DR. JOSEF STEINER KREBSFORSCHUNGSPREIS 2009

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Der Dr. Josef Steiner Krebsforschungspreis 2009
wird Herrn Dr. Manel Esteller verliehen.
Herr Esteller ist Spanier und arbeitet am
Katalanischen Institut für Onkologie und am Biomedizinischen
Forschungsinstitut, Bellvitge, Barcelona, Spanien.
Die Preissumme beträgt CHF 1‘000‘000.

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Doktor Josef Steiner, Inhaber der „Dr. Steiner Apotheke und Bahnhofdrogerie“ in Biel, hat bei seinem Tode im Jahre 1983 ein grosses Vermögen hinterlassen, welches entsprechend seinem letzten Willen die finanzielle Basis der Dr. Josef Steiner Krebsstiftung bildete. Ziel der Stiftung ist die Förderung der Krebsforschung und die Auszeichnung hochverdienter Wissenschafter auf allen Gebieten der Krebsforschung. Als erster Preisträger konnte 1986 ein Schweizer, Dr. Peter Cerrutti, geehrt werden. Seither wurden zahlreiche hervorragende Wissenschafter aus Europa, USA und Australien mit dem Dr. Josef Steiner Preis ausgezeichnet.

Im Bestreben, die Krebsforschung im Sinne des Stifters effizient und nachhaltig zu fördern, wird seit 1998 ein hervorragendes Forschungsprojekt für die Periode von vier Jahren mit einem Betrag von 1’000’000 Schweizerfranken unterstützt. Der Forschungsgruppenleiter oder die Forschungsgruppenleiterin wird zusätzlich mit einem persönlichen Preis in der Höhe von 50'000 Schweizerfranken ausgezeichnet.

Die Auswahl des preisgekrönten Projektes erfolgte nach einem mehrstufigen strengen Auswahlverfahren. Der Dr. Josef Steiner Preis 2009 wurde in renommierten Wissenschaftszeitschriften ausgeschrieben. Die eingereichten Projektskizzen sind vom Stiftungsrat und einer aus Fachvertretern zusammengesetzten Preiskommission gesichtet und bewertet worden. Als Kriterien wurden die wissenschaftliche Qualität und die Originalität der Projektskizzen, die Qualifikation der Projektverfasser sowie die Beurteilung der Machbarkeit der vorgeschlagenen Projekte in Betracht gezogen. Jüngeren Forschern gab man den Vorzug. Fünf hervorragende Projektskizzen wurden ausgewählt und die Verfasser aufgefordert, ein überarbeitetes und detailliertes Projekt einzureichen. Für jedes Projekt sind mindestens drei externe Gutachten eingeholt worden.

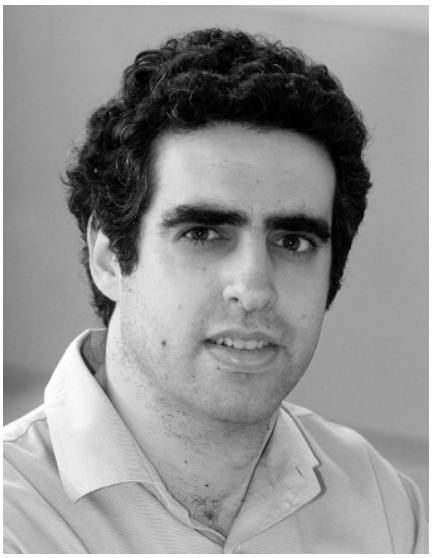
Zusätzlich haben die fünf Projektverfasser an einem Symposium, welches am 21. Januar 2009 an der Universität Bern stattgefunden hat, ihre Projekte vorgestellt.

Aus diesem strengen Auswahlverfahren ist Herr Prof. Dr. Manel Esteller als Sieger hervorgegangen.

Laudatio für Herrn Dr. Manel Esteller

Die Dr. Josef Steiner Stiftung verleiht den Josef Steiner Krebsforschungspreis an Herrn Dr. Manel Esteller in Anerkennung seiner grundlegenden Arbeiten zum Verständnis der Rolle der DNA Methylierung in der Regulation der Genexpression, speziell der Regulation von Genen, die in der Krebsentstehung eine Schlüsselrolle spielen; für seine überzeugende Beweisführung, dass Änderungen in der DNA Methylierung ursächlich an der Entstehung von Krebs beteiligt sind; sowie für seine originellen, systematischen Untersuchungen, die das Forschungsgebiet der Epigenetik in einen medizinisch hochrelevanten Zusammenhang gebracht haben und dadurch die Grundlagen für die Entwicklung neuartiger therapeutischer Ansätze gegen Krebs geschaffen haben.

Curriculum Vitae Manel Esteller (*1968)



10/1/86-6/30/92	Medical Student, University of Barcelona, Spain.
10/1/88-6/30/92	Assistant Fellow, Department of Biochemistry and Molecular Biology, School of Medicine, University of Barcelona, Spain.
5/1/95-9/1/95	Research Fellow, School of Biological and Medical Sciences, St. Andrews University, United Kingdom.
10/1/92-12/31/96	Graduate Student, Biomedical Research Unit, Hospital Universitari Maternal Vall d'Hebrón, Barcelona, Spain.

1/1/97-3/1/97	Postdoctoral Fellow, Biomedical Research Unit, Hospital Universitari Maternal Vall d´Hebrón, Barcelona, Spain.
4/1/97-5/31/00	Postdoctoral Fellow, The Johns Hopkins Oncology Center, The Johns Hopkins University and School of Medicine, Baltimore, USA.
6/1/00-5/31/01	Research Associate, The Johns Hopkins Oncology Center, The Johns Hopkins University and School of Medicine, Baltimore, USA.
6/1/01-12/31/07	Group Leader, Cancer Epigenetics Laboratory, Molecular Pathology Program, Spanish National Cancer Center (CNIO), Madrid, Spain.
1/1/08-Present	Director and Group Leader, Cancer Epigenetics and Biology Program (PEBC), Catalan Institute of Oncology (ICO) and Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Catalonia, Spain.

Honors and Awards Manel Esteller

1986	Prize young scientists CIRIT (Generalitat de Catalunya) 1985-1986.
1987	Prize young scientists CIRIT (Generalitat de Catalunya) 1986-1987.
1990-1992	Grant Consejo Superior de Investigaciones Científicas (CSIC-I.E.I.).
1992	Medical Graduate with Honors, Barcelona University.
1992	Grant "Agustí Pedro i Pons" Foundation.
1992	Grant "Spanish Association for Cancer Research".
1995	Grant I.E.S. (Institut d'Estudis de la Salut)
1992-1996	Predoctoral Grant Ministery of Education and Science. Rovira i Virgili University.
1997	Ph. D. Degree with Honors *"cum laude".*
1997-1999	Postdoctoral Fellowship Ministery of Education and Science. The Johns Hopkins Oncology Center, Johns Hopkins University and School of Medicine.
1998	Young Investigator Award American Association for Cancer Research (AACR-AFLAC).
1998	Gordon Research Conferences (GRC) Award in Cancer.
1998	European School of Medical Oncology (ESMO) Award.
1999	Young Investigator Award American Association for Cancer Research (AACR-Bristol-Myers Squibb).
1999	First Prize in Basic Research at The Johns Hopkins Oncology Center Fellows Day.
2000	Special Late-Breaking Abstract at the American Association for Cancer Research Meeting.

2000	European Association for Cancer Research “Young Cancer Researcher Award”.
2001	Young Investigator Award American Association for Cancer Research (AACR-AFLAC).
2002	Merit Award American Society of Clinical Oncology (ASCO)
2003	Mary Béve Lecturer, Nordic Society for Paediatric Haematology and Oncology
2005	Translational Research Award. Hospital of Madrid Foundation
2006	Magistral Lecturer, Universidad Internacional Menendez y Pelayo
2006	Beckman-Coultier Award Spanish Society of Biochemistry and Molecular Biology
2006	FPRC Young Investigator Award, Fondazione Piemontese per la Ricerca sul Cancro-ONLUs
2006	Foundation Francisco Cobos Award in Biomedical Research
2006	Swiss Bridge Cancer Award
2006	Carcinogenesis Award Oxford University Press
2007	National Research Award in Oncology "Maria Julia Castillo"
2007	"Dr Josep Trueta" Award, Academy of Medical Sciences of Catalonia
2007	Innovation Award, Commonwealth of Massachusetts.
2007	Human Frontier Science Program Award
2008	"Dr Jacint Vilardell" Award, Gastroenterology Foundation
2008	Debiopharm Life Sciences Award École Polytechnique Fédérale Lausanne
2009	Premio « Conde de Cartagena » Real Academia Nacional de Medicina

How aberrant epigenetics contributes to human cancer: Epigenetics refers to heritable changes in phenotype or gene expression caused by mechanisms other than changes in the underlying DNA sequence. Although, monozygous twins share a common genotype, most of them are not identical. Several types of phenotypic discordance may be observed, such as differences in susceptibilities to disease due to epigenetic differences i.e., content and genomic distribution of DNA methylation and histone acetylation, affecting their gene-expression portrait. When discordant twins are treated with the adequate drugs they become concordant. Epigenetic mechanisms include histone modification, positioning of histone variants, nucleosome remodelling, DNA methylation, small and non-coding RNA (such as microRNA), all of which cross-talk and interact with transcription factors and other DNA-binding proteins to regulate gene-expression pattern. These changes may remain through cell divisions for the remainder of the cell's life and may also last for multiple generations

In humans, **DNA methylation** occurs in CpG sites which are not randomly distributed in the genome. The 5´end of the regulatory region of many genes are rich in CpG and are called as CpG islands. These are usually not methylated in normal cells, except for particular subgroups of promoter CpG islands, e.g. of certain tissue-specific genes. Hypermethylation of repetitive genomic sequences may prevent chromosomal instability, translocations, and gene disruption caused by the reactivation of transposable DNA sequences. During development of cancer there is a progressive loss of total DNA methylation content, an increase of hypermethylated CpG islands and an increase histone-modification imbalance, in addition to phenotypic cellular changes and accumulation of genetic defects. Every tumor type has its DNA methylation pattern, and affects different hallmarks of cancer (apoptosis, proliferation, angiogenesis, etc). Dr. Manel Esteller has shown that transcriptional silencing of tumor suppressor genes by CpG island promoter hypermethylation is common hallmark in cancer cells. Thus, TLE1 epigenetic inactivation by promoter CpG island hypermethylation contributes to the development of hematologic malignancies, such as diffuse large B-cell lymphoma and AML, by disrupting critical differentiation and growth-suppressing pathways. TLE1 reintroduction in hypermethylated leukemia/lymphoma cells causes growth inhibition in colony assays and nude mice, whereas TLE1-short hairpin RNA depletion in unmethylated cells enhances tumor growth.

DNA methylation is not only important in protein-coding gene silencing, but also in silencing non-coding genes, such as **microRNAs** that regulate other genes as oncogenes in transformed cells. The group of Dr. Manel Esteller analyzed for miRNA expression in cancer cells genetically deficient for the DNA methyltransferase enzymes (Dnmt) and observed that DNA hypomethylation induces a release of miRNA silencing in cancer cells. One of the main targets is miRNA-124a, which undergoes transcriptional inactivation by CpG island hypermethylation in human tumors from different cell types. A functionally link for the epigenetic loss of miRNA-124a was described with the activation of cyclin D kinase 6 and the phosphorylation of the retinoblastoma. From the epigenetic point of view, a primary tumor is very different from a metastasis, although they are very similar from the oncogenetic point of view. Therefore, Dr. Manel Esteller analyzed de microRNA DNA methylation signature for human cancer metastasis by treating lymph node metastatic cancer cells with a DNA demethylating agent followed by hybridization to an expression microarray. Three miRNAs (miR-148a, miR-34b/c, and miR-9) were identified to have cancer specific CpG island methylation and were associated with metastatic behaviour, both *in vitro* (wound-healing assay,) and *in vivo* (xenograft mice model). The reintroduction of miR-148a and miR-34b/c in cancer cells with epigenetic inactivation inhibited their motility, reduced tumor growth, and inhib-

ited metastasis formation in xenograft models, with an associated down-regulation of the miRNA oncogenic target genes, such as C-MYC, E2F3, CDK6, and TGIF2. Moreover, the involvement of miR-148a, miR-34b/c, and miR-9 hypermethylation in metastasis formation was also suggested in human primary malignancies because it was significantly associated with the appearance of lymph node metastasis. DNA methylation-associated silencing of tumor suppressor miRNAs contributes to the development of human cancer metastasis. A clinical trial is ongoing to determine if DNA methylation profile can predict metastatic behaviour.

The third epigenetic parameter which DNA methylation regulates is **histone modifications** affecting nucleolar structure and thus synthesis of ribosomal RNA (rRNA) in the nucleus whose integrity is essential. The group of Dr. Manel Esteller has shown that Dnmt1 knockout cells, but not wild-type or Dnmt3b knockouts, present a severe DNA hypomethylation at ribosomal DNA associated with a loss of recruitment of the class III histone deacetylase SirT1 and an increase in the acetylation levels of lysine 16 of histone H4 at these genomic loci. The DNA methylation and chromatin changes at ribosomal DNA observed are associated with a structurally disorganized nucleolus, which is fragmented into small nuclear masses. Prominent nucleolar proteins, such as Fibrillarin and Ki-67, and the rRNA genes are scattered throughout the nucleus in Dnmt1 deficient cells. Dnmt1 has a role in the maintenance of nucleolar structure.

Many efforts have been focused to develop **epigenetic therapies**. Epigenetic inactivation of tumor suppressor genes is associated with dense CpG-islands promoter hypermethylation and the appearance of repressive histone markers such as Lysines 9 and 27 of histone H3. Unlike mutations, DNA methylation and histone modifications are reversible. Epigenetic drugs can partially restore the disturbed epigenetic picture by removing inactivation markers (DNA methylation) and including the presence of active markers (e.g., histone acetylation). Inhibitors of DNA methyltransferase (such as Zebularine) and histone deacetylase are already at clinical phases. Inhibitors to novel targets such as Histone methyltransferase (HMT) and Sirt1 are in preclinical phases. The efficacy of epigenetic drugs against solid tumor is limited. To maximize the potential of such drugs it is necessary to characterize the epigenetic changes that occur during normal development, adult cell renewal and disease, and the relation between genetic and epigenetic variation and their impact on health. Dr. Manel Esteller participates in the Alliance for Human Epigenome and Disease (AHEAD) project which studies the totality of epigenetic marks in a given cell type, i.e. the **epigenome map**. DNA methylation techniques permit the sensitive and quantitative detection of hypermethylated tumor-suppressor genes in all types of biologic fluids and biopsy specimens. The establishment of DNA methylation and histone-modification profiles of the primary tumor specimen

itself might be a valuable tool in determining the prognosis and predicting the patients' response to therapies.

Summary of Publications by Manel Esteller (number of manuscripts in parenthesis):
Nature Genetics (4), Nature (2), Science (2), New England Journal of Medicine (3), The Lancet (1), EMBO Journal (4), Nature Cell Biology (2), Proc Natl Acad Sci USA (3), Nature Reviews Genetics (1), Cancer Research (30), Oncogene (11), Molecular and Cellular Biology (2), Human Molecular Genetics (5), Journal of The National Cancer Institute (4), Lancet Oncology (1), Journal of Clinical Oncology (2), Nucleic Acids Research (2), Journal of Cell Science (2), EMBO Reports (1), Carcinogenesis (6), Clinical Cancer Research (5), Journal of Biological Chemistry (2), Human Genetics (1), Developmental Cell (1), Other Journals (51).