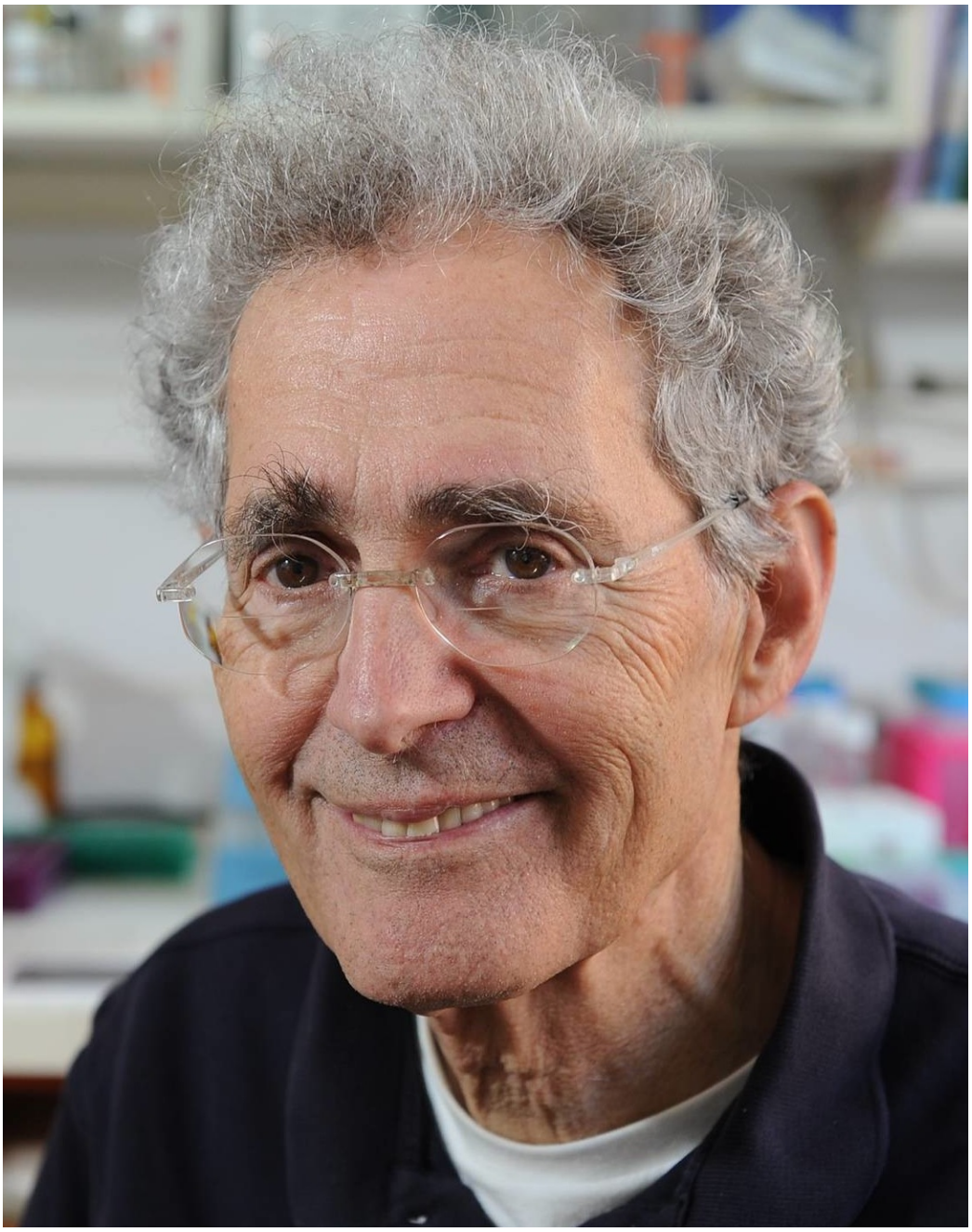

Professor Howard Cedar
Professor Emeritus
Faculty of Medicine
Hebrew University of Jerusalem
Israel

האוניברסיטה העברית בירושלים
THE HEBREW UNIVERSITY OF JERUSALEM

Prof. Eli Pikarsky | Dean | Faculty of Medicine
Brandman Foundation Chair in Cardiac and Pulmonary Disease
פרופ' אלי פיקרסקי | דיקן | הפקולטה לרפואה
הקתדרה ע"ש ברנדמן למחלות לב וריאה

November 20, 2023

I am pleased to nominate Prof. Howard Cedar for the 2024 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. Remarkably, Cedar's elucidation of DNA methylation paved the way for groundbreaking extensions to other chemical modifications of DNA, the associated proteins, and a diverse array of RNA molecules, significantly amplifying the fundamental importance of this pioneering discovery.

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.

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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 groundbreaking research and is highly worthy of this award.

Prof. Eli Pikarsky
Dean

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Institute for Medical Research Israel-Canada
INNOVATIONS TOUCHING LIVES

November 14, 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 2024 "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)

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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 maternal 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 founds 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 2024 "Albert Einstein" World Award of Science.

Sincerely,

Yuval Dor

Yuval Dor

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COLUMBIA UNIVERSITY
MORTIMER B. ZUCKERMAN MIND BRAIN BEHAVIOR INSTITUTE

RICHARD AXEL, M.D.
UNIVERSITY PROFESSOR

November 14, 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 2024 "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

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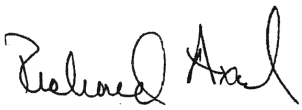
front of housekeeping genes. Specific demethylases are then responsible for removing methyl groups from tissue-specific genes only in appropriate tissues at appropriate times in development. Moreover, he has shown that a special class of genes that exhibit genomic imprinting is differentially methylated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



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.

Howard Cedar, M.D., Ph.D. **November, 2023**

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:

1973 - present	Lecturer, Senior Lecturer, Associate Professor, Professor, Hebrew University Medical School.
1971 - 1973	Research Associate, USPHS, National Institutes of Health with Dr. Gary Felsenfeld.
1970 - 1971	Fellow, Public Health Research Institute of NYC with Drs. James H. Schwartz and Eric R. Kandel.
1970 - 1971	Intern, New York University School of Medicine.

AWARDS:

1979	Hestrin Prize for Biochemistry.
1982	Member European Molecular Biology Organization
1991	Hebrew University Outstanding Investigator
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	Gairdner International Award
2012	Rothschild Prize in Biology
2016	Louisa Gross Horwitz Prize
2018	Pollack Prize
2022	Member, U.S. 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.

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Dr. Howard Cedar

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