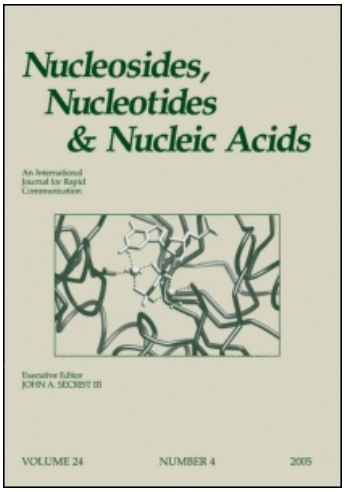

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BIOGRAPHY

Tohru Ueda

1931-1990

In 1955, the Faculty of Pharmaceutical Sciences was founded at Hokkaido University College of Medicine. By this time, chemical studies in Japan on nucleic acids had been performed only sporadically. For example, in 1913 Kodama found that histidine inosinate imparts the flavor to dried bonito. Vitamin L_2, the lactation factor discovered by Nakahara in 1943, was synthesized by Makino in 1954. Yoshihisa Mizuno, Professor of Medicinal Chemistry in the newly founded department, decided to devote the entire laboratory effort to the chemistry of nucleic acids. Tohru Ueda joined the faculty as a young research associate in the Laboratory of Medicinal Chemistry, and there began his brilliant scientific career. At that time, the days of P. A. Levene were already history, but an extremely exciting development was taking place with A. R. Todd and his Cambridge

group. G. H. Khorana's DCC method was just being introduced, and Leloir's group in the southern hemisphere discovered a group of coenzymes containing nucleotide 5'-pyrophosphate, such as uridine diphosphate glucose (UDPG). Tohru immediately attempted the chemical synthesis of guanosine diphosphate mannose (GDPM) and successfully completed the first total synthesis of this coenzyme with Eiko Ohtsuka, who later became the first and only woman professor at the Faculty of Pharmaceutical Sciences of Hokkaido University. No nucleoside was commercially available at that time. Thus, the starting nucleosides were prepared by hydrolysis from RNA, which was extracted from brewery yeast supplied by the nearby Sapporo Beer factory. Guanosine was obtained relatively easily in pure, crystalline form. Uridine, which was first crystallized in the laboratory by Tohru, was extremely difficult to isolate in pure form. Later, in 1961, Tohru received his Ph. D. degree from the University of Tokyo on the basis of his work on the chemical synthesis of modified nucleosides, nucleotides, and nucleotide coenzymes.

Tohru Ueda was born in Tokyo on November 4, 1931, and was the third son of Jiroh and Masako Sasaki. He was adopted by Umekichi and Hono Ueda, one of the close relatives of the Sasakis who did not have a child. In 1943, Tohru was admitted to Musashi High School, a five-year college preparatory school. He entered the University of Tokyo in 1949, and received his BA degree in 1953. He went on to graduate school, working in the laboratory of Professor Eiji Ochiai, who had developed alone the chemistry of aromatic amine oxides, while completely segregated from scientists in other parts of the world during the war. Tohru, however, did not work on the chemistry of amine oxides, but dealt with the metabolism of mesoxalic acid, and obtained his MS degree in 1955. He continued his studies toward the Ph. D. degree as a graduate student at the University of Tokyo. At the same time, he joined Mizuno's laboratory in Sapporo. Tohru wrote ten papers for publication. However, the most time-consuming work in which he engaged was to optimize conditions to isolate RNA from brewery yeast, and to efficiently prepare nucleosides and ribose (in the form of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose) from the RNA. During this period, he also successfully defended his Ph. D. thesis, and then got married to Sumiko Horikawa, one of his bright students.

In 1961, Tohru accepted a postdoctral research position in Dr. Jack J. Fox' laboratory at Sloan-Kettering Institute for Cancer Research in Rye, New York, living close by with Sumiko. The next two years were a most peaceful and happy period in Tohru's life. At Sloan-Kettering Tohru conducted a number of experiments, which resulted in six publications with Dr. Fox, but he also found time to enjoy his honeymoon with Sumiko, and they frequently attended Carnegie Hall concerts.

Tohru was promoted to the rank of Associate Professor shortly after returning to Hokkaido, and became Professor of Organic Chemistry in 1968. In 1981, Tohru was elected Dean of the Faculty. His scientific endeavor those days was focused on sulfur-containing nucleosides. He developed a direct method to convert uracil nucleosides into 2,4-dithiouracil derivatives using phosphorus pentasulfide and tetralin. Many 2-thiopyrimidine nucleosides were synthesized, including S-bridged anhydro-nucleosides. 2-Thiocytidine was prepared prior to its finding in tRNA as a minor component. Later on, it was further converted into lysidine, another minor component of tRNA. Also, Tohru introduced solvolysis of cytosine nucleosides and nucleotides with liquid hydrogen sulfide to prepare 4-thiouracil congeners. This was a useful method for elucidation of 5S ribosomal RNA structure.

Tohru was elected Dean again in 1983. He no longer played baseball in summer and soccer in winter in 1970's, as he had during the sixties, but he spent time with all of his group every summer for swimming. He enjoyed skiing with his family and his laboratory members in winter. He continued working on the chemistry of sulfur-containing nucleosides and nucleotides and made several important contributions to nucleoside chemistry during this period: The total synthesis of the natural nucleoside, bredinin was achieved. The discovery of the formation of 6-cyanouridine from 5-bromouridine, and 5-cyanouridine from 6-cyanouridine by treatment with cyanide was especially important, not only from the mechanistic view point but also for synthetic purposes. Using this reaction, orotidine and orotidylic acid were synthesized. Synthesis and properties of carbon-bridged cyclonucleosides were initiated during this period for elucidation of the relationships between glycosyl conformation and CD spectra of nucleosides and nucleotides. This line of work was continued until his death, and the studies of interactions of these nucleotides with enzymes were also important subjects in his mind.

The 1980s were, scientifically, a most fruitful period for Tohru. He started writing haiku, poetry with 5-7-5 syllables. He frequently traveled to Europe and the United States, giving lectures and participating in many international meetings, and occasionally accompanied by Sumiko. Tohru became Professor of Medicinal Chemistry in 1983. More than two-thirds of his papers (which total 207) were published in the 1980s. Although important chemical contributions were made, such as the chemistry of neplanocin A and bredinin, and sugar modified nucleosides, the direction of Tohru's research became more oriented to drug discovery, especially toward development of anticancer, antiviral, and antiparasitic drugs. For such purposes, methods were developed for the synthesis of nucleosides modified at the sugar and/or base. Such studies have resulted in the development of potential drugs including the anticancer 2'-deoxy-2'-methylidenecytidine (DMDC), the anticancer/antiviral 5-ethynyl-1-(β-D-

ribofuranosyl)imidazole-4-carboxamide (EICAR), the anti-HIV 2',3'-didehydro-2',3'-dideoxythymidine (D4T), and the antileishmanial 3'-deoxyinosine. Tohru also initiated more biochemically-oriented studies on DNAs, especially using restriction nucleases.

On September 19, 1990, Tohru Ueda passed away at the age of 58, after a few months treatment for lung cancer at the Sapporo Medical College Hospital. While Tohru was ill, Sumiko published his haiku collection privately, and distributed it among his friends as her present for his coming birthday. He is survived by his wife, two daughters (Nozomi and Hiromi), and a son (Masato). Tohru always lived seriously whether at the bench, at peace movements, or in the playground. He was true to himself, and did what he believed to be right. When Tohru joined Mizuno's group in 1955, the laboratory was housed in an old, abandoned wooden building. Water leaked through the ceiling on rainy days. Windows had to be wide open, even on cold winter days, because there was no fume hood functioning. My project was to prepare variously substituted benzyl esters of phosphoric acid by condensation of benzyl halides with silver phosphate. Tohru had no patience to watch me synthesize the starting halides unskillfully with inexperienced hands and suffering from benzyl halide poisoning. He volunteered to prepare the halides by himself for me. His hands, arms, and even face, just like mine, became swollen and red with poisoning by the halides. We had many heated arguments, but after calming down, Tohru usually took me out. In the 1980s, we met at scientific meetings and enjoyed many more relaxed conversations. When I visited him at the hospital just three weeks before his death, we talked on various subjects for more than an hour. Although Tohru was taking medication for pain, he did not complain about his condition. He was aware of his diagnosis, but still hoped to recover from the disease and return to work. Although this hope was not fulfilled, a few weeks before my visit, Tohru was able to enjoy a visit home for several hours. Now, Tohru is gone, but he will be remembered with respect by his former colleagues and friends.

K. A. Watanabe*

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