Making short work of malady

A TRADITIONAL CHINESE REMEDY FOR MALARIA HAS BEEN FOUND TO HELP DRUGS ACT MORE INTENSELY AGAINST TUBERCULOSIS, WRITES **S ANANTHANARAYANAN**

A third of the world's population harbours the tuberculosis bacterium, which causes nearly two million deaths every year. The disease is curable, but the deaths, mostly in developing countries, mainly occur because of insufficient or incomplete treatment. Apart from the fact that patients do not get completely cured, less treatment gives rise to antibiotic resistance.

An important reason for the treatment remaining incomplete is that it needs to be taken regularly over a period of six months or more. Patients in developing countries are frequently unable to stick with the medicine regimen and the bacterium is not destroyed, but revives, often in a form that may not respond to available antibiotics.

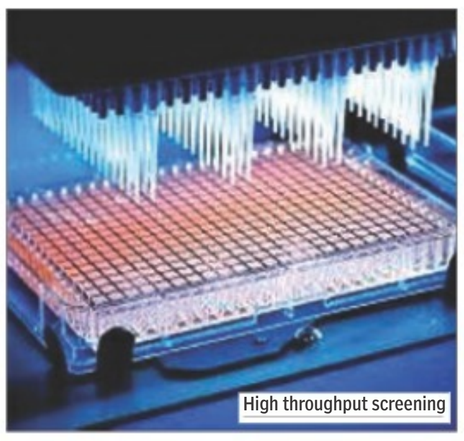
In this context, the discovery by Huiqing Zheng, Christopher J Colvin, Benjamin K Johnson, Paul D Kirchhoff, Michael Wilson, Katriana Jorgensen-Muga, Scott D Larsenand and Robert B Abramovitch of the Michigan State University, the University of Michigan and Sweet Briar College, Virginia, of a method to attack the TB bacterium effectively over a shorter period has widespread importance. The team of researchers report in the journal, *Nature Chemical Biology*, that artemisinin, the active component of an ancient Chinese herbal treatment for malaria, effectively interferes with the mechanism of the TB bacterium to evade the immune system and lurk in a dormant state, which is the reason that treatment needs to be maintained for a longer period.

Robert Abramovitch

The immune system in the body reacts to the presence of mycobacterium tuberculosis, which causes the disease by turning off the supply of oxygen and nutrients that the bacterium needs, and by regulating the level of acidity. The bacterium, in turn has evolved a mechanism of slowing down its metabolic activity and entering a state of dormancy so that it can survive the immune system attack. It has been found that the response is brought about by a set of genes called DosRST or Dormancy survival Regulator, along with components S and T. DosS and DosT sense the levels of nitrous oxide, carbon monoxide and oxygen, to promote a set of genes called the DosR regulon. It keeps the MTB quiescent and also imparts resistance to antibiotics.

There has hence been interest in finding ways to block dormancy, and one way would be to inhibit the working of the MTB's machinery to detect low levels of oxygen. In the course of automated trials conducted on over 540,000 small molecules, to assess their effect on DosRST, it was found that five compounds, including artemisinin, were able to prevent DosRST from responding to environmental oxygen levels. "If MTB cannot sense low oxygen, then it cannot become dormant and will die," says microbiologist and TB expert, Abramovitch, who led the study.

Abramovitch and his team used an automated technique, called high throughput screening, where organisms can be treated with a range of chemical or other agents, in an array of thousands of small containers, called wells, in trays called microtitre plates. The results are then surveyed, in an operation known as an "assay", and this can be automated, using robotic instrumentation.



High throughput screening

The method has been used effectively in drug discovery or to identify trace impurities or in quality control. The Abramovitch team made use of a fluorescent marker, or a chemical that glows when bathed in light of a suitable colour, that is activated by the presence of DosR in conditions of mild oxygen depletion. As DosR arises during oxygen depletion, the presence of DosR, which brings about dormancy of MTB, would be advertised by fluorescence. If fluorescence were absent, however, this would indicate that the growth of DosR had been suppressed by the compound that had been added to that well of the microtitre plate.

The method of high throughput screening enabled automated testing for fluorescence and rapid trials with 540,288 different compounds. The target of the test was a significant dip in the fluorescence, which would indicate that DosR had been suppressed. Artemisinin is believed to be effective against malaria because it affects an iron containing molecule, called heme, in cells. As the oxygen sensors DosS/T also contain iron, the artemisinin group was among the compounds tried out. And it is this group, along with five other compounds, that was found to have the strongest inhibiting action on DosR. The DosR regulon is composed of some 50 basic genes and another hundred, or so, are also expressed by variations of DosR. Analysis showed that artemisinin was able to inhibit the well-characterised genes and also a large part of the others.

Administering Artemisinin-based therapy could thus shut down the signal that tells the MTB bacterium that it is time to sleep and disappear. The bacteria would then stay awake and be starved of oxygen and nutrients and in position for antibiotics, to make short work of them. Apart from being empowered, the course of treatment would also be brief and capable of being more efficiently administered.

An important part of the arsenal against malaria, which affects much of Africa and South-east Asia, would thus join the forward line in the offensive against tuberculosis, a scourge in the poorest parts of the world.

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Ancient Chinese remedy

Artemisinin, known as *quinghao su* in Chinese, is a 2,000-year-old remedy for the falciparum, or the cerebral strain of malaria. Artemisinin occurs naturally in the plant Artemisia annua or sweet wormwood, from which it is now extracted. There is now also a means of producing the compound with the help of genetically engineered yeast.

While the drug has problems of being effective for a short time and of toxicity, it is still the best known rapid-acting drug against falciparum malaria and, in combination with other drugs, is now the standard protocol. Tu Youyou, the Chinese scientist who isolated the drug, shared the 2015 Nobel Prize for Medicine for her discovery.

Quinghao su or sweet wormwood.

PLUS POINTS

Ebola breakthrough

An experimental vaccine has been found to be highly successful against the deadly Ebola virus when used in a major trial in Guinea. The study, led by the World Health Organisation, was the first to find a way to stop infection from the pathogen. The drug has not yet been approved by regulatory authorities but an emergency stockpile of 300,000 doses has been created in case the virus flares up.

Keïta Sakoba, director of the National Agency for Health Security in Guinea, said, "Ebola left a devastating legacy in our country. And we are proud that we have been able to contribute to developing a vaccine that will prevent other nations from enduring what we endured." During the outbreak of 2014, the virus took the lives of more than 11,000 in Africa with Guinea among the worst-affected countries.

The study, published in the *Lancet* medical journal, involved 11,841 people and took place in coastal regions where Ebola cases were still occurring when the trial began in 2015. Nearly 6,000 people received the vaccine and all were free of the virus 10 days later.

The Ebola virus was first discovered in 1976 but until the 2014 outbreak, only about 1,600 people died from it and efforts to create a vaccine were hindered by a lack of funding.

"While these compelling results come too late for those who lost their lives during West Africa's Ebola epidemic, they show that when the next Ebola outbreak hits, we will not be defenceless," said Marie-Paule Kieny, Who's assistant director-general for health systems and innovation, and the *Lancet* paper's lead author.

SAFYA KHAN-RUF/THE INDEPENDENT

New species found

A rainbow-headed snake, a tiny frog and a lizard with dragon-like horns are among more than 150 new species confirmed by scientists last year in the ecologically diverse but threatened Mekong region, researchers said recently.

Winding its way from the Tibetan plateau through the mountains and jungles of South-east Asia, the Mekong River helps sustain one of the most diverse regions on the planet.

But there are fears many species may die out before even being discovered in an area of the world that is rapidly developing, where rule of law is notoriously shaky and wildlife smuggling rampant. The Greater Mekong region — which includes south-western China, Vietnam, Cambodia, Laos, Thailand and Myanmar — is under intense pressure from dam and road building as well as a thriving illegal wildlife trade, much of it centred around the lawless Golden Triangle area where the latter three meet.

In total, scientists described 163 new species in 2015 including nine amphibians, three mammals, 11 fish, 14 reptiles and 126 plants. Among the most eye-catching are *parafimbrios lao*, a snake found in the limestone karsts of northern Laos whose scales reflect rainbow-like colours around its head.

On the Thai tourist island of Phuket, which has seen huge development in recent decades, scientists found a lizard (*acanthosaura phuketensis*) with a fearsome-looking ridge of horns down its head and back.

And in the country's northern Chiang Rai province researchers found a newt (*tylototriton anguliceps*) with dazzling red and black markings that they likened to a Klingon's head from the *Star Trek* franchise.

In Cambodia and Vietnam, a new frog species that could fit on a finger tip was also discovered. At three centimetres long, *leptolalax isos*, can fit on a finger tip. It was first spotted in 2006 but peer-reviewed confirmation that it was indeed a new species took nearly a decade.

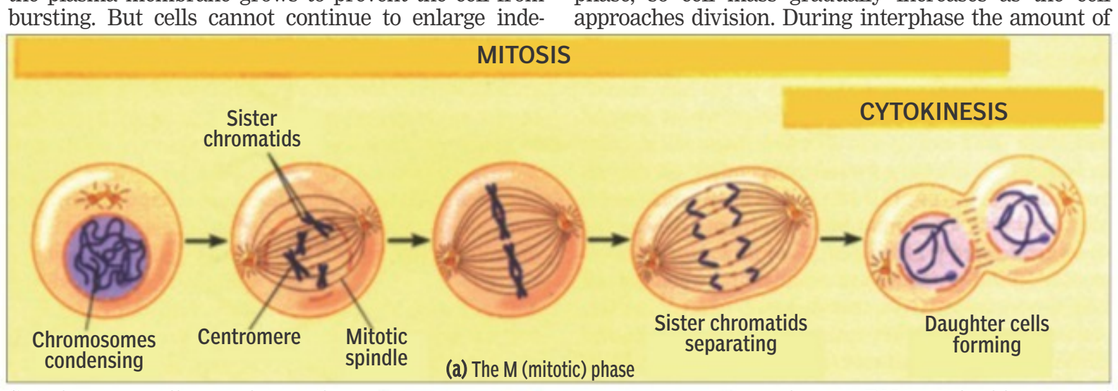
Between 1997 and 2015 there have been 2,409 new species described in the Greater Mekong, the equivalent of two new discoveries a week.

THE STRAITS TIMES/ANN

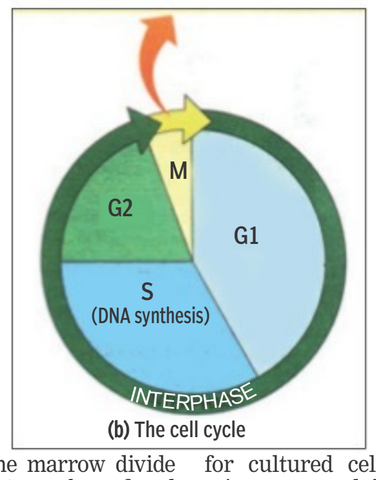
DIVIDING IN PHASES

TAPAN KUMAR MAITRA PROVIDES AN OVERVIEW OF THE CELL CYCLE

Cell growth is accomplished through the synthesis of new molecules of proteins, nucleic acids, carbohydrates and lipids. As the accumulation of these molecules causes the volume of a cell to increase, the plasma membrane grows to prevent the cell from bursting. But cells cannot continue to enlarge indefinitely — as a cell grows larger, there is an accompanying decrease in its surface area/volume ratio and hence in its capacity for effective exchange with the environment. Therefore, cell growth is generally accompanied by cell division, whereby one cell gives rise to two new daughter cells (The term daughter is used by convention and does not indicate that cells have gender.)



(a) The M (mitotic) phase



(b) The cell cycle

For single-celled organisms, division increases the total number of individuals in a population. In multi-cellular organisms, cell division either increases the number of cells, leading to growth of the organism, or replaces ones that have died. In an adult human, for example, about two million stem cells in bone marrow divide every second to maintain a constant number of red blood cells in the body.

A cell passes through a series of discrete stages, collectively known as the cell cycle. It begins when two new cells are formed by the division of a single parental cell and ends when one of these cells divides again into two cells. To early cell biologists studying eukaryotic cells with the microscope, the most dramatic events in the life of a cell were those associated with the point in the cycle when the cell actually divides. This division process, called the M phase, involves two overlapping events in which the nucleus divides first and the cytoplasm second. Nuclear division is called mitosis, and the division of the cytoplasm to produce two daughter cells is termed cytokinesis.

While visually striking, the events of the mitotic phase account for a relatively small portion of the total cell cycle; for a typical mammalian cell, the mitotic phase usually lasts less than an hour.

Cells spend the majority of their time in the growth phase between divisions called interphase. Most cellular contents are synthesised continuously during interphase, so cell mass gradually increases as the cell approaches division. During interphase the amount of nuclear DNA doubles, and experiments using radioactive DNA precursors have shown that the new DNA is synthesised during a particular portion of interphase named the S phase (S for synthesis). A time gap called Gl phase separates the S phase from the preceding M phase, and a second gap, the G2 phase, separates the end of S phase from the beginning of the next M phase.

Although the cells of a multicellular organism divide at varying rates, most studies of the cell cycle involve them growing in culture, where the length of the cycle tends to be similar for different types. We can easily determine the overall length of the cell cycle – the generation time – for cultured cells by counting the cells under a microscope and determining how long it takes for the population to double. In cultured mammalian cells, for example, the total cycle usually takes about 18-24 hours. Once we know the total length of the cycle, it is possible to determine the length of specific phases. For mammalian cells in culture, S phase is about six to eight hours in length. On the other hand, the M phase lasts less than an hour (usually 30-45 minutes).

In contrast to the S and M phases, whose lengths tend to be quite similar for different mammalian cells, the length of G1 is quite variable, depending on the cell type. G2 is shorter than G1 and is more uniform in duration among different cell types, usually lasting four to six hours.

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Blame it on friends

SCIENTISTS FROM THE US HAVE FOUND THAT VIOLENCE SPREADS THROUGH TEENAGERS LIKE A 'CONTAGIOUS DISEASE'. **IAN JOHNSTON** REPORTS

Violence spreads through young people like a disease, with adolescents up to 180 per cent more likely to attack someone if a friend has done so previously, according to new research in the US. The effect was so strong that new outbreaks of fighting were more likely even if a friend of a friend — and onwards up to four degrees of separation — had been violent.

One of the researchers, Professor Robert Bond of Ohio State University, said, "This study shows just how contagious violence can be. Acts of violence can ricochet through a community, travelling through networks of friends." He also said that the research showed why prevention of violence was so important. Bond added, "If we can stop violence in one person that spreads to their social network. We're actually preventing violence not only in that person, but potentially for all the people they come in contact with."

In London, there has long been a problem with stabbings, mainly carried out by teenage boys and young men. In August this year, there were 1,749 stabbings of people aged below 25 years in the city — a four-year high. However, gang activity was blamed for less than five per cent of knife crime in the city.

In 2006, Danny and Ricky Preddie, from Peckham, south London, were convicted of the manslaughter of 10-year-old Damilola Taylor, who bled to death after being stabbed in the leg with a broken bottle in November 2000 when the Preddie brothers were 12 and 13 years old.

In the US study, researchers studied information about nearly 6,000 people, most aged between 12 to 18 years, who took part in the National Longitudinal Study of Adolescent Health in the 1990s. The adolescents were asked how often in the past 12 months they had been in a serious physical fight, how often they hurt someone badly enough to need medical attention, and how often they had pulled a knife or gun on someone.

They were 183 per cent more like to have hurt someone badly, 140 per cent more likely to have drawn a weapon and 48 per cent more likely to have been in a serious fight if they had a friend who had done something similar.

Professor Brad Bushman, another of the researchers, said, "We now have evidence that shows how important social relationships are to spreading violent behaviour, just like they are for spreading many other kinds of attitudes and behaviours." The study echoes others that have looked into the effect of social networks on a range of different kinds of attitudes and behaviour, from happiness to obesity and smoking.

The researchers said part of the explanation was a "clustering effect", in which violent people tend to become friends with each other. But even after taking that into account, they found the chance that a boy or a girl had hurt someone else badly increased by 55 per cent for each friend they had who had done this. The figure was 82 per cent for the males alone.

Each degree of separate saw a reduction in the effect. While an adolescent was 48 per cent more likely to have had a serious fight if a friend had been in one, this figure dropped to 18 per cent if a friend of a friend had.

The research was published in the *American Journal of Public Health*.

THE INDEPENDENT