



Nobel Laureate David Baltimore a Revolutionary Molecular Biologist is No More: To Pay Homage a Brief Coverage of His Scientific Contribution with Precision

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Abstract

Nobel laureate David Baltimore an eminent virologist turned molecular biologist celebrated for his discovery of the enzyme reverse transcriptase, passed away on 6th September 2025. To pay tribute a deliberate attempt to explain his contribution in science.

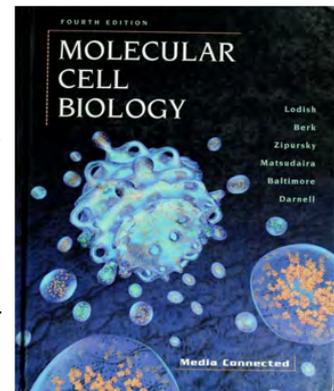
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Introduction

Enzyme discovery a memorable history

Nobel laureate David Baltimore, an international celebrity in biomedical research is no longer with us. Born in Manhattan, New York City, on March 7, 1938, David Baltimore, son of Richard and Gertrude (Lipschitz) Baltimore, passed away from cancer on 6th September 2025, at the age of 87 in Massachusetts. There is no denying that most of graduate students working

around molecular biology research are aware with David Baltimore's name and have probably gone through a Text book titled "Molecular Cell Biology" co-authored by David Baltimore. Earlier it was taken into granted that according to central dogma of life genetic information flows only in one direction from DNA to RNA to proteins, and never in reverse way as voiced by Francis Crick [1]. In 1970, David Baltimore at Massachusetts Institute of Technology (MIT), who concurrently but independently with Howard Temin from the University of Wisconsin discovered that murine leukaemia virus possesses an enzyme called reverse transcriptase, which could make a DNA copy from RNA template [2]. This discovery must also be familiar to medical and veterinary professionals, as Baltimore exclusively worked on animal viruses to establish his findings. Majority of scientists considered this proposal as deviation as it was conflicting with central dogma of life. In some viruses



Baltimore was able to find the flow went the other way and RNA became DNA with the help of the reverse transcriptase (RT) enzyme. One can say this was the most incredible scientific moment of the second half of the 20th century [3]. Regarding David Baltimore there is so much to say, so to pay tribute to him we will just hit the highlights here.

Curious about virus

Since early 1900s it is known that virus is one form of life that carry a genetic material either DNA or RNA as its genome. Virus needs simple basic requirement for transmission of its genome from generation to generation and a messenger RNA (mRNA) that direct the synthesis of essential viral proteins such as nucleoprotein (coat the genome) and replicase (help in genome replication) has been established century ago. Viral genetic system comprises of two major arms one is replication and another is transcription. Virus uses cellular ribosome and soluble factors to translate their mRNA has been authenticated by David Baltimore [4]. As on today with the advancement of DNA science we know that “what’s true for *E coli* is also true for the elephant.” In a simplified term we can say the fundamental unit of life science can be learned by dissecting, inexpensive, and easy to manipulate bacterial and viral genome as model systems. In the year 1975 David Baltimore shared Noble Prize in Medicine and Physiology along with two other recipients, Renato Dulbecco, and Howard Martin Temin “for their discoveries concerning the interaction between tumour viruses and the genetic material of the cell [5].

Time before Baltimore

Much earlier published work of Baltimore, in 1910 a women brought a hen having a large tumour to Rockefeller Institute, New York (now Rockefeller University). At that time Francis Peyton Rous who was working at Rockefeller Institute showed interest to investigate the reason behind the tumour. He used cell free tumour extract free from bacterial contaminant to confirm the transmissibility of tumour production in heathy chicken and observed tumour inducing agent was no other than a virus [6]. Initially oncogenic character of virus was harshly criticized. However, as multiple reports demonstrated that inoculating cell-free extract of tumour tissue may cause the onset of murine cancer, viral oncogenicity eventually gained scientific support [7]. According to the name of Francis Peyton Rous the virus has been named as Rous sarcoma virus (RSV) that can induce soft tissue tumour called sarcoma. It took 55 years for Peyton Rous to get the Nobel Prize for his discovery [8]. Oncogenes were confirmed when Rous demonstrated that certain malignancies have an infectious genesis. However, till that time oncogene were not established. Following this, several researchers became interested in RSV; in the end, Harold E. Varmus and J. Michael Bishop were given the Nobel Prize in 1989 for discovering the cellular genesis of the retroviral oncogenes, and Howard M. Temin and David Baltimore in 1975 for reverse transcriptase [9].

transcription and virus replication

The process of transferring information from a DNA strand into a new messenger RNA (mRNA) molecule referred to as transcription. Contrary to it the synthesis of DNA from an RNA template is known as reverse transcription. Reverse transcriptase (RTs) is the enzyme that mediates reverse transcription process. In terms of biochemistry, RTs are RNA-dependent DNA polymerases. Both prokaryotic and eukaryotic species, as well as retroviruses, possess reverse transcriptase. Reverse transcriptase has been detected in many organisms, including bacteria, viruses, animals, as well as in plants. Significance of reverse transcription has been observed in propagation of retroviruses, genetic diversity in eukaryotes via retrotransposons [10].

Carrier of Nobel Prize winner

Baltimore was excelling in mathematics as a student, but he soon became fascinated with biological science. Baltimore’s mother accidentally noticed a bulletin board displaying about a high school program being hosted at the Jackson Laboratory (Jax Lab) in Bar Harbor, Maine, during an upcoming summer when he was a junior in high school. After that, he applied and got admitted. He made the decision to focus on experimental biology for the remainder of his

life after witnessing research biologists in action and experiencing biology in real-world research settings at Jax Lab. He aspired to pursue a career as an experimental biologist because of his mother [11]. Due to this early encounter, he decided to major in biology at Swarthmore College in Pennsylvania, but subsequently he switched to chemistry for his research thesis. During a summer course at Swarthmore



College (1956–1960), he had the chance to collaborate with Dr. George Streisinger at Cold Spring Harbor Laboratories. In 1960 he obtained B.A. honours in Chemistry. Working experience with great teacher George Streisinger ignited his mind to become a molecular biologist. The influential teacher George Streisinger was a well-known geneticist trained under Salvador Edward Luria the Nobel Laureate of 1965. George Streisinger made significant contributions to the T-even bacteriophage's genetic makeup. By illustrating the effects of frameshift mutations, he established vital connections between genetics and biochemistry [12]. David Baltimore opted for biophysics, so he moved to Massachusetts Institute of Technology (MIT). Later he developed curiosity about animal viruses and joined a summer course with Dr. Philip Marcus at the Albert Einstein College of Medicine in New York. He continued by choosing to

enrol in additional animal virus courses; thus, he moved to Cold Spring Harbor to do so under Drs. Richard Franklin and Edward Simon. The main theme of his doctoral study was the replication of poliovirus as a model of RNA virus. Following the submission of his doctoral thesis under the mentorship of Dr. Franklin at Rockefeller Institute (1961-1964), Baltimore contributed as a postdoctoral fellow with Dr. James Darnell to continue his research interest in animal virology. In 1965 he was hired as a research associate at the Salk Institute of Biological Studies marking his first independent position. There he started his first laboratory and continued to study how the virus-infected cells become factories for virus production. His focus was on viral RNA synthesis. After a couple of years, he received an offer from Salva to return to MIT as an Associate Professor. He worked there along with several postdocs and graduate students for another 30 years, commencing on January 1, 1968 [11]. While working around he met fellow scientist, Alice S. Huang, and the two tied the knot in marriage on October 5, 1968. In 1972 Baltimore was appointed as a full-time professorship at MIT. In 1974 he joined the staff of the MIT Centre for Cancer Research under Salvador Luria [13]. There he got an opportunity for working with Renato Dulbecco with whom he shared Nobel Prize in 1975.

Innovation and publication

At the age of 32 he published a paper in Nature reporting the evidence of an enzyme in tumour causing RNA virus which synthesizes DNA from an RNA template, that has made a turning

point in DNA science to contradict the central dogma of life voiced earlier [1]. In the same year along with his wife Alice Huang he published another manuscript describing how a defective viral particle comprising of viral protein and incomplete viral genomic content is capable to interfere with the growth of homologous, standard virus and may play a major part in the evolution of viral diseases [14]. In one of his articles published in the year 1971 he placed his thought about viral genetic systems and classified the viruses into six classes: double-stranded DNA viruses, single-stranded DNA viruses, double-stranded RNA viruses, positive-strand RNA viruses, negative-strand RNA viruses, and retroviruses (having reverse transcriptase). Till that period virus classification had used a Linnean system of great complexity. Due to simplification, students grasped it easily and kept it in mind the key aspects of different types of viruses. Thereafter it became popular as the Baltimore classification [4]. Much before the tumour inducing nature of retrovirus was published by Baltimore, the experiment conducted by Renato Dulbecco in 1964 demonstrated that the DNA of the tumour-inducing SV40 can integrate into the DNA of the host cell, a critical step in changing the growth of the cell from normal to malignant [15]. David Baltimore later independently discovered that viral RNA can also be incorporated into host cells' DNA because of the existence of the virus-originated RT enzyme, which allows the information contained in viral RNA to be transferred to DNA. In MIT one of his team mate Alice Huang (his wife), had prior expertise on vesicular stomatitis virus (VSV) so after arriving at MIT, Baltimore decided to include VSV along

with polio virus in their work. They quickly observed that the mode of infection of polio virus was quite different than VSV. Polio virus having sense strand of RNA so during infection it inject the cell with a new messenger RNA, whereas in case of VSV it was antisense, or negative, strand in its infectious particles [16]. They assessed for this polymerase, and confirmed its presence in the virus particle [17].

The most persuasive and well-established argument was that genetic information could only be transferred in one direction, from DNA to RNA and then to protein. As a result, the new discovery from Baltimore's lab went against the accepted norm in biological science and was previously thought to be impossible for over two decades [18]. Baltimore continued to work with retroviruses for several years before turning his focus to immunology. One of his favourite challenges in immunology has been allelic exclusion. He was curious to explore how does a B cell know to stop rearrangement of immunoglobulin gene after successfully rearranging so that only one of its heavy chain loci and then one of its light chain loci is expressed? In later part of his active research Baltimore and his students initiated in cloning of recombination-activating genes (RAG genes) responsible for immunoglobulin gene diversity in mammals. David could able to demonstrate that human DNA encoding the RAG activity could be transferred in to 3T3 mouse embryonic fibroblast [19,20].

Institute development and social commitment

In 1982 David Baltimore initiated the launch of the Whitehead Institute for Biomedical Research at the Massachusetts Institute of Technology (MIT) with the support of private donation from the businessman Jack Whitehead. That institute has played contributory role in the Human Genome Project. In 2023, the Whitehead Institute established the endowed David Baltimore Chair in Biomedical Research, honouring Baltimore's six decades of scientific and academic contribution. During his tenure (1997 to 2006) as the president he led various fundraising initiatives for the biological sciences at California Institute of Technology (Caltech). Simultaneously, he initiated diversity, equity and inclusion policies in campus and brought more women into administrative roles [21].

Repute with petty dispute

In 1990 he had to depart MIT and Whitehead Institute to chair as President of the Rockefeller Institute New York. He crowned that

position through 1991, when a case of scientific misconduct against one of his associates damaged his reputation, forcing him to step down [22]. Baltimore has received numerous honours throughout his life, including the Nobel Prize however an unexpectedly controversial case of scientific misconduct in one of his studies published in *Cell* became public [23]. The debatable paper described the "altered repertoire of endogenous immunoglobulin gene expression mimicking the idotype of the transgene" was later retracted by the editor due to certain flaw in raw data (*Cell* 1991;65(4):536).

Rather than Baltimore himself, the work done by the co-author immunologist Thereza Imanishi-Kari remained in the centre of "David Baltimore fraud case". Upon being found guilty simply of sloppy science, Imanishi-Kari was reinstated in her Boston position. The US immunological establishment ultimately disagreed regarding responsibility or innocence after seven investigations that lasted for ten years, protecting Baltimore's respect and reputation [24]. During 2008 in an interview the anchor Errol Clive Friedberg an influential DNA repair scientist (deceased March 2023), who was the first Editor-in-Chief of the journal *DNA Repair* asked a tough question to David Baltimore; whether the incidence of scientific fraud is increasing? Baltimore replied "I am not sure; my impression is that most scientists are rigorously honest and sometimes honest errors are unfortunately labelled as fraud. So, one must be careful in that regard". [25].

Tribute for his attributes

David Baltimore's life is filled with wonderful experiments ended with glorious events. He has dedicated his entire life in biomedical research. Throughout his career, he authored more than 600 scholarly articles. The 2021 Lasker-Koshland Special Achievement Award in Medical Science often called as America's Nobels was awarded to David Baltimore. He is well-known for his diverse work on areas ranging from viral replication to allelic exclusion in immunoglobulin gene rearrangement following how transcription factor NF- κ B drives inflammation and many more in this line. We sincerely apologize for our inability to accommodate every aspect of his accomplishments in this brief report, yet we have taken it as an opportunity to pay tribute to David Baltimore from the scientific community.

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