Paul Reinhard Schimmel was born in Hartford, Connecticut in 1940. He attended Ohio Wesleyan University, where he received his A.B. in 1962, and then went to the Tufts University School of Medicine with the intention of being a doctor. However, he left after his first year of medical school to attend graduate school at the Massachusetts Institute of Technology. Working under Gordon Hammes in the department of biology, Schimmel studied thermodynamics and chemical kinetics and earned his Ph.D. in 1966.

After graduating, Schimmel went to Stanford University where he did a postdoctoral fellowship with 1974 Chemistry Nobel laureate Paul Flory, working on the application of polymer statistical mechanics to proteins. He returned to MIT a year later to become an assistant professor and was eventually promoted to the John D. and Catherine T. MacArthur Professor of Biochemistry and Biophysics.

At MIT, Schimmel established a research program that centered on the genetic code, transfer RNAs, and aminoacyl transfer RNA synthetases. He became the first to uncover what has been referred to as an early, “second genetic code” when he discovered that a single G-U base pair in a tRNA acceptor stem marked the molecule for aminoacylation with alanine (1) and inferred that specific sequences and structures in tRNA acceptor stems provide signals for aminoacylation. Schimmel also established that tRNA synthetases have modular designs, with distinct functional units for amino acid activation, tRNA binding, and oligomerization (2, 3).

A good portion of Schimmel’s research has also focused on editing functions in tRNA synthetases, i.e. the means by which the enzymes are able to remove misactivated amino acids and prevent them from being joined to the wrong tRNAs. His foray into this area began in 1972, when he became the first to show that tRNA synthetases had editing functions and could deacylate mischarged tRNAs (4, 5). Fifteen years later, while investigating the modular structure of tRNA synthetase, Schimmel and his colleagues discovered the CP1 insertion domain (6), which was later shown to encode the catalytic center for cleaving a mischarged amino acid from a tRNA (7). Further investigations by Schimmel revealed that specific
nucleotides in the tRNA cofactor were needed to trigger the editing reaction (8, 9). In 1999, 27 years after he discovered the editing function, Schimmel demonstrated how a misactivated valine was translocated from the active site to the editing center (10).

In the following years, Schimmel continued to investigate the editing reaction and published some of this work in the Journal of Biological Chemistry (JBC). Two of these papers are reprinted here as JBC Classics.

In the first Classic, Schimmel and Brian E. Nordin further investigate the tRNA determinants necessary for the editing reaction. Specifically, they looked at the discrimination between the structurally similar amino acids valine and isoleucine by isoleucyl-tRNA synthetase. Previously, Schimmel had shown that nucleotides in the D-loop of tRNA\textsubscript{Ile} trigger the translocation of the valyl group from the aminoacylation to the editing site (9). Following up on these observations, Schimmel and Nordin tested whether the translocation and editing responses could be recreated by dividing the critical domains of tRNA\textsubscript{Ile} into two pieces. The first was a minihelix that recreated the acceptor stem of the tRNA and could be recharged with isoleucine by isoleucyl-tRNA synthetase, and the second piece was an RNA hairpin ligand similar to the D-loop of tRNA\textsubscript{Ile}. They determined that the two pieces in concert could not reproduce the editing reaction, indicating that the native tertiary fold of tRNA\textsubscript{Ile} is required to promote efficient editing. Because the minihelix was thought to be the more ancestral part of the tRNA structure, these results were consistent with the idea that during the development of the genetic code, RNA determinants for editing were added after the establishment of an aminoacylation system.

In the second Classic, Schimmel, Kirk Beebe, and Eve Merriman took the above experiments a step further by making several chimeric tRNAs. They replaced the acceptor stem of several tRNA molecules with that of tRNA\textsubscript{Ala} and found that although the acceptor stem in isolation lacked determinants for editing, alanyl-tRNA synthetase effectively cleared a mischarged amino acid from each chimeric tRNA. Thus, they concluded that a covalently continuous two-domain structure was a major determinant for clearance of mischarged amino acids by alanyl-tRNA synthetase. Because errors of aminoacylation are known to be deleterious to cell growth, structure-specific determinants constitute a powerful selective pressure to retain the format of the two-domain L-shaped tRNA.

Schimmel’s work on editing also led to the discovery that, by disrupting the editing mechanism, noncanonical amino acids could be incorporated into proteins. He has recently connected editing defects to errors in protein synthesis that lead to neurological disorders.

In 1997, Schimmel joined the Skaggs Institute for Chemical Biology at The Scripps Research Institute, where he is currently the Ernest and Jean Hahn Professor of Molecular Biology and Chemistry. He also cofounded several companies, including Repligen Corp., Alkermes, Inc., and Cubist Pharmaceuticals, Inc. Schimmel has received many awards and honors for his contributions to science, including the American Chemical Society’s Pfizer Award in Enzyme Chemistry, the Biophysical Society’s Emily M. Gray Award for significant contributions to education in biophysics, and the Chinese Brilliant Achievement Award. He was also elected to membership in the American Academy of Arts and Sciences, the National Academy of Sciences, the American Philosophical Society, and the Institute of Medicine, and served as the chairman of the American Society for Biochemistry and Molecular Biology’s nominating committee and awards committee.

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