

Laboratory for Molecular Virology and Medical Genetics 2010 Studies on Epigenetics

Institute of Genetics, University of Cologne and

Institute for Clinical and Molecular Virology, Erlangen University Medical
School



The Research Group (from left to right: Anja Naumann, Stefanie Weber, Ellen Fanning, Humboldt Awardee 2010, Visiting Professor from Vanderbilt University, Nashville, TN, USA, Walter Doerfler. Painting by Dr. Silvia Stabel, Institute of Genetics graduate 1982).

The main interest of our research group is focused on the biological function of DNA methylation in the regulation of biological processes that are of interest in medicine and epigenetics. In these investigations, we have been using viral systems (adenoviruses and HIV1) and human genes (currently the fragile X mental retardation gene 1). DNA methylation patterns in mammalian genomes can be cell-type specific, are sometimes conserved, but can also be altered, and play an important role in genome structure and function. We have adduced evidence that the insertion of foreign DNA into an established mammalian genome can lead to genome-wide alterations in DNA methylation and transcription patterns. The laboratory is located in the Institute of Virology, Erlangen Medical School and maintains close ties to the Institute of Genetics, University of Cologne where the principal investigator has been on the active faculty between 1972 and 2002.

Principal Investigator: Walter Doerfler is Professor *emeritus*.active, University of Cologne and Guest Professor (since 2002), Institute for Virology, Erlangen University Medical School. After finishing Medical School in Munich (LMU) and postdoctoral education at the Max-Planck-Institute for Biochemistry in Munich (1961-1963) and the Department of Biochemistry at Stanford University (1963-1966), W.D. held faculty positions at Rockefeller University in New York City, NY (1966-1978) and at the Institute of Genetics in Cologne (1972-2002). During sabbaticals, he was guest professor at Uppsala (1971/72, 2002, 2006, 2007, 2009) as well as at Stanford (1978, 1993), Princeton (1986, 1999) and Vanderbilt (2006) Universities.

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Humboldt Research Awardee 2010: Dr. Ellen Fanning is the Stevenson Professor of Molecular Biology at Vanderbilt University in Nashville, TN, USA and has been awarded a Humboldt Research Prize. In 2010, Professor Fanning has been guest professor at the Institute of Virology, Erlangen University Medical School.

Group Members:

Anja Naumann, doctoral student.

Stephanie Weber, doctoral student.

Former group member: Dr. Norbert Hochstein, Qiagen, Hilden, Germany.

The Four Research Projects

1. The Epigenetic Status of an Adenovirus Trans-genome upon Long-term Cultivation in Hamster Cells

N. Hochstein, I. Muiznieks, L. Mangel, H. Brondke, and W. Doerfler

Journal of Virology **81**, 5349-5361, 2007.

The epigenetic status of integrated adenovirus type 12 (Ad12) DNA in hamster cells cultivated for about four decades has been investigated. Cell line TR12, a fibroblastic revertant of the Ad12-transformed epitheloid hamster cell line T637 with 15 copies of integrated Ad12 DNA, carries one Ad12 DNA copy plus a 3.9 kbp fragment from a second copy (Fig. 1). The cellular insertion site for the Ad12 integrate, identical in both cell lines, is a >5.2 kbp inverted DNA repeat (Fig. 1). The integrated Ad12 trans-genome is packaged around nucleosomes. The cellular junction is more sensitive to micrococcal nuclease at Ad12-occupied than at un-occupied sites. Hence, trans-gene insertion might destabilize the chromatin structure at the site of integration. Bisulfite sequencing reveals complete *de novo* methylation in most of the 1,634 CpGs of the integrated viral DNA, except for its termini (Fig. 2). Isolated un-methylated CpG isles extend over the entire Ad12 integrate. The fully methylated trans-genome segments are characterized by promoter silencing and histone H3 and H4 hyper-acetylation. Nevertheless, there is minimal transcriptional activity of the late viral genes controlled by the fully methylated major late promoter of Ad12 DNA, perhaps due to hemi-methylation of the trans-genome during replication.

Struktur des Ad12 Integrates in der Zelllinie TR12

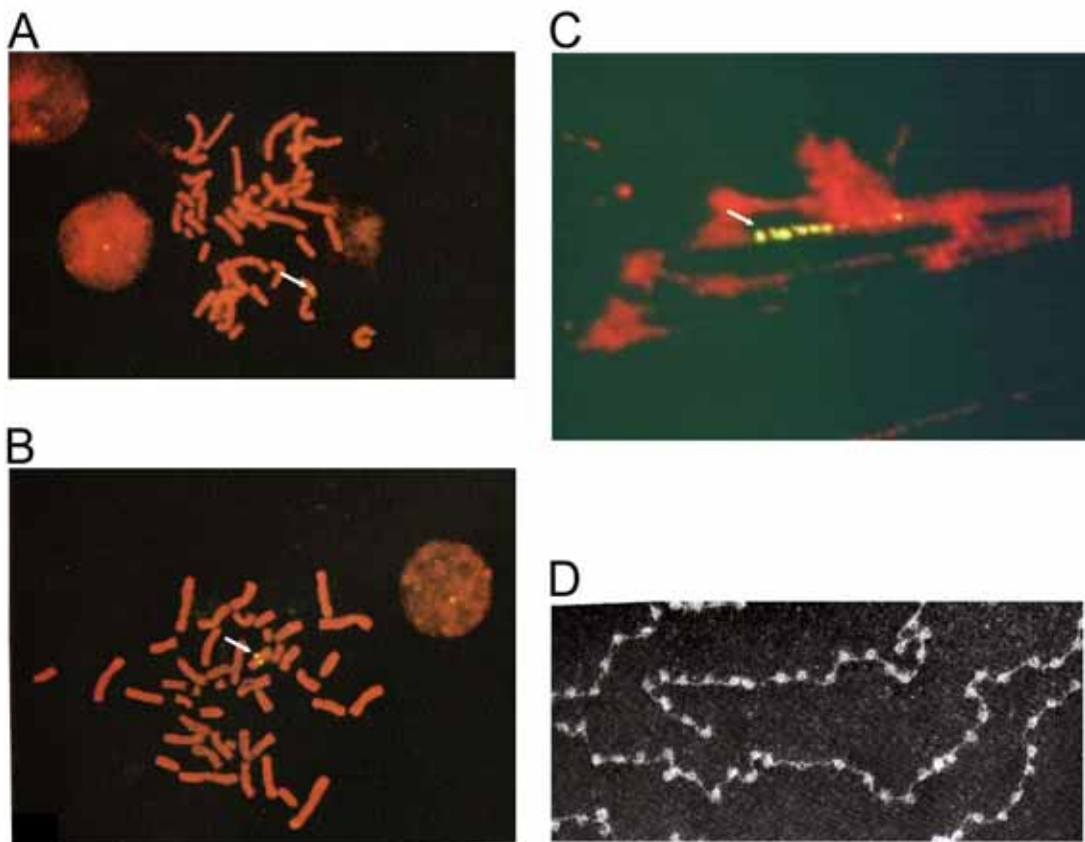
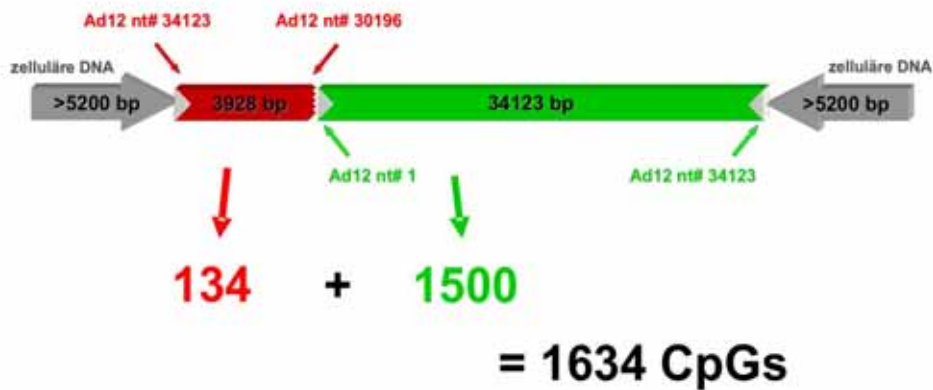


Figure 1 Anatomy of the adenovirus type 12 trans-genome in the transformed hamster cell line TR12

A complete Ad12 DNA molecule (34,123 bp) and an additional 3,928 bp Ad12 DNA fragment from the right terminus of the virion genome are integrated into hamster (cellular) DNA. For details see Hochstein et al. J. Virol. 81, 5349-5361, 2007. The integrated Ad12 DNA carries 1,634 CpGs which are the targets for *de novo* methylation. (A) Integrated Ad12 DNA in cell line T637 (white arrow) and (B) in the revertant cell line TR12 (white arrow) (from Orend et al., 1995). (C) Stretched chromosome from (A), multiple copies of Ad12 DNA are visualized (from Schröer et al., 1997). The integrated Ad12 DNA has assumed nucleosome structure (Hochstein et al., 2007).



Figure 2 Methylation profile of the Ad12 transgenome in cell line TR12

The methylation pattern was investigated at single-CpG resolution using the bisulfite conversion of genomic DNA. Both ends of the adenoviral integrate are unmethylated, and the remainder of the integrated viral DNA is heavily methylated with a small number of unmethylated CpG sites. Some CpG sites show variable methylation status. Unmethylated CpGs are indicated by open squares and methylated ones by filled squares. CpG sites with variable methylation status are assigned diagonally half-filled symbols. The results of all PCR clones that were sequenced are shown. Each horizontal array of symbols corresponds to one PCR clone. Individual CpGs are numbered; on top of these numbers Ad12 genome nucleotide positions of the PCR fragments are shown. Ad12 gene groups are indicated with gray bars. The methylation status of the rightward-transcribed strand of the transgenome has been determined throughout. Since the right and left-terminal transgenome segments containing 134 CpGs are in inverted orientations, the primers employed for PCR encompass both DNA complements in these regions. This Figure was taken from Hochstein et al., 2007.

2. A Distinct DNA Methylation Boundary in the 5'-Upstream Sequence of the *FMRI* Promoter Binds Nuclear Proteins and is Lost in Fragile X Syndrome

A. Naumann, N. Hochstein, S. Weber E. Fanning, and W. Doerfler.

American Journal of Human Genetics 85, 606-616, 2009.

We have discovered a distinct DNA methylation boundary at a site between 650 and 800 nucleotides upstream of the CGG repeat in the first exon of the human *FMRI* gene (Fig. 3). This boundary, identified by bisulfite sequencing, is present in all human cell lines and cell types, irrespective of age, gender, and developmental stage. The same boundary is found also in different mouse tissues, although sequence homology between man and mouse in this region is only 46.7%. This boundary sequence, both in the un-methylated and the CpG-methylated modes, binds specifically to nuclear proteins from human cells. We interpret this boundary to carry a specific chromatin structure that delineates a hyper-methylated area in the genome from the un-methylated *FMRI* promoter and protects it from the spreading of DNA methylation. In individuals with the fragile X syndrome (FRAXA), the methylation boundary is lost; methylation has penetrated into the *FMRI* promoter and inactivated the *FMRI* gene (Fig. 4). In one FRAXA genome, the upstream terminus of the methylation boundary region exhibits decreased methylation as compared to healthy individuals. This finding suggests changes in nucleotide sequence and chromatin structure in the boundary region of this FRAXA individual. In the completely *de novo* methylated *FMRI* promoter, there are isolated un-methylated CpG dinucleotides which are, however, not found when the *FMRI* promoter and upstream sequences are *in vitro* methylated with the bacterial *M-SssI* DNA methyltransferase. They may arise during *de novo* methylation only in DNA that is organized in chromatin and be due to the binding of specific proteins.

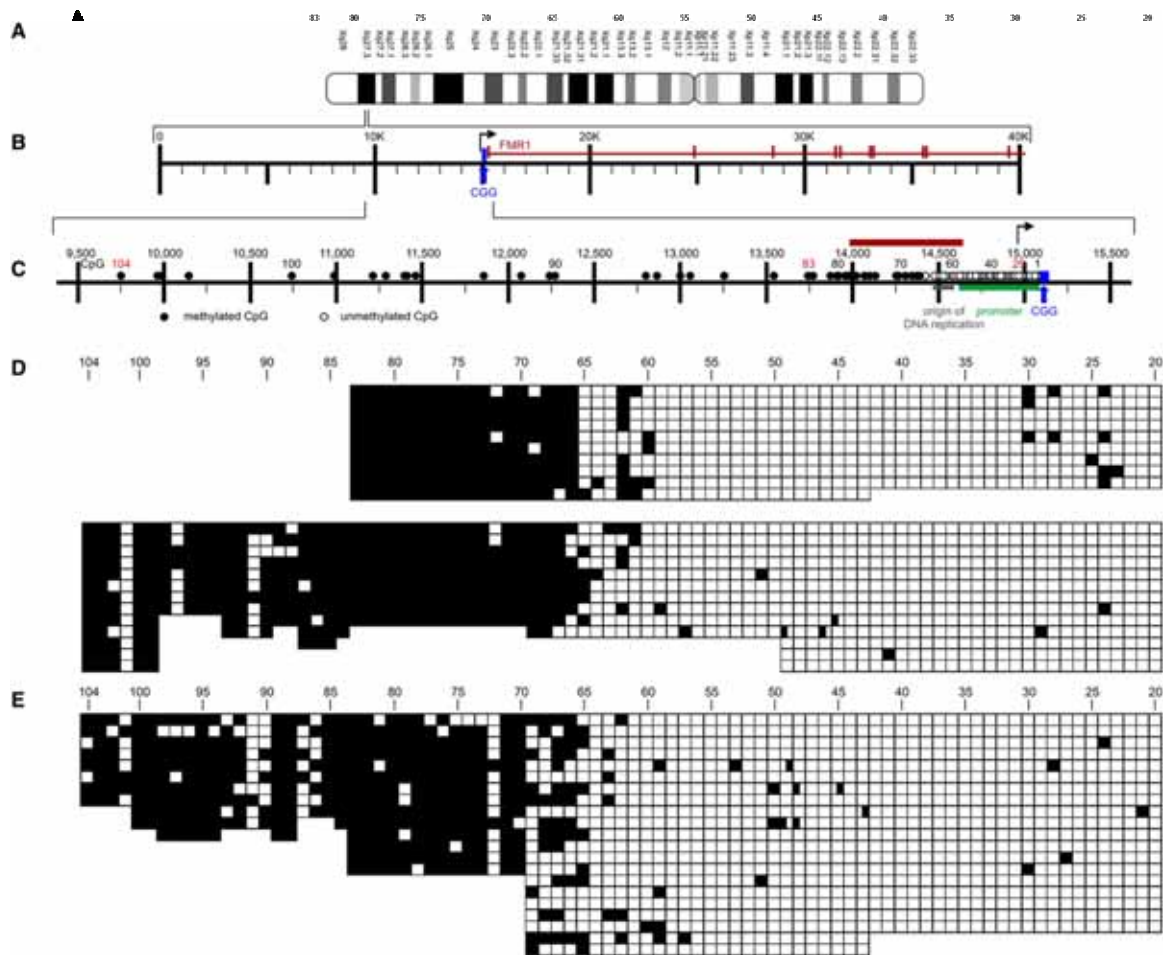


Figure 3 Methylation profiles in the *FMR1* promoter and 5'-upstream segment in the human cell line HCT116 and in primary human fibroblasts

(A) Ideogram of the human X chromosome. From *NCBI* with modifications.

(B) Partial map shows the first ten exons (vertical bars) and introns of the *FMR1* gene plus the upstream genome segment including the CGG repeat.

(C) Map of the 5'-upstream region of the *FMR1* gene. The graph presents all CpG dinucleotides (1 to 104) in the region: Open circles designate unmethylated, closed circles methylated CpG dinucleotides. The arrow indicates the start site of transcription. The promoter and an origin of DNA replication are also indicated. Nucleotide numbering in this and the following graphs was adapted from the *NCBI* nucleotide nomenclature: NC_000023:146,786,201-146,840,303 *H. sapiens FMR1* gene region (nucleotide numbers on the human X = 23rd chromosome). The boundary between unmethylated (○) and methylated (●) CpG dinucleotides is marked by these symbols and is designated by a red bar.

(D) In HCT116 DNA, both strands (upper and lower panels) were bisulfite sequenced between CpG pairs 20 and 83. Bisulfite sequencing in one strand was extended to CpG pair 104 (lower panel). □ – unmethylated, ■ – methylated CpGs.

(E) In primary human foreskin fibroblasts, DNA was bisulfite sequenced between CpG pairs 20 and 104.

This scheme and the figure legend were taken from Naumann et al., 2009.

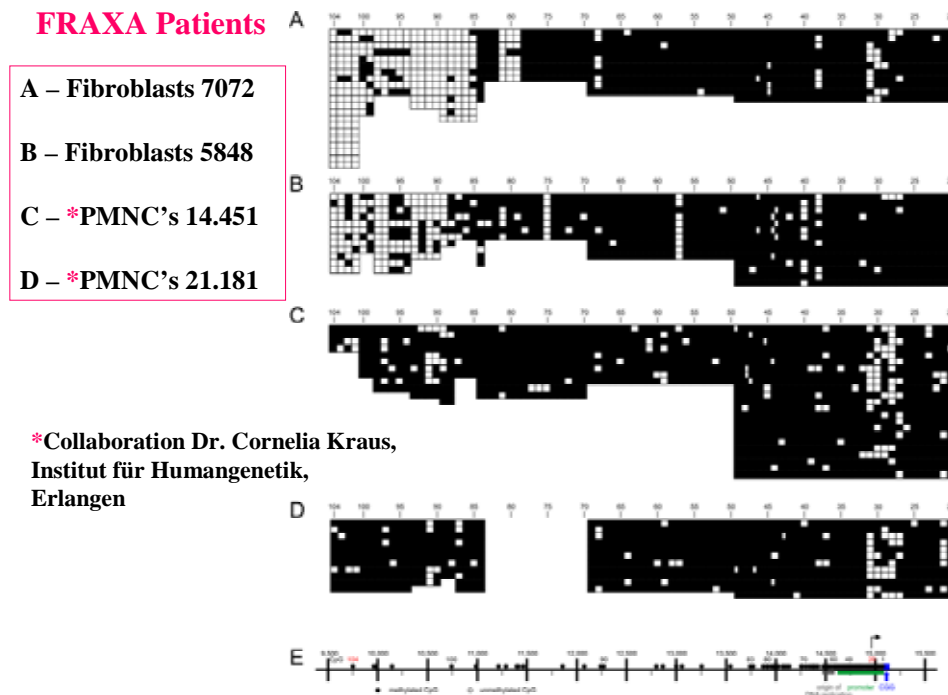


Figure 4 Loss of the methylation boundary in fibroblasts and PBMCs from male *FRAXA* individuals

In DNA from *FRAXA* individuals from commercially obtained fibroblasts GM07072 (A), GM05848 (B) or from PBMC samples 14,451 (C) and 21,181 (D) the methylation border was absent and methylation was observed throughout the promoter region downstream to the CGG repeat, except for a few unmethylated CpG dinucleotides. Bisulfite sequencing was extended upward to CpG dinucleotide 104. (E) *FMR1* map as in Figure 1C, except that all CpGs are indicated as methylated. Part of this scheme was taken from Naumann et al., 2009

3. Consequences of Foreign DNA Insertion into the Human Genome

S. Weber, and W. Doerfler, project in progress.

Based on the results of earlier work on adenovirus type 12 (Ad12) DNA- or bacteriophage lambda DNA-transgenic hamster cells, that showed alterations in DNA methylation patterns at sites remote from the insertion locus (Heller et al. Proc. Natl. Acad. Sci. USA **92**, 5515-5519, 1995; Remus et al. J. Virol. **73**, 1010-1022, 1999; Müller et al. J. Biol. Chem. **276**, 14271-14278, 2001), we pursue the notion that foreign DNA insertion into an established mammalian genome can lead to changes in cellular DNA methylation and transcription patterns. At present, we develop a human cell system in which different plasmid constructs have been chromosomally inserted. We currently assess preliminary findings that overall methylation and transcription patterns appear to be altered in the transgenic as compared to the non-transgenic clonal cell lines. Genome-wide methylation and transcription analyses will be performed in these two sets of cell clones.

4. The Epigenetic Profile of Integrated HIV Genomes: Correlations to the Course of the AIDS Disease in HIV Infections?

S. Weber, K Korn, and W. Doerfler – in collaboration with Harold Burger and Barbara Weiser, UC Davies Medical School in Sacramento, CA, USA.

Among the >214.500 publications on HIV and AIDS cited in PubMed, there are very few that describe the epigenetic profiles of integrated HIV genomes in AIDS patients or in people infected with HIV. We have started such a project to determine the extents of de novo methylation of integrated HIV genomes in peripheral white blood cells in people infected by HIV and/or in AIDS patients. We will also determine the modification of histones in specific segments of the integrated HIV genomes. Life-long persistence of HIV genomes and the variability in their expression levels render epigenetic mechanisms an interesting target for molecular analyses. The map in Fig. 5 locates the CpG dinucleotides currently being investigated for their methylation status. Preliminary data demonstrate that these CpGs have remained unmethylated in DNA from nine HIV patients so far analyzed. In contrast, in one long-term controlling individual, HIV-infected decades ago, with very low virus load, normal CD4⁺ T cell count and absence of disease, the CpG dinucleotides in the two LTR regions of the HIV proviral genomes are highly methylated. These data suggest that epigenetic modifications of proviral HIV genomes play a major role in the control of HIV infection.

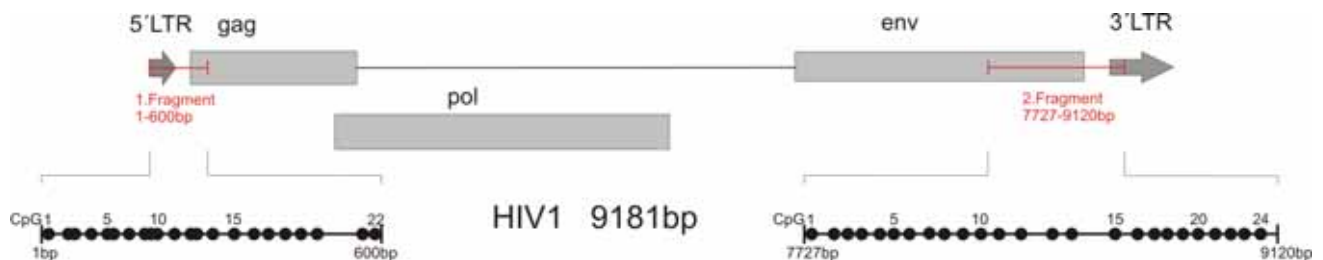


Figure 5 Map of the HIV genome. The CpG dinucleotides located at either LTR and adjacent regions of the HIV genome have been depicted. These CpGs are currently investigated for their methylation status in HIV-infected individuals.

Collaborations

- Professor Ellen Fanning, Vanderbilt University, Nashville, TN, USA, currently Humboldt Prize Award Winner at Erlangen University Medical School, Institute for Virology.
- Drs. Harold Burger and Barbara Weiser, UC Davies Medical School in Sacramento, CA, USA.
- Dr. Klaus Korn, Institute for Virology, Erlangen University Medical School.
- Professor Ulf Pettersson, Rudbeck Laboratoriet vid Uppsala Universitet i Uppsala, Sverige.
- Professor Hans-G. Ulrich, Theology (Ethics), University Erlangen-Nürnberg.
- Petra Böhm, Institute of Genetics, University of Cologne (Co-editor, CTMI).

Present Funding

- Fritz Thyssen Foundation, Cologne, Az. 10.07.2, 2010-2012.
- Institute for Clinical and Molecular Virology, Erlangen University Medical School.
- Nationale Akad. der Wissenschaften Leopoldina, Fourth Weissenburg Symposium 2011.

Teaching in 2009/2010

Since 1972, W.D. has regularly participated in the introductory and advanced lecture courses offered by the **Institute of Genetics, University of Cologne**.

He also teaches introductory molecular biology in the **Virology Department in Erlangen**.

At Erlangen University, Hans-G. Ulrich and W.D. have held a lecture course on **Molecular Genetics: Facts and Ethical Evaluation** since 2003 that has now been offered for the seventh time during the 2009/2010 winter semester.

During the summer semesters 2008, 2009, and again in September 2010, Dagmar Mörsdorf and Walter Doerfler have offered an advanced lecture and seminar course **Molecular and Medical Virology** at the **Institute of Genetics, University of Cologne**.

Visits of high school students from the **Werner-von-Siemens Gymnasium Weißenburg** in the Virology Department of **Erlangen University** and individual laboratory courses for high school students in molecular biology have been made possible by the Robert Bosch Foundation Stuttgart.

Current Selected Publications 2006 - 2010

W. Doerfler.

DNA methylation: *De novo* methylation, long-term promoter silencing, DNA methylation patterns and their changes.

Current Topics Microbiol. Immunol., **301**, 125-175, 2006.

S.J. Gray, J. Gerhardt, W. Doerfler, L.E.Small, and E. Fanning.

An origin of DNA replication in the promoter region of the human fragile X mental retardation (FMR1) gene.

Mol. Cell. Biol. **27**, 426-437, 2007.

N. Hochstein, I. Muiznieks, L. Mangel, H. Brondke, and W. Doerfler.

The epigenetic status of an adenovirus transgenome upon long-term cultivation in hamster cells.

J.Virol. **81**, 5349-5361, 2007.

H. Brondke, B. Schmitz, and W. Doerfler.

Nucleotide sequence comparisons between several strains and isolates of human cytomegalovirus reveal alternate start codon usage.

Arch. Virol., **152**, 2035-2046, 2007.

N. Hochstein, D. Webb, M. Hösel, W. Seidel, S. Auerochs, and W. Doerfler.

Human CAR gene expression in non-permissive hamster cells boosts entry of type 12 adenovirus and nuclear import of viral DNA.

J. Virol. **82**, 4159-4163, 2008.

W. Doerfler.

In pursuit of the first recognized epigenetic signal: DNA methylation. A 1976 to 2008 synopsis of work from the author's laboratory.

Epigenetics 3, 125-133, 2008.

W. Doerfler.

Epigenetic mechanisms in human adenovirus type 12 oncogenesis.

Seminars in Cancer Biology 19, 136-143, 2009.

A. Naumann, N. Hochstein, S. Weber E. Fanning, and W. Doerfler.

A distinct DNA methylation boundary in the 5'-upstream sequence of the FMR1 promoter binds nuclear proteins and is lost in fragile X syndrome **Americ. J. Hum. Genet. 85**, 606-616, 2009.

W. Doerfler, A. Naumann, N. Hochstein, and S. Weber.

DNA methylation profiles in the 5'-upstream region of the human *FMRI* promoter and in an adenovirus transgenome.

Handbook of Epigenetics: The New Molecular and Medical Genetics. Edited by Trygve Tollefsbol, pp. 495-509, 2010.

W. Doerfler.

DNA – a molecule in search of additional functions: recipient of *pool* wave emissions? - A hypothesis.

Medical Hypotheses 75:291-293, 2010.

Additional publications

W. Doerfler.

Conditio Humana as viewed by a geneticist.

In: *Theology, Disability and the New Genetics*, J. Swinton and B. Brock, eds.

T&T Clark, London, New York, pp. 117-131, 2007.

B. Brock, W. Doerfler, and H.-G. Ulrich.

Genetics, conversation and conversion: A discourse at the interface of molecular genetics and Christian ethics.

In: *Theology, Disability and the New Genetics*, J. Swinton and B. Brock, eds.

T&T Clark, London, New York, pp. 146-160, 2007.

W. Doerfler.

Molecular Virology and Medical Genetics at the Institute of Genetics in Cologne, 1972 to 2002. In: **S. Wenkel and U. Deichmann**, editors.

Max Delbrück and Cologne: An Early Chapter of German Molecular Biology.

World Scientific Publishing Co.Pte.Ltd., Singapore, Hackensack, N.J., London, pp. 159-177, 2007.

Books edited

W. Doerfler and P. Böhm (Eds).

DNA Methylation: Basic Mechanisms.

Current Topics in Microbiology and Immunology. Springer Verlag, Berlin, Heidelberg, New York, Tokyo, **vol. 301, 2006**.

W. Doerfler and P. Böhm (Eds).

DNA Methylation: Development, Genetic Disease, Cancer.

Current Topics in Microbiology and Immunology. Springer Verlag, Berlin, Heidelberg, New York, Tokyo, **vol. 310, 2006**.

W. Doerfler, H.-G. Ulrich, and P. Böhm (Eds).

Medicine at the Interface between Science and Ethics

Nova Acta Leopoldina, NF 98, Nr. 361, **2010** (see book cover at end of homepage).

Selected Publications 1968 to 1999: Integration of foreign DNA and DNA methylation

W. Doerfler.

The fate of the DNA of adenovirus type 12 in baby hamster kidney cells.

Proc. Natl. Acad. Sci. USA **60**, 636-643, 1968.

U. Günthert, M. Schweiger, M. Stupp, and W. Doerfler.

DNA methylation in adenovirus, adenovirus-transformed cells, and host cells.

Proc Natl Acad Sci USA **73**, 3923-3927, 1976.

J. Groneberg, Y. Chardonnet, and W. Doerfler.

Integrated viral sequences in adenovirus type 12-transformed hamster cells.

Cell **10**, 101-111, 1977.

D. Sutter, M. Westphal, and W. Doerfler.

Patterns of integration of viral DNA sequences in the genomes of adenovirus type 12-transformed hamster cells.

Cell **14**, 569-585, 1978.

D. Sutter, and W. Doerfler.

Methylation of integrated adenovirus type 12 DNA sequences in transformed cells is inversely correlated with viral gene expression.

Proc. Natl. Acad. Sci. USA **77**, 253-256, 1980.

R. Deuring, G. Klotz, and W. Doerfler.

An unusual symmetric recombinant between adenovirus type 12 DNA and human cell DNA. **Proc. Natl. Acad. Sci. USA** **78**, 3142-3146, 1981.

R. Deuring, U. Winterhoff, F. Tamanoi, S. Stabel, and W. Doerfler.

Site of linkage between adenovirus type 12 and cell DNAs in hamster tumour line CLAC3.

Nature **293**, 81-84, 1981.

L. Vardimon, A. Kressmann, H. Cedar, M. Maechler, and W. Doerfler.

Expression of a cloned adenovirus gene is inhibited by *in vitro* methylation.
Proc. Natl. Acad. Sci. USA 79, 1073-1077, 1982.

I. Kuhlmann, S. Achten, R. Rudolph, and W. Doerfler.

Tumor induction by human adenovirus type 12 in hamsters: loss of the viral genome from adenovirus type 12-induced tumor cells is compatible with tumor formation.
EMBO J. 1, 79-86, 1982.

I. Kruczek, and W. Doerfler.

Expression of the chloramphenicol acetyltransferase gene in mammalian cells under the control of adenovirus type 12 promoters: effect of promoter methylation on gene expression.
Proc. Natl. Acad. Sci. USA 80, 7586-7590, 1983.

W. Doerfler.

DNA methylation and gene activity.
Ann. Rev. Biochem. 52, 93-124, 1983.

K.-D. Langner, L. Vardimon, D. Renz, and W. Doerfler.

DNA methylation of three 5' C-C-G-G 3' sites in the promoter and 5' region inactivates the E2a gene of adenovirus type 2.
Proc. Natl. Acad. Sci. USA 81, 2950-2954, 1984.

K.-D. Langner, U. Weyer, and W. Doerfler.

Trans effect of the E1 region of adenoviruses on the expression of a prokaryotic gene in mammalian cells: resistance to 5'-CCGG-3' methylation.
Proc. Natl. Acad. Sci. USA 83, 1598-1602, 1986.

R. Jessberger, D. Heuss, and W. Doerfler.

Recombination in hamster cell nuclear extracts between adenovirus type 12 DNA and two hamster preinsertion sequences.
EMBO J. 8, 869-878, 1989.

M. Toth, U. Lichtenberg, and W. Doerfler.

Genomic sequencing reveals a 5-methylcytosine-free domain in active promoters and the spreading of preimposed methylation patterns.
Proc. Natl. Acad. Sci. USA 86, 3728-3732, 1989.

S. Kochanek, M. Toth, A. Dehmel, D. Renz, and W. Doerfler.

Interindividual concordance of methylation profiles in human genes for tumor necrosis factors α and β .
Proc. Natl. Acad. Sci. USA 87, 8830-8834, 1990.

S. Kochanek, A. Radbruch, H. Tesch, D. Renz, and W. Doerfler.

DNA methylation profiles in the human genes for tumor necrosis factors α and β in subpopulations of leukocytes and in leukemias.
Proc. Natl. Acad. Sci. USA 88, 5759-5763, 1991.

S. Kochanek, D. Renz, and W. Doerfler.

DNA methylation in the Alu sequences of diploid and haploid primary human cells.
EMBO J. **12**, 1141-1151, 1993.

H. Heller, C. Kämmer, P. Wilgenbus, and W. Doerfler.

Chromosomal insertion of foreign (adenovirus type 12, plasmid, or bacteriophage 1) DNA is associated with enhanced methylation of cellular DNA segments.
Proc. Natl. Acad. Sci USA **92**, 5515-5519, 1995.

R. Schubbert, D. Renz, B. Schmitz, and W. Doerfler.

Foreign (M13) DNA ingested by mice reaches peripheral leukocytes, spleen and liver via the intestinal wall mucosa and can be covalently linked to mouse DNA.
Proc. Natl. Acad. Sci. USA **94**, 961-966, 1997.

M. Zeschnigk, B. Schmitz, B. Dittrich, K. Buiting, B. Horsthemke, and W. Doerfler.

Imprinted segments in the human genome: different DNA methylation patterns in the Prader-Willi/Angelman syndrome region as determined by the genomic sequencing method.
Human Molecular Genetics **6**, 387-395, 1997.

S. Schwemmle, E. de Graaff, H. Deissler, D. Gläser, D. Wöhrle, I. Kennerknecht, W. Just, B.A. Oostra, W. Doerfler, W. Vogel, and P. Steinbach.

Characterization of FMR1 promoter elements by *in vivo*-footprinting analysis.
Americ. J. Hum. Genet. **60**, 1354-1362, 1997.

A. Schumacher, K. Buiting, M. Zeschnigk, W. Doerfler & B. Horsthemke.

Methylation analysis of the PWS/AS region does not support an enhancer competition model of genomic imprinting on human chromosome 15.
Nature Genet. **19**, 324-325, 1998.

J. Hertz, G. Schell, and W. Doerfler.

Factors affecting *de novo* methylation of foreign DNA in mouse embryonic stem cells.
J. Biol. Chem. **274**, 24232-24240, 1999.

Organisation of International Symposia 2001 – 2011

Weißenburg Symposium 2001: *Medicine and Molecular Biology*

Second Weißenburg Symposium 2004: *DNA Methylation, an Important Genetic Signal*

Third Weißenburg Symposium 2007: *Medicine at the Interface between Science and Ethics*

Organizer and Speaker at the **Annual Meeting of the American Association for the Advancement of Science (AAAS)**, 12-16 February, 2009 in **Chicago, IL, USA: *Epigenetics: Mechanisms and Impact on Biomedicine.***

Organizer and Speaker at the **Annual Meeting of the American Association for the Advancement of Science (AAAS)**, 18-22 February, 2010 in **San Diego, CA, USA**: *Science and Divinity – Genetics and Ethics*.

Co-organizer of Symposium on *Methylating the Mind* **Annual Meeting of the American Society of Human Genetics (ASHG)**, 02-06 November 2010 in **Washington, DC, USA**.

Fourth Weissenburg Symposium 2011, Walter Doerfler, Bernhard Fleckenstein and Ulf Petteresson, co-organizers: *Epigenetics and the Control of Genetic Activity*. June 20 to 22, 2011. All speakers and finances confirmed.



**Impressions from Cheekwood Botanical Garden in Nashville Tennessee –
Walter Doerfler's Sabbatical Stay in the Spring of 2006**

