Increasing the stability and biocompatibility of chemically synthesised oligonucleotides

Oxford researchers have developed a chemical synthesis strategy for producing DNA incorporating non-natural backbone structures and locked nucleic acid functions which convey desirable properties such as more selective and robust binding to complementary nucleic acids and greater resistance to enzymatic degradation.

Nucleic acids – Encoding life

DNA and RNA are biomolecules that are fundamental to all known forms of life. In recent years, many successful attempts have been made to harness the myriad functions of nucleic acids and apply them in the fields of human medicine, forensics and genetic testing. In general, these applications utilise DNA and or RNA produced through well-established solid phase synthesis methods. These mostly contain chemical modifications that have been established for very many years. Emerging applications, particularly in therapeutics, require more robust nucleic acid structures, with customisable properties to improve *in vivo* stability and delivery, so new designs and synthetic approaches are required.

New nucleic acid analogues - Improving on nature

To meet the demand for increased efficacy created by breakthroughs such as the recent development of several clinically approved therapeutic oligonucleotides, researchers have sought novel nucleic acid analogues. One such approach utilises azide-alkyne “Click” chemistry to generate a triazole surrogate of the natural phosphodiester backbone. However the presence of such groups in the DNA/RNA backbone renders the resulting biomolecules unable to efficiently bind (by Watson-Crick base pairing) to complementary DNA/RNA sequences. The selectivity and strength of this binding is crucial to its application.

LNA – Locking in new features

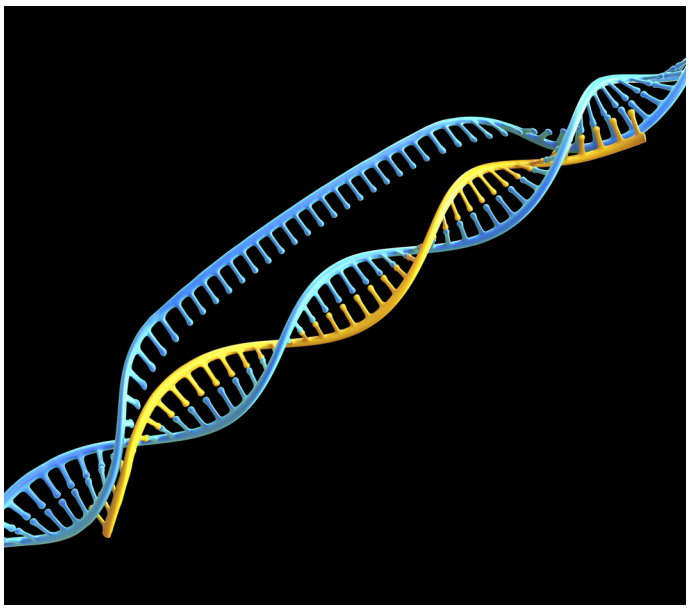
Researchers at the University of Oxford have exploited the triazole linkage in combination with locked nucleic acids (LNAs) to yield oligonucleotides which display higher target binding affinities and greater resistance to enzymatic degradation. In addition, reagents have been developed which allow for facile incorporation of this functionality by standard automated solid phase synthesis methods.

The main benefits of the Oxford Triazole-LNA approach are as follows:

- Significant increase in DNA:RNA duplex stability (target affinity) compared to triazole alone
- Less susceptibility to enzymatic degradation than native DNA/RNA
- Synthesis by rapid, efficient and scalable solid phase techniques
- Ability to modulate or eliminate anionic charge on DNA/RNA analogue

Protection and Applications

This technology is the subject of two patent applications and Oxford University Innovation is keen to talk to anyone who is interested in their commercialisation.



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Technology Transfer from the University of Oxford