Susumo Ohno

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1 Curriculum Vitae

Susumu Ohno
February 1, 1928 – January 13, 2000; By Ernest Beutler

SUSUMU OHNO was born of Japanese parents in Seoul, Korea, on February 1, 1928. The second of five children, he was the son of the minister of education of the Japanese Viceroyship of Korea. He was born at a time when Japan was in many ways isolated from Western thought with its chief scientific links firmly established with Germany, and he was schooled in the years when a bitter war was fought between Japan and the United States and its Western allies. Yet, he was to emerge as one of America's greatest scientists, exerting an enormous influence on our ideas about biology and evolution.

Ohno's family was aristocratic and well educated. His maternal grandfather had been a justice of the Supreme Court of Korea and his paternal grandfather had been a scholar of Chinese language and history. As a high government official his father had traveled extensively, and Susumu lived in Korea and Japan during his childhood. His father nurtured ideas that were unusually liberal for someone in his position. He believed, for example, that people of all races were equal, an idea that impressed Susumu and one that he carried with him for his whole life. Susumu's liberal views influenced the educational opportunities that were afforded him. He was denied entry into the government public school because, he said, of his liberal propensities. Instead, he was sent by his family to one of the best private schools. In addition, he was taught by tutors to learn Chinese language and Chinese history. Of his siblings Susumu was the only one to leave Japan; all of his brothers and his sister lived their entire lives on the Japanese islands.

His love of animals, particularly of horses, proved to be one of the most pervasive influences in his life. His father was entitled to maintain both an automobile and a horse on his property,

and he normally traveled to his office on horseback. That's how Susumu began riding--while waiting for his father. His interest in genetics began, Ohno said, when he realized that "when a horse is no good, there is not much you can do." His interest in horses also strongly influenced his career choice. He wanted to attend veterinary school. At first his father was opposed to this choice, suggesting a career in medicine instead. Nevertheless, veterinary school it was, and Ohno received a D.V.M. degree from the Tokyo University of Agriculture and Technology in 1949. It was also a common interest in horses that brought Susumu together with the charming Midori, who was to be his life's mate for nearly 50 years. Indeed, it was owning and training horses that were to be a lifetime avocation for both Susumu and Midori. Ohno selected the Hokkaido University Faculty of Sciences for his graduate studies, because a professor there, Sajiro Makino, was well known for his study of chromosomes, a topic that had begun to interest Ohno. His doctoral dissertation concerned the role of plasma cells in the production of antibody, and in 1953 Ohno was awarded his Ph.D. degree. His graduate work in the area of immunology brought him in contact with Keiji Aoyama, and it was through this acquaintanceship that he met Aoyama's daughter Midori. Although their romance flourished in a society in which, at the time, arranged marriages were common, they did not marry in Japan. Ohno saw that the future of science lay in the United States, and before they could be married, he had obtained an appointment at the University of California, Los Angeles, in the department of Charles Carpenter. At UCLA Ohno began to work with a well-known professor, Riojun Kinosita. Although he was of Japanese origin, Kinosita had traveled extensively abroad and had worked in Germany and England. There he had discovered that butter yellow was a carcinogen, and largely because of this discovery he had become internationally known. Soon after Ohno arrived at UCLA, Kinosita was asked to initiate a research program at the City of Hope National Medical Center in Duarte, some 50 miles northeast of UCLA. He asked young Ohno to join him in establishing this new research program. Apparently it was an exciting challenge for both of them, and Ohno moved to the institution where he was to spend his entire highly productive career. It was very difficult for a Japanese woman to obtain a visa to enter the United States in the early 1950s, so Midori stayed behind in Japan and married Susumu by proxy while she was in Japan and he in the United States. In 1953 she was able to join him. Their marriage produced three children. The oldest, a son named Azusa, was born in 1955 and is now a film director in southern California. The second child was a daughter, Yukali, who studied philosophy and now lives with her husband in Hawaii. The youngest son lives in Las Vegas, where he works as a croupier.

2 Contributions to Science

Ohno's productive career may be divided into several overlapping phases. When beginning his work at the City of Hope Medical Center he skillfully devised cinematographic techniques for the study of living bone marrow. While these studies hardly foretold the

profound insights that Ohno would have into biologic mechanisms, they established him as a highly skilled experimentalist. With these skills he moved into the second phase of his career as a scientist, the study of chromosomes. Here his abilities as an experimentalist complemented his deep biologic insights and led him to a discovery that was to influence our understanding of genetic mechanisms. He recognized that the chromatin body that was found in female cells was not, as had been previously thought, the two X chromosomes lying in apposition but rather that one X chromosome was heterochromatic. This discovery, which Ohno later singled out as being possibly the most important of his career, served to focus his attention upon chromosomal function, particularly with respect to sex determination, and it was in this area that he made additional highly original contributions. Since it was known that in insects heterochromatin was genetically inactive, this suggested independently to a number of scientists that one of the two mammalian female chromosomes might be genetically inactive.

In studying the phylogenetic derivation of the X chromosomes, he recognized that they must have developed from a pair of autosomes, one of which underwent specialized development. In mammals this ultimately led to the nearly functionless Y chromosome. For a time he became fascinated with the H-Y antigen but began to realize that the antisera that were available were of such poor quality that the results were not reliable. He later acknowledged that he had been, for a short time, misled by the results obtained. In studying the chromosomes of mammals he noted that while there was great diversity in the number of chromosomes in different species, even species that were closely related, the total amount of chromosomal material appeared to be the same.

At a time that many were doing much less profound work, using highly sophisticated techniques, Ohno carefully made chromosome spreads, photographed them, and cut the chromosomes from photographic paper. He then weighed the cutout chromosomes showing in this way that whether there were 17 pairs of chromosomes as in the creeping vole, Microtus oregoni, or 84 pairs as in the black rhinoceros, the amount of chromosomal material was the same. But he found that this was not the case in organisms lower on the phylogenetic tree. Here it seemed to him that there had been successive doublings of the amount of chromosomal material. He somewhat whimsically designated the extra DNA as "junk DNA," presciently recognizing that most of the DNA in higher organisms does not consist of coding sequences. Ohno undertook to write three monographs in which he developed his innovative ideas about chromosomes and sex determination. These were Sex Chromosomes and Sex-Linked Genes published in 1967, Evolution by Gene Duplication published in 1970, and Major Sex-Determining Genes published in 1979. Although his ample bibliography is replete with multiauthored papers in leading scholarly journals, it is in these monographs that he was able to most fully explore his innovative ideas about biology. The preface of the first of these books reads as follows:

> *On the premise that each field of natural science has become too complex to be comprehended by a single man, it is more fashionable today to organize a committee of specialized scientists to write one book. While a book, written by a committee tends to present an objective appraisal of current knowledges, it suffers from disunity of thoughts. It is my sincere desire that this book will manifest more merits than shortcomings in having been written by one author.*

This monograph dealt with the evolution of the X and the Y chromosomes in mammals and the Z and W chromosomes in avian and ophidian species. It discussed in detail the X-inactivation hypothesis to which Ohno contributed so much and considered various mechanisms of dosage compensation.

The second monograph on gene duplication was far ahead of its time. In the preface he wrote:

> *Had evolution been entirely dependent upon natural selection, from a bacterium only numerous forms of bacteria would have emerged. The creation of metazoans, vertebrates, and finally mammals from unicellular organisms would have been quite impossible, for such big leaps in evolution required the creation of new gene loci with previously nonexistent function. Only the cistron that became redundant was able to escape from the relentless pressure of natural selection. By escaping, it accumulated formerly forbidden mutations to emerge as a new gene locus.*

Thus, he recognized that this DNA could serve as a powerful means by which new genes or new functions of old genes could be created. This concept had been expressed earlier by Haldane, but the explosion in modern biology and molecular genetics made it possible to assess for the first time the important role that gene duplication played in evolution.

The third volume dealt in greater detail with sex determination. Ohno was fascinated by the testicular feminization syndrome, in which XY persons do not only develop into phenotypic females but into females who are particularly beautiful. A mutation on the X chromosome that causes resistance to the effect of male hormones is responsible for this disorder. In the middle 1980s Ohno became interested in the evolution of DNA sequences. He realized that the decamers that might be formed in the primordial soup through known chemical reactions would not be sufficient to contain the information required for even the most primitive life forms. Accordingly, he proposed that the primordial oligonucleotides were repeating pentamers that hybridized with one another, forming templates for elongation. The result would be a repeating sequence, but because the repeating unit was five nucleotides long, there would be a frameshift in a triplet code, resulting in the formation of longer amino acid sequences, which however, would also be repeating in nature. Such sequences he proposed could well give rise to the # helices and ß sheets so common in protein structure. In searching the rapidly increasing number of sequences that were becoming available, Ohno saw many

recurring motifs and thought it would be interesting to assign notes to nucleotides, converting the sequences into musical passages. This made it possible to appreciate the repeating nature of motifs in the DNA sequence in a much more pleasant fashion than scanning the monotonous repeating letters of the sequences. This approach had a great deal of popular appeal and Susumu and Midori, who was musically proficient as a singer, were often called upon to perform some of their transcriptions of sequences into music.

Ohno's enormous contributions to science did not go unnoticed during his lifetime. He was elected to the American Academy of Arts and Sciences in 1974 and to the National Academy of Sciences in 1981. He was elected as a foreign member of the Royal Danish Academy of Sciences and Letters in 1992. In 1968 he received the Peter Volid special tribute award; the silver medal of the Bell Museum of Pathology at the University of Minnesota in 1972; the Japanese human genetics society prize in 1981; the Francis Amory Prize for Reproductive Biology of the American Academy of Arts and Sciences in 1981; the Kihara Prize of the Japanese Society of Genetics in 1983; and the Inaugural Queen Margarethe Prize from the Royal Danish Academy of Arts and Sciences in 1998. On the latter occasion Lennart Olsen stated,

> *He has thought at least half of the thoughts that form the basis of the work being carried out all over the world in respect to genetic analysis. In particular, the notion that every new gene arises from an already existing gene has revolutionized research.*

Honorary degrees were conferred upon him by the University of Pennsylvania in 1984 and by the Tokyo University of Agriculture and Technology in 1997. In the last year of his life he made a final journey to Japan with Midori. On that occasion Ohno was accorded the rare privilege of a personal meeting with the emperor of Japan, and upon his passing the emperor and empress sent their personal condolences to Mrs. Ohno.

THE ORAL HISTORY INTERVIEW conducted by Steven J. Novak, director of professional education and scientific reports at the City of Hope National Medical Center, was a great aid in writing this biographical memoir, and the author appreciates this valuable resource being made available.

3 Selected Bibliography

- 1958 With W. D. Kaplan and R. Kinosita. A photographic representation of mitosis and meiosis in the male of Rattus norvegicus. Cytologia 23:422-28.
- 1959 With W. D. Kaplan and R. Kinosita. On the end-to-end association of the X and Y chromosomes of Mus musculus. Exp. Cell Res. 18:282-90.
- With W. D Kaplan and R. Kinosita. The centromeric and nucleolus-associated heterochromatin of Rattus norvegicus. Exp. Cell Res. 16:348-57.

- With W. D. Kaplan and R. Kinosita. Formation of the sex chromatin by a single X-chromosome in liver cells of Rattus norvegicus. Exp. Cell Res. 18:415-18. 1960 With T. S. Hauscka. Allocycly of the X-chromosome in tumors and normal tissues. Cancer Res. 20:541-45.
- With W. D. Kaplan and R. Kinosita. On isopycnotic behavior of the XX-bivalent in oocytes of Rattus norvegicus. Exp. Cell Res. 19:637-39.
- 1961 With S. Makino. The single-X nature of sex chromatin in man. Lancet 1:78-79.
- With J. Trujillo, V. F. Fairbanks, and E. Beutler,. Chromosomal constitution in glucose-6-phosphate-dehydrogenase deficiency. Lancet 2:1454-55.
- With W. D. Kaplan and R. Kinosita. X-chromosome behavior in germ and somatic cells of Rattus norvegicus. Exp. Cell Res. 22:535-44.
- 1964 With W. Beçak and M. L. Beçak. X-autosome ratio and the behavior pattern of individual X-chromosomes in placental mammals. Chromosoma 15:14-30.
- 1965 With C. Mathai, J. Trujillo, and E. Beutler. Sex-linkage of G-6-PD in the horse and donkey. Fed. Proc. 24:440.
- With J. Poole and I. Gustavsson. Sex-linkage of erythrocyte glucose-6-phosphate dehydrogenase in two species of wild hares. Science 150:1737-38.
- 1966 With C. K. Mathai and E. Beutler. Sex-linkage of the glucose-6-phosphate dehydrogenase gene in Equidae. Nature 210:115-16.
- With H. W. Payne, M. Morrison, and E. Beutler. Hexose-6-phosphate dehydrogenase found in human liver. Science 153:1015-16.
- 1967 Sex Chromosomes and Sex-Linked Genes. Heidelberg: Springer-Verlag.
- 1970 Evolution by Gene Duplication. Berlin: Springer Verlag.
- 1973 With L. Christian, B. J. Attardi, and J. Kan. Modification of expression of the testicular feminization (tfm) gene of the mouse by a "controlling element" gene. Nature (New Biol.) 245:92-93.
- 1974 With U. Drews, S. R. Blecher, and D. A. Owen. Genetically directed preferential X-activation seen in mice. Cell 1:3-8.
- 1978 With B. Beutler, Y. Nagai, G. Klein, and I. Shapiro. The HLA-dependent expression of testis-organizing H-Y antigen by human male cells. Cell 13:509-13.
- 1979 Major Sex Determining Genes. Berlin: Springer-Verlag.
- 1985 The notion of primordial building blocks in construction of genes and transcriptional and processing errors due to random occurrence of oligonucleotide signal sequences. Adv. Exp. Med. Biol. 190:627-36.
- 1986 With M. Ohno. The all pervasive principle of repetitious recurrence governs not only coding sequence construction but also human endeavor in musical composition. Immunogenetics 24:71-78.
- 1987 Evolution from primordial oligomeric repeats to modern coding sequences. J. Mol. Evol. 25:325-29.

- 1996 The notion of the Cambrian pananimalia genome. Proc. Natl. Acad. Sci. U. S. A. 93:8475-78.
- 1998 The notion of the Cambrian pananimalia genome and a genomic difference that separated vertebrates from invertebrates. Prog. Mol. Subcell. Biol. 21:97-117.

4 Ohno at Science Connections: Lectures and Articles

- Repetition as the Essence of Life on this Earth: Music and Genes (1987)
- OF WORDS, GENES AND MUSIC, 1988
- Cellular Oncogenes as the Ancestors of Endocrine and Paracrine Growth Factors and Their Evolutionary Relic Status in Vertebrates (1985)
- Atavistic Mutations Reflect the Long Life Span of Dispensable Genes (1987)
- Immunological Self-Nonself Discrimination and Numerous Peptide Fragments Shared by Unrelated Proteins (1992)
- Ohno's Evolution by Duplication and DNA Correlations, Wentian Li, Ph.D (2005)