The newly synthesized nucleic acid, Xenonucleic Acid, offers exciting possibilities in scientific research and understanding the bounds of what it means to be alive.

Bryson, in his book *A Short History of Nearly Everything*, muses about the fickle and mindless particles – atoms – that join in an intricate and curiously obliging manner to create life. Isn’t it interesting to note that of all the bizarre forms of molecules present in the universe only two, namely the DNA and RNA, assembled themselves in a fashion that allowed them to store information, replicate to propagate information and evolve?

This thinking changed in a breakthrough in molecular genetics in April 2012 when Vitor Pinheiro and Philip Hollinger and their team at the MRC Laboratory of Molecular Biology, Cambridge, UK developed six alternative polymers called XNAs. These XNA molecules can store genetic information and evolve through natural selection. The discovery forms a turning point in the era of synthetic genetics, which expands the chemistry of life in new uncharted directions.

A Look Back in Time
In order to understand the significance of this discovery we have to trace the development back in time when the nature of genetic material was still unknown to man. The discovery of DNA dates back to 1869, more than 140 years ago when
Researchers are now working on the development of enzymes and mechanisms that can build XNAs directly from XNAs cutting out the intermediate involvement of DNA.

Friedrich Miescher, the Swiss doctor, isolated DNA for the first time. Miescher was performing experiments on the chemical composition of leukocytes when he noticed the precipitate of an unknown substance, which was resistant to protein digestion enzymes, proteases. Analyses of its composition revealed that, unlike proteins, this curious substance contained large amounts of phosphorous and lacked sulphur. Recognising that he had discovered a novel molecule, Miescher named it nuclein as it was isolated from the cells’ nuclei – a name preserved in today’s designation of deoxyribonucleic acid.

However, it took another 83 years for scientists to prove that this nuclein was actually the genetic material. In 1952, Alfred Hershey and Martha Chase showed that, when bacteriophages (composed of DNA and protein) infect bacteria, their DNA enters the host bacterial cell, but most of their protein does not. This led to a conclusion that DNA could actually be the genetic material.

One more year passed before James D. Watson and Francis Crick, using X-ray diffraction data collected by Rosalind Franklin and Maurice Wilkins, proposed the double helix structure of the DNA molecule and confirmed the hereditary nature of DNA. Following these discoveries, a lot of work was done to understand the nature of genetic code and particularly the types, structure and function of another molecule that seemed similar to DNA, which was called the RNA or the ribonucleic acid, until 1968.

Francis Crick and Leslie Orgel proposed that the first information molecule was RNA. Since then numerous studies have gone into this field, exploring the nature and function of these molecules. Over the years it has been established that of all the molecules, only DNA and RNA have a unique chemistry that allows information storage, and follow unique replication mechanisms that allow accurate transfer of this information and evolution thus accounting for life.

**Xenonucleic Acid (XNA)**

This thinking could soon change. Synthetic biologists from MRC laboratory under the leadership of Vitor Pinheiro and Philip Hollinger have developed six alternative polymers called XNAs that can also store genetic information, replicate and evolve like the genetic systems consisting of DNA and RNA. The “X” in XNA stands for “xeno” a Latin prefix that means exotic or foreign. Scientists have used this term to indicate the synthetic nature of these molecules – that one of the ingredients typically found in the building blocks that make up RNA and DNA has been replaced by something different from what occurs naturally.

Strands of DNA and RNA are formed by joining together individual structural units called nucleotides. A nucleotide in turn is made up of two units – a nucleoside and a phosphate group. The nucleoside consists of one of 5 nitrogenous bases – adenine, guanine, cytosine, thymine or uracil – and a five-carbon sugar. In case of RNA, the backbone is composed of ribose sugar (“R” in RNA), rather than 2-deoxyribose sugar. While making the rungs of the ladder-like structure RNA uses uracil (U) instead of thymine (T) and finally unlike the double helix of DNA, RNA forms half a ladder – a single helix.

In case of XNAs, the sugars in the backbone ladder structure differ from that of four-carbon sugars 2-deoxy ribose and ribose sugar. The MRC team used various kinds of sugars varying from four-carbon sugars to seven-carbon sugars in order to polymerize and form the helix structure. If arabinose sugar is used for the backbone instead of deoxyribose, it is called an ANA. Similarly, if the sugar is cyclohexane (a six-member ring) or threon (a four-carbon sugar) or a hexitol, it is called a CeNA, TNA, and then HNA respectively.

One of these synthetic molecules FANA even contains a flouine atom. All the XNAs use the same bases and the same phosphate groups as an ordinary DNA and any of them can pair up with a complementary strand of DNA or RNA. These substitutions make XNAs functionally and structurally analogous to DNA and RNA, but they remain foreign molecules.

**How was XNA Synthesized?**

Geneticists have earlier tried to create DNA with base pairs other than A-T and C-G, and also XNAs that incorporate foreign sugars. But the synthesis of XNA has been accomplished using machines such that the resulting nucleic acids were short chains that had limited functionality and evolution potential. Hence, it was necessary to create novel XNA from enzymes that could replicate and evolve. In order to do this, researchers have developed new kinds of XNA building enzymes.

DNA replicates with the help of a special enzyme called DNA polymerase. DNA polymerase has a specific mechanism to read the information
As of now to replicate XNA from XNA, the process of XNA replication demands a two-step mechanism in which XNA can be copied into DNA, which can then be copied back to XNA, thus replicating it.

Hence, after the successful synthesis of XNA from DNA the researchers tried to create an enzyme that could do the reverse – convert XNA into DNA. To achieve this, Pinheiro and his team selected a different polymerase, and randomly mutated it. Such mutated versions were then checked for their ability to convert XNA to DNA. Eventually, they created a version that could accomplish the task and could create enzymes that could copy information between XNA and DNA, with an accuracy of at least 95 per cent. This may not be the most efficient method of replication as it involves a DNA intermediary, but has high degree of accuracy, which makes the transmission of genetic information and evolution feasible.

Researchers are now working on the development of enzymes and mechanisms that can build XNAs directly from XNAs cutting out the intermediate involvement of DNA. The team has so far managed to copy FANA from FANA, CeNA from CeNA, and even HNA from CeNA. However, all these steps were far less efficient than working through DNA.

Implications of XNA Synthesis
Scientists consider the discovery of XNAs extremely important owing to their far reaching implications and their special properties.

Synthetic Life: It is believed that XNAs might, in the future, help in the creation of synthetic genetic systems based on alternative chemical platforms, and hence entirely synthetic alternative novel forms of life that will not require DNA or RNA for functioning.

Origin of Life: It is also assumed that XNAs and their enzymes might shed light on the origin of life and provide an answer to why life as we know it is based on the dominance of only two molecules – DNA and RNA. Some researchers believe that life might have been based on simpler genetic systems before the emergence of RNA and DNA. The capability of XNA to evolve strengthens the hypothesis of existence of a genetic system predating DNA and RNA and that DNA and RNA might have emerged as the building blocks of life, sheen accidentally, by what scientists call ‘frozen accident’ from the origin of life.

Medicine and Therapeutics: Medicine, too, could benefit from XNAs because of their non-biodegradable nature. Generally biomolecules like RNA, DNA, enzymes and antibodies are used as therapeutics, diagnostics and in biosensing applications. But a serious drawback of this technique is the short lifespan of such treatments and the difficult time they have in reaching their therapeutic targets as they are degraded quickly in the stomach and the blood stream. In such a scenario, XNA can be used as a potential therapeutic agent targeting diseased cells as they are more resistant to degradation and biological systems don’t have enzymes evolved enough to digest them.

Exobiology: Researchers feel that this discovery will have a strong impact on exobiology – the branch of science that is involved with looking for life on other planets. Till now DNA and RNA were being used as markers to monitor the presence of life on other planets but the emergence of XNA as a molecule that can store genetic information and evolve strengthens the hypothesis of existence of a genetic system predating DNA and RNA. Some researchers believe that life as we know it is based on the dominance of only two molecules – DNA and RNA and that DNA and RNA might have emerged as the building blocks of life, sheen accidentally, by what scientists call ‘frozen accident’ from the origin of life.

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