An Alternative Genetic System for Complex Alien Life Forms

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One question in Exobiology asks whether molecules different in structure from DNA and RNA can support genetics in water. Work to answer this question falls squarely into the purview of organic chemistry, which provides tools needed to synthesize alternative genetic systems to see if they can function. Over a decade ago, we proposed an alternative genetic system having 12 nucleotides, instead of the 4 found in contemporary terran DNA. This proposal found its way into popular culture, including an episode of the *X-files* and the movie *Evolution*. As a spin-off, our alien genetic system today manages the care of over 400,000 patients having HIV and hepatitis virus infections. Nevertheless, certain chemical properties of the expanded genetic alphabet suggested that it might not serve advanced forms of life having large genomes. Thus, the nucleobase proposed to implement the puDDA hydrogen bonding pattern had an tautomeric form that caused substantial mismatching. The nucleoside proposed for the pyAAD pattern had a propensity to depyrimidinylate. Nucleosides implementing the pyDDA and pyADD

patterns readily epimerized. Early work with terran polymerases suggested that C-glycosides and N-glycosides might not be combinable in an efficient, highly faithful genetic system. We have now resolved these issues, identifying puDDA, pyAAD, pyDDA, and pyADD implementations that do not display their respective undesirable properties. Further, we have implemented a fully efficient six-letter polymerase chain reaction involving both C- and N-glycosides. This establishes that our expanded genetic system could support complex life, and sets the stage for a full synthetic biology using it.