Manel Esteller received EACR’s prestigious 2011 Cancer Researcher Award in Stockholm where he gave his award lecture in a Special Session at The European Multidisciplinary Cancer Congress (ECCO).

Cancer Epigenetics
Manel Esteller

We cannot fully blame our genome for our behaviour and susceptibility to disease. The base pair nucleotide sequence of DNA, the typical subject of study of classical genetics, cannot completely explain the functionality of our cells, their disruption in complex diseases or the definition of our species. We need something else. Part of the explanation is provided by the field of Epigenetics. Waddington defined Epigenetics in 1939 as “the causal interactions between genes and their products, which bring the phenotype into being.” From our current knowledge we can define Epigenetics as “the inheritance of DNA activity that does not depend on the naked DNA sequence.” This “inheritance” is most simply understood during mitosis, the process of transmission when a cell divides to produce daughter cells during the cell cycle; or even, and in a more provocative manner, during meiosis in our germ cells and thus the epigenetic information is transmitted to our progeny.

Epigenetics refers to the dynamic chemical modifications that occur to our DNA, and its subsequent association with regulatory proteins (Berdasco and Esteller, Dev Cell 19(5):698-711, 2010).

DNA methylation has critical roles in the controlling of gene activity and nuclear architecture. In humans, DNA methylation occurs at cytosine within CpG dinucleotides. These CpG sites are not randomly distributed in the human genome; CpG-rich regions, known as CpG islands, are often associated with the 5’-end regulatory region of many genes and are usually unmethylated in normal cells. This unmethylated status corresponds with the ability of CpG-island-containing genes to be transcribed in the presence of the necessary transcriptional activators. However, there is a subset of promoter CpG islands that are heavily methylated in normal tissues, and these are often associated with tissue-specific and germline-specific genes, imprinted genes and genes that undergo X-chromosome inactivation in females. In addition, repetitive genomic sequences are also heavily methylated. The maintenance of this methylation state may have a role in protecting chromosome integrity by preventing chromosomal instability. DNA methylation is not an isolated epigenetic mark. It is often associated with chemical modifications to the N-terminal tails of histone proteins. Once considered only mere DNA-packaging proteins, histones now take centre stage as stores of epigenetic information through a complex set of post-translational modifications such as lysine acetylation, arginine and lysine methylation or serine phosphorylation, among others. It has been proposed that distinct patterns of modifications presented on histone tails form a ‘histone code’ for gene activity.

Epigenetic disruption is a major hallmark of human cancer. The reduction of the total DNA methylation levels of human tumours versus their normal counterparts was one of the first epigenetic alterations described in tumours. This loss is accomplished mainly through DNA hypomethylation of repetitive DNA sequences and demethylation of the gene ‘bodies’ (coding regions and introns). Global DNA hypomethylation contributes to the origin of cancer cells by generation of chromosomal instability, reactivation of transposable elements and loss of imprinting. Most importantly, and referred to as the “DNA methylation paradox”, there are local areas of DNA that gain CpG methylation:
the promoter CpG islands of many tumour-suppressor genes, such as hMLH1, BRCA1 and p16\(^{INK4a}\), leading to the inactivation of these cancer-protecting proteins. Even more recently, it has been shown that microRNAs with tumour suppressor functions, and other types of non-coding RNAs, are also silenced in cancer cells by DNA hypermethylation (Esteller, Nat Rev Genet 12(12):861-74). From the histone standpoint, human tumours also present with a distorted code; and for leukaemia, we know that the patognomonic translocations involve histone acetyltransferase and methyltransferase genes.

If we analyse cancer at a cellular evolution level, epigenetics seems to play a central role. Human tumours undergo massive and adaptive changes in their natural history: the cancer may metastasise to distant sites, it can create new blood and lymph vessels to feed on and eliminate its metabolites, it can also change if we try and treat it with chemotherapy, hormone therapy or radiotherapy. The capacity of the cancer cell to undergo fast genetic changes to adapt to the hostile cellular microenvironment is limited. However, Darwinian selection of cancer cells is permitted by the production of “fit” cells through rapid epigenetic changes within forty-eight hours of an external stimulus the DNA methylation and histone modification patterns of transformed cells can be completely altered. We can take the example of a breast cancer to illustrate this phenomenon. The cell adherence E-cadherin gene may become methylated and silenced, inducing the formation of metastases in the rib, but the cancer cells now located in that bone “need” to establish an interaction with their new surroundings and a subsequent loss of the DNA methylation at this loci will promote the survival of these cells. Another interesting case: a glioma with DNA methylation-associated inactivation of the DNA repair enzyme MGMT is predictive of a good response to a family of chemotherapy drugs, however, once the treatment has started the tumour may evolve, survival selecting those cells which are unmethylated at MGMT, producing chemoresistance on a purely epigenetic basis.

One of the essential differences between human cancer genetics and epigenetics is that DNA methylation and histone modification changes are reversible under the right circumstances. Thus, epigenetic alterations are one of the weakest points in the armour of the cancer cell, because those hypermethylated tumour suppressor genes in their long “sleep” can be awoken and reactivated with the right drug regimes and exert their normal growth inhibitory functions. Two families of epigenetic drugs, DNA demethylating agents and histone deacetylase inhibitors, have emerged as the most promising compounds in this area, and five drugs have received approval for the treatment of specific leukaemia and lymphoma subtypes (Rodriguez-Paredes and Esteller, Nat Med 17(3):330-92011). The successful story in these malignancies needs now to be translated to epithelial solid tumours and medical oncologists should be encouraged in this regard.

Manel Esteller

The EACR Cancer Researcher Award Highly Commended

Jesús Gil

Cellular senescence was first identified as an irreversible growth arrest that occurs when cells reach the end of their lifespan and that it is potentially connected with organism ageing. Since then senescence has been proven to be a cellular response that can be triggered by stresses such as oncogene signalling or chemotherapeutic drugs. As such, senescence influences ageing and a broad range of pathological conditions from cancer to fibrosis, cirrhosis or diabetes.

During the past 10 years, first as a post-doc and later heading my own group, I have focused in identifying novel regulators of senescence. During this time, my research contributed to show that senescence acts as a tumour suppressor mechanism in vivo and limits reprogramming to induced pluripotent stem cells (iPSCs, Banito et al. Genes & Dev 2009; 23, 2134-2139). Through the use of functional screens, we have identified novel molecular mechanisms controlling senescence, such as an unexpected role for pro-inflammatory CXCR2-binding chemokines in reinforcing growth arrest (Acosta et al. Cell 2008; 133, 1006–1018).

While studying senescence, my laboratory has developed an interest in understanding the epigenetic regulation of the INK4/ARF locus. This locus is frequently altered in cancer and encodes for p16\(^{INK4a}\) and ARF, regulators of the Rb and p53 tumour suppressor networks (reviewed in Gil and Peters. Nat Rev Mol Cell Biol 2006; 7, 667-677). Our research has identified how the INK4/ARF locus is kept repressed by Polycomb proteins such as Cbx7, and long non-coding RNAs, such as ANRIL. In addition, we identified a role for the histone demethylase JMJD3 in the induction of p16\(^{INK4a}\) during senescence (Barradas et al. Genes & Dev 2009; 23, 1177-1182). More recently, our investigations on Polycomb have contributed to identify differential role for the members of the Cbx-family proteins on pluripotency and differentiation (O’Loghlen et al. Cell Stem Cell 2012; 10, 33-46).

For a more detailed summary and a full publication list, please check: 

[http://www.csc.mrc.ac.uk/Research/Groups/EPI/CellProliferation](http://www.csc.mrc.ac.uk/Research/Groups/EPI/CellProliferation)
2012 sees the establishment of two new EACR Awards where scientific excellence is celebrated via a Plenary Lecture and with award presentations at the Association’s biennial congress.

The EACR Awards Committee is delighted to announce that the inaugural award of the Mike Price Gold Award Medal will be made in Barcelona to José Baselga, M.D., Ph.D. and that Dr. Baselga will give the award lecture on ‘The Future of Personalised Medicine’ at the culmination of the EACR congress.

Dr. Baselga will be presented with the first Mike Price Gold Medal by EACR President Julio Celis.

His research interests are in clinical breast cancer and in translational and early clinical research. He conducted the initial clinical trials with the monoclonal antibodies cetuximab and trastuzumab and is leading the clinical development of several new agents including pertuzumab and PI3K inhibitors. His main focus in the laboratory and in the clinic is in the area of novel anti-HER2 agents, in the identification of mechanisms of resistance to anti-HER2 agents and therapeutic approaches to target the PI3K pathway. He is also leading a number of neo-adjuvant trials in breast cancer and has been at the forefront of developing biomarker-based early and translational clinical trials.

“We are delighted that José Baselga will receive our new award the ‘Mike Price Gold Award Medal’. Dr. Baselga’s work and achievements are impressive and stand as an inspiration to all of us active in cancer research. The committee is also delighted that Dr. Baselga has accepted our invitation to receive his award in person at EACR-22 and give an essential keynote talk highlighting the principal theme of our congress.”

Julio Celis, EACR President

Dr. Baselga received his M.D. and Ph.D. degree from the Universidad Autonoma of Barcelona. He completed a fellowship in Medical Oncology at Memorial Sloan-Kettering Cancer Center in New York and subsequently stayed on as a faculty member of the Breast Medicine Service at Memorial Sloan-Kettering. From 1996 to 2010 he was the Chairman of the Medical Oncology Service and Founding Director of the Vall d’Hebron Institute of Oncology (VHIO) at the Vall d’Hebron University Hospital in Barcelona, Spain.

A recipient of many awards during his distinguished career, Dr. Baselga was most recently the recipient of the Queen Sofia Spanish Institute’s Gold Medal. He was selected for this prestigious award for representing Spain’s leadership in the area of cancer research.

Mike Price

The Mike Price Gold Medal Award and previously the Mike Price Travel Fellowship, commemorates the life and work of perhaps the most significant figure in EACR’s history.

Mike Price graduated from the university in 1969 and was awarded his Ph.D in 1972 and devoted his life to cancer research.

Mike Price served as Secretary General for 21 years and his scientific career was based at the University of Nottingham where the Association still has its Secretariat offices.

Mike Price died in 2000, he had fought bravely for just over a year against an unusual form of cancer. Edith Olah, EACR President at the time, wrote that his death brought immense sadness to all the many members of EACR who knew and loved him.

Mike Price was an excellent educator and countless students benefitted from his enthusiasm and understanding. Among many initiatives, he was instrumental in setting up the EACR Travel fellowship scheme which continues to give young scientists the opportunity to visit and train in centres of excellence throughout Europe and beyond.
The 1st Pezcoller Foundation - EACR Cancer Researcher Award has been awarded to Eric So, who will present a plenary lecture at EACR-22.

Eric C.W. So obtained his PhD in Pathology in 1997 from the University of Hong Kong and received most of his postdoctoral training at Stanford University. In 2004, he joined the newly formed Haemato-Oncology Department in the Institute of Cancer Research. He was appointed the as Professor of Leukaemia Biology in King’s College London in 2009.

Over the past few years, his team has made many seminal discoveries that are critical to the current understanding of leukaemia biology and to design effective therapy for the disease. Professor So is the main proposer of the idea that forced dimerization is a common mechanism for oncogenic activation of truncated transcription factors involved in acute leukaemia. He has made important contributions in identification and targeting of distinctive transcriptional/epigenetic components essential for LSC functions in different AML subtypes including acute promyelocytic leukaemia (APL). Recently, he also revealed a novel and unexpected crosstalk between Polycomb Group (PcG) and Trithorax/MLL/Hox proteins in development of normal and leukemic stem cells. Professor So made the original discovery of the critical role of \(\beta\)-catenin in mediating the establishment and drug resistance of MLL LSC, which provides a paradigm for differential targeting of drug resistant LSC. His work has featured in many highly respected journals.

Professor So serves in the review panels and advisory committees of many scientific and medical journals as well as international funding agencies in Europe, the US and Asia. He has won many personal awards throughout his scientific career. The most recent of these are an International Fellowship from the Association for International Cancer Research (AICR) in the UK (2005-2011) and the Young Investigator’s Award from the European Molecular Biology Organisation (EMBO) (2008-2011). He is also an elected Fellow of the Academy of Life Science for Chinese in the UK (ALSC-UK) and an elected Member of the European Research Institute for Integrated Cellular Pathology (ERI-ICP).