

**Professor Howard Cedar
Professor Emeritus
Faculty of Medicine
Hebrew University of Jerusalem
Israel**



February 12th, 2023

To
World Cultural Council Awards
Albert Einstein Award

Re: Letter of nomination – Prof. Howard Cedar

Dear Respected committee members,

I am pleased to nominate Prof. Howard Cedar for the 2023 Albert Einstein World Award of Science in recognition of his major role in the discovery of DNA methylation and his ground-breaking contributions to the field of epigenetics, in general.

While the discovery of the genetic code in the 1950s was instrumental in elucidating the basic language of biology, Cedar has beautifully demonstrated that this genetic text is also chemically annotated by DNA methylation, thus providing a brand-new layer of essential information that directs how genes are properly regulated in a stable manner throughout the body. This annotation system constitutes the molecular foundation for epigenetics and, in this way plays a seminal role in all aspects of biology and medicine. The evolution of this concept was the result of Cedar's lifetime devotion to understanding this process. Over the past 40 years, he has made major contributions to understanding the biochemistry of DNA methylation, uncovering the molecular mechanisms of gene regulation, unraveling the role of this modification as a device for long-term memory of cell identity, and explaining how it controls the process of development. He has also helped decipher how this entire process is actually programmed in the genome.

Cedar's ongoing research is continuously uncovering how DNA methylation is involved in many different key biological phenomena. His early work, for example, serves as the basis for a new and exciting blood test for the early detection and monitoring of many different diseases, including cancer. Recent studies are opening a new era in understanding how the environment causes long-term changes in behavior and are now uncovering the mechanisms by which DNA methylation serves as the basis for disease susceptibility and aging.

All of Cedar's research accomplishments have been reported in an ongoing series of over 80 papers published in the highest-profile scientific journals and his life work has attained wide recognition, including a large number of prestigious international awards. There is no doubt that Howard Cedar deserves recognition for his extensive and ground-breaking research and is highly worthy of this award.

Respectfully,

Prof. Tamir Sheaffer
Rector



Prof. Yuval Dor
Developmental Biology and Cancer Research
The Institute for Medical Research Israel-Canada (IMRIC)
The Hebrew University-Hadassah Medical School
Jerusalem 91120, Israel
Tel 972-2-6757181, Fax 972-2-6757482
Email yuvald@ekmd.huji.ac.il



January 18, 2023

Selection Committee
"Albert Einstein" World Award of Science
New York

Dear Colleagues:

I write to support, in the strongest possible terms, **the nomination of Howard Cedar for the 2023 "Albert Einstein" World Award of Science, for his discovery of the principles governing DNA methylation.**

DNA methylation, involving the covalent addition of a methyl group to specific cytosine residues in DNA, is a fundamental process in biology, functioning to achieve a key mission of living organisms: the accurate maintenance of cell identity (the subset of expressed and repressed genes) through many years and multiple rounds of cell division(1)(2).

While the elucidation of the double stranded structure of DNA explained how genetic information can be duplicated and transmitted to the next generation, it could not explain how differentiated cells can give rise to daughter cells that maintain the same differentiation state. Prof. Cedar has discovered that the methylation of a cytosine followed by a guanosine (CpG dinucleotide) is the basis for transmission of such information. CpG methylation occurs symmetrically on both strands of the DNA, and serves to repress the expression of genes via impacting chromatin structure and accessibility to transcription factors. When a cell replicates, each strand instructs one daughter cell to copy its methylation pattern to the newly synthesized strand, thus ensuring accurate transmission of DNA methylation patterns. This is the molecular basis of epigenetics, namely the establishment of stable, heritable phenotypes that do not involve changes to the sequence of DNA. The significance and impact of DNA methylation are comparable to that of other key processes affecting the building blocks of life such as the splicing of RNA and the degradation of proteins via the ubiquitin system.



Cedar's studies established the key principles of DNA methylation, including:

- (1) The demonstration that DNA methylation constitutes a unique layer of biological information that is fundamentally different from the genetic code itself. While DNA methylation patterns are inherited accurately through somatic cell divisions, they are erased and re-established each time a new organism is formed.
- (2) The demonstration that DNA methylation provides molecular memory. That is, once established, DNA methylation patterns are autonomously maintained through all future cell divisions, via a semi-conservative enzymatic process. This provides a unique memory mechanism whereby decisions made at one stage of development persist even though the original protein factors responsible for the decision are no longer present. No other chromatin mark has this property.
- (3) The demonstration that DNA methylation provides stable long-term gene regulation by virtue of controlling chromatin structure and preventing access of transcription factors. This chemistry enables the permanent repression of genes that ought to be silenced in a given cell type.

Prof. Cedar carried out the key experiments that revealed the role of DNA methylation as a regulator of gene expression. He first showed that methylation is present only at fixed CpG residues in DNA, and that methylation patterns are maintained through cell division (3,4). He then discovered that the mechanism for copying methylation profiles is based on nucleotide symmetry. That is, a CpG pair is hybridized with a CpG pair in the opposite strand of DNA, and the methylation pattern of the parent strand is copied to the newly synthesized strand (5,6). These results form the basis for understanding the stability of epigenetic marks.

In the next steps, Prof. Cedar and others showed that DNA methylation represses gene expression. His group proved experimentally that methylation inhibits expression *in vivo* and discovered the mechanism for this effect. He demonstrated that methylation alters chromatin structure, thereby blocking access of the transcription machinery to DNA (3,7–9). He further contributed to the understanding that CpG islands are clusters of constitutively unmethylated promoter sequences that serve to drive expression of housekeeping genes (10).

Prof. Cedar also demonstrated that during normal development, DNA methylation patterns are erased in the early embryo, reestablished anew at the time of implantation, and then undergo tissue- and gene-specific changes during later development. He further deciphered the molecular elements involved in these events. These studies showed how methylation patterns are established *in vivo*, and proved that these patterns are based completely on regulatory sequence information in the DNA (11–13).



Prof. Cedar and his colleagues and students next approached the multiple roles of DNA methylation in development, cell differentiation and cancer. They demonstrated that de-methylation is essential for B-cell differentiation and function, disproving the prior claim that methylation plays no role in differentiation (14,15). They showed that postnatal de-methylation represents a response to the internal organismal environment and can be mediated by hormones (16–18). They deciphered the mechanism by which oncogenes may be de-methylated and tumor suppressor genes may be methylated in previously normal cells, elucidating the role of DNA methylation in tumorigenesis (19–21).

These basic results have informed our understanding of a wide variety of processes in human health and disease. DNA methylation controls genomic imprinting, whereby only the maternal or only the paternal allele of given gene is expressed; it is a key mechanism for stable X-inactivation in females; and it plays a central role in allelic exclusion in the immune and olfactory systems. Aberrations of methylation lead to diseases, including Prader-Willi and Angelman syndromes, familial dysautonomia, fragile X. As shown by Cedar and others, reprogramming of DNA methylation also contributes to disrupted gene expression in tumors, and participates in the process of organismal aging. Therapies based on demethylation (e.g. 5-azacytidine) are broadly used in oncology, for example in acute myeloid leukemia.

In recent years, the fundamental principles of DNA methylation elucidated by Prof. Cedar have made a surprising impact in diverse fields, particularly in medicine. I will mention here just a few striking examples out of many.

1. Diagnostic medicine. It turns out that DNA methylation patterns are retained on fragments of cell-free DNA (cfDNA) that are released from dying cells to blood. This includes cell type-specific patterns of DNA methylation, which can be used to infer the tissue origins of such fragments. Thus analysis of DNA methylation on cfDNA fragments can provide extremely specific and sensitive information on the rate of cell death in specific tissues, opening a minimally-invasive window into human tissue dynamics. I was fortunate to collaborate with Prof. Cedar on one of the earliest demonstrations of this technology (22,23). Strikingly, it is now appreciated that methylation patterns of cfDNA contain sufficient information for the detection of cancer-associated cell turnover at an early, actionable stage. Consequently, cfDNA methylation analysis is now considered the preferred approach for early cancer detection (24,25). This has been shown in multiple high-profile publications in recent years, and is already in practical use. For example, the multi-cancer early detection (MCED) blood test (Galleri) sold by the biotech company Grail, is based on analysis of methylation patterns in cfDNA, and it is estimated that a quarter of cancer deaths can be prevented by early detection using this method. Methylation-based blood tests for cancer detection are being developed by many other diagnostic biotech companies, e.g. the colon cancer test developed by Guardant Health. Methylation-based liquid biopsies inspired by Cedar's discoveries in fact apply to the detection and monitoring



of many pathologies beyond cancer including liver disease, inflammation, degenerative diseases, drug toxicity and more.

2. **Forensics.** In criminal investigations, the question is often not who has left DNA in a crime scene, but what is the tissue source of that DNA. For example, is suspect's DNA found on a weapon derived from saliva or skin? Is suspect's DNA found in a rape case derived from sperm or skin or saliva? Cell type-specific DNA methylation patterns are emerging as the most accurate approach for answering such questions, and are finding their way into mainstream forensics (26).

3. **Ancient DNA.** The extreme stability of DNA allows to interrogate patterns of DNA methylation on ancient DNA. This has allowed to infer gene expression programs in ancient humans (long after RNA and proteins have been degraded), and helped the reconstitution of facial morphology of the Denisovans (27,28).

In summary, DNA methylation plays a crucial role in the chemistry of life, in normal development and in human disease and medicine. Our understanding of this fundamental process is based on the work of Prof. Cedar over more than 40 years. It would be most appropriate to recognize the centrality of this work to modern medicine by awarding Prof. Cedar the 2023 "Albert Einstein" World Award of Science.

Sincerely,

Yuval Dor

Yuval Dor

References

1. Cedar H. DNA methylation and gene activity. *Cell*. 1988 Apr 8;53(1):3–4.
2. Bergman Y, Cedar H. DNA methylation dynamics in health and disease. *Nat Struct Mol Biol*. 2013 Mar;20(3):274–81.
3. Pollack Y, Stein R, Razin A, Cedar H. Methylation of foreign DNA sequences in eukaryotic cells. *Proc Natl Acad Sci USA*. 1980 Nov;77(11):6463–7.
4. Stein R, Gruenbaum Y, Pollack Y, Razin A, Cedar H. Clonal inheritance of the pattern of DNA methylation in mouse cells. *Proc Natl Acad Sci USA*. 1982 Jan;79(1):61–5.
5. Gruenbaum Y, Naveh-Many T, Cedar H, Razin A. Sequence specificity of methylation in higher plant DNA. *Nature*. 1981 Aug 27;292(5826):860–2.
6. Gruenbaum Y, Cedar H, Razin A. Substrate and sequence specificity of a eukaryotic DNA methylase. *Nature*. 1982 Feb 18;295(5850):620–2.
7. Naveh-Many T, Cedar H. Active gene sequences are undermethylated. *Proc Natl Acad Sci USA*. 1981 Jul;78(7):4246–50.



8. Stein R, Razin A, Cedar H. In vitro methylation of the hamster adenine phosphoribosyltransferase gene inhibits its expression in mouse L cells. *Proc Natl Acad Sci USA*. 1982 Jun;79(11):3418–22.
9. Keshet I, Lieman-Hurwitz J, Cedar H. DNA methylation affects the formation of active chromatin. *Cell*. 1986 Feb 28;44(4):535–43.
10. Stein R, Sciaky-Gallili N, Razin A, Cedar H. Pattern of methylation of two genes coding for housekeeping functions. *Proc Natl Acad Sci USA*. 1983 May;80(9):2422–6.
11. Frank D, Keshet I, Shani M, Levine A, Razin A, Cedar H. Demethylation of CpG islands in embryonic cells. *Nature*. 1991 May 16;351(6323):239–41.
12. Kafri T, Ariel M, Brandeis M, Shemer R, Urven L, McCarey J, et al. Developmental pattern of gene-specific DNA methylation in the mouse embryo and germ line. *Genes Dev*. 1992 May;6(5):705–14.
13. Brandeis M, Frank D, Keshet I, Siegfried Z, Mendelsohn M, Nemes A, et al. Sp1 elements protect a CpG island from de novo methylation. *Nature*. 1994 Sep 29;371(6496):435–8.
14. Lichtenstein M, Keini G, Cedar H, Bergman Y. B cell-specific demethylation: a novel role for the intronic kappa chain enhancer sequence. *Cell*. 1994 Mar 11;76(5):913–23.
15. Orlanski S, Labi V, Reizel Y, Spiro A, Lichtenstein M, Levin-Klein R, et al. Tissue-specific DNA demethylation is required for proper B-cell differentiation and function. *Proc Natl Acad Sci USA*. 2016 May 3;113(18):5018–23.
16. Reizel Y, Spiro A, Sabag O, Skversky Y, Hecht M, Keshet I, et al. Gender-specific postnatal demethylation and establishment of epigenetic memory. *Genes Dev*. 2015 May 1;29(9):923–33.
17. Reizel Y, Sabag O, Skversky Y, Spiro A, Steinberg B, Bernstein D, et al. Postnatal DNA demethylation and its role in tissue maturation. *Nat Commun*. 2018 May 23;9(1):2040.
18. Falick Michaeli T, Sabag O, Fok R, Azria B, Monin J, Nevo Y, et al. Muscle injury causes long-term changes in stem-cell DNA methylation. *Proc Natl Acad Sci USA*. 2022 Dec 27;119(52):e2212306119.
19. Keshet I, Schlesinger Y, Farkash S, Rand E, Hecht M, Segal E, et al. Evidence for an instructive mechanism of de novo methylation in cancer cells. *Nat Genet*. 2006 Feb;38(2):149–53.
20. Schlesinger Y, Straussman R, Keshet I, Farkash S, Hecht M, Zimmerman J, et al. Polycomb-mediated methylation on Lys27 of histone H3 pre-marks genes for de novo methylation in cancer. *Nat Genet*. 2007 Feb;39(2):232–6.
21. Klutstein M, Moss J, Kaplan T, Cedar H. Contribution of epigenetic mechanisms to variation in cancer risk among tissues. *Proc Natl Acad Sci USA*. 2017 Feb 28;114(9):2230–4.
22. Lehmann-Werman R, Neiman D, Zemmour H, Moss J, Magenheimer J, Vaknin-Dembinsky A, et al. Identification of tissue-specific cell death using methylation patterns of circulating DNA. *Proc Natl Acad Sci USA*. 2016 Mar 29;113(13):E1826–34.



23. Dor Y, Cedar H. Principles of DNA methylation and their implications for biology and medicine. *Lancet*. 2018 Sep 1;392(10149):777–86.
24. Jamshidi A, Liu MC, Klein EA, Venn O, Hubbell E, Beausang JF, et al. Evaluation of cell-free DNA approaches for multi-cancer early detection. *Cancer Cell*. 2022 Dec 12;40(12):1537-1549.e12.
25. Hasenleithner SO, Speicher MR. How to detect cancer early using cell-free DNA. *Cancer Cell*. 2022 Dec 12;40(12):1464–6.
26. Frumkin D, Wasserstrom A, Budowle B, Davidson A. DNA methylation-based forensic tissue identification. *Forensic Sci Int Genet*. 2011 Nov;5(5):517–24.
27. Gokhman D, Mishol N, de Manuel M, de Juan D, Shuqrun J, Meshorer E, et al. Reconstructing denisovan anatomy using DNA methylation maps. *Cell*. 2020 Feb 6;180(3):601.
28. Mathov Y, Batyrev D, Meshorer E, Carmel L. Harnessing epigenetics to study human evolution. *Curr Opin Genet Dev*. 2020 Jun 20;62:23–9.



MORTIMER B. ZUCKERMAN MIND BRAIN BEHAVIOR INSTITUTE

RICHARD AXEL, M.D.
UNIVERSITY PROFESSOR

January 23, 2023

The “Albert Einstein” World Award of Science

Dear Sirs and/or Madams:

It is with great pleasure and the strongest enthusiasm that I support the nomination of Professor Howard Cedar for the 2023 “Albert Einstein” World Award of Science. Howard Cedar's elegant and incisive experimental approach has provided profound new insights into how genes are controlled. Cedar has combined insight into important problems in biology with an ability to devise extremely clever yet simple experimental approaches to affect their solution. By coupling ideas with experimental rigor, Cedar has shown how DNA modification controls gene expression in animal cells.

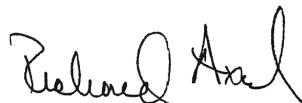
Early in his career, Cedar recognized that one simple yet elegant mechanism of gene control that can be inherited is DNA modification. The placement of methyl groups on DNA could affect the way regulatory molecules interact with specific DNA sequences, such that a maintenance methylase could assure that this information is retained from generation to generation. Through a thoughtful series of experiments in the Cedar lab, considerable support for this important model of gene control has emerged. In early studies with Aaron Razin, Cedar demonstrated that methyl groups in eukaryotic DNA were found only on CpG residues. With the emergence of recombinant DNA technologies, Cedar's was among the first laboratories to demonstrate that developmentally regulated sequences were undermethylated in expressing cells, such that the extent of methylation at specific loci correlated inversely with gene expression. This immediately posed the question as to whether demethylation of DNA was the cause or consequence of gene expression. In a novel series of experiments, Cedar employed gene transfer techniques to demonstrate that the methylation of DNA *in vitro* inhibited expression of this newly introduced gene. Moreover, Cedar provided firm evidence that the introduction of methylated sequences into the chromosome led to the stable inheritance of this modified state. This immediately suggested the existence of a maintenance methylase capable of modifying any methylated sites in DNA that are generated during replication. Cedar identified this activity and defined its substrate specificity, providing a simple mechanism for the clonal inheritance of the pattern of DNA methylation in mouse cells.

Moving from these model systems, Cedar initiated an analysis of the patterns of DNA modification in the developing embryo. He showed that in the preimplantation embryo, virtually all DNA methylation is erased by demethylase activity, such that the modification pattern must be established anew at each generation. This process is accomplished by a simple mechanism involving non-specific *de novo* methylation sparing islands of regulatory sequences that reside in

front of housekeeping genes. Specific demethylases are then responsible for removing methyl groups from tissue-specific genes only in appropriate tissues at appropriate times in development. Moreover, he has shown that a special class of genes that exhibit genomic imprinting is differentially methylated in the gametes and that this pattern is preserved in early development.

Thus, through a series of extremely thoughtful yet rigorous experiments, Cedar has moved from a demonstration of DNA modification to an elucidation of the mechanisms whereby DNA methylation plays a critical role in gene control. Cedar's career is characterized by consistent creativity and productivity directed toward central issues in molecular biology. I support his nomination for the "Albert Einstein" World Award of Science.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Richard Q Axel".

Richard Axel, M.D.
University Professor

Howard Cedar Resume

Howard Cedar played a major role in the discovery of DNA methylation and in deciphering its role in biology and medicine. All of the fundamental principles of this elegant annotation system were elucidated by Cedar in a series of pioneering studies. He was the first to show that methylation serves as a chemical mark on the DNA itself that causes gene repression and demonstrated that this operates by altering chromatin structure and accessibility. He introduced the concept of epigenetic memory by proving that DNA methylation patterns are maintained autonomously through cell division and he was the first to actually decipher this molecular copying mechanism. Cedar also showed that the methylation state is reprogrammed by erasure in the early embryo and then succeeded in deciphering the DNA-sequence rules that govern how overall modification patterns are re-established during normal development. These studies have laid the foundation stones for finally understanding how genetic information from our parents is actually used and properly controlled to generate a functioning human being.

On the basis of this basic work, DNA methylation has emerged as a completely new concept of gene repression. Unlike mechanisms based on protein–DNA interactions, DNA methylation is covalently maintained even after initiating protein factors are no longer present in the cell, thus enabling long-term stability of key developmental decisions, a process that appears to be essential for long-lived organisms, like man. This idea serves as the basis for explaining global gene repression in general, as well as parental genomic imprinting and X chromosome inactivation in females. DNA methylation is also relevant to our understanding of stem cell biology and is the critical molecular switch that must be reset in order to reprogram somatic cells to pluripotency. [These findings are essential for enabling us to use stem cells for tissue replacement technology in modern day medicine.](#)

The fundamental mechanisms elucidated by Cedar have brought about a total change in the way we understand cancer by demonstrating that tumor biology

is dictated largely by epigenetic as opposed to genetic alterations. Abnormal methylation takes place in almost every form of cancer and has an enormous influence on tumor phenotype. Recent studies by Cedar have contributed to our understanding of abnormal methylation by showing that these changes actually occur through a programmed mechanism that counteracts differentiation, strongly suggesting that this modification is indeed part of a basic cancer biology program. Unlike molecular defects of cell markers that are normally limited to specific cancers, aberrant methylation is associated with every known tumor and occurs as a very early event in the tumorigenesis process, [making this a key target for cancer treatment and prevention.](#)

DNA methylation is a fundamental aspect of animal cell biology that is implicated in the regulation of a large number of physiological, developmental and pathological processes. Ongoing studies support the idea that this modification serves as a molecular memory mechanism that mediates changes in gene function as an adaptive response to environment. [In this way, DNA methylation has far-reaching consequences as the key link for understanding aging, disease susceptibility and human behavior.](#) Cedar has also laid the foundations for an amazing new methylation-based blood test for assessing the disease state of almost every tissue in the body, which is now being used for the early detection of cancer.

While many scientists have contributed to our knowledge of methylation, the foundations of this field were clearly established by the seminal work of Cedar. Beyond methylation itself, he has pioneered in deciphering the basic paradigms behind the establishment and maintenance of epigenetic information in general, and this has served as a model for almost all studies on chromatin structure and gene regulation. [These discoveries are having a tremendous influence on molecular medicine.](#)

CURRICULUM VITAE

BIOGRAPHICAL: Born January 12, 1943, New York, N.Y.

EDUCATION:

1964 - B.Sc. Massachusetts Institute of Technology, Sigma Xi
1970 - M.D., Ph.D. New York University

MAJOR RESEARCH INTEREST:

Molecular Biology

PROFESSIONAL BACKGROUND:

1970 - 1971 Intern, Department of Pathology, New York University School of Medicine.
1970 - 1971 Fellow, Department of Neurobiology, Public Health Research Institute of the City of New York, in the laboratory of Drs. James H. Schwartz and Eric R. Kandel.
1971 - 1973 Research Associate, USPHS, National Institutes of Health, in the laboratory of Dr. Gary Felsenfeld.
1973 - present Lecturer, Senior Lecturer, Associate Professor, Professor of Molecular Biology, Hebrew University Medical School.

AWARDS:

1979 Hestrin Prize for Biochemistry.
1982 Member European Molecular Biology Organization
1987 Israel Cancer Research Fund Professorship
1988 Member Human Genome Organization (HUGO)
1991 Hebrew University Outstanding Investigator
1997 FEBS Lecturer Award
1999 Israel Prize in Biology
2003 Member Israel Academy of Sciences
2008 Wolf Prize in Medicine
2009 Safra Distinguished Professor
2009 Emet Prize in Medicine
2011 Member Academia Europaea
2011 Gairdner International Award
2012 Rothschild Prize in Biology
2016 Louisa Gross Horwitz Prize
2022 Member, US National Academy of Sciences

Howard Cedar

10 Most Important Papers

1980 Pollack, Y., Stein, R., Razin, A. and Cedar, H. Methylation of foreign sequences in eukaryotic cells. *Proc. Natl. Acad. Sci. USA* **77**, 6463-6467.

1981 Gruenbaum, Y., Naveh-Many, T., Cedar, H. and Razin, A. Sequence specificity of methylation in higher plant DNA. *Nature* **292**, 860-862.

1981 Naveh, T. and Cedar, H. Active gene sequences are undermethylated. *Proc. Natl. Acad. Sci. USA* **78**, 4246-4250.

1982 Gruenbaum, Y., Cedar, H. and Razin, A. Substrate and sequence specificity of a eukaryotic DNA methylase. *Nature* **295**, 620-622.

1986 Keshet, I., Lieman-Hurwitz, J. and Cedar, H. DNA methylation affects the formation of active chromatin. *Cell* **44**, 535-543.

1994 Brandeis, M., Frank, D., Keshet, I., Siegfried, Z., Mendelsohn, M., Nemes, A., Temper, V., Razin, A. and Cedar, H. Sp1 elements protect a CpG island from de novo methylation. *Nature* **371**, 435-438.

2006 Keshet, I., Schlesinger, Y., Farkash, S., Rand, E., Hecht, M., Segal, E., Pikarski, E., Young, R.A., Niveleau, A., Cedar, H. and Simon, I. Evidence for an instructive mechanism of de novo methylation in cancer cells. *Nature Genet.* **38**, 149-153.

2007 Schlesinger, Y., Straussman, R., Keshet, I., Farkash, S., Hecht, M., Zimmerman, J., Eden, E., Yakhini, Z., Ben-Shushan, E., Reubinoff, B.E., Bergman, Y., Simon, I. and Cedar, H. Polycomb mediated histone H3(K27) methylation pre-marks genes for de novo methylation in cancer. *Nature Genet.* **39**, 232-239.

2018 Reizel, Y., Sabag, O., Skversky, Y., Spiro, A., Steinberg, B., Bernstein, D., Wang, A., Keickhaefer, J., Li, C., Pikarsky, E., Levin-Klein, R., Goren, A., Rajewsky, K., Kaestner, K.H. and Cedar, H. Postnatal DNA demethylation and its role in tissue maturation. *Nature Comm.* **9**, 2040-2050.

2018 Dor, Y. and Cedar, H. Principles of DNA methylation and their implications for biology and medicine. *The Lancet*, **392**, 777-786.

Dr. Howard Cedar

BIBLIOGRAPHY

1967 Cedar, H. and Schwartz, J.H. Localization of the two L-asparaginases in anaerobically grown *Escherichia coli*. *J. Biol. Chem.* **242**, 3753-3754.

1968 Cedar, H. and Schwartz, J.H. The production of L-asparaginase II by *Escherichia coli*. *J. Bacteriol.* **96**, 2043-2048.

1969 Cedar, H. and Schwartz, J.H. The asparagine synthetase of *Escherichia coli*. I. Biosynthetic role of the enzyme, purification, and characterization of the reaction products. *J. Biol. Chem.* **244**, 4112-4121.

1969 Cedar, H. and Schwartz, J.H. The asparagine synthetase of *Escherichia coli*. II. Studies on mechanism. *J. Biol. Chem.* **244**, 4122-4127.

1969 Cedar, H. The asparagine synthetase of *Escherichia coli*. Doctoral dissertation. N.Y.U. School of Medicine.

1971 Ehrman, M., Cedar, H. and Schwartz, J.H. L-asparaginase II of *Escherichia coli*. Studies on the enzymatic mechanism of action. *J. Biol. Chem.* **256**, 88-94.

1972 Cedar, H. and Schwartz, J.H. Cyclic AMP in the nervous system of *Aplysia californica*. II. Effect of various putative transmitter substances. *J. Gen. Physiol.* **60**, 570-587.

1972 Cedar, H., Kandel, E.R. and Schwartz, J.H. Cyclic AMP in the nervous system of *Aplysia californica*. I. Increased synthesis of cAMP in response to synaptic stimulation. *J. Gen. Physiol.* **60**, 558-569.

1973 Cedar, H. and Felsenfeld, G. Transcription of chromatin *in vitro*. *J. Mol. Biol.* **77**, 237-254.

1973 Axel, R., Cedar, H. and Felsenfeld, G. The synthesis of globin RNA from duck reticulocyte chromatin *in vitro*. *Proc. Natl. Acad. Sci. USA* **70**, 2029-2032.

1973 Cedar, H., Axel, R. and Felsenfeld, G. Chromatin, structure and function. Fogarty International Symposium **26**, 243-256.

1973 Axel, R., Cedar, H. and Felsenfeld, G. Chromatin template activity and chromatin structure. *Cold Spring Harbor Symp. Quant. Biol.* **38**, 312-330.

1973 Felsenfeld, G. and Cedar, H. Chromatin structure in solution. In, FOGARTY INTERNATIONAL SYMPOSIUM OF REGULATION OF GENE EXPRESSION IN EUKARYOTIC CELLS; Control of Transcription and Translation, eds. M. Hans and B. Thompson. pp. 3-16.

1975 Felsenfeld, G., Axel, R., Cedar, H. and Sollner-Webb, B. The Specific Template Activity of Chromatin. In, THE STRUCTURE AND FUNCTION OF CHROMATIN. Ciba Foundation Symposium 28. ASP (Elsevier Excerpta Medica North-Holland), Amsterdam. pp. 29-57.

1975 Axel, R., Cedar, H. and Felsenfeld, G. The structure of the globin genes in chromatin. *Biochemistry* **14**, 2489-2495.

1975 Schwartz, J.H., Eisenstadt, M.L. and Cedar, H. Metabolism of acetylcholine in the nervous system of *Aplysia californica*. I. Source and uptake of choline. *J. Gen. Physiol.* **65**, 255-273.

1975 Cedar, H. Transcription of DNA and chromatin with calf thymus RNA polymerase B in vitro. *J. Mol. Biol.* **95**, 257-269.

1976 Cedar, H. Annealing and hybridization properties of *Herpes simplex* virus type 1 DNA. *J. Gen. Virol.* **32**, 337-347.

1976 Bloch, S. and Cedar, H. Methylation of chromatin DNA. *Nucleic Acids Res.* **3**, 1507-1519.

1976 Cedar, H., Solage, A. and Zurucki, F. Control of RNA synthesis by chromatin proteins. *Nucleic Acids Res.* **3**, 1659-1670.

1976 Solage, A. and Cedar, H. The kinetics of *E. coli* RNA polymerase. *Nucleic Acids Res.* **3**, 2207-2222.

1976 Solage, A. and Cedar, H. RNA chain elongation on a chromatin template. *Nucleic Acids Res.* **3**, 2223-2231.

1977 Panet, A. and Cedar, H. Selective degradation of integrated murine leukemia proviral DNA by deoxyribonucleases. *Cell* **11**, 933-940.

1977 Razin, A. and Cedar, H. Distribution of 5-methylcytosine in chromatin. *Proc. Natl. Acad. Sci. USA* **74**, 2725-2728.

1978 Weinstock, R., Sweet, R., Weiss, M., Cedar, H. and Axel, R. Intragenic DNA spacers interrupt the ovalbumin gene. *Proc. Natl. Acad. Sci. USA* **75**, 1299-1303.

1978 Garel, A., Weinstock, R., Sweet, R., Cedar, H. and Axel, R. The organization of the ovalbumin gene in the chromosome. *THE CELL NUCLEUS VI, Chromatin Part C*, Academic Press (Harris Busch, ed.), New York, N.Y., p 75-93.

1978 Solage, A. and Cedar, H. The organization of 5-methylcytosine in chromosomal DNA. *Biochemistry* **17**, 2934-2938.

1978 Panet, A. and Cedar, H. Arrangement of Murine leukemia proviral genes integrated in chromatin. *Adv. in Comp. Leukemia Res.* 1977, Editors Bentvelzen et al., Elsevier/North-Holland Biomedical Press. pp 446-447.

1979 Levitt, A., Axel, R. and Cedar, H. Nick translation of active genes in intact nuclei. *Dev. Biol.* **69**, 496-505.

1979 Cedar, H., Solage, A., Glaser, G. and Razin, A. Direct detection of methylated cytosine in DNA by use of the restriction enzyme Mspl. *Nucleic Acids Res.* **6**, 2125-2132.

1979 Cedar, H. and Panet, A. Activation of the endogenous proviral genes in mouse cells is not followed by increased sensitivity to deoxyribonuclease I digestion. *J. Gen. Virol.* **45**, 765-770.

1980 Gazit, B., Panet, A. and Cedar, H. Reconstitution of a deoxyribonuclease I - sensitive structure on active genes. *Proc. Natl. Acad. Sci. USA* **77**, 1787-1790.

1980 Solage, A. and Cedar, H. Hybridization analysis of the methylated bases of *Escherichia coli* DNA. *Biochim. Biophys. Acta* **606**, 387-389.

1980 Guttman-Bass, N., Cedar, H. and Panet, A. Quantitation of newly synthesized virus RNA in Moloney murine leukemia virus infected cells. *J. Gen. Virol.* **48**, 341-350.

1980 Pollack, Y., Stein, R., Razin, A. and Cedar, H. Methylation of foreign sequences in eukaryotic cells. *Proc. Natl. Acad. Sci. USA* **77**, 6463-6467.

1980 Gazit, B. and Cedar, H. Nuclease sensitivity of active chromatin. *Nucleic Acids Res.* **8**, 5143-5155.

1981 Quint, A. and Cedar, H. In vitro methylation of DNA with HpaII methylase. *Nucleic Acids Res.* **9**, 633-646.

1981 Gruenbaum, Y., Stein, R., Cedar, H. and Razin, A. Methylation of CpG sequences in eukaryotic DNA. *FEBS Letters* **124**, 67-71.

1981 Naveh, T. and Cedar, H. Active gene sequences are undermethylated. *Proc. Natl. Acad. Sci. USA* **78**, 4246-4250.

1981 Gruenbaum, Y., Naveh-Many, T., Cedar, H. and Razin, A. Sequence specificity of methylation in higher plant DNA. *Nature* **292**, 860-862.

1981 Gruenbaum, Y., Cedar, H. and Razin, A. Restriction enzyme digestion of hemimethylated DNA. *Nucleic Acids Res.* **9**, 2509-2515.

1981 Vardimon, L., Kuhlmann, I., Doerfler, W. and Cedar, H. Methylation of adenovirus genes in transferred cells and in vitro-influence on the regulation of gene expression. *European J. Cell Biol.* **25**, 13-16.

1982 Stein, R., Gruenbaum, Y., Pollack, Y., Razin, A. and Cedar, H. Clonal inheritance of the pattern of DNA methylation in mouse cells. *Proc. Natl. Acad. Sci. USA* **79**, 61-65.

1982 Vardimon, L., Kressmann, A., Cedar, H., Maechler, M. and Doerfler, W. Expression of a cloned adenovirus gene is inhibited by *in vitro* methylation. *Proc. Natl. Acad. Sci. USA* **79**, 1073-1077.

1982 Gruenbaum, Y., Cedar, H. and Razin, A. Substrate and sequence specificity of a eukaryotic DNA methylase. *Nature* **295**, 620-622.

1982 Stein, R., Razin, A. and Cedar, H. In vitro methylation of the hamster APRT gene inhibits its expression in mouse L-cells. *Proc. Natl. Acad. Sci. USA* **79**, 3418-3422.

1982 Naveh-Many, T. and Cedar, H. Topographical distribution of 5-methylcytosine in animal and plant DNA. *Mol. Cell. Biol.* **2**, 758-762.

1982 Gazit, B., Cedar, H., Lerer, I. and Voss, R. Active genes are sensitive to DNaseI during metaphase. *Science* **217**, 648-650.

1983 Cedar, H., Stein, R., Gruenbaum, Y., Naveh-Many, T., Gallili-Sciaky, N. and Razin, A. Metabolism and function of DNA methylation in animal cells. *Cold Spring Harbor Symposium* **47**, 605-609.

1983 Stein, R., Sciaky-Gallili, N., Razin, A. and Cedar, H. The pattern of methylation of two genes coding for housekeeping functions. *Proc. Natl. Acad. Sci. USA* **80**, 2422-2426.

1983 Gruenbaum, Y., Szyf, M., Cedar, H. and Razin, A. Methylation of replicating and post-replicated mouse L-cell DNA. *Proc. Natl. Acad. Sci. USA* **80**, 4919-4921.

1983 Kerem, B., Goitein, R., Richler, C., Marcus, M. and Cedar, H. In situ nick-translation distinguishes between active and inactive X chromosomes. *Nature* **304**, 88-90.

1983 Keshet, E. and Cedar, H. Effect of CpG methylation on Mspl. *Nucleic Acids Res.* **11**, 3571-3580.

1984 Razin, A., Webb, C., Szyf, M., Yisraeli, J., Rosenthal, A., Naveh-Many, T., Sciaky-Gallili, N. and Cedar, H. Variations in DNA methylation during mouse cell differentiation *in vivo* and *in vitro*. *Proc. Natl. Acad. Sci. USA* **81**, 2275-2279.

1984 Razin, A. and Cedar, H. DNA methylation in eukaryotic cells. In "International Reviews of Cytobiology" **92**, 159-185.

1984 Cedar, H. DNA methylation and gene expression. In "DNA Methylation and its Biological Significance" (A. Razin, H. Cedar and A.D. Riggs, eds), Springer-Verlag Inc., N.Y., pp. 147-164.

1984 Kerem, B., Goitein, R., Diamond, G., Cedar, H. and Marcus, M. Mapping of DNasel sensitive regions on mitotic chromosomes. *Cell* **38**, 493-499.

1984 Rosenthal, A., Wright, S., Cedar, H., Flavell, R. and Grosveld, F. Regulated expression of an introduced MHC H-2K¹ gene in murine embryonal carcinoma cells. *Nature* **310**, 415-418.

1985 Keshet, I., Yisraeli, J. and Cedar, H. Effect of hybrid methylation on gene transcription. *Proc. Natl. Acad. Sci. USA* **82**, 2560-2564.

1985 Rosenthal, A., Wright, S., Quade, K., Gallimore, P., Cedar, H. and Grosveld, F. MHC H-2K gene transcription in cultured mouse embryo cells is increased following adenovirus infection. *Nature* **315**, 579-581.

1985 Jablonka, E., Goitein, R., Marcus, M. and Cedar, H. DNA hypomethylation causes an increase in DNase-I sensitivity and an advance in the time of replication of the entire inactive X chromosome. *Chromosoma* **93**, 152-156.

1985 Sperling, K., Kerem, B., Goitein, R., Kottush, V., Cedar, H. and Marcus, M. DNase-I sensitivity in facultative and constitutive heterochromatin. *Chromosoma* **93**, 38-42.

1986 Keshet, I., Lieman-Hurwitz, J. and Cedar, H. DNA methylation affects the formation of active chromatin. *Cell* **44**, 535-543.

1986 Yisraeli, J., Adelstein, R., Melloul, D., Nudel, U., Yaffe, D. and Cedar, H. Muscle-specific activation of a methylated chimeric actin gene. *Cell* **46**, 409-416.

1987 Jablonka, E., Goitein, R., Sperling, K., Cedar, H. and Marcus, M. 5-aza-C-induced changes in the time of replication of the X chromosomes of *Microtus agrestis* are followed by non-random reversion to a late pattern of replication. *Chromosoma* **95**, 81-88.

1988 Yisraeli, J., Frank, D., Razin, A. and Cedar, H. Effect of *in vitro* DNA methylation on beta-globin gene expression. *Proc. Natl. Acad. Sci. USA* **85**, 4638-4642.

1988 Selig, S., Ariel, M., Goitein, R., Marcus, M. and Cedar, H. Regulation of mouse satellite DNA replication time. *EMBO J.*, **7**, 419-426.

1988 Cedar, H. DNA methylation and gene activity. *Cell* **53**, 3-4.

1989 Handeli, S., Klar, A., Meuth, M. and Cedar, H. Mapping replication units in animal cells. *Cell* **57**, 909-920.

1989 Frank, D., Mintzer-Lichenstein, M., Paroush, Z., Bergman, Y., Shani, M. and Cedar, H. Demethylation of Genes in Animal Cells. *Philos. Trans. Royal Soc.* **326**, 241-251.

1990 Razin, A., Frank, D., Lichtenstein, M., Paroush, Z., Bergman, Y., Shani, M. and Cedar, H. Changing methylation patterns during development. In *Nucleic Acid Methylation* (Clowson, G., Willis, D., Weissbach, A. and Jones, P., eds.) *UCLA Symposia on Molecular and Cellular Biology, New Series Vol. 128*. Alan R. Liss, Inc., New York, pp. 257-274.

1990 Cedar, H. and Razin, A. DNA methylation and development (Review) *Biochim. Biophys. Acta* **1049**, 1-8.

1990 Paroush, Z., Keshet, I., Yisraeli, Y. and Cedar, H. Dynamics of demethylation and activation of the α -actin gene in myoblasts. *Cell* **63**, 1229-1237.

1991 Ariel, M., McCarey, J. and Cedar, H. Methylation patterns of testis-specific genes. *Proc. Natl. Acad. Sci. U.S.A* **88**, 2317-2321.

1991 Frank, D., Keshet, I., Shani, M., Levin, A., Razin, A. and Cedar, H. Demethylation of CpG islands in embryonic cells. *Nature* **351**, 239-241.

1991 Razin, A. and Cedar, H. DNA methylation and gene expression. *Microbiol. Rev.* **55**, 451-458.

1991 Kitsberg, D., Selig, S. and Cedar, H. Chromosome structure and eukaryotic gene organization. *Curr. Opinion Gen. Dev.* **1**, 534-537.

1992 Selig, S., Okumura, K., Ward, D.C. and Cedar, H. Delineation of DNA replication time zones by fluorescence *in situ* hybridization. *EMBO J.* **11**, 1217-1225.

1992 Kafri, T., Ariel, M., Brandeis, M., Shemer, R., Urven, L., McCarey, J., Cedar, H. and Razin, A. Developmental pattern of gene specific DNA methylation in the mouse embryo and germ line. *Genes Dev.* **6**, 705-714.

1993 Razin, A. and Cedar, H. DNA methylation and embryogenesis. In *DNA Methylation, Molecular Biology and Biological Significance* (Post, J.P. and Saluz, H.P., eds.). Birkhauser Verlag, Basel, pp. 343-357.

1993 Stoger, R., Kubicka, P., Liu, C.-G., Kafri, T., Razin, A., Cedar, H. and Barlow, D.P. Maternal-specific methylation of the imprinted mouse Igf2r locus identifies the expressed locus as carrying the imprinting signal. *Cell* **73**, 61-71.

1993 Brandeis, M., Ariel, M. and Cedar, H. Dynamics of DNA methylation during development. *BioEssays* **15**, 709-713.

1993 Brandeis, M., Kafri, T., Ariel, M., Chaillet, J.R., McCarey, J., Razin, A. and Cedar, H. The ontogeny of allele-specific methylation associated with imprinted genes in the mouse. *EMBO J.* **12**, 3669-3677.

1993 Kitsberg, D., Selig, S., Brandeis, M., Simon, I., Keshet, I., Driscoll, D.J., Nicholls, R.D. and Cedar, H. Allele specific replication timing of imprinted gene regions. *Nature* **364**, 459-463.

1993 Ariel, M., Selig, S., Brandeis, M., Kitsberg, D., Kafri, T., Weiss, A., Keshet, I., Razin, A. and Cedar, H. Allele specific structures in the mouse Igf2-H19 domain. *Cold Spring Harbor Symposium* **58**, 307-313.

1993 Kitsberg, D., Selig, S., Keshet, I. and Cedar, H. Replication structure of the human β -globin gene domain. *Nature* **366**, 588-590.

1994 Lichtenstein, M., Keini, G., Cedar, H. and Bergman, Y. B-cell specific demethylation: a new role for the intronic κ -chain enhancer sequence. *Cell* **76**, 913-923.

1994 Razin, A. and Cedar, H. DNA methylation and genomic imprinting. *Cell* **77**, 473-476.

1994 Ariel, M., Cedar, H., and McCarrey, J. Developmental changes in methylation of spermatogenesis-specific genes include reprogramming in the epididymis. *Nature Genet.* **7**, 59-63.

1994 Eden, S. and Cedar, H. Role of DNA methylation in the regulation of transcription. *Curr. Op. Genet. Dev.* **4**, 255-259.

1994 Chess, A., Simon, I., Cedar, H. and Axel, R. Allelic inactivation regulates olfactory receptor gene expression. *Cell* **78**, 823-834.

1994 Brandeis, M., Frank, D., Keshet, I., Siegfried, Z., Mendelsohn, M., Nemes, A., Temper, V., Razin, A. and Cedar, H. Sp1 elements protect a CpG island from de novo methylation. *Nature* **371**, 435-438.

1995 Simon, I. and Cedar, H. Regional regulation of allele-specific gene expression. In: *Genomic Imprinting, Causes and Consequences*. (R. Ohlsson, K. Hall and M. Ritzen, ed.). Cambridge University Press. pp. 195-206.

1995 Ariel, M., Robinson, E., McCarrey, J.R. and Cedar, H. Gamete-specific methylation imprints on the Xist gene. *Nature Genet.* **9**, 312-315.

1995 Eden, S. and Cedar, H. Genomic imprinting: action at a distance (News and Views). *Nature* **375**, 16-17.

1996 Simon, I. and Cedar, H. Temporal order of DNA replication. In: *DNA Replication in Eukaryotic Cells* (M.L. DePamphilis, ed.). Cold Spring Harbor Laboratory Press, 387-408.

1996 Weiss, A., Keshet, I., Razin, A. and Cedar H. DNA demethylation in vitro: involvement of RNA. *Cell* **86**, 709-718.

1996 Kistler, B., Kirillov, A., Mostoslavsky, R., Cedar, H., Wirth, T. and Bergman, Y. A role for nuclear NF- κ B in B cell specific demethylation of the Ig κ locus. *Nature Genet.* **13**, 435-441.

1997 Siegfried, Z. and Cedar, H. DNA methylation: A molecular lock. *Curr. Biol.* **7**, R305-R307.

1997 Weiss, A. and Cedar, H. The role of DNA demethylation during development. *Genes to Cells* **2**, 481-486.

1998 Mostoslavsky, R., Singh, N., Kirillov, A., Pelanda, R., Cedar, H., Chess, A. and Bergman, Y. κ chain monoallelic demethylation and the establishment of allelic exclusion. *Genes Dev.* **12**, 1801-1811.

1998 Eden, S., Hashimshony, T., Keshet, I., Thorne, A.W. and Cedar, H. DNA methylation models histone acetylation. *Nature* **394**, 842-843.

1998 Swisher, J. F., Rand, E., Cedar, H., and Pyle, A.M. Analysis of putative RNase sensitivity and protease insensitivity of demethylation activity in extracts from rat myoblasts. *Nucleic Acids Res.* **26**, 5573-5580.

1999 Cedar, H. and Verdine, G.L. The amazing demethylase. *Nature* **397**, 568-569.

1999 Siegfried, Z., Eden, S., Mendelsohn, M., Feng, X., Tzubari, B. and Cedar, H. DNA methylation represses transcription in vivo. *Nature Genet.* **22**, 203-206.

1999 Simon, I., Tenzen, T., Reubinoff, B.E., Hillman, D., McCarrey, J.R. and Cedar, H. Asynchronous replication of imprinted genes is established in the gametes and maintained during development. *Nature*, **401**, 929-932.

1999 Cedar, H. and Bergman, Y. Developmental regulation of immune system gene rearrangement. *Curr. Opin. Immunol.* **11**, 64-69.

1999 Mostoslavsky, R., Kirillov, A., Ji, Y.-H., Goldmit, M., Holzman, M., Wirth, T., Cedar, H. and Bergman, Y. Demethylation and the establishment of κ allelic exclusion. *Cold Spring Harbor Symp. Quant. Biol.* **64**, 197-206.

2000 Shemer, R., Hershko, A.Y., Perk, J., Mostoslavsky, R., Tsuberi, B.-Z., Cedar, H., Buiting, K. and Razin, A. The imprinting box of the Prader-Willi/Angelman Syndrome domain. *Nature Genet.* **26**, 440-443.

2000 Rhoades, K.L., Singh, N., Simon, I., Glidden, B., Cedar, H. and Chess, A. Allele-specific expression patterns of interleukin-2 and Pax-5 revealed by a sensitive single-cell RT-PCR analysis. *Curr. Biol.* **10**, 789-792.

2000 Ben-Porath, I., and Cedar, H. Imprinting -- focusing on the center. *Curr. Op. Genet. Dev.* **5**, 550-554.

2001 Eden, S., Constancia, M., Hashimshony, T., Dean, W., Goldstein, B., Johnson, A.C., Keshet, I., Reik, W. and Cedar, H. An upstream repressor element plays a role in Igf2 imprinting. *EMBO J.* **20**, 3518-3525.

2001 Simon, I., Tenzen, T., Mostoslavsky, R., Fibach, E., Lande, L., Milot, E., Gribnau, J., Grosveld, F., Fraser, P. and Cedar, H.. Developmental regulation of DNA replication timing at the human β globin locus. *EMBO J.* **20**, 6150-6157.

2001 Mostoslavsky, R., Singh, N., Tenzen, T., Goldmit, M., Gabay, C., Elizur, S., Qi, P., Reubinoff, B.E., Chess, A., Cedar, H., and Bergman, Y. Asynchronous replication and allelic exclusion in the immune system. *Nature* **441**, 221-225.

2001 Ben-Porath, I. and Cedar, H. "Epigenetic crosstalk." *Mol. Cell* **8**, 1-2.

2002 Perk, J., Lande, L., Cedar, H., Razin, A. and Shemer, R. On the imprinting mechanism of the Prader Will/Angelman regional control center. *EMBO J.* **21**, 5807-5814.

2002 Goldmit, M., Schlissel, M., Cedar, H. and Bergman, Y. Differential accessibility at the κ chain locus plays a role in allelic exclusion. *EMBO J.* **21**, 5255-5261.

2002 Rand, E. and Cedar, H. Regulation of imprinting: a multi-tiered process. *J. Cellular Biochem.* **88**, 400-407.

2002 Zhang, J., Feng, X., Hashimshony, T., Keshet, I. and Cedar, H. The establishment of transcriptional competence in early and late S-phase. *Nature* **420**, 198-202.

2002 Goren, A. and Cedar, H. Replicating by the clock. *Nature Rev. Mol. Cell Biol.* **4**, 25-32.

2003 Hashimshony, T., Zhang, J., Keshet, I., Bustin, M. and Cedar, H. The role of DNA methylation in setting up chromatin structure during development. *Nature Genet.* **34**, 187-192.

2003 Singh, N., Bergman, Y., Cedar, H. and Chess, A. Biallelic germline transcription at the κ immunoglobulin locus. *J. Exp. Med.* **197**, 743-750.

2003 Bergman, Y., Fisher, A.G. & Cedar, H. Epigenetic mechanisms that regulate antigen receptor gene expression. *Curr. Opin. Immunol.* **15**, 176-181.

2003 Ji, Y., Zhang, J., Lee, A.I., Cedar, H. and Bergman, Y. A multi step mechanism for the activation of rearrangement in the immune system. *Proc. Natl. Acad. Sci. USA* **100**, 7557-7562.

2004 Rand, E., Ben-Porath, I., Keshet, I. and Cedar, H. CTCF elements direct allele specific undermethylation at the imprinted H19 locus. *Curr. Biol.* **14**, 1007-1012.

2004 Lande-Diner, L., Zhang, J., Hashimshony, T., Goren, A., Keshet, I., and Cedar, H. Gene repression paradigms in animal cells. *Cold Spring Harbor Symp. Quant. Biol.* **69**, 1-8.

2004 Bergman, Y., and Cedar, H. A step-wise epigenetic process controls immunoglobulin allelic exclusion. *Nature Rev. Immunol.* **4**, 753-761.

2005 Goldmit, M., J. Yanhong, J. Skok, E. Roldan, S. Jung, H. Cedar, and Y. Bergman. Epigenetic ontogeny of the κ locus during B cell development. *Nature Immunol.* **6**, 198-203.

2005 Lande-Diner, L. and Cedar, H. Silence of the Genes – mechanisms of long term repression. *Nature Rev. Genet.* **6**, 648-654.

2006 Keshet, I., Schlesinger, Y., Farkash, S., Rand, E., Hecht, M., Segal, E., Pikarski, E., Young, R.A., Niveleau, A., Cedar, H. and Simon, I. Evidence for an instructive mechanism of de novo methylation in cancer cells. *Nature Genet.* **38**, 149-153.

2006 Feldman, N., Gerson, A., Fang, J., Li, E., Zhang, Y., Shinkai, Y., Cedar, H. and Bergman, Y. G9a-mediated irreversible epigenetic inactivation of Oct-3/4 during early embryogenesis. *Nature Cell Biol.* **8**, 188-194.

2006 Goren, A., Simchen, G., Fibach, E., Szabo, P.E., Tanimoto, K., Chakalova, L., Pfeifer, G.P., Fraser, P.J., Engel, J.D. and Cedar, H. Fine Tuning of Globin Gene Expression by DNA Methylation. *PLoS ONE* **1**, e46.

2007 Schlesinger, Y., Straussman, R., Keshet, I., Farkash, S., Hecht, M., Zimmerman, J., Eden, E., Yakhini, Z., Ben-Shushan, E., Reubinoff, B.E., Bergman, Y., Simon, I. and Cedar, H. Polycomb mediated histone H3(K27) methylation pre-marks genes for de novo methylation in cancer. *Nature Genet.* **39**, 232-239.

2007 Lande-Diner, L., Zhang, J., Ben-Porath, I., Amariglio, N., Keshet, I., Hecht, M., Azuara, V., Fisher, A.G., Rechavi, G. and Cedar, H. Role of DNA methylation in stable gene repression. *J. Biol. Chem.* **282**, 12194-12200.

2007 Fraenkel, S., Mostoslavsky, R., Novobrantseva, T.I., Pelada, R., Chaudhuri, J., Esposito, G., Jung, S., Alt, F.W., Rajewsky, K., Cedar, H. and Bergman, Y. Allelic choice governs somatic hypermutation at the Ig κ locus in vivo. *Nature Immunol.* **8**, 715-722.

2008 Goren, A., Tabib, A., Hecht, M. and Cedar, H. DNA replication timing of the human β globin domain is controlled by histone modification at the origin. *Genes Dev.* **22**, 1319-1324.

2008 Cedar, H. & Bergman, Y. Choreography of Ig allelic exclusion. *Curr. Opin. Immunol.* **20**, 308-317.

2008 Epsztejn-Litman, S., Feldman, N., Abu-Remaileh, M., Shufaro, Y., Gerson, A., Ueda, J., Deplus, R., Fuks, F., Shinkai, Y., Cedar, H. and Bergman, Y. G9a-mediated de novo methylation is necessary and sufficient to prevent embryonically-silenced gene reprogramming. *Nature Struct. Mol. Biol.* **15**, 1176-1183.

2009 Bergman, Y. and Cedar, H. Linking DNA methylation and histone modification: patterns and paradigms. *Nature Rev. Genet.* **10**, 295-304.

2009 Lande-Diner, L., Zhang, J. and Cedar, H. Shifts in replication timing actively affect histone acetylation during nucleosome reassembly. *Mol. Cell.* **34**, 767-774.

2009 Straussman, R., Nejman, D., Roberts, D., Steinfeld, I., Blum, B., Benvenisty, N., Simon, I., Yakhini, Z., and Cedar, H. Developmental programming of CpG island methylation profiles in the human genome. *Nature Struct. Mol. Biol.* **16**, 564-571.

2009 Schlesinger, S., Selig, S., Bergman, Y. and Cedar, H. Allelic inactivation of rDNA loci. *Genes Dev.* **23**, 2437-2447.

2009 Cedar, H. and Bergman, Y. Epigenetic silencing during early lineage commitment. *StemBook* [Internet]

2010 Shufaro, Y., Lacham-Kaplan, O., Tzuberi, B.-Z., McLaughlin, J., Trounson, A., Cedar, H. and Reubinoff, B.E. Reprogramming of DNA replication timing. *Stem Cells*, **28**, 443-449.

2010 Bergman, Y. and Cedar, H. Epigenetic control of recombination in the immune system. *Semin. Immunol.* **22**, 323-329.

2011 Cedar, H. and Bergman, Y. Epigenetics of hematopoietic cell development. *Nature Rev. Immun.* **11**, 478-488.

2012 Cedar, H. and Bergman, Y. Programming of DNA Methylation Patterns. *Annu. Rev. Biochem.* **81**, 97-117.

2012 Farago, M., Rosenbluh, C., Tevlin, M., Fraenkel, S., Schlesinger, S., Masika, H., Gouzman, M., Teng, G., Schatz, D., Rais, Y., Hanna, J.H., Mildner, A., Jung, S., Mostoslavsky, G., Cedar, H. and Bergman, Y. Clonal allelic predetermination of immunoglobulin-kappa rearrangement. *Nature* **490**, 561-565.

2013 Bergman, Y., Cedar, H. DNA methylation dynamics in health and disease. *Nature Struct. Mol. Biol.* **20**, 274-281.

2014 Sabag, O., Zamir, A., Keshet, I., Hecht, M., Ludwig, G., Tabib, A., Moss, J. and Howard Cedar, H. Establishment of methylation patterns in ES cells. *Nature Struct. Mol. Biol.* **21**, 110-112.

2014 Nejman, D., Straussman, R., Steinfeld, I., Ruvolo, M., Roberts, D., Yakhini, Z. and Cedar, H. Molecular rules governing de novo methylation in cancer. *Cancer Res.* **74**, 1475-1483.

2014 Ludwig, G., Nejman, D., Hecht, M., Orlanski, S., Abu-Remaileh, M., Yanuka, O., Sandler, O., Marx, A., Roberts, D., Benvenisty, N., Bergman, Y., Mendelsohn, M. and Cedar, H. Aberrant DNA methylation in ES cells. *PLOS One* **9**, e96090.

2014 Levin-Klein, R., Kirillov, A., Rosenbluh, C., Cedar, H. and Bergman, Y. A novel pax5-binding regulatory element in the igkappa locus. *Front Immunol.* **5**, 240.

2015 Reizel, Y., Spiro., A., Sabag, O., Skversky, Y., Hecht, M., Keshet, I., Berman, B.-P. and Cedar, H. Gender-specific post-natal demethylation and establishment of epigenetic memory. *Genes Dev.* **29**, 923-933.

2015 Stoyanov, E., Ludwig, G., Mizrahi, L., Olam, D., Schnitzer-Perlman, T., Tasika, E., Sass, G., Tiegs, G., Jiang, Y., Nie, T., Kohler, J., Schinazi, R.F., Vertino, P.M., Cedar, H., Galun, E. and Goldenberg, D. Chronic liver inflammation modifies DNA methylation at the precancerous stage of murine hepatocarcinogenesis. *Oncotarget* **6**, 11047-11060.

2016 Almouzni, G. and Cedar, H.. Maintenance of epigenetic information. In *Epigenetics, Second Edition.* (Allis, C. D., Caparros, M.-L., Jenuwein, T., Reinberg, D. and Lachlan, M., ed.). Cold Spring Harbor Laboratory Press, pp 575-597.

2016 Lehmann-Werman, R., Neiman, D., Zemmour, H., Moss, J., Magenheimer, J., Vaknin-Dembinsky, A., Rubertsson, S., Nellgård, B., Blennow, K., Zetterberg, H., Spalding, K., Haller, M., Wasserfall, C., Schatz, D., Greenbaum, C., Dorell, C., Grompe, M., Zick, A., Hubert, A., Maoz, M., Fendrich, V., Bartsch, D.K., Golan, T., Ben-Sasson, S., Zamir, G., Razin, A., Cedar, H., Shapiro, A.M.J., Glaser, B., Shemer, R. and Dor, Y. Identification of tissue specific cell death using methylation patterns of circulating DNA. *Proc. Natl. Acad. Sci. USA*, **113**, E1826-1834.

2016 Orlanski, S., Labi, V., Reizel, Y., Spiro, A., Lichtenstein, M., Levin-Klein, R., Koralov, S., Skversky, Y., Rajewsky, K., Cedar, H. and Bergman, Y. Tissue-specific DNA demethylation is required for proper B-cell differentiation and function. *Proc. Natl. Acad. Sci. U.S.A.* **113**, 5018-5023.

2016 Klutstein, M., Nejman, D., Greenfield, R., Cedar, H. DNA methylation in cancer and aging. *Cancer Res.* **12**, 3446-3450.

2017 Klutstein, M., Moss, J., Kaplan, T., Cedar, H. Contribution of epigenetic mechanisms to variation in cancer risk among tissues. *Proc. Natl. Acad. Sci. U.S.A.* **114**, 2230-2234.

2017 Levin-Klein, R., Fraenkel, S., Lichtenstein, M., Matheson, L.S., Bartok, O., Nevo, Y., Kadener, S., Corcoran, A.E., Cedar, H. and Bergman, Y. Clonally stable Vkappa allelic choice instructs Igkappa repertoire. *Nature Commun.* **8**, 15575.

2017 Masika, H., Farago, M., Hecht, M., Condiotti, R., Makedonski, K., Buganim, Y., Burstyn-Cohen, T., Bergman, Y. and Cedar, H. Programming asynchronous replication in stem cells. *Nature Struct. Mol. Biol.* **24**, 1132-1138.

2017 Neiman, D., Moss, J., Hecht, M., Magenheimer, J., Piyanzin, S., Shapiro, A.M.J., de Koning, E.J.P., Razin, A., Cedar, H., Shemer, R. and Dor, Y. Islet cells share promoter hypomethylation independently of expression, but exhibit cell-type-specific methylation in enhancers. *Proc. Natl. Acad. Sci. U.S.A.* **114**, 13525-13530.

2017 Hecht, M., Tabib, A., Kahan, T., Orlanski, S., Gropp, M., Tabach, Y., Yanuka, O., Benvenisty, N., Keshet, I. and Cedar, H. Epigenetic mechanism of FMR1 inactivation in Fragile X syndrome. *Int. J. Dev. Biol.* **61**, 285-292.

2017 Cedar, H. and Razin, A. Annotating the genome by DNA methylation. *Int. J. Dev. Biol.* **61**, 137-148.

2018 Reizel, Y., Sabag, O., Skversky, Y., Spiro, A., Steinberg, B., Bernstein, D., Wang, A., Keickhaefer, J., Li, C., Pikarsky, E., Levin-Klein, R., Goren, A., Rajewsky, K., Kaestner, K.H. and Cedar, H. Postnatal DNA demethylation and its role in tissue maturation. *Nature Comm.* **9**, 2040-2050.

2018 Dor, Y. and Cedar, H. Principles of DNA methylation and their implications for biology and medicine. *The Lancet* **392**, 777-786.

2018 Greenfield, R., Tabib, A., Moss, J., Sabag, O., Goren, A. and Cedar, H. Role of transcription complexes in the formation of the basal methylation pattern in early development. *Proc. Natl. Acad. Sci. U.S.A.* **115**, 10387-10391.

2021 Blumenfeld, B., Masika, H., Farago, M., Yehuda, Y., Halaseh, L., Vardi, O., Rapoport, R., Levin-Klein, R., Cedar, H., Bergman, Y., Simon, I. Chromosomal coordination and differential structure of asynchronous replicating regions. *Nature Comm.* **12**, Article number:1035.

2021 Bergman, Y., Simon, I., and Cedar, H. Asynchronous replication timing: A mechanism for monoallelic choice during development. *Front. Cell Dev. Biol.* **9**, Article 737681.

2022 Cedar, H., Sabag, O., and Reizel, Y. The role of DNA methylation in genome-wide gene regulation during development. *Development* **149**(2):dev200118.

2022 Falick Michaeli, T., Sabag, O., Fok, R., Azria, B., Monin, J., Nevo, Y., Gielchinsky, Y., Berman, B.P., Cedar, H., and Bergman, Y. Muscle injury causes long-term changes in stem-cell DNA methylation. *Proc. Natl. Acad. Sci. U.S.A.* **119**(52):e2212306119.