral scientist at the Oncology department at Amgen, WA, USA. The main project developed by Dra Gonzalez Suarez in Amgen was the characterization of the role of RANK and RANKL in mammary gland development and tumorigenesis. Her results demonstrated that RANK signaling activation in MECs promotes proliferation, impairs terminal differentiation (Gonzalez-Suarez et al., MCB, 2007) and increases the susceptibility to mammary tumors in the transgenic mouse model, MMTV-RANK (González-Suarez et al., manuscript in preparation). She has designed the experiments to test the efficiency of RANK-Fc in blocking the progression of mammary tumors in both, preventive and therapeutic settings. The corresponding results have a big impact within Amgen, as they have developed a monoclonal antibody that blocks RANK/RANKL interaction (Denosumab), that is currently effective for the treatment of osteoporosis and bone metastasis. Further applications of Denosumab within the primary breast cancer site are expected based on the work of Dra. Gonzalez Suarez.



**Technician:** Laura Barberá Ferrando  
**PhD Students:** Sara Hernández Ortega,  
Pasquale Pellegrini

**Vicious Cycle Hypothesis of Osteolytic Metastases**  
 Explanation For Bone-tropism of Breast, Prostate Cancer?



In 2008 Dra Eva Gonzalez Suarez was awarded a Ramon y Cajal research contract and joined the Cancer Epigenetics and Biology Program (PEBC) integrated in the Biomedical Research Institute of Bellvitge (IDIBELL) in Barcelona as a Young Investigator and leader of the "Transformation and Metastasis" group. Her current research lines are within the mammary gland biology and breast cancer field, particularly in understanding the events that drive transformation of the mammary epithelial cells and metastasis and the stem cell pathways that become deregulated during carcinogenesis.

**Research at the "Transformation and Metastasis" group Overview**

Breast cancer is the most common type of cancer in women with a mortality of 30-40% mainly due to metastasis. Breast cancer is currently managed by surgery, hormone therapy, chemotherapy and radiation. However, these approaches are non-specific, have severe side effects, and many are ineffective, specially in the treatment of metastatic disease. Our work in the Transformation and Metastasis group lead by Eva Gonzalez-Suarez is focused in the identification of the main proteins and pathways that drive mammary epithelial cell transformation and metastasis in order to find targets for future therapeutics and elucidate mechanisms of resistance to current breast cancer drugs.

**Tools and methods**

We are generating orthotopic mouse models of breast cancer. Our aim is to generate models that resemble different breast cancer subtypes and use them to identify new potential targets for breast cancer treatment, to test novel therapies and to characterize "in vivo" the mechanisms of resistance to drugs currently used in the clinics. In addition we use several transgenic mouse models prone to develop mammary epithelial tumors to complement the xenograft models. Our experimental models also include three-dimensional (3D) and suspension cultures of primary mouse and human breast cancer cells from fresh mouse and human tumors. 3D models of epithelial cells are physiologically relevant as they recapitulate the structural organization and multi-cellular complexity of the mammary epithelia. Suspension cultures are extensively used to expand and characterize the population of tumor initiating cells in vitro.

**Research Lines:**

RANK signaling in bone metastasis and breast cancer

Metastasis is responsible of most of cancer-related deaths. Metastasis to the bone is a common complication of multiple myeloma (90-95%), prostate and breast cancer (65-70%). In pathological conditions such as bone metastasis, there is an imbalance between bone resorption, mediated by osteoclasts, and bone formation, mediated by osteoblasts. In the bone microenvironment tumor cells stimulate osteoclastogenesis throughout RANKL signaling. Blocking RANKL interaction with its receptor RANK effectively prevents or reduces tumor-induced bone lesions. RANK and RANKL are also expressed in normal and tumor mammary epithelial cells (MECs) and are essential for mammary gland development in mice. Mammary epithelial cell differentiation is impaired when RANK signalling is de-regulated. We recently demonstrated using a model of RANK overexpression (MMTV-RANK transgenic mice), that RANK/RANKL signalling promotes proliferation and impairs alveolar secretory differentiation during pregnancy. In 3D cultures MMTV-RANK acini show hallmarks of transformation in a RANKL dependent manner. We aim to elucidate the RANKL-dependent and the factors that control RANK and RANKL expression pathways in mammary epithelial cells. Additionally, we explore whether there is a connection between RANK signalling in bone and mama in physiological and pathological conditions (breast cancer and bone metastasis).

**Breast cancer stem cells**

There is increasing evidence that cells with stem characteristics are targets of transformation. A population of cancer stem cells has been described in breast cancer, as well as other solid tumors and leukemia. The hypothesis that only these cancer stem cells have the ability to regenerate tumors has a deep impact for the current treatments that do not target the population of cancer stem cells. We will identify and isolate this population of cancer initiating cells from fresh mouse and human cancer samples and test their self-renewal potential in suspension and by serial transplants into the emptied mammary fat pad of host mice. Ultimately we aim to elucidate the stem cell pathways that become deregulated during carcinogenesis and that could be inhibited as a therapeutic approach to target cancer stem cells.

**Selected publications:**

- Gonzalez-Suarez E., Jacob A., Jones J., Miller R., Roudier-Meyer M., Erwert R., Pinkas J., Branstetter D., and Dougall WC. "RANK Ligand (RANKL) is a Critical Mediator of Progesterone-induced Breast Epithelial Proliferation and Progression to Adenocarcinoma". In preparation.
- Gonzalez-Suarez E., Branstetter, D., Armstrong, A., Dinh, H., Blumberg, H. and Dougall, W.C. (2007). *RANK promotes mammary epithelial proliferation in MMTV-RANK mice and disrupts luminal formation in cultured acini*. *Mol. Cell. Biol.* 27,1442-1454.
- Arnett, H.A., Escobar, S.S., Gonzalez-Suarez E., Budelsky, A.L., Steffen, L.A., Boiani, N., Zhang, M., Siu, G., Brewer, A.W. and Viney J.A. (2007). *BTNL2, a butyrophilin/B7-like molecule, is a negative costimulatory molecule modulated in intestinal inflammation*. *J. Immunol.* 178, 1523-1533.
- Geserick, C., Tejera A., Gonzalez-Suarez E., Klatt, P. and Blasco, M.A. (2006). *Expression of mTert in primary murine cells links the growth-promoting effects of telomerase to transforming growth factor- $\beta$  signaling*. *Oncogene.* 25 4310-4319.
- Gonzalez-Suarez E., Geserick, C., Flores, J.M. and Blasco, M.A (2005). *Antagonistic effects of telomerase on cancer and aging in K5-mTert transgenic mice*. *Oncogene.* 24, 2256-2270.
- Gonzalez-Suarez E., Goytisolo, F., Flores, J.M. and Blasco, M.A (2003). *Telomere dysfunction results in enhanced organismal sensitivity to the alkylating agent MNU*. *Can. Res.* 63, 7047-7050.
- Gonzalez-Suarez E., Flores, J.M. and Blasco M.A. (2002). *Cooperation between p53 mutation and high telomerase transgenic expression in spontaneous cancer development in mice*. *Mol. Cell. Biol.* 22, 7291-7301.
- Gonzalez-Suarez E., Samper, E., Ramirez, A., Flores, J.M, Martín-Caballero, J., Jorcano, J.L., and Blasco, M.A. (2001). *Increased epidermal tumors and increased wound healing in transgenic mice overexpressing the catalytic subunit of telomerase, mTERT, in basal keratinocytes*. *EMBO J.* 20, 2619-2630.
- Samper, E., Goytisolo, F., Ménissier-de Murcia, J., Gonzalez-Suarez E., Cigudosa, J.C., de Murcia, G., and Blasco M.A. (2001). *Normal telomere length and chromosomal end-capping in poly (ADP-ribose) polymerase deficient mice and primary cells despite increased chromosomal instability*. *J. Cell Biol.* 154, 49-60.
- Gonzalez-Suarez E., Samper, E., Flores, J.M. and Blasco, M.A. (2000). *Telomerase-deficient mice with short telomeres are resistant to skin tumorigenesis*. *Nat Genet* 26, 114-117

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## Dr Maribel Parra

### Cellular Differentiation Group

- **Maribel Parra** (Granollers, Barcelona, 1972) graduated in Chemistry in 1998 from the University Autonomous of Barcelona (UAB). In 2003, she received her PhD under the supervision of Dr. Pura Muñoz Cánoves at the Oncology Research Institute (IRO) and the University of Barcelona. Dr. Parra's PhD project was focused on the investigation of the signaling pathways involved in the transcriptional activation of components of the Plasminogen Activation system in response to genotoxic stress.

After finishing her PhD in 2003, Dr. Parra joined the laboratory of Dr. Eric Verdin (Gladstone Institute of Virology and Immunology (GIVI), University of California, San Francisco (UCSF) as a postdoctoral researcher. In Dr. Verdin's laboratory, Dr Parra identified the kinase and the phosphatase responsible for the phosphorylation/dephosphorylation and subcellular distribution of the histone deacetylase HDAC7 in response to T cell receptor activation. HDAC7 is a transcriptional co-repressor key in the negative selection of thymocytes during T cell development.

In 2006, Dr. Parra was awarded with a Ramón y Cajal contract from the Spanish Ministry of Science and Education (MEC). In 2007, she joined the laboratory of Dr. Thomas Graf at the Centre for Genomic Regulation (CRG) in Barcelona to initiate her studies on the role of chromatin modifying enzymes in the hematopoietic system.

Since 2007, Dr. Parra has obtained funding from the European Commission (Marie Curie International Reintegration Grant) and from the Spanish Ministry of Science and Innovation (I+D+i Grant, Plan Nacional). Since February 2009, Dr. Parra is leader of the Cell Differentiation Group at the Cancer Epigenetics and Biology Program (PEBC) of the Bellvitge Institute for Biomedical Research (IDIBELL) in Barcelona. Her current research is focused in the study of the epigenetic mechanisms involved in the lineage commitment and the differentiation of hematopoietic cells, as well as, their potential involvement in hematological disease.



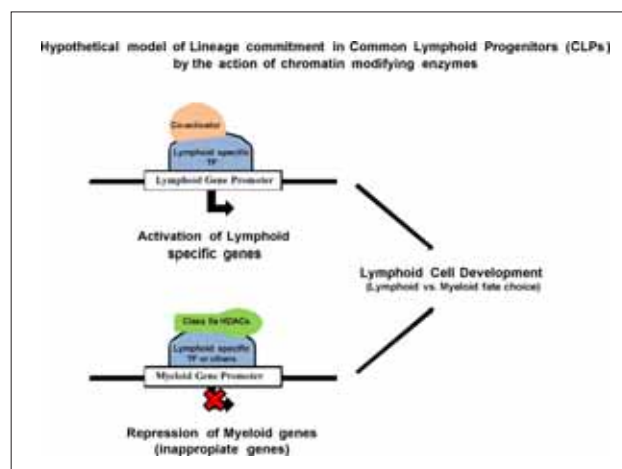
**Technician:** Olga Collazo

The hematopoietic system is a complex and fascinating model of cell commitment and differentiation. Hematopoietic stem cells (HSC) have the potential to generate all mature blood cell types. To achieve this, HSC and multipotent progenitors (MMP) develop into more lineage-restricted cell fates, common lymphoid progenitors (CLP) and common myeloid progenitors (CMP). CMPs will differentiate into megakaryocyte/erythrocyte progenitors (MEPs) and granulocyte/macrophage progenitors (GMPs), whereas CLPs will differentiate into pro-B and pro-T cells. Since the stability of every differentiation step is critical, each transition is tightly regulated at the transcriptional level through the action of lineage-restricted transcription factors that induce genes characteristic of particular cellular states. Importantly, deregulation of particular transcriptional programs leads to hematological malignancies.

Surprisingly, very little is known on the potential epigenetic control of HSC differentiation events to date. Indeed, the role of chromatin modifying enzymes, such as histone acetyl transferases (HATs) and histone deacetylases (HDACs), as well as chromatin remodeling complexes in the lineage commitment and differentiation of hematopoietic cells is poorly understood.

The main goals of our laboratory are:

1. To investigate the role of HDACs in the lineage commitment of hematopoietic cells. Once a progenitor has chosen to become a particular cell type, it will both up-regulate lineage specific genes, and repress inappropriate genes characteristic of other cellular lineages.
2. To investigate the role of chromatin remodeling complexes, such as the SWI/SNF complex, in the lineage commitment and differentiation of hematopoietic cells.
3. To investigate the potential role of chromatin regulators in the development of hematological malignancies.

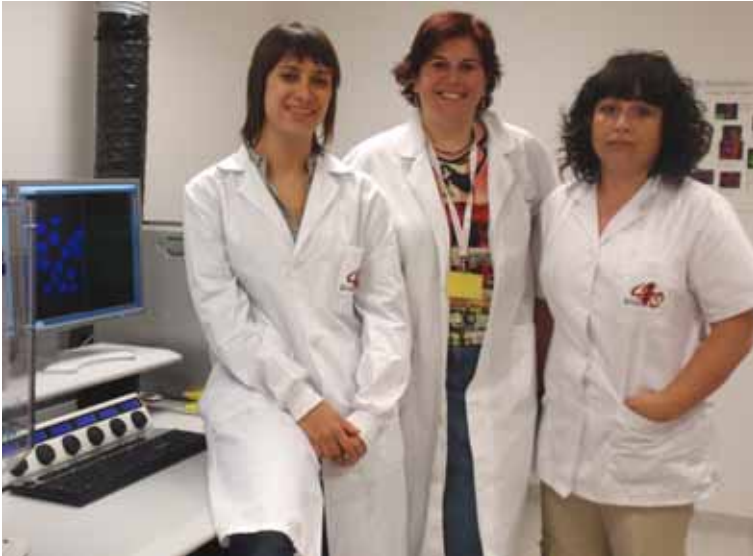


#### Selected publications

- Wang S, Li X, Parra M, Verdin E, Bassel-Duby R, Olson EN. *Control of endothelial cell proliferation and migration by VEGF signaling to histone deacetylase 7*. *Proc Natl Acad Sci U S A*. 2008. 105(22):7738-43.
- Parra M, Mahmoudi T and Verdin E. *Myosin phosphatase dephosphorylates HDAC7, controls its nucleo-cytoplasmic shuttling and inhibits apoptosis in thymocytes*. *Genes and Development*. 2007. 21(6):638-43.
- Mahmoudi T, Parra M, Vries R, Kauder S, Verrijzer P, Ott M and Verdin E. *The SWI/SNF Chromatin-Remodeling Complex is a Cofactor for Tat Transactivation of the HIV Promoter*. *Journal of Biological Chemistry*. 2006. 281(29): 19960-8.
- Mahmoudi T, Parra M, Vries R, Kauder S, Verrijzer P, Ott M and Verdin E. *The SWI/SNF Parra M, Kasler H, McKinsey TA, Olson EN and Verdin E. Protein kinase D1 phosphorylates HDAC7 and induces its nuclear export after T-cell receptor activation*. *Journal of Biological Chemistry*. 2005. 280(14): 13762-70.
- Vidal B, Parra M, Jardí M, Saito S, Appella E and Muñoz-Cánoves P. *The alkylating carcinogen N-methyl-N'-nitro-N-nitrosoguanidine activates the plasminogen activator inhibitor-1 gene through sequential phosphorylation of p53 by ATM and ATR kinases*. *Thrombosis and Haemostasis*. 2005. 93(3): 584-91.
- Parra M, Jardí M, Koziczak M, Nagamine Y and Muñoz-Cánoves P. *p53 phosphorylation at serine 15 is required for transcriptional induction of the plasminogen activator inhibitor-1 (PAI-1) gene by the alkylating agent MNNG*. *Journal of Biological Chemistry*, 2001. 276:36303-10

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## PEBC Technical Support



**Imaging Technician:** Jemina Moreto  
**Managing Technician:** Laura España  
**Support Technician:** Sonia del Oro

## PEBC Technical Administration



**Senior Administrative Assistant:** Anne Legrand  
**Administrative Assistant:** Anna Verges  
**National Grant Officer:** Merce Manyos  
**International Grant Officer:** Sonja Noss

## PEBC Educational and Training Dimension



- 24 PhD Students:
- 14 Universitat de Barcelona (UB)
  - 4 Universidad Autonoma de Madrid (UAM)
  - 2 Universitat Autonoma de Barcelona (UAB)
  - 2 Universitat Pompeu Fabra (UPF)
  - 2 Universidade do Porto, Portugal

- 3 Master Students:
- Master en Biologia del Desenvolupament i Genetica, UB
  - Master en Investigación y Desarrollo de Medicamentos, UB
  - Master en Biotecnologia, UB

- Visiting Scientists:
- Universita degli Studi di Milano, Italy
  - Universita degli Studi di Firenze, Italy
  - University of Patras, Greece
  - University of Coimbra, Portugal

Training Technician Course Institut Roger de Lluria, Barcelona

Training Course in Genetics for 100 Undergraduate Students from the School of Medicine, UB

Training Course in Biomedical Master for 20 Students, UB

# PEBC Invited Lectures

Hosted by Dr Manel Esteller

Director, Cancer Epigenetics and Biology Program (PEBC)  
Institut d'Investigació Biomèdica de Bellvitge (IDIBELL)  
Institut de Recerca i Estudis Avançats (ICREA)  
Catalan Institute of Oncology (ICO)

**November 21 2008**

**Dr Jose Maria Mato**

"Abnormal methionine metabolism leads to impaired liver function and hepatocellular carcinoma."  
Director, CIC bioGUNE & CIBERehd, Parque Tecnológico de Bizkaia, Derio, Bizkaia.

**December 19, 2008**

**Dr Lluís Montuenga**

"Searching for molecular biomarkers: in early lung cancer: the challenge of crossing the translational bridge."  
Head, Division of Oncology, Center of Applied Medical Research (CIMA), Pamplona.

**January 16th, 2009**

**Dr Eugenio Santos**

"Functional specificity and activation of Ras proteins. Studies in genetically modified animal models."  
Director, Centro de Investigación del Cáncer (CIC), Salamanca.

**January 23, 2009**

**Dr Manuel Hidalgo**

"Individualize Approaches to the Treatment of Pancreatic Cancer"  
Director, Centro Integral Oncológico Clara Campal, Madrid

**February 6, 2009**

**Dr Cesar Nombela**

"The yeast signalling network in the control of cell integrity".  
Chairman of Microbiology and MSD Genomics and Proteomics, School of Pharmacy, Universidad Complutense de Madrid

**February 13, 2009**

**Dr Eduardo Diaz-Rubio**

"Targeted Therapy in metastatic Colorectal Cancer"  
Head, Medical Oncology Department, Hospital Clínico San Carlos, Madrid.

**February 20, 2009**

**Dr Elías Campo**

"Mantle Cell Lymphoma: from morphology to molecular biology and back to the clinics"  
Director of Biomedical Diagnostic Center, Head of Hematopathology Unit, Hospital Clinic de Barcelona

**March 6, 2009**

**Dr Jose Luis Jorcano**

"Relevance of Genomics in the Future of Biomedicine: the view of Genoma España"  
Director General, Fundación Genoma España

**March 13, 2009**

**Dr Miguel Angel Piris**

"Lymphoma: therapy driven by molecular diagnosis"  
Director, Molecular Pathology Program, Spanish National cancer Research Centre (CNIO), Madrid.

**March 20, 2009**

**Dr Josep Baselga**

"New directions in targeting the HER receptor family: a voyage to the centre of the cell"  
Head, Medical Oncology Department, Hospital Universitari Vall d'Hebron, Barcelona.

**April 3, 2009**

**Dra Margarita Salas**

"Protein-primed regulation of bacteriophage  $\phi$ 29 DNA"  
Centro de Biología Molecular "Severo Ochoa", Madrid.

**May 15, 2009**

**Dr Miguel Beato**

"Chromatin Structure and Gene Regulation"  
Director, Center for Genomic Regulation, Barcelona.

**June 19, 2009**

**Dr Angel Carracedo**

"Finding genes that underlie cancer using genetic tools"  
Director, Instituto de Medicina Legal, Universidad de Santiago de Compostela.

Location: Sala d'Actes, Planta Baixa, Hospital Duran i Reynals, Gran Via 199-203, 08907 L'Hospitalet, Barcelona.  
Time: 12.00h

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## PEBC Invited Lectures



Professor Margarita Salas's presentation at the PEBC Invited Lectures

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## Selected PEBC Ad Hoc Seminars

Chris Van Oevelen, New York University  
School of Medicine, New York, USA

Alberto Font, Roche

Juan Luis Monteagudo, Leica

Bernat Crosas, CSIC, Barcelona

Albert Jordan, Centre de Regulacio Genomica,  
Barcelona

Josep Vilardell, Centre de Regulacio Genomica,  
Barcelona

Bill Dougall, Amgen Seattle, USA



Professor Lluís Montuenga at a PEBC Invited Lecture

## PEBC Retreat December 2008



A great occasion to bring together all the personnel working at the PEBC for a fruitful discussion about the scientific goals and perspectives of the research program in a relaxed atmosphere at Platja d'Aro in the Costa Brava of Catalonia.

## PEBC Funding

### Main Patron



### International Competitive Grants

European Commission (FP7), CANCERDIP  
European Commission (FP6), MCSC, ESTOOLS and SMARTER  
Human Frontiers Science Program (HFSP)  
European Network on Rett Syndrome (EuroRETT)  
Marie Curie People-European Union



### Catalonia / Spain Competitive Grants

Ministerio de Ciencia e Innovación, Gobierno de España  
Ministerio de Sanidad, Gobierno de España



### Foundations

Asociación Española contra el Cáncer (AECC)  
Junta de Barcelona- Asociación Española contra el Cáncer  
Fundación Marcelino Botín  
Fundación Mutua Automovilística Madrileña  
Fundación Sandra Ibarra de Solidaridad frente al Cáncer  
Fundación Genoma España



### Competitive Positions and Fellowships

Institució Catalana de Recerca i Estudis Avançats (ICREA)  
Agència de Gestió d'Ajuts Universitaris i de Recerca (AGAUR)  
Ramon y Cajal Research Program, Ministerio de Ciencia e Innovación  
Ministerio de Asuntos Exteriores, Gobierno de España  
Fundación Ramon Areces

## PEBC Opening Acts



Top left, Molt Honorable President of the Catalan Government (Generalitat de Catalunya) Sr. José Montilla at his first visit at the PEBC and presentation of the PEBC Program in the Catalan Parliament.

## PEBC Awards and Recognitions

### Scientific Awards

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#### Dr Manel Esteller

- 2008 "Dr Jacint Vilardell" Award, Gastroenterology Foundation
- 2008 Debiopharm Life Sciences Award, École Polytechnique Fédérale Lausanne, Switzerland
- 2009 Premio «Conde de Cartagena», Real Academia Nacional de Medicina, Spain
- 2009 Premio Fundacion Lilly de Investigacion Biomedica, Spain
- 2009 Dr Josef Steiner Cancer Research Foundation Award, Switzerland

#### Dr Manel Esteller

- 2008-2009 President, Epigenetics Society

#### Dr Manel Esteller

- 2008 Elected to the Editorial Board of Journal of Pathology
- 2008 Elected to the Editorial Board of Molecular Cancer Therapeutics
- 2009 Elected to the Editorial Board of European Journal of Clinical Investigation

#### Dr Manel Esteller

- 2008 Elected for the Scientific Advisory Board of IPATIMUP, Portugal
- 2009 Elected for the Scientific Advisory Board of Centro de Investigación Biomédica de La Rioja (CIBIR)

#### Dr Eva Gonzalez-Suarez

- 2009 Grant award Junta de Barcelona, Asociación Española contra el Cancer

#### Dr Alejandro Vaquero and Dr Sonia Guil

- 2009 Grant awards breast cancer, Fundación Solidaridad frente al Cancer Sandra Ibarra

#### Dr Dave Monk

- 2009 Merck Serono Investigation Award



Catalan of the Year Award Gala



Nobel Laureate in Medicine Dr. Michael Bishop with Dr. Manel Esteller at the Debiopharm Life Science Award EPFL ceremony

### Social Awards and Honors

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#### Dr Manel Esteller

- 2009 Finalist for the "Catalan of the Year" Award, El Periodico de Catalunya
- 2009 Premio Dulcinea Asociación Mujeres Cáncer de Mama Castilla-La Mancha

## PEBC in International Scientific Meetings

AACR Annual Meeting, 2008. San Diego, CA, USA  
International Cancer Genome Consortium (ICGC) Scientific Workshop, 2008. Bethesda, MD, USA  
AACR Conference on Cancer Epigenetics, May 2008. Boston, USA  
Workshop on Genome Bioinformatic Techniques. MC-GARD Conferences and Training Courses. September 2008, Madrid  
Interplay among Genetics, Epigenetics and non-coding RNAs congress. MC-GARD Conferences and Training Courses. Madrid. May 4-7, 2008.  
Simposio Internacional de Oncología Traslacional, Barcelona. April 24-25, 2008.  
EuroSTELLS Workshop: Stem Cell Niches. January 2008, Barcelona  
Conference Debate on Genetic Testing: The Age of Personal Genomes. Nature Publishing Group, Fundación Ramón Areces. Madrid, 2009-04-29  
Mechanisms of Eukaryotic Transcription, Cold Spring Harbor Laboratory. August 2008, Cold Spring Harbor, NY (USA)  
7th European Lupus Meeting, Amsterdam, The Netherlands. May 7-10, 2008  
Keystone Symposia: Epigenetics, Development and Human Disease, Beaver Run Resort, Breckenridge, Colorado. January 2009, USA  
MCC Cluster Review, Sasakawa Lyon, France, IARC, 2008  
MCSCs 2nd Annual Meeting of the EU FP6 STREP Consortium Seon, Germany, 2008  
NOW-CW study groups Amsterdam, The Netherlands, NKI, 2008  
SMARTER Annual Project Meeting Basel, Switzerland, Friedrich Miescher Institute for Biomedical Research, 2008  
CancerDip Coordination and Management Meeting, Napoli, S.U.N. Naples, Italy, 2008  
Dr. Josef Steiner Cancer Research Award 2009, Bern, Switzerland, Josef Steiner Foundation, 2009  
International TNF Meeting Madrid El Escorial, 2009  
Workshop ENBDC Weggis Switzerland, 2009  
Gordon Conference on mammary gland biology, Barga, Italy, 2008  
Keystone Symposia Emerging Themes in Tumor Suppressors: Function and Clinical Implications in the Post-Genomic Era. Taos, New Mexico, USA, 2009



Emerging Evidence for Epigenomic Changes in Human Disease NIH Roadmap Epigenomics Program Bethesda, MD, USA, 2009  
Welcome Trust/Cancer Research UK Gurdon Institute for Cancer and Developmental Biology Cambridge, UK, 2009  
15th Scientific Symposium of the Lilly Foundation. Molecular Markers in Cancer Therapy: Present and Future Perspectives El Escorial, Madrid, Spain, Fundación Lilly, 2009  
100th AACR Annual Meeting Denver, CO, USA, 2009  
The DNA-proteome: recent advances towards establishing the protein-DNA interaction space Barcelona, Spain, IRB, 2009  
ESMO Impact Breast Cancer Conference Brussels, Belgium, 2009



# PEBC International Coverage

**USNews** Wednesday, April 28, 2009

**Genes Help Cancer-Linked Viruses Elude Immune System**  
**Pathogens such as HPV tweak their DNA to escape detection, study suggests**  
 Posted February 25, 2009

TUESDAY, Feb. 24 (HealthDay News) — The DNA of cancer-related viruses may actually change to disguise themselves from the immune system, a new study has found.

An international team of scientists studied the entire genomes of three common viruses — Epstein-Barr, the human papilloma virus (HPV) and hepatitis B. Each of these pathogens can progress into cancer — for example, HPV is strongly linked to cervical tumors, and hepatitis B has been tied to liver cancer. About 15 percent of all cancer cases worldwide are linked to a viral infection.

The researchers found that the genomes were generally similar between people who had the virus but no symptoms, those with the disease caused by the virus, and those who developed the virus-related cancer. However, the epigenome — a layer of biochemical reactions that turn genes on and off — appeared much different, with the virus increasingly experiencing methylation in patients who had developed cancer.

According to the researchers, methylation (an enzyme-mediated modification to DNA) may prove to be a type of camouflage to help the virus evade the body's natural defense system.

The findings were published online in *Genome Research*.

"This is a very exciting result that can explain why some of these viruses can survive for such prolonged times in our body," senior author Marel Esteller, of the Bellvitge Institute for Biomedical Research (IDIBELL) in Barcelona, said in a news release issued by the journal.

**NewScientist**

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**Gene caps may turn viruses cancerous**

11 February 2009 by Bob Holmes  
 Magazine issue 2555, Subscribe and get 4 free issues.

CANCER-CAUSING viruses undergo genetic changes as their host cells become malignant. The finding could allow doctors to predict when people infected with a virus will develop cancer, and possibly point to new treatments.

It is already known that cells turning cancerous accumulate chemical "tags", called methyl groups, on crucial tumour-suppressor genes. These caps silence the genes, often speeding up the onset of cancer.

Marel Esteller, an epigenetics researcher at the Bellvitge Institute for Biomedical Research in Barcelona, Spain, wondered whether similar methylations were taking place on viral genes as their host cells turned cancerous.

To investigate, Esteller and his colleagues looked up the methylations on the entire genome of various types of cancer-causing virus. These included strains 16 and 18 of the human papilloma virus (HPV), which can cause cervical cancer, and hepatitis B virus, which can lead to liver tumours. They also looked for methylations in Epstein-Barr virus, which is associated with some types of lymphoma.

For each virus, the team obtained three sets of samples: from people who were carriers but had no cancer symptoms, from those who had precancerous lesions, and from people with full-blown cancer.

In all four viruses, the degree of methylation correlated with disease progression. One gene found in HPV-16, for example, was not methylated in any of 30 asymptomatic carriers, but was in 21 of 92 people with precancerous lesions, and 18 of 17 with cervical cancer (*Genome Research*, DOI: 10.1101/300550, 2009). "When you start to get methylation, you start to get tumorigenesis," says Esteller.

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**TheScientist**  
 News  
 Posted by Laura Jermolova  
 [Entry posted at 10:51 February 2009 10:01 PM GMT]  
 View comments(1) | Comment at this news story

Epigenetic changes in certain viruses can make the difference between a simple infection and cancer, according to a new study published early online tomorrow (Feb 25th) in *Genome Research*.

Stephen Beck, a medical geneticist at University College London who was not involved in the research, said he was "excited" by the findings, which identify "the connection between cancer progression and methylation."

Researchers have been examining the link between DNA methylation, which generally causes gene silencing, and cancer, and to date, "this is the most comprehensive study of a complete methylome" — or methylation map — of a virus, Benk SMC.

Some 15% of cancer worldwide can be linked to viral infection, *David Esteller*, Director of the Cancer Epigenetics and Biology Program (CEBP) at Bellvitge in Barcelona, and his collaborators set out to create maps of DNA methylation patterns in three known oncogenic viruses: human papilloma virus (HPV), Hepatitis B virus (HBV), and the Epstein Barr Virus (EBV).

**METASTASIS**  
**Micro silencing**  
 The deregulated expression of microRNAs has been implicated in the development of tumour metastases. New evidence from Marel Esteller and colleagues indicates that hypomethylation of microRNAs could be responsible for this deregulated expression.

Evidence that non-coding microRNAs are subject to epigenetic regulation led Esteller and colleagues to ask whether a microRNA hypomethylation profile is evident in human tumours. These human metastatic cancer cell lines were treated with the DNA methylation inhibitor 5-aza-2'-deoxycytidine.

RNA analyses of the treated and untreated cells showed that 57 of 369 microRNAs showed increased expression in the presence of 5-aza-2'-deoxycytidine, and 27 of these were embedded in a canonical CpG island — stretches of DNA that are commonly associated with DNA methylation. MiR-145a, miR-34b, and miR-9 were specifically hypomethylated in cancer cells and their re-expression in these cells suppressed tumour growth, motility and metastasis in xenograft models. This correlated with reduced expression of some of their known target genes, including MYC and E2F3.

Importantly, the authors also showed that hypomethylation of these microRNAs correlated with the appearance of lymph node metastasis in 207 primary human tumour samples. If verified, such information could be used to predict patients that are more likely to develop metastasis. These findings also indicate that drugs that lead to DNA demethylation might be useful for the treatment of metastatic disease.

*Marel Esteller*

**abc NEWS**  
 start here

TUESDAY, Feb. 24 (HealthDay News) — The DNA of cancer-related viruses may actually change to disguise themselves from the immune system, a new study has found.

An international team of scientists studied the entire genomes of three common viruses — Epstein-Barr, the human papilloma virus (HPV) and hepatitis B. Each of these pathogens can progress into cancer — for example, HPV is strongly linked to cervical tumors, and hepatitis B has been tied to liver cancer. About 15 percent of all cancer cases worldwide are linked to a viral infection.

The researchers found that the genomes were generally similar between people who had the virus but no symptoms, those with the disease caused by the virus, and those who developed the virus-related cancer. However, the epigenome — a layer of biochemical reactions that turn genes on and off — appeared much different, with the virus increasingly experiencing methylation in patients who had developed cancer.

The findings were published online in *Genome Research*.

"This is a very exciting result that can explain why some of these viruses can survive for such prolonged times in our body," senior author Marel Esteller, of the Bellvitge Institute for Biomedical Research (IDIBELL) in Barcelona, said in a news release issued by the journal.

**NATURE REVIEWS | CANCER**

## Selected PEBC National and International Collaborations

### Catalonia

Universitat de Barcelona  
Universitat Autònoma de Barcelona  
Universitat Pompeu Fabra, Barcelona  
Hospital Sant Joan de Deu, Barcelona  
Hospital de la Santa Creu i Sant Pau,  
Barcelona  
Centre de Regulació Genòmica (CRG),  
Barcelona  
Hospital Universitari Vall d'Hebron,  
Barcelona  
Municipal Institute for Medical Research  
(IMIM-Hospital del Mar), Barcelona

### Spain

Fundación Instituto de Investigación  
Príncipe Felipe  
Universitat de Valencia  
Hospital Virgen de la Arrixaca, Murcia  
Hospital 12 de Octubre, Madrid  
Centro de Investigaciones del Cancer  
(CIC), Salamanca  
Centro Nacional de Investigaciones  
Oncológicas (CNIO), Madrid  
CIMA, Pamplona  
Universidad del País Vasco, Lejona,  
Vizcaya, Euskadi  
CIC Biomagune, San Sebastian,  
Guipuzcoa, Euskadi  
National Center of Biotechnology (CNB),  
Madrid  
Hospital La Paz, Madrid  
Gregorio Marañón Hospital, Madrid  
Centro Nacional de Microbiología,  
Instituto de Salud Carlos III, Madrid  
Biomedical Research Center, Department  
of Surgery, Navarra Health Service,  
Pamplona  
Centro de Biología Molecular Severo  
Ochoa, Madrid  
Centro Andaluz de Biología Molecular y  
Medicina Regenerativa (CABIMER),  
CSIC, Sevilla  
School of Chemistry-Química-Kimika  
Fakultatea, Donostia, Euskadi

### International

Cancer Research UK  
National Cancer Center Research  
Institute, Tokyo, Japan.  
National Cancer Institute, National  
Institutes of Health, Bethesda,  
Maryland  
Università degli Studi di Napoli Federico II,  
Napoli, Italy  
Harvard Medical School, Dana Farber  
Cancer Institute, Boston, USA  
Medical Research Council, National Institute  
for Medical Research, London UK  
John Hopkins University and Medical  
Institutions, Baltimore USA  
Kings College London, UK.  
CNRS Montpellier, France.  
Unité de Recherche en Génomique  
Végétale, CNRS, France  
London Research Institute, Cancer  
Research UK, London  
National Institute of Environmental Health  
Sciences, National Institutes of Health  
(NIH), Bethesda MD, USA  
Institute of Human Genetics, Christian-  
Albrechts-University Kiel, Kiel, Germany  
Broad Institute, Cambridge, MA, USA  
Gladstone Institute of Virology and  
Immunology (GVI), University of California  
at San Francisco (UCSF), USA  
Rutgers University, USA  
NYU medical school, USA  
Université Libre De Bruxelles, Belgium  
Radboud Universiteit Nijmegen - Stichting  
Katholieke Universiteit, The Netherlands

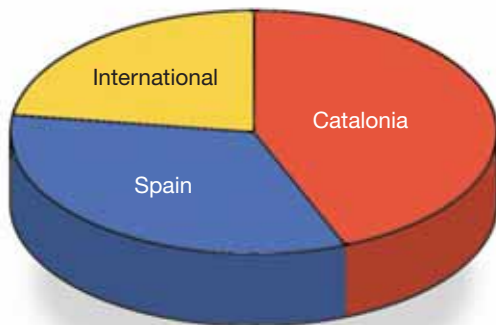
Seconda Università Degli Studi Di Napoli,  
Italy  
Max Planck Gesellschaft Zur Foerderung  
Der Wissenschaften E.V., Germany  
University of Sheffield (UK)  
SCS UK Ltd (UK)  
University of Basel (CH)  
Hebrew University of Jerusalem (Israel)  
University of Turku (FI)  
University of Bonn (GER)  
University of Milan (IT)  
Medical Research Council (UK)  
Institute of Experimental Medicine (CZ)  
University of Lund (SE)  
Karolinska Institutet (SE)  
Netherlands Cancer Institute (NL)  
Hesiging yliopisto (FI)  
SCT Stem Cell Technologies Ltd (Israel)  
University of Edinburgh, Institute for Stem  
Cell Research (UK)  
University of Technology Dresden (GER)  
University of Cambridge (UK)  
Imperial College London (UK)  
Tampere University of Technology (FI)  
Inserm U491, Faculté de Médecine de La  
Timone, Marseille (F)  
Institut Cochin, Inserm U567 Génétique et  
Développement, Paris (F)  
San Raffaele Scientific Institute, DIBIT,  
Milano (I)  
Max Delbrück Center for Molecular  
Medicine, Molecular and Cell Biology of  
the (Epi)genome, Berlin (GER)  
SHEBA MEDICAL CENTER, Genetics  
Institute, Tel Hashomer (IL)  
Georg August University - Faculty of  
Medicine, Pediatrics and Pediatric  
Neurology, Göttingen (GER)  
Istituzione Istituto Superiore di Sanità, Cell  
Biology and Neurosciences, Section  
Behavioural Neurosciences, City Roma (I)  
UMR5166 CNRS/MNHN, RDDM, Paris (F)  
Istituto Auxologico Italiano, Laboratorio di  
Biologia Molecolare, Milano (I)  
RIKEN Brain Science Institute (JP)  
University of British Columbia (CAN)  
VU University Medical Centre (NL)  
The University of Edinburgh (UK)



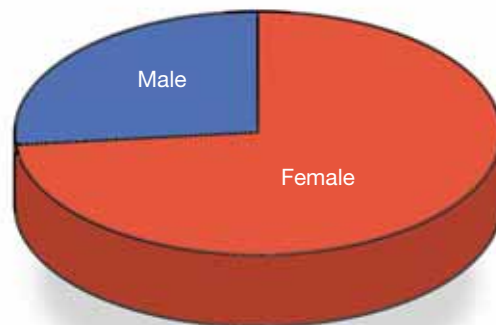
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## PEBC Demography and Personnel Data

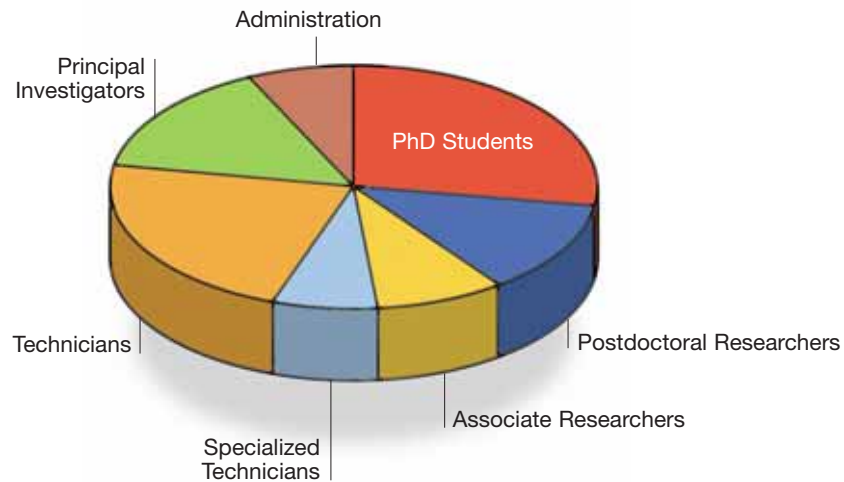
Geographical Origin of PEBC Personnel



Gender of PEBC Personnel



Job Distribution of PEBC Personnel



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## PEBC International Consulting Committee

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University of Southern California, Los Angeles,  
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Wellcome Trust Sanger Institute,  
Hinxton, Cambridge CB10 1SA, UK.







Forthcoming  
PEBC Meetings  
and Conferences



# CANCERDIP

## MEDIP CANCER CONSORTIUM



### Mid-Term Workshop

# DNA Methylomes in Health and Disease

Thursday, July 2nd, 2009

Hospital Duran i Reynals, ICO Auditorium

**François Fuks, PhD,**  
Group Leader, Cancer Epigenetics Group,  
Faculty of Medicine, Université Libre de  
Bruxelles, Belgium  
*"Mechanisms of DNA methylation and its  
intimate link with histone modifications".*

**Irina Panteleeva, PhD,**  
R&D Epigenetics, Diagenode SA, Liège,  
Belgium  
*"Methylated DNA analysis: Diagenode  
new tools and standardisation".*

**Christoph Bock, PhD\*,**  
Research scholar at the Broad Institute,  
Boston, USA  
*"Epigenome analysis with bioinformatic  
methods and applications to cancer  
biomarker discovery".*

**Manel Esteller, M.D., PhD,**  
Director, Cancer Epigenetics and Biology  
Program (PEBC), Bellvitge Institute  
for Biomedical Research (IDIBELL), Barcelona,  
Spain  
*"Human Cancer Epigenetics".*

**Arjen Brinkman, PhD,**  
Associate Researcher, Department of  
Molecular Biology, Radboud University  
Nijmegen, The Netherlands  
*"Cancer methylome profiling using  
Methyl-DNA Capture".*

**Dirk Schuebeler, PhD,**  
Group Leader, Propagation and Dynamics of  
Epigenetic States Group,  
Friedrich Miescher Institute, Basel, Switzerland  
*"Epigenetic restriction during stem cell  
differentiation".*

**Lucia Altucci, M.D., PhD,**  
Associate Professor, Department of General  
Pathology, Seconda Università degli Studi di  
Napoli, Italy  
*"Broad-spectrum epigenetic inhibition as a novel  
anti-cancer approach in vivo".*

**Stephan Beck, PhD,**  
Professor of Medical Genomics, UCL Cancer  
Institute, University College London, UK  
*"Reverse Phenotyping: towards an integrated  
(epi)genomic approach to complex phenotypes  
and common disease".*



Website: [www.cancerdip.eu](http://www.cancerdip.eu)

Contact: [snoss@iconcologia.net](mailto:snoss@iconcologia.net)

\* Also Junior Group Leader for Computational Epigenetics at the Max Planck Institute for Informatics, Saarbruecken, Germany



# ICC on Sirtuins 2009



## October 22-23, Barcelona, Spain

### Invitation to Attend

As organisers, we invite you to attend the IDIBELL Cancer Conference on Sirtuins. The meeting will be held in the Bellvitge Institute for Biomedical Research, IDIBELL, Barcelona.

The *ICC on Sirtuins* meeting will begin on Thursday morning, October 22, 2009, and will conclude with lunch on Friday, October 23, 2009. The goal of this meeting is to highlight the latest advances in the Sirtuin field from a multidisciplinary point of view, from the molecular to the physiological level, and to create an exceptional framework for scientific discussion.

Applicants are encouraged to submit Poster presentations. A limited number of these abstracts will be selected for oral presentation.

For registration visit [www.pebc.cat](http://www.pebc.cat). All meeting questions should be directed to Anne Legrand, Meeting Manager, [alegrand@iconcologia.net](mailto:alegrand@iconcologia.net)

### Invited Speakers

**Fred Alt**  
Harvard Medical School  
Cambridge, MA, USA

**Johan Auwerx**  
Ecole Polytechnique Federale de Lausanne  
Lausanne, Switzerland.

**Antonio Bedalov**  
Fred Hutchinson Cancer Research Center  
Seattle, WA, USA.

**Eva Bober**  
Max-Planck-Institute for Heart and Lung Research  
Bad Nauheim, Germany.

**Katrin Chua**  
Stanford University School of Medicine  
Stanford, CA, USA.

**John Denu**  
University of Wisconsin-Madison School of Medicine and  
Public Health  
Madison, WI, USA.

**Manel Esteller**  
Cancer Epigenetics and Biology Program PEBC-IDIBELL,  
Barcelona, Spain.

**Ingrid Grummt**  
German Cancer Research Center  
Heidelberg, Germany.

**Wei Gu**  
Columbia University  
New York, NY, USA.

**Pere Puigserver**  
Dana-Farber Cancer Institute  
Boston, MA, USA.

**Danny Reinberg**  
NYU School of Medicine  
New York, NY, USA.

**Ed Seto**  
H.Lee Moffit Cancer Center  
Tampa, FL USA.

**Alejandro Vaquero**  
Cancer Epigenetics and Biology Program, PEBC- IDIBELL,  
Barcelona, Spain.

**Eric Verdin**  
Gladstone Institute of Virology and Immunology  
San Francisco, CA, USA.

**Francesc Villarroya**  
University of Barcelona (UB)  
Barcelona, Spain.

### Organisers

Alejandro Vaquero (Cancer Epigenetics and Biology program (PEBC)/Bellvitge Institute for Biomedical Research, IDIBELL)  
Manel Esteller (Cancer Epigenetics and Biology program (PEBC)/Bellvitge Institute for Biomedical Research, IDIBELL)

meeting sponsored by:



Contact Meeting Management:  
[avaquero@iconcologia.net](mailto:avaquero@iconcologia.net)  
[mesteller@iconcologia.net](mailto:mesteller@iconcologia.net)



# ICC on the Cell Cycle 2009



## November 26-27, Barcelona, Spain

### Invitation to Attend

As organisers, we invite you to attend the IDIBELL Cancer Conference on the Cell Cycle (ICC on the Cell Cycle). The meeting will be held in the Bellvitge Institute for Biomedical Research, IDIBELL, Barcelona.

The ICC on the Cell Cycle will begin on Thursday morning, November 26, 2009, and will conclude with lunch on Friday, November 27, 2009. The goal of this meeting is to highlight the latest advances in cell cycle regulation in a broad spectrum of experimental organisms.

Applicants are encouraged to submit Poster presentations. A limited number of these abstracts will be selected for oral presentation.

For registration visit [www.pebc.cat](http://www.pebc.cat). All meeting questions should be directed to Anne Legrand, Meeting Manager, [alegrand@iconcologia.net](mailto:alegrand@iconcologia.net)

### Invited Speakers

**Tim Hunt**  
Cancer Research UK, Clare Hall Laboratories  
South Mimms, UK.

**John Diffley**  
Cancer Research UK, Clare Hall Laboratories  
South Mimms, UK.

**Etienne Schwob**  
Institute of Molecular Genetics  
Centre National de la Recherche, Montpellier, France.

**Marti Aldea**  
Dept. Ciències Mèdiques Bàsiques  
Universitat de Lleida, Lérida, Spain.

**Christian Lehner**  
University of Zurich, Institute of Zoology  
Zurich, Switzerland.

**Wolfgang Zachariae**  
Max Planck Institute of Molecular Cell Biology and Genetics  
Dresden, Germany.

**Jean-Michael Peters**  
Research Institute of Molecular Pathology IMP  
Vienna, Austria.

**Prasad Jallepalli**  
Memorial Sloan-Kettering Cancer Center  
New York, USA.

**Karim Labib**  
Paterson Institute for Cancer Research  
Manchester, UK.

**Erich A. Nigg**  
Marx Planck Institute of Biochemistry  
Martinsried, Germany.

**Bela Novak**  
Oxford Centre for Integrative Systems Biology  
Department of Biochemistry  
University of Oxford, Oxford, UK.

**Angel Nebreda**  
Centro Nacional de Investigaciones Oncológicas  
CNIO, Madrid, Spain.

**Sergio Moreno**  
Centro de Investigación del Cáncer  
Salamanca, Spain.

**Marcos Malumbres**  
Centro Nacional de Investigaciones Oncológicas  
CNIO, Madrid, Spain.

**Frank Uhlmann**  
Cancer Research UK, London Research Institute  
London, UK.

**Ethel Queralt**  
Cancer Epigenetics and Biology Program PEBC-  
IDIBELL, Barcelona, Spain.

### Organisers

Frank Uhlmann (Cancer Research UK London Research Institute)  
Ethel Queralt (Cancer Epigenetics and Biology program (PEBC)/Bellvitge Institute for Biomedical Research, IDIBELL)

meeting sponsored by:



Contact Meeting Management:  
[frank.uhlmann@cancer.org.uk](mailto:frank.uhlmann@cancer.org.uk)  
[equeralt@iconcologia.net](mailto:equeralt@iconcologia.net)

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## ICC on Tumor Suppressor Genes

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May 2010

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Organizers: Montse Sanchez-Cespedes,  
Conxi Lazaro and David Sidransky

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## ICC on Mice Models of Cancer

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October 2010

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Organizers: Eva Gonzalez-Suarez,  
Puri Muñoz and Jos Jonkers

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Genoma España



epigenetics



# Cancer Epigenetics and Biology Symposium

and presentation of the PEBC research program

28-29 May 2009  
Barcelona