Editing genes like alphabets

There are now tools to alter parts of DNA without cutting the chain and putting things back

S ANANTHANARAYANAN

The journal, *Nature*, has selected David R Liu, a researcher at the Massachusetts Institute of Technology, Boston, as the first of the 10 people who mattered in 2017. Liu has "developed gene-editing tools that are new to nature, and that could one day save lives", says the write-up in the journal.

In October 2017, the journal had carried a paper by David Liu with Nicole M Gaudelli, Alexis C Komor, Holly A Rees, Michael S Packer, Ahmed H Badran and David I Bryson, working at Harvard University and the Broad Institute of MIT and Harvard, which described a technique of targeting a single component of a vast DNA molecule and making a correction in that component, without disturbing the rest of the molecule.

It is this DNA molecule, of course, which is present in the nucleus of every cell of an organism, which contains the action programme of what proteins the cell will produce, and hence the characteristics of the organism. If there are errors in that programme, naturally, cells do not produce the right proteins, and there is disease or malfunction of the organism. The DNA itself is a chain of millions of units, in the form of two complementary strands in the shape of a helix, but folded and compact, to fit inside the cell nucleus. The millions of units in the DNA are grouped in segments, which are the codes for specific proteins. The segments, in turn, consist of groups of three links in the chain, and each group of three, called a triad, codes for one of 20 possible amino acids, which are the components of proteins.

A segment of DNA thus entails a large collection, in a specific order, of amino acids from a menu of 20 possible ones. As the segment can be long indeed, a huge sequence of amino acids, and hence a huge number of distinct proteins can be specified by the code. There is also the device of more than one coding for some amino acids, to take care of errors in the structure of the units. Errors, however, do occur and these change the specific structure of proteins, leading to disease with a genetic origin.

A promising method to repair such errors has been with the recent technique, CRISPR, which cuts the DNA at a place that can be specified by the clinician. If this cut is made at the place where an error has crept in, there is a possibility for the error not to persist when the two parts rejoin, resulting in a remedy of the genetic error.

The units that make up the triads, a sequence of which make up the segments of DNA, consists of just four basic kinds, which are named, A,T,G and C. These units occur in the two strands of the DNA in only four possible combinations — G-C or C-G and A-T or T-A. Occurrence of any one in one strand thus determines the units of the other strand, and this is the principle behind each strand being able to build up the complementary strand when a cell divides.

Now, as each unit, called a base pair, can thus be one of four kinds, a triad can be in 4x4x4=64 forms. These are the combinations of base pairs that code, with redundancy built in, for the 20 amino acids of which all proteins consist.

The CRISPR technique has derived from a system that is native to bacteria, in their defence against viruses. Viruses are little more than their own DNA and what they do to the cells that they infect is to monopolise the cells' resources for their own proliferation. The defence that bacteria employs is to copy a segment of the virus' DNA into its own DNA and use this template, at a subsequent virus attack, to chop the attacker at the place where the segment appears, with the help of associated segment, called the CAS (CRISPR Associated) gene. CRISPR/CAS is thus a powerful tool which makes use of a portion of a strand of DNA, along with the enzyme, CAS9, to cleave DNA at an identified place.

The authors of the paper in *Nature* note that about half of all known "point mutations" or single point errors in genes, which cause disease, are because a C in a base pair changes to T and the CG pair becomes a TA pair. The ability to change an AT pair back to a GC pair could thus have great value in correcting genetic features that cause disease. Carrying out such correction with the help of CRISPR/CAS9 and related paths, which involve a break in the DNA, has undesirable outcomes. As the methods only create a break at a specific location and have little control on how the two parts of a divided DNA would rejoin, there could be chance insertion or deletion of a part of the DNA, or the movement of a segment to another part of the DNA. Methods that directly target the error in the DNA structure, by converting one base pair into another, called base editing, have thus been developed.

A number methods have been developed, the paper says, to convert a C into a U (a form related to a T) and lead to permanently converting a CG base pair into a TA. This is also the change that occurs spontaneously. No methods, however, had been developed to convert AT to a GC, which would help reverse a great many CG to TA base pair changes that are associated with disease. This is the task Liu and his group, particularly Nicole Gaudelli and Holly Rees, undertook and is described in the *Nature* paper. While the conversion of GC to TA has used enzymes found in nature, the reverse conversion required the creation of a new and unknown enzyme in the laboratory.

The *Nature* citation that recognises Liu's work says that his lab pioneered the development of new enzymes and the first methods to convert G to T in many organisms. The methods were successfully used in bacteria, yeast, plants, zebra fish, and animals and recently in China to correct a single base pair mutation in a human embryo. But there was no assurance that Liu's team would be able to find an enzyme that could make it possible to reverse, or change TA to CG. Till the relentless efforts of Nicole Gaudelli, in Liu's team, nobody could come up with the evasive enzyme.

The enzyme has been tried out with the base, A, in different environments and has even succeeded in correcting a genetic cause of building up of iron in tissue and organs. The efficiency of base editing was found to average a high 53 per cent and there were no adverse effects. This advance in "single base pair editing", could be refined to give clinicians access and control over patients' genetic heritance.

The writer can be contacted at response@simplescience.in

PLUS POINTS

Bob Marley spider

A new species of semi-aquatic spider has been discovered scuttling over corals exposed by the receding tides on an Australian beach. The spider has been named *Desis bobmarleyi* in honour of the legendary reggae musician and his song "High tide or low tide", by the scientists who discovered it.

Desis bobmarleyi belongs to a family of marine spiders with special behaviours that allow them to survive submersion in water. They seem to have adapted to an underwater lifestyle by hiding in air-filled pockets in rock cavities, shells and seaweed.

While the tide is high and the spiders' homes are covered by water, they build silk chambers in these pockets to seal themselves inside, allowing them to breath. Then, at low tide, they emerge from their chambers to feed on small shore-dwelling creatures, which they pierce with their large jaws.

It is partly this behaviour that inspired the unusual name for the new species, but it's not the only reason. "The song 'High tide or low tide' promotes love and friendship through all struggles of life," said Barbara Baehr, a spider expert at Queensland Museum, Australia, who co-authored the study describing the new spider, "It is Bob Marley's music that aided a field trip to Port Douglas in coastal Queensland to collect spiders with a highly unique biology."

The description of the species was published in the journal *Evolutionary Systematics*. Male and female specimens were found living on coral along the shoreline by the Great Barrier Reef.

Mike Gray at the Australian Museum described in a blog post how marine spiders had once been common residents of Sydney harbour but were relatively unknown now. "Although marine spiders are known from many areas of the Australian coast, it appears that people rarely notice them," wrote Gray.

The Independent

Oldest sea monster

The remains being carried away

Scientists in Argentina have found the remains of a giant carnivorous marine reptile, or plesiosaur, which lived 150 million years ago in Antarctica. The four-finned reptile, which measured up to 12m long, dates from the late Jurassic period and is the most ancient creature ever discovered on the continent.

Soledad Cavalli, a palaeontologist at Argentina's National Scientific and Technical Research Council, said, "At this site, you can find a great diversity of fish, ammonites, some bivalves but we did not expect to find such an ancient plesiosaur."

The "surprising" discovery has never been documented, according to a statement from the National University of La Matanza, near Buenos Aires. "The discovery is pretty extraordinary, because the rock types at the site weren't thought conducive to the preservation of bones, like the vertebrae of this marine reptile," Cavalli said. The discovery site was a two-hour helicopter journey from Argentina's Marambio Base on the tip of Antarctica, with the researchers set to continue their work in January, during the southern hemisphere's summer.

Marcelo Reguero of the Argentine Antarctic Institute added that Antarctica was at the time part of the Gondwana continent, which also included Australia, New Zealand, India, Madagascar, Africa and South America, before continental drift pushed them apart.

The Straits Times/ANN

Reintroducing jellyfish

The species have a lot more going for them than blobby bodies and a sting

PHILIP LAMB

People rarely enjoy meeting a jellyfish. On the beach they appear limp, amorphous and blistered in the sun. In the water it's often a brush of a tentacle on exposed skin followed by a sting.

They hardly evoke the serene elegance of a turtle or the majesty of a breaching humpback whale. But despite making a poor first impression, jellyfish are among the most unusual animals on Earth and deserve a second chance to introduce themselves.

They're survival masters

Jellyfish are among the most abundant organisms in the sea. Recent research suggests there are about 38 million tonnes of them just in the mesopelagic: the upper 200 metres of ocean.

What's more, they are common in all oceans and have colonised the majority of marine habitats, including the deep sea.

One reason they are so common is that contrary to appearances, a body made from jelly is a very successful strategy. Gelatinous bodies have evolved independently three times and have existed, largely unchanged, for at least 500 million years, surviving all five major extinction events in the Earth's past that wiped out 99 per cent of all life.

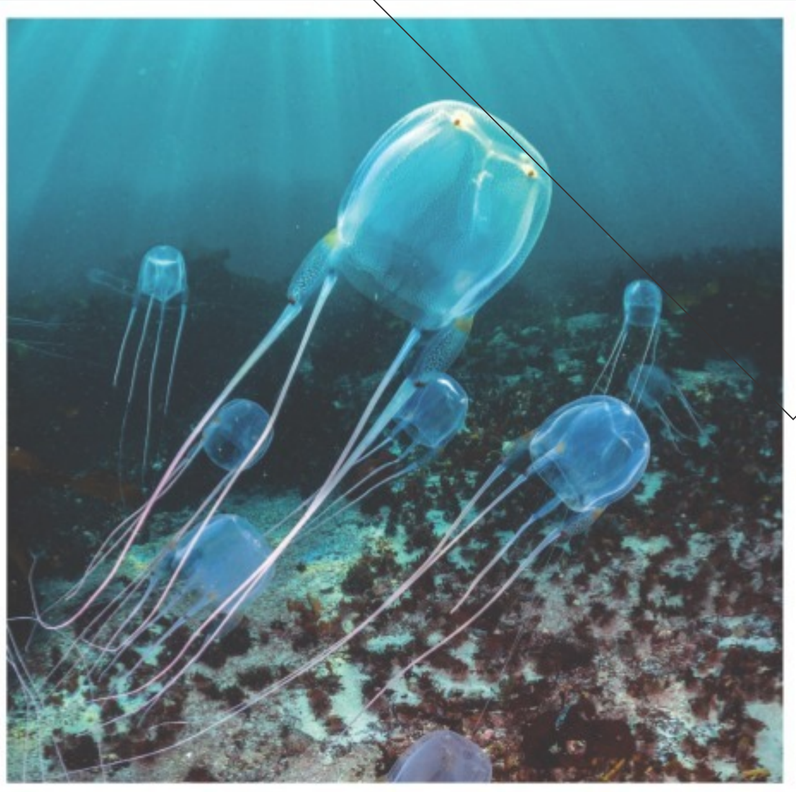
They have superpowers

Many jellies have evolved unique abilities, some of which seem almost supernatural. Comb jellies produce mesmerising bioluminescent displays. One tropical species has formed a symbiotic relationship with photosynthetic algae, which act like their own personal solar panels and let them obtain energy straight from the sun. Other species can produce copious amounts of offspring: large moon jellyfish females have been witnessed releasing over 400,000 young at a time.

Their piece de résistance is surely their second chance at youth. When conditions are unfavourable, certain species including compass, barrel, and moon jellyfish can reverse their development and effectively turn back into jelly-juveniles in order to wait out the hard times.

They have an amazing childhood

Many jellyfish belonging to the class scyphozoa have a remarkable and complex life cycle. These different life stages are so varied they were thought to represent entirely different species for a long time. Adult jellyfish reproduce sexually, releasing thousands of babies known as planulae into the plankton. Planulae spend a handful of days floating around before settling on hard substrata such as rocks, or artificial surfaces such as concrete or plastic.



Each planula then develops into a polyp, a small (two mm to three mm), stationary life form that feeds off floating bits of plankton. These polyps reproduce asexually, forming a colony of clones. When the time is right, the clones undergo a process known as strobilation, which transforms each one into something that looks like a stack of pancakes on a string. One by one, they are then released into the surrounding plankton. Although only a few millimetres in size, and lacking the obvious characteristics of an adult, the "pancakes" are in fact tiny jellyfish. Eventually they will mature into sexually reproducing adults and begin the cycle anew (assuming they don't reverse-develop if conditions are poor).

Depending on the species, a polyp can produce one, a handful, hundreds or even thousands of jellyfish at a time, sometimes over a period of many years. The combination of the amazing reproductive ability of adult jellyfish, coupled with the asexual reproduction of polyps, is thought to be one of the reasons why vast swarms, known as blooms, of jellyfish can apparently appear out of nowhere.

They have been a boon for mankind

Jellyfish can undoubtedly cause ecological and economic problems for humans. Mass outbreaks of jellyfish can overrun fish farms, block cooling pipes of power stations, burst fishing nets and damage tourist businesses. Their stings can also cause a severe allergic reaction known as anaphylaxis and even kill people. But jellyfish are also a source of medical collagen, which can be used in wound dressings or reconstructive surgery, and they are considered a delicacy in Japan and China.

But the greatest jellyfish contribution to humankind must be the green fluorescent protein, a common biomarker synthesised from crystal jellies. GFP allows scientists to monitor how certain genes work in real time, and has proved invaluable in medical research, being used in well over 30,000 studies including the study of HIV and Alzheimer's disease. As such, the scientists behind the synthesis of GFP were awarded the Nobel Prize in Chemistry in 2008. Jellyfish may well have started out as the villain, but to many scientists around the world, they have become the inadvertent hero.

They remain a fascinating mystery

There is still so much to discover about these amazing organisms. There is a lot of evidence to suggest jellyfish numbers are increasing in certain areas due to climate change and overfishing of other species. This has lead to the idea they may be increasing worldwide. However, at present, we simply lack the hard data to say with any confidence what is happening to the majority of these populations.

Another mystery is the actual role jellyfish play in ecosystems. Until recently it was thought that jellyfish may not be eaten by anything aside from the occasional turtle or sunfish, and they didn't make a significant contribution to the food chain. This prompted concerns that as jellyfish populations swelled there would be no natural control, and ecosystems may become jelly-dominated.

This concern is not totally trivial and a jellyfish-dominated ecosystem seems to have established off the coast of Namibia. But new analytical techniques involving acoustics, marine cameras, chemical analysis and DNA analysis have shown a variety of species actually do eat jellyfish. This means jellyfish likely play a more important role in marine ecosystems than previously thought. Documenting and understanding this is a top priority for jellyfish researchers.

The writer is a PhD candidate in marine biology at the University of East Anglia, UK

The Independent