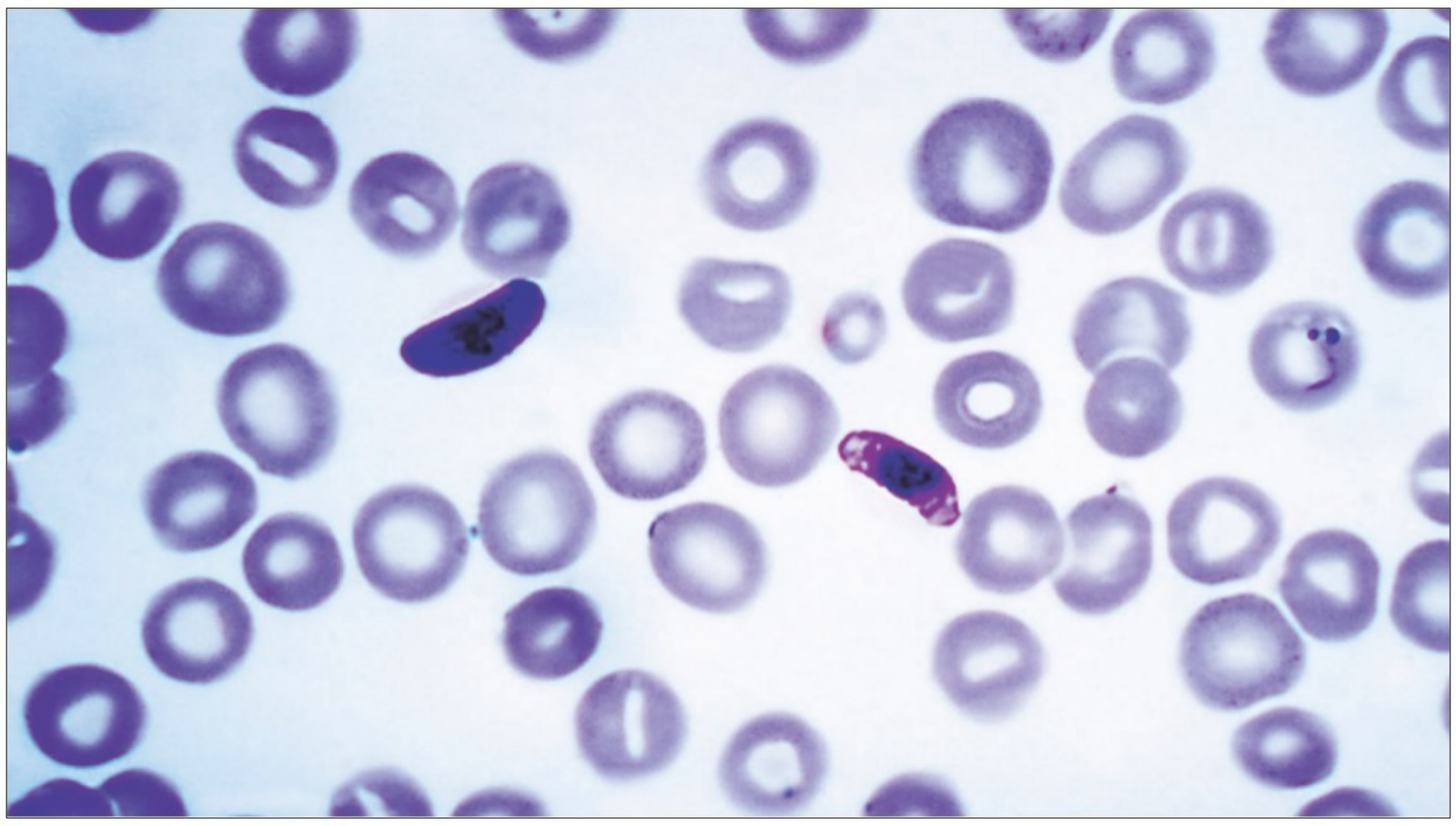
# Plugging escape routes

**The malaria parasite is known for proficiency in evading the effect of drugs, especially in the tropics**



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Pathogens have a tendency to develop resistance. The usual pathway is through chance mutations that have inborn resistance. These mutants, though in small numbers, survive the attack by drugs and the body's mechanisms against the original organisms, and they thrive, because the drugs reduce their competitors for resources. Mutants hence multiply and grow into a drug-resistant strain, in good numbers.

Malaria is a notable example of this method of keeping a step ahead of drugs and has been rampant in the tropics, where the temperature and humidity favour the growth of the malaria parasite. In a paper just published in the journal, *Science* (of the American Association for the Advancement of Science), Elizabeth A Winzeler and a team of scientists from California, Missouri, Massachusetts, New York, Geneva and Madrid describe an innovative strategy to track down the sensitive spot in the parasite's genome, to block the facility with which it changes form.

The authors explain that a single human infection may result in more than a thousand billion blood-stage parasites. With even a mutation rate of one instance in a billion, at least one parasite that resists known drugs or body defences can turn up in a few reproductive cycles. And this mutant strain can grow unopposed, for months, till effective drugs are developed.

While this rapid proliferation and turnaround of generations leads to successive, new drugs becoming obsolete, the same features allow the process of evolution, under pressure of anti-malarial substances, to be initiated and observed in the laboratory. As drug-resistant forms arise in the laboratory cultures, minute genetic changes can be traced, by analyses of the genome of the succession of parent and mutant offspring, to uncover the changes that bring about drug resistance. The paper notes that watching for the changes that accompany the onset of resistance is also an effective method of isolating the target, or mechanism of action, of a known anti-malarial agent. These methods, however, have focused, so far, on isolated genetic effects of single compounds.

In the present study, the group systematically examined the changes in the DNA of the falciparum malaria parasite, over its life cycle, as it evolved and developed resistance against a range of anti-malarial substances. The bulk of therapeutic drugs consist of organic chemical molecules that are small in comparison with structures like proteins. These molecules act by binding at specific regions of large biological molecules or cells or act as initiators of immune or other responses. As small molecules can be absorbed through the intestinal wall, it is possible for such drugs to be administered orally. The study was hence conducted with a collection of plasmodium falciparum parasites of the same genealogy, which had developed resistance against an array of 37 different small molecules. Most of these were known anti-malarials, while the others had significant chemical structures.

To isolate the genetic bases of the drug-resistance developed, the DNA structures of 204 mutant varieties of the falciparum parasite were fully sequenced. The DNA structure is a pair of strings, each of which is a series made up of four kinds of chemical units known as A,T,G and C. The units in the pair of strings are interconnected, to form the shape of a spiralling ladder, with the rule that A must pair with T and C must pair with G. The sequence of bases in one string thus defines the sequence in the other string and this is what makes it possible for each string to build up the complementary string when the DNA splits into two during cell division.

Segments of DNA, each one called a gene, are the code on the basis of which the cells of an organism generate different proteins. The structure of the DNA thus administers the functional viability of a species and permitted variations in the DNA structure lead to differences in the individuals of the species. These are the differences among the descendents of pathogen organisms that may lead to some growing resistant to drugs or other agents that threaten the organism.

In 262 analyses of the sequences of millions of units (which are called base pairs) in the DNA, the study discovered 1,277 instances of a change in a single base pair and 668 small insertions or deletion of base pairs. Single base pair damage, called point mutations, can have far ranging effects and there is a list of serious genetics disorders arising from them. This study, like others that have gone before, thus finds single base pair damage implicated in malarial drug resistance.

In addition to single pair variations, the study found frequent instances of base pairs or series of base pairs being repeated, a feature known as copy number variants, which contribute to drug-resistance. While the human DNA, with three billion base pairs, codes for 30,000 genes, it was believed that the DNA usually had two copies of each gene. But it has been discovered that there are often many copies and great variety in the number of copies of even large sections of DNA, often in parts that do not code for genes.

Such variations lead to individual differences, due to which functional genes are differently presented for becoming active. That leads to differences in traits, including susceptibility to disease, or, in the case of the malaria parasite, in the sensitivity to drugs. True to being difficult to handle, the paper notes that even in this feature of copy number variants, the structure of p falciparum is "A-T rich", which makes it problematic to detect copy number variation. The team hence developed a case specific algorithm for detecting copy number variants.

The team notes that the study, through "a controlled examination of anti-malarial drug resistance acquisition", has identified a collection of genes that would aid clinical studies and drug development. "It is notable that we were able to identify a likely target or resistance gene for every compound for which resistant parasites were generated. Our characterisation of the chemo genetic landscape of p falciparum will guide the design of small-molecule inhibitors against this deadly eukaryotic pathogen," the paper says.

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### Deadliest parasite

Plasmodium falciparum is a single celled parasite and the deadliest species of Plasmodium that cause malaria in humans. It is transmitted through the bite of a female Anopheles mosquito. It is responsible for roughly 50 per cent of all malaria cases. It causes the disease's most dangerous form, called cerebral malaria and is regarded as the deadliest parasite in humans, causing a conservative estimate of one million deaths every year.

Elizabeth A Winzeler

PLUS POINTS

## Female majority

Over 99 per cent of green turtles born in parts of the Great Barrier Reef are female because of increasing temperatures linked to climate change. A turtle's sex is dependent on the temperature at which it is incubated, so warmer nests result in more females.

As a result scientists and conservationists have warned that as global temperatures rise, Australian turtle populations face "complete feminisation" in the near future. "Finding that there are next to no males among young northern green turtles should ring alarm bells," said Dermot O'Gorman, the chief executive officer of the World Wide Fund for Nature, Australia.

In some northern beaches near Australia's Great Barrier Reef, scientists found that virtually every juvenile turtle was female and over 85 per cent of the adults. Even in cooler beaches to the south, nearly 70 per cent of young turtles were female.

The research was published in the journal *Current Biology*. The study's leader author, Michael Jensen, a marine biologist at the National Oceanic and Atmospheric Administration, said skewed sex ratios over the last two decades have resulted in an "extreme female bias" in the populations.

If this trend continues, the turtle populations are likely to collapse, he warned. "This research is so important because it provides a new understanding of what these populations are dealing with," he said. "Knowing what the sex ratios in the adult breeding population are today and what they might look like five, 10 and 20 years from now when these young turtles grow up and become adults is going to be incredibly valuable."

The scientists caught turtles at their foraging sites, identified their sex and used genetic tests to determine their nesting origin. They combined this information with recent temperature data to deduce the cause of this "feminisation".

The plight of turtles has been highlighted recently, as they are some of the many animals known to consume plastic in the oceans, often with fatal consequences. "But all is not lost for this important population," O'Gorman said, adding that scientists and wildlife managers can use this knowledge to work out practical ways to help these turtle populations.

The Independent

# Messenger from afar

**Last year a mysterious, cigar-shaped object traversed our solar system — its speed and orbit indicated it had originated from outside our galaxy. Now, somebody has said he knows where it came from**

FABO FENG

One of the highlights of 2017 was the discovery of the first object in our solar system that definitely came from somewhere else. At first we thought it was a comet, then an asteroid, and now the International Astronomical Union has reclassified it as something new entirely — an interstellar object. The Hawaiian astronomers who discovered it aptly named it Oumuamua, which means "a messenger from afar arriving first", reflecting that this object is like a scout sent from the past to reach out to us.

Research has already helped us learn a lot about Oumuamua's rare cigar-like shape, what it's made of (ice with a carbon-rich surface) and its highly unusual orbit, which will take it out of our solar system at a speed of around 26km/s. The Breakthrough Listen research programme has even investigated whether Oumuamua is an alien space ship by scanning the object for life forms with the Green Bank telescope. No intelligent signals have been identified so far, though further observations are planned.

Now my latest study gives us a glimpse of exactly where Oumuamua may have come from. Reconstructing the object's motion, my research suggests it probably came from the nearby "Pleiades moving group" of young stars, also known as the "Local Association". It was likely ejected from its home solar system and sent out to travel interstellar space.

Based on Oumuamua's trajectory, I simulated how it has probably travelled through the galaxy and compared this to the motions of nearby stars. I found the object passed 109 stars within a distance of 16 light years. It went by five of these stars from the Local Association (a group of young stars likely to have formed together) at a very slow speed relative to their movement.

It's likely that when Oumuamua was first ejected into space, it was travelling at just enough speed to break away from the gravity of its planet or star of origin, rather than at a much faster speed that would require even more energy. This means we'd expect the object to move relatively slowly at the start of its interstellar journey, and so its slow encounters with these five stars suggests it was ejected from one of the group.

Stars typically move with an average speed when they are formed and gradually change speed as they encounter very large objects, such as massive stars and molecular clouds and are affected by their gravity. Unlike most nearby stars, Oumuamua moves very slowly compared to the average motion of the rest of the galaxy. This suggests it has only been travelling in interstellar space for a relatively short time and hasn't had a chance to encounter many massive objects that would speed it up.

We also have evidence for Oumuamua's relatively young age from the colour of its surface. Outside of the protection of a star's magnetic field, objects in space are bombarded with cosmic rays and interstellar dust and gas that gradually alter their surfaces and turn them very red in colour. But Oumuamua has a more neutral colour, suggesting it has only been impacted by cosmic rays for, at most, hundreds of millions of years rather than for the billions of years that our solar system has existed. Oumuamua is extremely elongated and has quite a different shape from other objects in our solar system. It was probably formed by a relatively high-energy process, such as a collision, or ejected from a forming star. Most objects in the outer part of a planetary system are made more of ice and most objects in the inner regions are made more of rocks. Since Oumuamua is a more even mix of ice and rocks, it's likely it came from the middle part of a solar system, similar to the asteroid belt between Mars and Jupiter that features a mixture of icy and rocky asteroids.

Perhaps the most plausible scenario is that Oumuamua was ejected from a closely separated binary star system made of two stars closely orbiting each other. Objects orbiting one of the stars in a binary system will be strongly affected by the gravity of the other and so can be more easily ejected from the system than if it had just one star.

Oumuamua is probably just the tip of the iceberg. My research suggests there are likely more than 46 million similar interstellar objects crossing the solar system every year. Most of them will be too far away for us to see with our current telescopes. But new telescopes and surveys should soon be able to find these interstellar messengers, which may be sending us important information about how stars and planets are formed. Studying more objects like Oumuamua will enable us to work out how much debris is left over from star formation and how much this adds to the mass of our galaxy.

Another reason to study these interstellar objects is that they could one day threaten to collide with the Earth and cause catastrophic events such as mass extinctions. The more we know, the better prepared we'll be if that day ever comes.

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The Independent

## Warmer & rarer

Climate change has made severe cold spells like the one that recently gripped North-eastern US far less common than they used to be, a team of researchers has found.

The reason is straightforward. The Arctic has warmed so much — twice as fast in recent decades than other parts of the world — that when polar air descends to lower latitudes, the cold snaps are warmer on average. So a spell of extremely cold weather like the recent one is rare, about 15 times rarer than a century ago, the scientists said.

"Although this cold spell would not have been unusual before global warming, it is now a relatively rare event in any one region," the study's authors, from a loose-knit international group called World Weather Attribution, wrote.

Put another way, the most intense cold waves are on average about 2 degrees Celsius warmer now than previously, they said. "The trend in general for these cold waves is that they're warming," said Claudia Tebaldi, a research fellow with Climate Central, a news organisation that focuses on climate science and coordinated the study.

While Arctic air is milder because of climate change, the question whether global warming is actually leading to more cold spells has been much debated.

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