At the time of its elucidation the genetic code was suggested to be universal in all organ­isms, and the result of a ‘frozen accident’ unable to evolve further even if the current state were suboptimal (1). How do we see the genetic code today – 45 years after the familiar ‘alphabet’ with 20 amino acids was established?

There are 22 natural amino acids (2-4): selenocysteine, the 21st, and pyrrolysine, the 22nd, are di­rectly inserted into growing polypeptides during translation. Selenocysteine is synthesized via a tRNA-dependent pathway and decodes UGA codons (5-7). The incorporation of seleno­cysteine requires the concerted action of specific RNA and protein elements. In contrast, pyrro­lysine is ligated directly to a suppressor tRNAPyl and inserted into proteins in response to UAG codons without a complex re-coding machinery (8-11).

Based on the realization that protein plasticity is a feature of living cells (12), man-made expansion of the genetic code has begun by adding non-standard amino acids to the repertoire of the cell (13, 14). These present evolutionary developments are the underpinning for the creation of new organisms in the realm of synthetic biology.

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