Sciences biologiques,
Écologie et Environnement
CONFÉRENCES
JACQUES-MONOD

Roscoff (France), 16-20 novembre 2015

Méthylation et déméthylation de l'ADN

DNA methylation and demethylation

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Rapport sur la Conférence

Conference Report

Conference overview

A first **DNA Methylation and Demethylation (DMD I)** Conference was launched in September 2013 by Pierre-Antoine Defossez (president) and Heinrich Leonhardt (vice-president). Following the success of this first conference and in regards of the most recent advancements in the field, Déborah Bourc'his (Institut Curie, Paris- president) and Michiel Weber (Radboud Institute, Netherlands- vice-president) organized a second edition of this thematic conference, which took place in 2015 in Roscoff, from November 16th to 20th.

The aim of the « **DMD II** » conference was to discuss the latest insights and future developments in the field of DNA methylation and other forms of cytosine modifications, with experts in molecular and cellular biology, development and biochemistry, working on mammalian or plant models. It was organized along six sessions :

1) *Trans* and *cis* determinants of DNA methylation patterns
2) Readers of DNA methylation patterns
3) Instructing DNA methylation during development
4) Preparing and perpetuating DNA methylation to the next generation
5) DNA methylation in health and disease
6) Innovative methods of DNA methylation detection

Of note, this meeting started right after the dreadful terrorist attacks that took place in Paris on November 13th. Despite the fear that spread across the world and the massive travel disturbances that followed these tragic events, the vast majority of the conference attendees maintained their participation to the conference. We experienced only sparce cancelations, from a poster presenter and a selected speaker. We are thankful to all the participants for their support and for having actively chosen to attend this scientific meeting to exchange and discuss with their colleagues during these troubled times.

Conference statistics

96 participants registered to the 2015 **DNA Methylation and Demethylation II** Meeting.

The program comprised the following presentations :
- 1 Keynote lecture (1h)
- 25 long talks from invited speakers (20min + 10min for questions)
- 20 short talks selected on abstracts (12min + 3min questions)
- 43 poster presentations, split into two poster sessions (1h45 each)
- among them, 10 flash talks were selected for for poster teasing (2min)

The flash talks were a new addition compared to the first 2013 edition of this meeting : it allowed young scientists to highlight their work and to attract the conference audience to their poster. This exercise was performed in a lively (and sometimes funny) manner and met a great enthusiasm.

Each session was assigned dedicated chairs, who were chosen among the invited speakers.

Geographical origins

	France	Europe	Rest of the world
Whole conference	43	42#	11##
Invited speakers	8	11*	7**
Selected speakers	7	12°	1°°

#United Kingdom 18, Germany 11, Netherlands 4, Switzerland 4, Belgium 2, Italy 1, Israel 1, Lithuania 1
USA 7, Japan 2, Taiwan 1, Australia 1
* United Kingdom 5, Germany 3, Switzerland 2, Netherlands 1,
**USA 5, Japan 1, Australia 1
° United Kingdom 7, Germany 2, Belgium 1, Netherlands 1, Italy 1
°°USA 1

Gender ratio

	Women : absolute numbers	Women : %
Whole conference	36	37.5
Invited speakers	6	23
Selected speakers	6	30

Despite our efforts, the percentage of women among invited speakers was below the requirements according to the EMBO gender equality rules (23 instead of 30%). The imbalance is mostly due to male over-representation among principal investigators in the field, which we have not been able to resolve during the invitation process. We were nonetheless able to fix this imbalance upon selection of young scientists for short talks and poster presentations, which allowed us to reach a final percentage of 37.5% of female attendees.

Financial support

We obtained financial support from Conseil Général du Finistère, Région Bretagne, Diagenode and Cambridge Epigenetix. The EMBO organization also participated financially to this event by sponsoring the travel and accomodation of three young EMBO Principal Investigators (Lionel Navarro, Maria Elena Torres Padilla and Petra Hajkova).

Scientific program

Keynote lecture

The first evening, after the reception cocktail and a dinner, was occupied by a Keynote Lecture given by **Timothy Bestor** *(Columbia University, USA)*. His lecture aimed at resolving the long pending question as to how methylated promoters are trancriptionally silenced. Latest studies performed in his lab suggest that the chromatin factor TRIM28/KAP1 is genetically required for the repression of methylated promoters. The binding of TRIM28 on methylated promoters may be mediated by the multiple zing fingers proteins it constitutively interacts with. Interestingly, TRIM28 interacts with the O-N-acetylglucosamine methyltransferase (OGT) only in presence of DNA methylation : the GlcNAcylation of transcription factors or the RNA polymerase itself could lead to their eviction from methylated promoters and subsequent lack of activation of associated genes.

Session 1 : Trans and cis determinants of DNA methylation patterns

Chair : Déborah BOURC'HIS, Michiel VERMEULEN, Rebecca OAKEY

The first scientific session, which was dedicated to *trans* and *cis* determinants of DNA methylation patterns, was launched by **Alexander Meissner** *(Broad Institute, USA)* : he reported the differential requirement of ground state embryonic stem cells (ESCs) versus primed epiblast stem cells (EpiSCs) towards DNA methylation. This may explain why human ESCs, which are developmentally more advanced that mouse ESCs and are more similar to an EpiSC state cannot tolerate *Dnmt1*-KO-induced loss of DNA methylation, while mouse ESCs can. **Toru Nakano** *(Osaka University, Japan)* focused on piRNA-based targeting of DNA methylation to transposon sequences, which occurs during male germ cell development in the mouse. Using artificial transgenic systems *in vivo*, he provided evidence that piRNA production or local recruitment of the PIWI protein MIWI2 is enough to promote *de novo* DNA methylation and repression of a given sequence. **Ehsan Habibi** *(Radboud Institute, Netherlands)* reported on the molecular determinants of the culture-induced DNA demethylation that occurs upon conversion of serum- to 2i-based medium of mouse ESCs.

By experimental means combined with mathematical modelling, he concluded that the mere transcriptional downregulation of the *de novo* DNA methyltransferases *Dnmt3A* and *Dnmt3B* induced by the 2i addition is not enough to explain the rapid DNA demethylation. Moreover, it appeared that TET-driven active demethylation is not essential for reprogramming genome-wide methylation patterns in 2i but is only required for a very discrete set of genomic loci. It was hypothetized that 2i components may have an effect on the maintenance enzyme DNMT1. **Albert Jeltsch** *(UniStutt, Germany)* summarized the latest knowledge about the role of post-translational modifications and binding partners in the allosteric regulation of DNA methyltransferases, and their influence on their nuclear localization and activity in experimental cell systems. In particular, DNMT3A phosphorylation counteracts DNMT3L role in targeting this enzyme to euchromatic foci and in enhancing its activity. Similarly, interaction with MeCP2 also reduces DNMT3A activity. **Achim Breiling** *(DKFZ, Germany)* reported that Tet1 and Tet2 double knock-out (DKO) mice exhibit various developmental defects. Using whole-genome bisulfite and transcriptome sequencing he showed that hypermethylation of so-called DNA methylation canyons (large genomic regions with low average methylation levels) is a key genomic feature of DKO embryonic fibroblasts. Canyon-hypermethylation significantly disturbs the regulation of associated genes, thus providing a mechanistic explanation for the observed defects in DKO mice, including impaired in vitro adipocyte differentiation of DKO MEFs. **Peter Sarkies** *(MRC London, UK)* presented an evolutionary analysis revealing that different species of nematodes exhibit a surprisingly diverse range of cytosine DNA methylation enzymes. Furthermore, by investigating enzymes that coevolve with DNMTs across nematodes he uncovered a striking relationship between DNA methylation and DNA repair enzymes (ALBH2&3), which also holds in other eukaryotic species. Strikingly, less mutagenesis is observed in cells which do not contain DNA methylation, providing a potential explanation why certain species have dispensed cytosine methylation altogether. **Daniel Zilberman** *(UC Berkeley, USA)* talked about his latest published work on the role of a new family of DNA methyltransferases, Dnmt5, in maintaining high levels of CG methylation in the linker DNA of nucleosomes in the genomes of many evolutionary ancient algae lineages: this activity contributes to nucleosome positioning and high level of genome compaction. In addition, latest unpublished findings regarding the interplay between DNA methylation, nucleosome positioning, DNA transposon activity and intron evolution in these eukaryote species were presented. Finally, **Jean Molinier** *(IBMP, France)* presented the latest intriguing findings on the relationship between the DNA repair, small RNA, and DNA methylation pathways in *Arabidopsis thaliana*, suggesting that this crosstalk plays a significant role in the homeostasis of DNA methylation in plants.

Session 2 : Readers of DNA methylation patterns
Chair : Anne FERGUSON-SMITH

Michiel Vermeulen *(Radboud Institute, Netherlands)* showed that the ZMYND8 protein bridges the NUcleosome Remodeling and Deacetylase (NuRD) complex to a number of putative DNA binding zinc finger proteins, namely ZNF687, ZNF592 and ZNF532. ZMYND8 directly interacts with the NuRD subunit GATAD2A, which is mutually exclusive with GATAD2B, through its MYND domain. He further showed that recruitment of GATAD2A/NuRD by the ZMYND8/ZNF module serves a dual purpose as part of the transcription-coupled DNA damage response and to fine-tune expression of NuRD target genes. **Dirk Schübeler** (FMI, Switzerland) summarized his very recently published work on the influence of DNA methylation states on the binding of transcription factors. By comparing the distribution of DNase-hypersensitive sites in wildtype versus DNA methylation-deficient *Dnmt*-tKO ESCs, he identified NRF1 as a methyl-sensitive transcription factor. This suggests that this type of transcription factors rely on others factors to demethylate their sequence targets before they can get access to them during critical developmental windows. **Andrea Riccio** (Institute of Genetics and Biophysics, Italy) presented the genome-wide mapping of the methyl-sensitive zing finger protein ZFP57-which is required for maintenance of methylation at imprinted loci in mammals- in mouse hybrid ESCs. Beside the canonical hexanucleotide motif TGCCGC previously identified, he reported the existence of motif

variants (notably CGCCGC), which are also required for the maintenance of proper repressive chromatin at imprinting control regions. **Pierre-Antoine Defossez** *(Paris Diderot University/CNRS UMR7216, France)* reported about a novel interaction between the Tudor domain of UHRF1 and an H3-like histone mimic within DNA ligase I. This interaction, which requires methylation of the DNA ligase I histone mimic by either G9a or GLP, was found to promote the recruitment of UHRF1 to sites of DNA replication. This study thus provides a first example of a histone mimic that coordinates DNA replication and DNA remethylation during S-phase. Finally, **Christian Muchardt** (Institut Pasteur, France) provided an update on the previously found link between H3K9me3, alternative splicing and the nuclear RNAi machinery (Argonaute proteins). He now showed that reducing DNA methylation affects alternative splicing of the CD44 gene and this is correlated with decreased accumulation of RNA polymerase II on this gene. Furthermore, Argonaute protein-dependent inducibility of RNA polymerase II accumulation on the CD44 gene in response to pro-inflammatory cues is lost when DNA methylation is reduced, suggesting an intricate interplay between the RNAi machinery and DNA methylation in regulating alternative splicing.

Session 3 : Instructing DNA methylation during development
Chair : Dirk SCHUBELER, Petra HAJKOVA

Anne Ferguson-Smith *(Cambridge University, UK)* delved deeper into the ZFP57 binding scenery, by describing the presence of ZFP57 to all imprinted regions, but also to non-imprinted regions. These last targets are mainly bound in a strain-specific manner, frequently due to the presence of SNPs at the C of the central CpG of the TGCCGC binding motif, which likely impact the epigenetic state. She also reported the binding of ZFP57 to retroviral elements and the presence of H3K9me3 at these sites, event in cells devoid of ZFP57. **Fanny Decarpentrie** *(The Francis Crick Institute, UK)* presented some preliminary data about the role of DNA methylation in X chromosome inactivation in female marsupials. Using *Monodelphis domestica* as an opossum representative, she investigates during key developmental periods the methylation profiles of the potential determinant of X inactivation in marsupials, the long non-coding *Rsx* RNA, as well as the genes undergoing X inactivation. **Joan Barau** *(Institut Curie France),* who talked for Déborah Bourc'his, revealed the unexpected existence of a third member of the *de novo* DNA methyltransferase family in mammals, DNMT3C. This gene occurred by tandem duplication of the *Dnmt3B* gene, and is exclusively expressed in the testis. Although it was previously annotated as a pseudogene, his work provides undoubtful evidence that DNMT3C has *de novo* DNA methylation activity, which is essential for repressing transposons in the mouse male germline and for protecting fertility. **Alexei Aravin** *(Caltech, USA)* presented the last whole-genome bisulfite sequencing analyses of DNA methylation patterns performed in his lab upon MILI or MIWI2 deficiency in mouse male germ cells. While being part of the same pathway, it appears that MILI is required for methylating a larger subset of transposons families than MIWi2. **Michael Weber** *(CNRS UMR7242, France)* showed that the H3K9 methyltransfrase G9a regulates DNA methylation at specific sequences that include CpG-rich promoters of germ-line specific genes. These loci are marked by H3K9me2 and show strongly decreased DNA methylation levels in G9a$^{-/-}$ embryos. Finally, DNA methylation was found to be instrumental for G9a-mediated gene silencing during embryogenesis, thus revealing extensive crosstalk between G9a, H3K9me2 and DNA methylation during early embryogenesis. **Maria Elena Torres Padilla** *(IGBMC, France)* presented the strategies for the analysis of large, multivariate datasets collected using different experimental approaches (including single cell analyses) for the purpose of capturing, understanding, and predicting the "totipotency signature" of the cells of the mouse peri-implantation embryo. **Till Bartke** *(MRC London, UK)* showed that the KDM2A protein contains a nucleosome recognition module consisting of a CXXC zinc finger and a PHD domain, which facilitates a high-affinity interaction with unmodified nucleosomes. He also showed that KDM2A directly interacts with HP1 via a LxVxL motif, thus allowing recruitment of HP1 to unmodified nucleosomes. Furthermore, genetic and transcriptome analyses of zebrafish carrying mutations in the KDM2A orthologue kdm2aa uncovered a critical role for kdm2aa in gene expression regulation and early embryonic development.

Session 4 : Preparing and perpetuating DNA methylation to the next generation
Chair : Michaël WEBER, Alexei ARAVIN

The fourth session was extensive and started with a presentation by **Vincent Colot** *(ENS, France)*. He found an unexpected increase in the patterns of CHH methylation during very early embryonic development in Arabidosis, suggesting the existence of some extent of epigenetic reprogramming in plants. Interestingly, this phenomenon coincides with an activity peak of the RdDM machinery : identified CHH-enriched DMRs in the embryo matched a subpopulation of small RNAs produced in the endosperm, pointing to the existence of a communication between these two tissues to cooperatively sets reprogramming in early Arabidopsis development. **Mario Iurlaro** *(Babraham Institute, UK)*, who talked for Wolf Reik, further expanded on the genome-wide demethylation of mouse ESCs in 2i culture conditions. Interestingly, he found that the protein levels of UHRF1, which targets DNMT1 to hemimethylated DNA at replication forks, is lowered in 2i medium ; this may be secondary to the reduction of H3K9me2 levels he also observed. All together with the work that Ehsan Habibi reported on the first day, this indicates that 2i-induced demethylation mostly occurs by downregulation of both *de novo* and maintenance DNA methylation, while active demethylation processes driven by TETs have only a subtle, locus-specific effect. **Didier Trono** *(EPFL, Switzerland)* presented the provocative idea that the evolution of KRAB-ZFP proteins reflects a massive entreprise of mammalian genomes towards the domestication of transposable elements (TEs). Using an ChIP-Exo approach in human cells to identify the genomic targets of KRAB-ZFPs, he found that 1) half of the 303 KRAB-ZFPs that he analyzed are bound to TEs, the majority of which are HERVs, 2) KRAB-ZFPs can bind several TEs and TEs can be bound by several KRAB-ZFPs, and 3) TEs bound by KRAB-ZFPs are fairly old and transposition incompetent, indeed providing an argument that these could have been co-opted for other functions. **Stéphane Maury** *(LBLGC Orléans, France)* provided evidence for the existence of abnormally methylated regions in the genome of meristem cells from the apical shoot of crop plants that underwent drought stress. These could be correlated with alterations in gene expression and phenotypic plasticity in response to environmental stresses. **Ryan Lister** *(University of Western Australia)* presented the dynamics of whole-genome DNA methylation profiles across different vertebrate species (frog, zebrafish and mouse) during the phylotypic period of embryogenesis. He uncovered thousands of shared sites showing signatures of TET1/2/3-dependent active demethylation at sites that act as enhancers of developmental genes among evolutionary-distant vertebrate species. These findings implicate TET proteins in the setting of the regulatory landscape of an ancient, common developmental program of vertebrates. **Kathleen Stewart** *(Babraham Institute UK)* depicted the time-scenery of the histone modifications changes that accompany DNA methylation acquisition during mouse oogenesis. She showed that the acquisition of H3K36me3 marks precedes the removal of H3K4me3 at CpG islands destined to be methylated in mature oocytes. **William Pastor** *(UCLA, USA)* talked about the role of the GHKL ATPase MORC1 in the mouse male germline. MORC1 is required for the repression of transposons, by helping the deposition of DNA methylation specifically at the TSS of transposons. Only three genes are upregulated upon *Morc1* deletion, and these all happen to have a promoter coinciding with a transposon. **Colum Walsh** *(University of Ulster, Ireland)* presented a stable, differentiated human cell line system for studying the effects of short-term, reversible ablation of DNMT1 and subsequent transient demethylation. This allowed his group to uncover regions that fail to recover previous levels of DNA methylation, including some imprinting control regions. This system may allow defining the characteristics (sequence, chromatin) of the genomic regions that require germline passage for the proper setting and/or recovery of DNA methylation profiles. Finally, **Petra Hajkova** *(MRC London, UK)* reported the intriguing demonstration (through precise analysis of 5mC and 5hmC kinetics combined with genetic mutations and chemical inhibitors) that TET-driven hydroxymethylation is involved in counteracting *de novo* DNA methylation activities during mouse development, rather than promoting global, active DNA demethylation. This rule seems to apply to both the early zygote after fertilization and to primordial germ cells, which

represent two typical contexts where genome-wide erasure of DNA methylation patterns occur.

<u>Session 5 : DNA methylation in health and disease</u>
<u>Chair</u> : Vincent COLOT, Pierre-Antoine DEFOSSEZ

Rebecca Oakey *(King's College London, UK)* started this session with a detailed analysis of DNA methylation maps associated with the specification of the different cell lineages of the heart endocardium in the mouse. Combined with transcription analyses, she identified inter- but also intra-population differences between the endocardial and the epithelial cells of the heart ; this may reveal the origin of congenital heart diseases. **Lionel Navarro** *(ENS, France)* presentation dealt with the role of DNA methylation in host defense responses in the plant Arabidopsis. His works showed that RNA-directed DNA methylation negatively regulates antibacterial innate immunity by repressing a subset of immune response genes that contain repeats in their promoter regions. Conversely, the ROS1 glycosylase promotes the expression of these genes by targeting demethylation. This raises the interesting question as to whether the immune system could also be influenced by DNA methylation in humans. Still in Arabidopsis, **Charles Underwood** *(CSHL, USA)* used fluorescent reporters to measure recombination frequency in various epigenetic mutants. Contrary to CG methylation, which was previously shown to be required for recombination at pericentrometic repeats, he found that CHH methylation and H3K9 trimethylation act in concert to suppress recombination at these regions. These results have implication for the breeding of crop species with repeat-dense genomes. **Robert Dante** *(Cancer Research Lyon, France)* presented ChIP-sequencing data for the methyl CpG binding protein MBD2 in a cellular model of oncogenic transformation of human mammary cells. MBD2 was mainly found to be associated with silenced, methylated genes. Genes down-regulated during oncogenic transformation frequently gain MBD2 on their promoter and depletion of MBD2 from cells resulted in transcriptional upregulation of these genes. **Claire Francastel** *(Paris Diderot University/CNRS UMR7216, France)* discussed the genetic heterogeneity of the Immunodeficiency, Centromeric Instability and Facial Anomalies (ICF) syndrome : mutations in four different genes-the *de novo* DNA methyltransferase *DNMT3B*, the zing finger *ZBTB24*, the cell cycle-associated *CDCA7* and the chromatin helisace *LSH*- have now been associated with this rare syndrome, which leads to common and different constitutive DNA methylation defects among patient types. This raises the question of the genetic and physical interactions between the aforementioned factors and the possibility that this pathology is underdiagnosed. **Nicolas Bouché** *(Institut Pierre Bourgin Versailles, France)* reported on the isolation of a new so-called epiallele in Arabidopsis resulting from the complete silencing of a whole genomic region. He further showed that methylated epialleles can convert the unmethylated allele in F1 and methylated alleles can also spontaneously revert within the population. This observation may have importance for understanding the origin of epigenetic incompatibilities in natural plant populations. **Irina Stancheva** *(University of Edinburgh, UK)* reported on the generation of a novel conditionally reversible LSH knock-out mouse model. These mice exhibit global and locus-specific DNA hypomethylation, survive postnatally but display growth retardation and neurological problems such as tremor and limb paralysis. Further analysis revealed that these mice display a severe lack of myelin in the central nerve system (CNS) and a lack of mature oligodendrocytes. Strikingly, this phenotype is completely rescued by reintroducing LSH in the CNS of the LSH knock-out mice. The last talk of the session held by **Hélène Kiefer** *(INRA Jouy-en-Josas, France)* raised interesting insights into the potential roles of DNA methylation in the occurrence of nuclear reprogramming-related pathologies that are inherent somatic cloning. Using the cow as a model, she reported many differentially methylated regions in the liver of pathological perinatal clones that matched the methylation patterns of older adults. She proposed that these could be a response to metabolic defects these animals bear in response to incomplete genome reprogramming.

Session 6 : Innovative methods of DNA methylation detection
Chair : Ryan LISTER

Thomas Carell *(LMU Munich, Germany)* described some of their recent data on Tet proteins and 5hmC. He showed that 5hmC is acquired during postnatal retinal development in mice, coinciding with eye opening in the pups and elevated expression of genes involved in retinal and/or neuronal functions. He also showed a comprehensive interaction proteomics screening, which revealed that Tet proteins interact with a number of transcriptional regulators, including REST, NSD2/3 and the NuRD complex. This indicates that Tet proteins may be involved in a variety of transcription-coupled processes. **Daniel Grimanelli** (*IRD, CNRS UMR232 Montpellier, France)* has developed an elegant real-time, live-cell detection method of CG and nonCG methylation in Arabidopsis. This methodology gives access to new information about the dynamics of DNA methylation patterns at a single cell level in key developmental periods, such as the developing female germ line. **Christina Bauer** *(LMU Munich, Germany)* presented the diversity of applications derived from the MIN-Tag strategy, which is based on the insertion of a MIN sequence through CRISPR-Cas9 editing and the use of this sequence as a genomic entry point for Bxb1-mediated insertion of functional cassettes, for GFP or BirA+ tagging or for deriving knock-out and knock-in models. Notably, using an anti-MIN immunoprecipitation approach in mouse ESCs, she was able to identify some new protein partners of DNMT3B (such as DNMT3A, and some various centromeric proteins) and the post-translational modifications undergone by this DNA methyltransferase. **Vincent Croquette** *(ENS, Paris)* has developed a new method of detection of modified bases at the single molecule level by DNA hairpin manipulation. Preliminary results based on available antibodies allowed his lab to detect five different kinds of chemical base modifications at a single base pair resolution, including cytosine methylation, on artificial ds DNA fragments of hundreds to a few thousands bases. **Kian Koh** *(KU Leuven, Belgium)* ended this session and the meeting with a talk on the biological significance of TET1-driven hydroxymethylation for the mouse post-implantation embryo : *in situ* detection of this protein reveals its presence in the embryonic part of the conceptus, where it counteracts *de novo* DNA methylation at specific developmentally important genes, but also in the extra-embryonic part of the embryo, where its function has yet to be resolved.

Conclusions and recommendations

As organizers, we are very grateful for the practical organization and support provided by Nathalie Babic. She also was of great help to the participants as she was able to solve several problems, such as baggage loss.

In terms of local organization, the location was very well appreciated, and the cooking and waitering team was recognized by all as outstanding.

Combining the two poster sessions with snacks and drinks before dinner was really appreciated. This format should be kept.

We would like to encourage the CNRS to set up a proper system for online registration and abstract submission. Not having such tool is a major weakness, as the current emailing system is not convenient at all : it generates some major overflow of the email boxes of the organizers, can lead to the loss of important information and requires some additional tasks (as abstract formating for example or gathering of contact details), which are time consuming. To avoid this, we ourselves set up a conference website through scienceconf (*http://dnamethylation.sciencesconf.org/*): this really helped us managing the registration requests and abstract selection in a much more efficient and less troublesome way. We think that having such website platform is a major necessity for the organization of the Jacques Monod conferences.

Finally, we received many testimonies of enthousiasm throughout the conference and afterwards by email (see further below). The scientific program, the high quality of the

presentations, the friendly atmosphere, and the right participant size were particularly praised by the attendees. The participants stressed the need of having a conference specifically dedicated to the theme of DNA Methylation, as there is no equivalent in Europe. They were unanimous in their support to continue the series of the meeting.

Michiel Vermeulen accepted to be the president of a potential next meeting of this kind, and to put together, with the help of a vice-president to be identified, an application for a third edition to be held in two years.

Email extracts received after the conference

« I wanted to say thanks very much for the invitation, it was a really excellent meeting that you put together, and I had a great time. »

« Everyone was delighted with the meeting; we were all talking together at the airport. You did a great job in keeping things organized with a firm hand but a gentle touch. I loved the site too. »

« Congratulations on a great meeting! I really enjoyed it, and had some very useful discussions there. »

« Thanks again for all your efforts! You did a great job and I think you put together a great meeting. »

« This meeting should be held again in two years ! »

« Thank you very much for a great meeting, I really enjoyed it. »

« I really enjoyed the conference, great talks and right size. »