New way to fight superbugs

Synthesis of a powerful class of antibiotic may help combat resistant bacteria

S ANANTHANARAYANAN

The discovery of penicillin in 1928 brought about a sea change in the approach to disease and surgery. A first revolution was even earlier, in the mid 1800s, when hygiene and the use of antiseptics entered medical practice. Before Lister's 1867 discovery of the dramatic effect of using carbolic acid to sterilise surgical instruments, there was no saying whether a person undergoing surgery would recover from the procedure.

Even with antiseptics, however, medical science was powerless against a host of pathogens. While epidemics that broke out from time to time took a heavy toll, casualties in the battlefield were often more from infection of wounds than the battle itself. This also changed, with the second revolution, the discovery of penicillin and other antibiotics that followed.

The virtual conquest of bacterial infection, thanks to antibiotics, however, is in danger of being reversed because many pathogens have started developing resistance to antibiotics. The race is hence on to find new antibiotics faster than pathogens can evade them. The trouble is that antibiotics are complex molecules and the sources are normally molds, fungi or plant-based. This is the context of the report by Zihua Lin, Xiaobo Xu, Sheng Zhao, Xiaohong Yang, Jian Guo, Qun Zhang, Chunmei Jing, Shawn Chen and Yun He from Chongqing, Huanguai, Tsingua and Chongqing Medical Universities, in the journal, *Nature Communications*, that a method has been found to produce a class of antibiotics that pathogens would have difficulty in finding ways around.

The way antibiotics work is that they do to the pathogen the same thing that the pathogen does to the body cell. Now, the intelligence of body processes is all contained in the profiles or surface features that cells and chemicals present to each other. Thus, an enzyme switches on a function of a particular cell by attaching to the portion of the cell, which the structure of the enzyme exactly matches. It is this "lock and key" mechanism that makes biological processes both highly specific as well as efficient. The bacterium also makes use of the same machinery, of being able to attach to or enter body cells, to block or divert body processes.

The antibiotic, in turn, uses the same machinery to thwart the pathogen. Mainly by chance, certain substances, found in infinite variety among plants, are able to act against some bacterial and pathogenic organisms. Over centuries, some of these were identified for their curative action, as folk remedies. That the molds, or the fungi that grow on old bread, had an effect on infected wounds, for instance, was known. That is what led Alexander Fleming to discover penicillin. Methods were then developed to create penicillin, and other compounds of the same nature, by culturing samples or by biological processes, like fermentation. Antibiotics, effective against most known diseases caused by bacteria, are now known and manufactured.

The trouble is that the bacteria affected by antibiotics also need to survive and the intelligence built into living things gets active. Over several generations of bacterial reproduction, there are occasional offspring that are not exactly like their parents in some significant respect. If the difference is in a vital feature, of course, the offspring do not survive. But if the difference is in the feature that the antibiotic uses to identify the bacterium, for instance, the newborn has an advantage.

While the normal bacteria get killed off, the new strain faces less competition for resources and grows in numbers. If the antibiotic is used frequently, this could result in the old strain being replaced and we have an epidemic of a "resistant" bacterium. With rampant "off the counter" use of antibiotics, even use for fattening cattle, more bacteria are proving resistant and there are "superbugs", which resist most known antibiotics.

As the sources of antibiotics are mostly in plants, or biological processes, the quest for new antibiotics, to combat resistant pathogens, has to be fresh assays of plant sources or possible modification of the biological process. Advances in microbiology and genetics have helped but there has been no breakthrough in synthesising a "made to order" antibiotic.

The advance that the group from Chongqing, Huanguai and Tsingua report is synthesis of a naturally occurring substance that uses a body substance, on which the bacteria themselves depend, to smuggle itself in and destroy the bacteria. This class of substances is called sideromycins, as they are attached to siderophores, the substances that bacteria need.

Siderophores are molecules that can attach to iron, and bacteria secrete these to harvest iron from the environment. Iron is vital for all life processes but is rarely available except in the form of oxides, which are not soluble in water. This is why bacteria need this special machinery to go out and get it.

The advantage of using siderophores in drug delivery is that siderophores have free passage through the bacteria walls. A sideromycin, an antibiotic attached to a siderophore, can thus be effective at low doses and would clearly present a challenge to a bacterium to develop resistance.

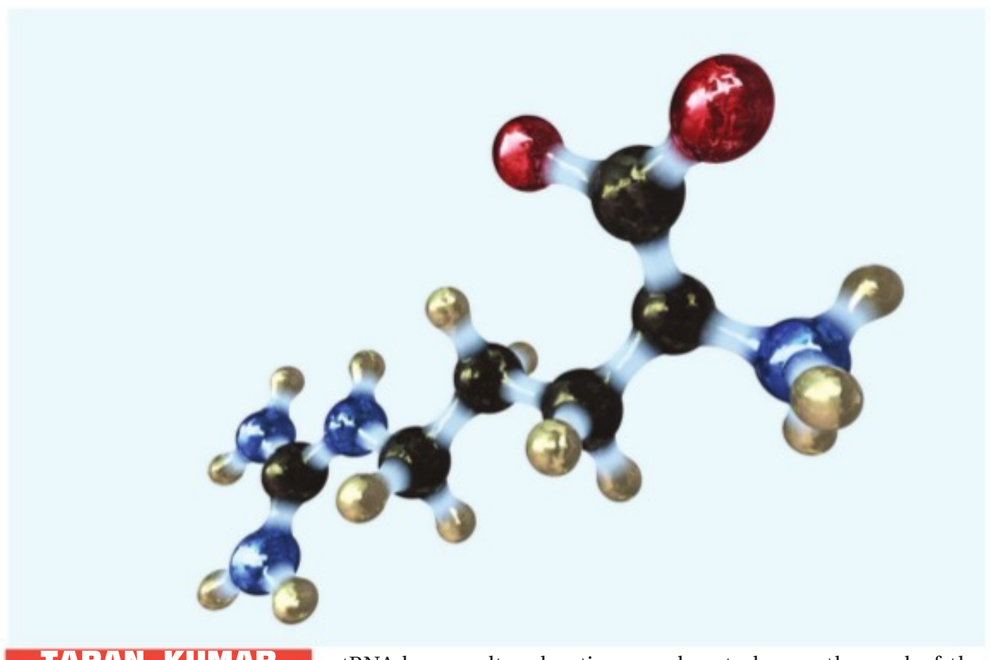
The paper in *Nature Communications* says that a few naturally occurring siderophores have been discovered. Among them are albomycins, which were first isolated from a soil-dwelling species of bacteria, from which several antibiotics, including streptomycin have been derived. Albomycins have been found to be effective against several disease causing bacteria, and against pneumonia and *E coli* infection, they are 10 times as effective as penicillin, the paper says.

The point of the paper, however, is that the team has succeeded in total synthesis of three albomycins, which show potent activity against multi-drug resistant bacteria that cause pneumonia and MRSA, a virulent form of Staph."The minimum concentrations required were well below those of ciprofloxacin, vancomycin, and penicillin G, and in a number of cases reaching 1,000 times lower", the paper says. Their success has opened the door to synthesise other forms of albomycins, the paper says.

The writer can be contacted at response@simplescience.in

Nonsense mutation

Here's the lowdown on a unique process of cellular translation



TAPAN KUMAR MAITRA

The normal process of translation happens when mRNAs containing mu-tant codons are translated. It provides an overview of the main types of mutations and their impact on the polypeptide chains produced by mRNAs. Most codon mutations simply alter a single amino acid, and mutations in the third base of a codon frequently do not change the amino acid at all. However, mutations that add or remove stop codons, or alter the reading frame, can severely disrupt mRNA translation.

Mutations that convert amino acid-coding codons into stop codons are referred to as nonsense mutations. A case in point is the mutation of a single base pair in DNA to an AAG lysine codon in mRNA to a UAG stop signal. Nonsense mutations like this one typically lead to production of incomplete, nonfunctional polypeptides that prematurely terminate the mutant stop codon.

Although nonsense mutations in essential genes are often lethal, phages with such mutations can nonetheless grow in certain strains of bacteria. These special bacteria "suppress" the normal chain-terminating effect of nonsense mutations because they have a mutant tRNA that recognises what would otherwise be a stop codon and inserts an amino acid at that point. A mutant tRNA has an altered anti-condon that allows it to read the stop codon UAG as a coda for tyrosine. The inserted amino acid is almost always different from the amino acid that would be present at that position in the wild-type protein but the crucial feature of suppression is that chain termination is averted and a full-length polypeptide can be made.

A tRNA molecule that somehow negates the effect of a mutation is called a suppressor tRNA. Suppressor tRNAs exist that negate the effects of various types of mutations in addition to nonsense mutations. For the cell to survive suppressor tRNAs must be relatively inefficient; otherwise, the protein-synthesising apparatus would produce too many abnormal proteins. An overly efficient nonsense suppressor, for example, would cause normal stop codons to be read as if they coded for an amino acid, thereby preventing normal termination.

In fact, the synthesis of most polypeptides is terminated properly in cells containing nonsense suppressor tRNAs, indicating that a stop codon located in its proper place at the end of an mRNA coding sequence still triggers termination, whereas the same codon in an internal location does not. This suggests that besides requiring the presence of a stop codon, normal termination involves the recognition of a special sequence or three-dimensional configuration located near the end of the mRNA coding sequence.

In the absence of an appropriate suppressor tRNA, a nonsense stop codon will cause mRNA translation to stop prematurely, thereby generating an incomplete polypeptide chain. To avoid this problem, mammalian cells (which typically lack suppressor tRNAs) destroy mRNAs containing premature stop codons by a mechanism called nonsense-mediated decay. The key to this mechanism is the exon-junction complex, a multi-protein complex deposited during mRNA splicing at each point where an intron is removed from pre-mRNA. Thus a newly made mRNA molecule will have one or more EJCs bound to it, one near the beginning of each exon-exon junction.

During translation, the distinction between normal and premature stop codons is made on the basis of their relationship to EJCs. If a stop codon is encountered in an mRNA prior to the last EJC-in other words, before the last exon — it must be a premature stop codon. This stop codon will cause translation to be terminated while the mRNA still has one or more EJCs bound to it, and the presence of any remaining EJCs marks the mRNA for degradation.

The writer is associate professor, head, department of botany, ananda mohan college, kolkata, and also fellow, botanical society of bengal, and can be contacted at tapanmaitra59@yahoo.co.in

Breaking barriers

Controversially omitted from the Nobel Prize awarded to her male colleagues in 1974, astrophysicist Dame Jocelyn Bell Burnell has donated the entirety of a recent prize to boost diversity in science

Dame Jocelyn Bell Burnell

TOM BARNES

A British astrophysicist has donated the entirety of her £2.3m prize from one of the world's most prestigious science awards to promote diversity among researchers. Professor Dame Jocelyn Bell Burnell announced the money will be used to fund scholarships to help women, refugees and people from ethnic minority groups into the sciences.

The professor was awarded the Breakthrough Prize in Fundamental Physics last week for the role she played in the discovery of pulsars during the mid-1960s. Two of her male colleagues, Anthony Hewish and Martin Ryle, were handed the 1974 Nobel Prize in Physics for the research, but Bell Burnell was controversially overlooked as a co-recipient. "I don't want or need the money myself and it seemed to me that this was perhaps the best use I could put to it," she told *BBC News*.

Bell Burnell was a young research student at Cambridge University when she became the first scientist to observe radiation omitted from pulsars, small stars with huge masses that rotate at tremendous speeds. The precise and consistent timing at which pulsars spin makes them extremely reliable natural clocks for astrophysicists, who have since used them to help map the visible universe. The Belfast-born, York-educated scientist has in the past been diplomatic about her omission from the 1974 Nobel Prize, conceding at the time it was seen as a prize awarded only to senior male scientists.

However, she hopes her donation will pave the way for more ground-breaking discoveries by scientists from diverse backgrounds in the future. "I found pulsars because I was a minority person and feeling a bit overawed at Cambridge," she added, "I was both female but also from the northwest of the country and I think everybody else around me was southern English.

"So I have this hunch that minority folk bring a fresh angle on things and that is often a very productive thing. In general, a lot of breakthroughs come from left field."

The Breakthough Prize is awarded each year to recognise scientists who have made "profound contributions to human knowledge". Sponsors of the prize include *Facebook* chief executive Mark Zuckerberg and *Google* co-founder Sergey Brin. Bell Burnell's cash prize will be handed over to the Institute of Physics, which said the money would be used to "open the door" to the sciences for underrepresented groups. "This prize is an excellent and hugely appropriate acknowledgement of Jocelyn's work," said IOP president Dame Julia Higgins, "Her discovery of pulsars still stands as one of the most significant discoveries in physics and inspires scientists the world over.

"Her example of using insight and tenacity to make a discovery that rings through the ages stands her alongside the greatest of scientists. Alongside her scientific achievement, Jocelyn has become a hugely respected leader in the scientific community.

"She has been instrumental in making sure the issue of access to science by people from under-represented groups is at the very top of the science community's agenda."

The independent

PLUS POINTS

Clean & green

The world's largest offshore wind farm, capable of supplying enough green energy to power around 600,000 homes, has opened off the coast of England. The Walney Extension, a Danish-led and funded project in the Irish Sea, consists of 87 turbines covering an area of 145 square kilometres — roughly equivalent to 20,000 football pitches.

Nearly 12 miles off the coast of Walney Island, Barrow-in-Furness, the wind farm is capable of generating 695 megawatts and has been connected to the National Grid by 300km of cables. It becomes the largest wind farm currently operational in the world; overtaking London Array located around seven miles off Kent in the Thames Estuary.

Construction of the project started in 2015, and has been completed by Danish energy firm Orsted, with the backing of two Danish pension funds. Matthew Wright, Orsted UK managing director, said, "We want to ensure that the local community becomes an integral part of the renewable energy revolution that's happening along its coastline."

Britain is considered to be the best location to generate wind power in Europe and the UK is the sixth highest producer of the renewable energy source in the world. In 2017, wind met a total of 15 per cent of the UK's entire electricity demand, the highest in history. The first quarter of this year also marked the first time in British history that wind power outstripped electricity production by nuclear power stations. Renewable energy of all forms now makes up almost a third of the electricity generated in the UK each year.

UK's energy minister, Claire Perry, said, "Record-breaking engineering landmarks like this huge offshore wind farm help us consolidate our global leadership position, break records for generating renewable energy, and create thousands of high quality jobs."

The independent

Missing remains

Seventeen years later, more than 1,100 victims of the hijacked plane attacks on the World Trade Center have yet to be identified. But in a New York lab, a team is still avidly working to identify the remains, with technological progress on its side. Day in, day out, they repeat the same protocol dozens of times.

At first, they examine a bone fragment found in the wreckage of the Twin Towers. It has yet to be matched to DNA. Cut and ground to a fine dust, the remains are then mixed with two chemical products that can expose and then extract DNA. But success is not guaranteed.

"The bone is the hardest biological material to work with," said Mark Desire, assistant director of forensic biology at the Office of Chief Medical Examiner in New York, "And, on top of that, when they're exposed to things that were present at Ground Zero like fire, mold, bacteria, sunlight, jet fuel, diesel fuel, all these destroy DNA. So you could physically have a sample with very small amounts of DNA there."

The 22,000 pieces of human remains found at the site since the attacks have all been tested — some 10 or 15 times already. So far, only 1,642 of the 2,753 people who died in the attacks in New York have been formally identified. The 1,111 others have yet to yield identifiable information.

Several years have sometimes passed without the lab adding a name. But no one is giving up. Teams from all over the world — from Argentina to South Africa — now come to New York to learn from the team.

When meeting with the families of victims, Desire said the team talks "about the future, what we're working on right now that helps making more identifications."

The straits times/ann