Changing tack in pathogen pursuit

FINDING NEW ANTIBIOTICS AS FAST AS BACTERIA EVADE EXISTING ONES HAS BEEN AN UNEQUAL FIGHT, SAYS **S ANANTHANARAYANAN**

Resistant bacteria and the growth of "super bugs" could convert even a simple surgery into a high-risk procedure and common infections could become as dangerous as they were before the discovery of antibiotics. A study in the UK has estimated that by 2050 antibiotic-resistant bacteria could kill one person every three seconds and cost the world trillions of dollars in economic loss.

Apart from uncontrolled use of antibiotics, the higher human population and increased communications that help resistant strains to spread have led to exponential multiplication of new bacterial forms. The speed with which bacteria are able to evolve has begun to outstrip the capacity of pharmaceutical research to come up with new drugs. In the context, a method to quickly assemble antibiotic molecules from basic constituents, which has been described in the journal *Nature*, may be the answer to the grim prospect of bacteria becoming progressively immune.

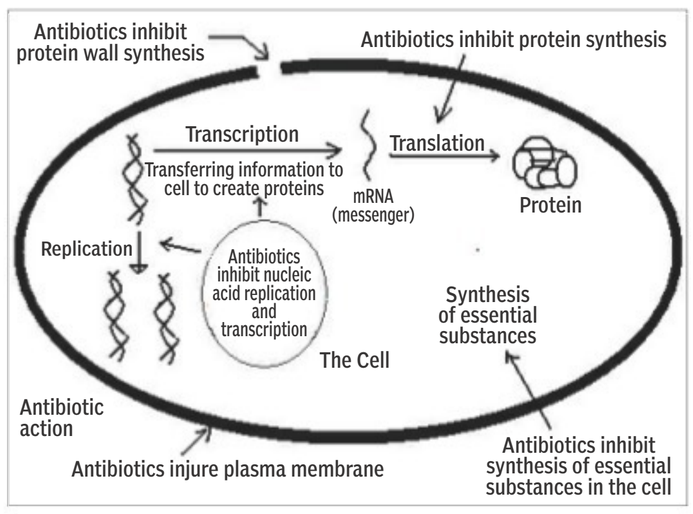
Ian B Seiple, Ziyang Zhang, Pavol Jakubec, Audrey Langlois-Mercier, Peter M Wright, Daniel T Hog, Kazuo Yabu, Senkara Rao Allu, Takehiro Fukuzaki, Peter N Carlsen, Yoshiaki Kitamura, Xiang Zhou, Matthew L Condakes, Filip T Szczypi?ski, William D Green and Andrew G Myers, at Harvard University, Massachusetts, report in their paper that they have built over 300 different molecules with antibiotic activity, including some that are akin to the antibiotic *erythromycin*, starting from basic components. Some of the variations are even active against bacteria that are resistant to existing antibiotics, the paper says.

The era of antibiotics started with the identification of penicillin by Alexander Fleming in 1928. He noticed that bacterial cultures were killed or their growth impeded by an accidental scrap of a fungal growth, or mould. Fleming was then able to show that the mouldy material was effective against a number of bacteria. This explained the use of mouldy bread, for instance, to help wounds heal, but isolating the active agent, which was called penicillin, was challenging. It was only after the efforts by Howard Florey and others in 1939 that penicillin could be used as a drug and research efforts during World War II led to methods of largescale production. A number of other penicillin-like antibacterial substances have since been discovered and antibiotics are now the mainstay of surgeons and physicians.

The way antibiotics act is that their complex molecular structure has portions that are able to attach to specific parts of the exterior of a bacterium, and hence to suppress its life processes or impede its action. Specific antibiotics are then able to deal with specific pathogens or a class of bacteria without serious effects on the body processes of the infected person. The actual antibiotic molecules, however, are too complex to fabricate and need to be formed by bacterial action or fermentation of complex, biological starting materials, a process known as *semisynthesis*. Modifications are still necessary for the substance to have the desired antibacterial effect, and these are carried out using chemical means.

The process is painstaking and involves first treating the molecule so that its major portions are protected, carrying out the change in the target portion and then uncovering the protected parts. Manufacture in quantity, after this, is again through biological processes.

Just as antibiotics need special structural features to be useful, bacteria are also sensitive to antibiotics on account of their own specific surface features. Hence, if a bacterium evolves, by chance mutation, to change those specific surface features, the strain of the bacterium could be as effective in causing disease as before, but immune to some antibiotics. This is the mechanism by which resistant strains of bacteria arise and indiscriminate use of antibiotics in low doses can result in the resistant proportion dominating the population.



Scientists then need to get busy trying to make changes in the structure of available antibiotics to restore effectiveness against the bacterium. This has generally been possible using sophisticated methods to identify the changes needed and then the complex chemical procedure. In this way, with many trials and experimentation, a new antibiotic to deal with the resistant strain can be developed from the previous version of the antibiotic.

With many rounds of such modification, however, and also rapid changes in the features of bacteria, this process has started getting more difficult or the changes required are not feasible. The rise in human population brings about a crowding of hosts and greater mobility of bacteria. International travel and trade also facilitates the transport of bacteria and a resistant strain is easily able to spread over a wide area and establish itself. The numbers of resistant strains of bacteria have thus started increasing. In 2013, the number of new cases of *multi-drug-resistant tuberculosis* reported was 480,000. *Extensively drug-resistant tuberculosis*, which needs longer and less effective treatment, has been identified in 100 countries. And the trend with many other infections and diseases is the same. The World Health Organisation has, hence, approved an emergency global plan to combat antibiotic resistance and the bleak forecast for 2050 put out by the UK-based study.

Antibiotic assembly

The Harvard University researchers have gone about creating modified antibiotics by a different route. They took on the synthesis of a group of antibiotics called *Macrolides* — whose structure includes the large ring in the left half of the Erythromycin molecule, which is shown in the picture. To this ring are attached different chemical groups, to give rise to different Macrolides, a section of which are antibiotics. Building this structure in the laboratory has not been feasible, and the route to macrolide antibiotics has been only through biological templates.

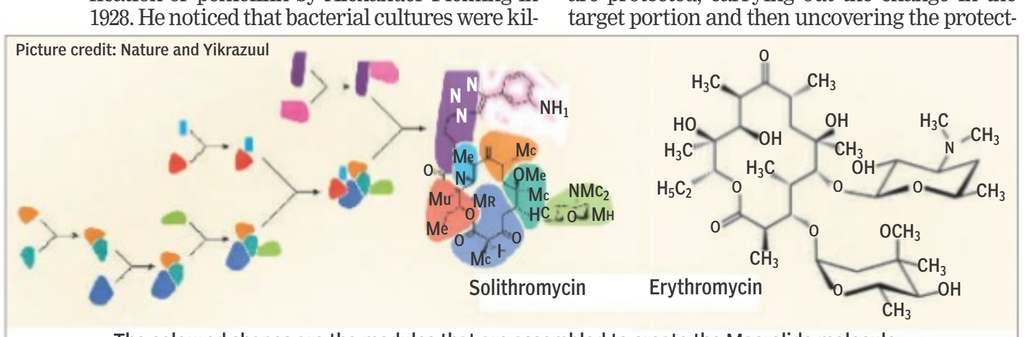
What the Harvard researchers did was to split the Macrolide molecule into eight different modules, or building blocks, as shown by the different colours in the picture, and undertook only the task of synthesising the simple modules. When dealing with simpler modules to create the Macrolide ring, it is also relatively easy to attach the different chemical groups that we may like to have in the final molecules. When the building blocks were ready, the researchers carried out seven key coupling manoeuvres to progressively link the modules together, as shown in the picture. This process sidestepped the difficulties in the conventional way of building the Macrolide molecule, where most attempts failed while creating the ring structure.

The variety of chemical groups that can be attached to the separate portions of the final molecule, and also the process of linking the parts together enable a very high degree of variations. The Harvard group was, hence, able to create over 300 variations of the Macrolide structure, as candidates for development as useful antibiotics. One was the antibiotic, Solithromycin, which is currently produced by carrying out 16 modifications to Erythromycin, the papers says. Three hundred and five of the Macrolides created were tested against a panel of pathogens, including well known and notorious antibiotic resistant bacteria. Most of the Macrolides showed promising potency, the paper says.

The work done is hence a platform for creating an unequalled variety, with simple permutations of the components of Macrolide antibiotics, for experimentation and synthesis if found useful. There would be need for more study of the side effects and effectiveness of these Macrolides in use as a drug, but the industry now has a starting point that is most of the way to the finishing line, the paper says. Finding similar ways to synthesise other naturally occurring antibiotic families would be a logical sequel, it adds.

THE WRITER CAN BE CONTACTED AT
response@simplescience.in

Picture credit: Nature and Yikrazuul



The coloured shapes are the modules that are assembled to create the Macrolide molecule. Notice the same basic structure as Erythromycin, shown on the right.

PLUS POINTS

Supercomputer for India

India will get an indigenously-built supercomputer next year as part of the government's Rs 4,500-crore programme

aimed at taking the country into an elite league of nations that have made advancements in the field.

The Centre for Development of Advanced Computing that built India's first supercomputer, Param, is handling the project, said Ashutosh Sharma, secretary in the Union ministry of science and technology.

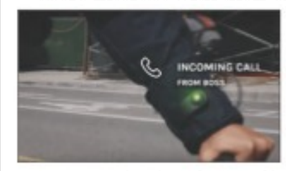
In March last year, the government had approved the plan of the National Supercomputing Mission, under which 80 supercomputers will be built in the next seven years. "Some of them will be imported and the rest will be built be indigenously. The first one will come up by August 2017," Sharma said. "We are working on how to control heat. The cost of power to run these supercomputers alone will be around Rs 1,000 crore."

The new supercomputers will be kept in different institutes across the country. "A supercomputer can be used for various purposes like climate modelling, weather forecasts, discoveries of drugs among others," he said.

Currently, countries like the USA, Japan, China and the European Union account for a major share of the top supercomputing machines in the world.

Smartphone control

Google and denim jeans company Levi's have developed a new jacket that lets users interact with their smartphones by



swiping at the garment in various ways. Called the "Commuter Trucker Jacket", the garment is aimed at cyclists who may be too busy riding and concentrating on their surroundings to reach into their pockets and fiddle with their phones, *Forbes* reported citing Paul Dillinger, company head of global product innovation.

The jacket is apparently waterproof — except for a detachable electronic smart tag that activates a wireless connection between the clothing and a mobile device. "If you get this thing dirty, you put it in the washing machine," said Dillinger during Google's annual developer conference in Mountain View, California, recently.

The garment is powered by Google's Project Jacquard technology developed by the Internet giant's Advanced Technology and Projects Group.

'Green desert'

Invasive species can have unpredictable impacts on new habitats. They can alter the food chain and overpopulate entire regions at the expense of local animals

and plants. Living creatures have always moved at different rates around the planet. but human transport can rapidly carry animals and plants around the world. Those who thrive in new places will irreparably change local biodiversity.

The Opuntia stricta cactus, known as the erect prickly pear, is native to the Americas. It was introduced to East Africa decades ago as an ornamental plant, but has since spread throughout the continent with a devastating effect on people's lives, reducing land productivity and harming livestock.

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'One step closer'

Scientists have said they are "one step closer" to providing commercial hypersonic flight jets fast enough to fly passengers from London to Sydney in just

two hours. An experimental aircraft, launched as part of the Hypersonic International Flight Research Experimentation project, successfully reached Mach 7.5 during a recent trial at the Woomera Test range in South Australia.

"The success of this test launch takes us one step closer to the realisation of hypersonic flight," said Dr Zelinsky, chief defence scientist at the Australian department of defence. "It's a game-changing technology… and could revolutionise global air travel, providing cost-effective access to space."

The experimental rocket, HIFiRE 5B, reached a speed of around 9,200 km per hour, 278 km from the earth. Led by Australia's department of defence science and technology group in collaboration with the US air force, the HIFiRE programme is a $54-million research project aimed at exploring the potential for hypersonic speed aeronautical systems — aircraft that can travel at more than five times the speed of sound, or around 6,700 kmph.

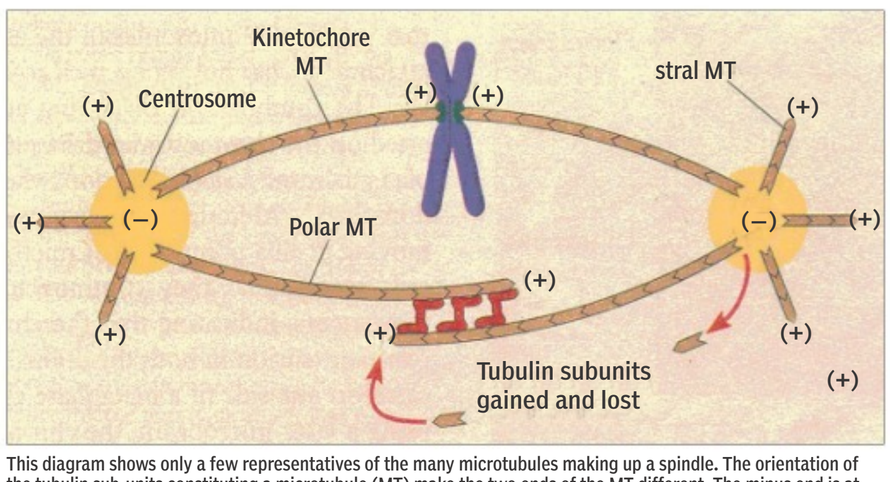
THE INDEPENDENT

GOING BACK & FORTH

THE MITOTIC SPINDLE IS RESPONSIBLE FOR CHROMOSOME MOVEMENTS DURING MITOSIS, WRITES **TAPAN KUMAR MAITRA**

The central purpose of mitosis is to separate two sets of daughter chromosomes and partition them into an equal number of newly-forming daughter cells. To understand the mechanisms that allow this to be accomplished, one needs to take a closer look at the microtubule-containing apparatus responsible for these events, which is called the mitotic spindle.

First, let's address the process by which the spindles assemble and attach to the chromosomes. The fact that the tubulin sub-units of a microtubule all face in the same direction gives them an inherent polarity; that is, the two ends of each microtubule are chemically different. The end where microtubule assembly is initiated — located at the centrosome for spindle microtubules — is the minus (-) end while the end where most growth occurs, located away from the centrosome, is the plus (+) end. Microtubules are dynamic structures, in that tubulin sub-units are continually being added and subtracted from both ends. When more sub-units are being added than removed, the microtubule gets longer. In general, the plus end



This diagram shows only a few representatives of the many microtubules making up a spindle. The orientation of the tubulin sub-units constituting a microtubule (MT) make the two ends of the MT different. The minus end is at the initiating centrosome; the plus end points away from the centrosome. MTs lengthen by adding tubulin sub-units and shrink by losing sub-units. In general, lengthening is due to addition at the plus ends and shortening to loss at the minus ends, but sub-units can also be removed from the plus ends. The red structures between the plus ends of the polar MTs shown here represent proteins that crosslink them.

is the site favoured for the addition of tubulin sub-units and the minus end is favoured for sub-unit removal.

During late prophase, microtubule-forming activity speeds up dramatically and the initiation of new microtubules at the centrosomes increases. Once the nuclear envelope disintegrates at the beginning of prometaphase, contact between microtubules and chromosomal kineto-chores becomes possible. When contact is made between a kinetochore and the plus end of a microtubule, they bind to each other and the microtubule is thereafter known as a kinetochore microtubule. This binding slows down the depolymerisation rate at the plus end of the microtubule, although polymerisation and depolymerisation can still occur there.

The plus ends of the microtubules are embedded in the two kinetochores. Each kinetochore is a plate-like, three-layered structure made of proteins attached to CEN sequences located in the centromere's DNA. Kinetochores of different species vary in size. In yeast, for example, they are small and bind only one spindle microtubule each, whereas the kinetochores of mammalian cells are much larger, each binding 30-40 microtubules.

Because the two kinetochores are located on opposite sides of a chromosome, they usually attach to microtubules coming from opposite poles of the cell. (The orientation of each chromosome is random; either kinetochore can end up facing either pole.) Meanwhile, the polar microtubules make direct contact with those coming from the opposite centrosome. When the plus-end regions of two microtubules of opposite polarity start to overlap, cross-linking proteins bind them to each other. Like the cross-linking between kinetochores and kinetochore microtubules, the process stabilises the polar microtubules. Thus, one can picture a barrage of microtubules rapidly shooting out from each centrosome during late prophase and prometaphase. The ones that successfully hit a kinetochore or a microtubule of opposite polarity are stabilised while the others retreat by disassembling. It was once thought that the process by which microtubules find a kinetochore was entirely random but recent evidence suggests that signalling molecules may help guide microtubules toward the chromosomes.

When spindle microtubules first become attached to chromosomal kinetochores during early prometaphase, the chromosomes are randomly distributed throughout. The chromosomes then migrate toward the central region of the spindle through a series of agitated, back-and-forth motions generated by at least two different kinds of forces. First, the kinetochore microtubules exert a "pulling" force that moves the chromosomes toward the pole to which the microtubules are attached. That force can be demonstrated experimentally by using glass micro-needles to tear individual chromosomes away from the spindle. A chromosome that has been removed from the spindle remains motionless until new microtubules attach to its kinetochore, at which time the chromosome is drawn back into the spindle.

The second force tends to "push" chromosomes away if they approach either spindle pole. The existence of this pushing force has been demonstrated by studies in which a laser microbeam is used to break off one end of a chromosome. Once the broken chromosome fragment has been cut free from its associated centromere and kinetochore, the fragment tends to move away from the nearest spindle pole, even though it is no longer attached to it by microtubules. The nature of the pushing force that propels chromosomes in the absence of microtubule attachments has not yet been clearly identified.

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

Europa could support life

DOUG BOLTON REPORTS ON A NASA STUDY

Jupiter's moon Europa could have the right chemical balance to support life, according to a new study by the National Aeronautics and Space Administration. The balance of hydrogen and oxygen production on the small moon is comparable to that on earth, meaning the core building blocks of life could be present. The study hinges on the theorised salty ocean of liquid water that sits underneath the moon's icy shell.

To estimate the ratios of chemical production on Europa, the Nasa team looked at how much hydrogen could be produced as the ocean's salty water reacts with rock in a process known as serpentinisation. During this process, which also takes place on earth, water filters through minerals and reacts with rocks to form new minerals, producing hydrogen as a byproduct. Using complex models based on our knowledge of Europa, the team figured out how cracks in the moon's sea floor had opened up over time, allowing them to predict how much fresh rock was made available for serpentinisation.

The study is a vital step in discovering whether the moon's ocean could harbour life. Steve Vance, a planetary scientist at Nasa's Jet Propulsion Laboratory, said: "The cycling of oxygen and hydrogen in Europa's ocean will be a major driver for its ocean chemistry and any life there, just as it is on earth."

Kevin Hand, another JPL researcher, compared the interaction between Europa's surface and sea bed as a giant battery that could power life in the ocean. "The oxidants from the ice are like the positive terminal of a battery, and the chemicals from the seafloor, called reductants, are like the negative terminal. Whether or not life and biological processes complete the circuit is part of what motivates our exploration of Europa."

The results of the study have been published in the *Geophysical Research Letters* journal, but we could know more soon. Nasa is currently planning a mission to Europa, in which a probe will pass close to its surface and take high-resolution pictures.

THE INDEPENDENT

Europa's streaked surface could tell us more about the composition of its ocean.