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DNA analogues for CRISPER/CAS fidelity and exon skipping

New thiomorpholino oligonucleotide analogues (TMO) containing morpholino and deoxyribonucleoside joined through thiophosphate-phosphor inter nucleotide linkages were chemically synthesized. These analogues have higher melting temperatures when compared to natural DNA/RNA and DNA/RNA duplexes. Moreover, the TMO/RNA duplexes exhibit the A-form structure and are RNase H1 active. Treatment of HeLa cells with fluorescently labeled TMO and TMO/DNA chimeras demonstrated that these analogues were efficiently taken up by cells and stimulates biological activity in a HeLa cell dual luciferase assay. Recently thiomorpholino oligonucleotides were found to be more active than any other tested analogue in exon skipping assays with a mouse model for Duchenne muscular dystrophy. Recently imidoamidate DNA was synthesized. Imidoamidate DNA forms duplexes with complementary DNA, is positively charged and can be transfected in the absence of lipid, and is RNase H1 active. In collaboration with Agilent Technologies, we have developed methods and instruments for the chemical synthesis on glass chips of DNA and RNA containing upto 300 nucleotides per segment. RNA containing phosphonoacetate nucleotides at the 3'/5' ends have much higher fidelity than any other analogue in the CRISPER/CAS system.

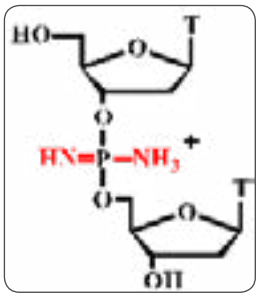

Figure 1: Imidoamidate DNA.

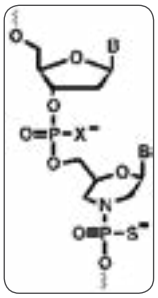

Figure 2: Thiomorpholino DNA

Recent Publications

1. Shang et al. (2016) Peptide substituted oligonucleotide synthesis & non-toxic passive cell delivery. Signal Transduction & Targeted Therapy 1:e16019.
2. Paul et al. (2015) Oxidative substitution of borane-phosphonate di-esters as a route to post-synthetic modified DNA. Journal of the American Chemical Society 137(9):3253-3264.
3. Caruthers M (2013) The chemical synthesis of DNA/RNA: our gift to science. Journal of Biological Chemistry 288(2):1420-1427.
4. Dellinger et al. (2011) Streamlined process for the chemical synthesis of RNA using 2'-O-thionocarbamate protected nucleoside phosphoramidites in the solid phase. Journal of the American Chemical Society 133:11540-11556.
5. Le Proust E et al. (2010) Synthesis of high quality libraries of long (150mer) oligonucleotides by a novel depurination controlled process. Nucleic Acids Research 38(8):2522-2540.

Biography

Marvin H Caruthers is a distinguished Professor at the University of Colorado. He is a Guggenheim Fellow, completed PhD at Northwestern University and Post-doctoral Studies at MIT. His interests include nucleic acids chemistry and biochemistry. Approximately 35 years ago, the methodologies for chemically synthesizing DNA/RNA were developed in his laboratory and incorporated into instruments for synthesizing DNA/RNA as used by biochemists, biologists and molecular biologists. He is the recipient of several academic and research awards including The National Academy of Sciences Award in the Chemical Sciences, The Prelog Medal, The Economists Award in Biotechnology and The US National Medal of Science. He is an elected member of The US National Academy of Sciences, The American Academy of Arts & Sciences, The National Inventors Hall of Fame and a Corresponding Member of the German Academy of Science Gottingen. He is also a co-founder of Amgen and Applied Biosystems.

Notes: