Total Synthesis of a Tyrosine Suppressor tRNA: the Work of H. Gobind Khorana


Har Gobind Khorana was born in 1922 in Raipur, a little village in Punjab, which is now part of eastern Pakistan. Although his family was poor, his father was committed to educating his children, and as a result they were practically the only literate family in the village of about 100 people. Khorana studied at Punjab University in Lahore where he earned a B.Sc. in 1943 and an M.Sc. in 1945 with Mahan Singh as his supervisor.

Khorana left India in 1945, when a Government of India Fellowship made it possible for him to go to England to earn a Ph.D. with Roger J. S. Beer at the University of Liverpool. After receiving his Ph.D. in 1948, Khorana spent a year at the Eidgenössische Technische Hochschule in Zurich, doing a postdoctoral fellowship with Vladimir Prelog. He then went to Cambridge University where he worked on nucleic acids with Nobel laureate Alexander R. Todd.

In 1952, Khorana took a position as director of the British Columbia Research Council's Organic Chemistry Section, located at the University of British Columbia in Vancouver. There, he and John G. Moffat developed a process for synthesizing acetyl coenzyme A relatively
cheaply, thereby making it widely available for research. Khorana remained in British Columbia for 8 years and then moved to the University of Wisconsin to become co-director of the Institute for Enzyme Research. He became a professor of biochemistry in 1962, and in 1964 was named Conrad A. Elvehjem Professor of Life Sciences. At this time, Khorana began to focus on genetics, specifically on deciphering the genetic code.

By this time, Marshall W. Nirenberg had successfully deciphered a good portion of the genetic code. Khorana added important information, such as the observation that three nucleotides specify an amino acid and that codons do not overlap, and also revealed the identities of the stop codons. Khorana also synthesized specific polynucleotides, proving that an RNA intermediary is involved in translating DNA into protein. For this work, Khorana was awarded the 1968 Nobel Prize in Physiology or Medicine, along with Robert W. Holley and Nirenberg.

In 1970, Khorana moved again, this time to Cambridge, Massachusetts to become the Alfred P. Sloan Professor of Biology and Chemistry at the Massachusetts Institute of Technology. There he focused on gene structure–gene function relationships and studies of DNA–protein interactions. To understand gene expression, he turned to DNA synthesis and sequencing and decided to synthesize the DNA sequence that coded for yeast alanine tRNA (1). In 1970, when Khorana announced this total synthesis of the first wholly artificial gene, his achievement was honored as a major landmark in molecular biology.

Although the availability of a synthetic alanine tRNA made it possible to study certain aspects of transcription and DNA enzymology, the molecule proved unsuitable for other biochemical studies such as elucidating the mechanism of transcription initiation and termination and the structure–function relationship in tRNA. To study these problems, Khorana undertook the total synthesis of the 126-nucleotide DNA for the precursor to an Escherichia coli tyrosine suppressor tRNA. His methodology involved the chemical synthesis of 26 deoxyribonucleotides, a polynucleotide ligase-catalyzed joining of several segments at a time to form a total of four DNA duplexes with appropriate complementary single-stranded ends, and the joining of the duplexes to form the entire DNA complex. Khorana published a series of 17 papers in the Journal of Biological Chemistry (JBC) describing this work (2–18). Three of the papers in this series are reprinted here as JBC Classics.

The first Classic describes the synthesis of the final two segments of the tRNA promoter. The second Classic reports on the how Khorana and his colleagues used polynucleotide kinase and polynucleotide ligase to join the 10 deoxyoligonucleotide segments to form the 62-nucleotide-long DNA corresponding to the promoter region of the tRNA gene. In the final Classic, Khorana and his colleagues show how they joined the DNA duplexes to complete the total synthesis of the gene.

In a subsequent paper, Khorana was able to successfully transcribe his synthetic gene.

Khorana currently lives in Cambridge, Massachusetts, serving as MIT’s Alfred P. Sloan Professor of Biology and Chemistry, Emeritus. His later research explored the molecular mechanisms underlying the cell signaling pathways of vision in vertebrates. His studies were concerned primarily with the structure and function of rhodopsin and the mutations in rhodopsin that are associated with retinitis pigmentosa, which causes night blindness.

In addition to the Nobel Prize, Khorana has received numerous awards and honors. These include the Merck Award from the Chemical Institute of Canada (1958), the Dannie-Heinneman Prize (1967), the Remsen Award from Johns Hopkins University (1968), the American Chemical Society Award for Creative Work in Synthetic Organic Chemistry (1968), the Louisa Gross Horwitz prize (1968), the Lasker Foundation Award for Basic Medical Research (1968), and the National Medal of Science (1987). Khorana was elected a member of the National Academy of Sciences and the American Academy of Arts and Sciences. He is also a foreign member of the USSR Academy of Sciences and an Honorary Fellow of the Indian Chemical Society.  

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