material medium to propagate. On page 243, Fong *et al.*[1] report experimental evidence that phonons can travel across a vacuum gap and therefore induce heat transfer between vacuum-separated objects because of the effect of quantum fluctuations.

In simple terms, quantum fluctuations can be understood as being the source of an electromagnetic signal that a perfectly sensitive detector would detect in a vacuum, even when this vacuum is shielded from all possible internal and external sources of electromagnetic waves, such as charges and currents[2]. The fluctuations are a consequence of a law in quantum mechanics known as Heisenberg's uncertainty principle[3], which states that certain pairs of physical quantities cannot be determined at the same time with absolute precision. The presence of quantum fluctuations subtly influences surrounding matter, leading to several observable effects.

One of these effects, relevant to Fong and colleagues' work, is the Casimir force[4] — the force that two neutral atoms separated by a vacuum gap exert on each other. The Casimir force results when quantum fluctuations induce fluctuating charge densities in these atoms; the charge densities then interact through their electric fields. The force that sticks a gecko's foot to a wall is an example of a macroscopic manifestation of the Casimir force. It arises from the combined interactions between fluctuating charge densities in all the atomic constituents of the two objects.

To understand how the Casimir force can induce phonon transfer between vacuum-separated objects, consider an object that is maintained at a particular temperature by being kept in contact with a heat source (Fig. 1). Thermal agitation of the object's atoms, which can be thought of as being interconnected by elastic springs, gives rise to phonons. In the presence of these phonons, the surface of the object undulates over time. When a second object is brought close to the first one, it is subjected to a time-varying Casimir force owing to its interaction with the undulations of the first object's surface. The second object's surface is thus subjected to tugging that then gives rise to phonons in the object's interior. Phonons are therefore transmitted from the first object to the second one.

Because phonons are heat carriers, when they are transported from one object to another across a vacuum gap, as a result of the Casimir force, they induce heat transfer if the second object is maintained at a lower temperature than that of the first one. This phenomenon of heat transport facilitated by the Casimir force has been predicted previously using theoretical models[5–7]. Fong *et al.* have now measured such a heat-transfer mode experimentally.

The authors used a technique called optical interferometry to observe the thermal agitation of atoms (Brownian motion) at the surface of a membrane. This membrane was kept in contact with a heat source held at a constant temperature. Measurements of thermal agitation can be related to, and therefore used as a gauge for, the temperature of the atoms at the membrane's surface. Moreover, the difference in this temperature with and without Casimir interaction with another, closely juxtaposed membrane is directly proportional to the resulting heat transfer between the two interacting membranes. The authors used these features to estimate the amount of heat transmitted between the membranes for vacuum gaps of different sizes. They found that their measurements accurately conform to theoretical estimates of such heat transport.

"Fong and colleagues' work provides conclusive evidence that the Casimir force can induce heat transfer."

Fong and colleagues' work provides conclusive evidence that the Casimir force can induce heat transfer. However, the use of this method to transport heat between two objects is limited, because the Casimir force decreases rapidly in strength as the space between the objects is increased. It is only when the gap between two objects is of the order of a few nanometres that the Casimir force is strong enough for this heat-transfer mode to dominate over competing modes, such as photon tunnelling[8].

The authors discovered a way to amplify the Casimir mode of heat transfer so that it remains dominant even when the gap between the membranes is in the range of hundreds of nanometres. The membranes were carefully designed in such a way that their dimensions and the temperatures at which they were maintained allowed them to vibrate with their maximum possible displacements — in other words, at their natural frequencies. Thus, applications that are devised to exploit this heat-transfer mode to dissipate heat (such as in a hard-disk drive, where the distance between the writing head and the storage disk is a few nanometres) would require such careful design to ensure that the mode is amplified. Achieving this would be a challenge for the future.

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Structural biology

Malaria parasites fine-tune mutations to resist drugs

Leann Tilley & Philip J. Rosenthal

Drug resistance in malaria parasites is mediated by mutations in a transporter protein. The transporter's structure reveals the molecular basis of how key mutations bring about resistance to different drugs. **See p.315**

About half a million people, most of them children living in Africa, are killed each year by malaria[1]. Management of malaria, particularly that caused by the highly virulent protozoan parasite *Plasmodium falciparum*, is challenged by the emergence of resistance to antimalarial drugs[2]. On page 315, Kim *et al.*[3] report the structure and molecular properties of a key protein that facilitates resistance, the *P. falciparum* chloroquine-resistance transporter (PfCRT). The structure reveals the consequences of finely tuned mutations of the amino-acid residues that line a crucial central cavity in PfCRT. These mutated residues allow resistant parasites to transport certain antimalarial drugs away from their site of action — and the effect of the mutations is different for closely related drugs.

Malaria parasites spend part of their life cycle inside human red blood cells. There, they use a specialized membrane-bound compartment known as the digestive vacuole to degrade the protein haemoglobin, thereby generating amino-acid building blocks for growth[4]. Haemoglobin digestion also produces a toxic side product called haem,

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which is exploited by antimalarials from the quinoline family of drugs (which includes chloroquine and piperaquine). These drugs bind to the released haem in the digestive vacuole and prevent the compound's detoxification by the parasite – in effect, poisoning the parasite with its own metabolic debris[4].

Chloroquine's affordability, safety and efficacy made it the drug of choice for combating malaria, until widespread resistance developed in the 1980s. Piperaquine is a structurally related compound that retains activity against chloroquine-resistant parasites and is currently used in combination with another antimalarial drug, dihydroartemisinin. Unfortunately, resistance to piperaquine is now widespread in parts of southeast Asia[5]. Paradoxically, piperaquine-resistant parasites are often more sensitive to chloroquine than are piperaquine-sensitive parasites[6].

Drug resistance can arise because of mutations either in the drug's target or in biological machinery that transports the drug to or from the target. A landmark report[7] in 2000 identified PfCRT as the main mediator of chloroquine resistance in *P. falciparum*. Resistance emerged independently at different locations around the world, but is always associated with a particular mutation in the transporter – the substitution of a lysine amino-acid residue by a threonine residue (a K76T mutation). K76T combines with other geographically specific PfCRT mutations to mediate resistance and improve the fitness of the mutant parasites[6–8].

PfCRT is a member of the superfamily of proteins known as drug/metabolite transporters[9] and is located in the membrane of the parasite's digestive vacuole. Structural and biochemical studies of related proteins suggest that resistance to chloroquine arises as a result of the transporter passing chloroquine out of the digestive vacuole, thus removing it from its site of action[8]. Interestingly, piperaquine resistance emerges when parasites harbouring the K76T mutation acquire further mutations[6].

Efforts to design new resistance-busting quinoline antimalarials have been stymied by a lack of information about the structures of mutated PfCRT. But in the past few years, advances in a technique called cryo-electron microscopy[10] (cryo-EM) have revolutionized structural biology by enabling the direct imaging of membrane-embedded proteins, such as PfCRT, that are not amenable to study using X-ray crystallography. Kim *et al*. used single-particle cryo-EM to determine the structure of PfCRT in South American 7G8 parasites, which harbour mutations that confer high-level chloroquine resistance.

The authors first had to work out a protocol for efficiently expressing, purifying and reconstituting PfCRT into a membrane-like environment, to maintain a native conformation of the protein. PfCRT is relatively small (49 kilodaltons) compared with proteins that are typically studied using cryo-EM, and so Kim *et al*. prepared an antibody fragment (known as an antigen-binding fragment, or Fab) that binds to PfCRT, thereby forming a complex that has sufficient mass and stability to allow cryo-EM-based structural elucidation. This approach yielded a structure with 3.2-ångström resolution.

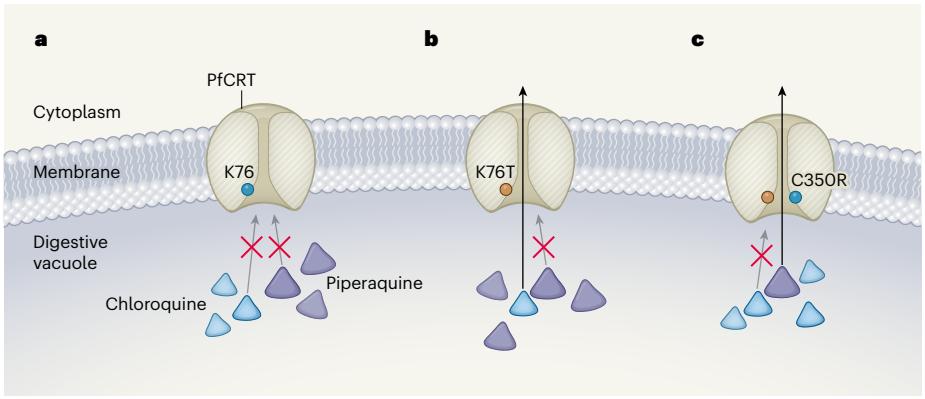

Figure 1 | Mutations affect the transport of antimalarial drugs through the PfCRT protein. **a**, The drugs chloroquine and piperaquine target a membrane-bound organelle in the malaria parasite, called the digestive vacuole. *Plasmodium falciparum* chloroquine-resistance transporter (PfCRT) resides in the membrane of the digestive vacuole of the most virulent species of malaria parasite. A positively charged lysine amino-acid residue (K76) in wild-type PfCRT is thought to repel the positively charged drugs, preventing transport out of the vacuole (arrow) – which would lead to drug resistance. **b**, Kim *et al*.[3] report the structure of PfCRT that contains a mutation known as K76T. The authors find that K76T alters the charge distribution of the lining of the PfCRT cavity. Both chloroquine and piperaquine bind to the mutated cavity, but only chloroquine passes through it (possibly because it has a lower positive charge than piperaquine), enabling resistance to chloroquine, but not to piperaquine. **c**, Further mutations in PfCRT (such as the C350R mutation) cause piperaquine to bind more weakly to the cavity than in **b**. This potentially underpins the drug's ability to pass through PfCRT and leads to piperaquine resistance. In this scenario, the transport of chloroquine out of the digestive vacuole is less efficient than the transport of piperaquine.

PfCRT was revealed to have ten transmembrane domains and a negatively charged central cavity. The cavity opens on to the digestive vacuole, but closes about halfway through the membrane. The Fab-bound cavity has an opening 25 Å in diameter, which is large enough to contain chloroquine (the maximum dimension of which is about 14 Å) and piperaquine (with a maximum dimension of about 21 Å). The structure shows that wild-type PfCRT has a positively charged lysine residue (K76) positioned in the cavity. This residue is thought to repel both chloroquine (which has two positive charges) and piperaquine (which has four positive charges), thereby trapping them in the digestive vacuole (Fig. 1a).

Interestingly, Kim and colleagues' biochemical experiments show that PfCRT from 7G8 parasites can bind both chloroquine and piperaquine, but transport only chloroquine; thus, parasites with the K76T mutation are resistant to chloroquine, but not piperaquine (Fig. 1b). By contrast, when the authors introduced further mutations to 7G8 that have been observed in South American[11] and southeast Asian[6] parasites in the past five years, piperaquine efflux increased – an effect that was associated with decreased sensitivity to piperaquine, but increased sensitivity to chloroquine (Fig. 1c).

Kim *et al*. used their cryo-EM structure to carry out molecular modelling and electrostatic analysis of PfCRT, to help explain why mutations can have opposite effects on the sensitivity of malaria parasites to chloroquine and piperaquine. The modelling suggests that mutations associated with piperaquine resistance can reduce the negative charge or alter the conformation of the PfCRT central cavity. This might prevent piperaquine from binding too tightly to the cavity and thus increase its transport out of the digestive vacuole. The authors propose that the distribution of surface charges in the cavity can be fine-tuned so that the initial binding of a drug to PfCRT, and its subsequent release for transport, is different for different drugs, thereby producing distinct effects on drug sensitivity. Taken together, Kim and colleagues' findings show that *P. falciparum* is engaged in an ongoing balancing act, generating mutations that block the action of different drugs while maintaining optimal fitness of the parasite.

A limitation of the new structure is that PfCRT is locked in a conformation in which it is open to the digestive vacuole, as a result of Fab binding in its central cavity. Further studies will be required to work out how drug binding couples to the conformational rearrangements that permit drug transport.

On a practical level, it is particularly important to understand the mechanisms of resistance that are likely to arise in Africa, where more than 90% of cases of malaria caused by *P. falciparum* occur[1]. Compared with other parts of the world, there are fewer PfCRT mutations

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in Africa, where resistance to chloroquine is decreasing in many countries and where the combination of piperaquine and dihydroartemisinin remains highly effective[12]. We can look forward to further studies of PfCRT, including visualization of the drug-bound and open-to-cytoplasm structural conformations, which will further explain the effects of resistance mutations and might help to identify drugs that circumvent resistance. For now, we can appreciate the insights gained from Kim and colleagues' beautiful marriage of structure, biochemistry, genetics and parasitology, and particularly from the first atomic-resolution structure of PfCRT — the fine-tuned, resistance-mediating machine of malaria parasites.

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Solar physics

A step closer to the Sun's secrets

Daniel Verscharen

NASA's Parker Solar Probe is currently making a series of close encounters with the Sun. Initial observations from the spacecraft have improved our understanding of both the Sun and its environment. **See p.223, p.228, p.232 & p.237**

Although the Sun is quite near to us compared with other stars, it has always kept intriguing and fundamental scientific secrets from us. For instance, we still don't know how the solar corona — the Sun's outermost atmosphere — maintains temperatures in excess of one million kelvin, whereas the visible surface has temperatures of just below 6,000 K (ref. 1). The corona produces the solar wind, an outflow of plasma particles (free ions and electrons) that expands into the space between the planets. In 2018, NASA launched the Parker Solar Probe[2] (PSP) with the aim of identifying the mechanisms behind the heating of the corona and the acceleration of the solar wind. Four papers in *Nature*[3–6] report the first results from the PSP.

The measurements from the PSP were taken when the spacecraft was as close as 24 million kilometres to the Sun (for comparison, the average distance between Mercury and the Sun is about 58 million kilometres). They show that the solar wind near the Sun is much more structured and dynamic than it is at Earth (Fig. 1). On page 237, Bale *et al.*[3] present measurements of the direction and strength of the Sun's magnetic field, which is dragged out into space by the solar wind. The authors find rapid reversals in the direction of the field that last for only minutes. Although some similar magnetic structures have been seen before[7], the large amplitude and the high occurrence rate of these reversals are surprising. In fact, the nature of these structures remains unknown.

Bale and colleagues also report that the PSP's sensors detected fluctuations in the local electric and magnetic fields in the solar wind that are larger than those detected near Earth. These fluctuations can be generated by turbulence in the solar wind or by plasma instabilities that are driven by ions or electrons. The presence of such fluctuations suggests that plasma instabilities have a much larger effect on the dynamics and energetics of the solar wind than previously expected.

On page 228, Kasper *et al.*[4] present observations of the Sun's plasma ions and electrons. They find that the reversals in the Sun's magnetic field are often associated with localized enhancements in the radial component of the plasma velocity (the velocity in the direction away from the Sun's centre). The authors use the extremely clear signal of the solar wind's strahl — a collimated and fast beam of electrons that stream along the magnetic field — to study the field's geometry and configuration. This method leads Kasper and colleagues to interpret the magnetic-field reversals as travelling S-shaped bends in the field lines coming from the Sun.

These authors also report a surprisingly large azimuthal component of the plasma velocity (the velocity perpendicular to the radial direction). This component results from the force with which the Sun's rotation slingshots plasma out of the corona when the plasma is released from the coronal magnetic field — much like a spinning hammer-thrower slingshots the hammer when releasing it from their hands. However, the reason for the large observed value of the azimuthal velocity is currently unclear.

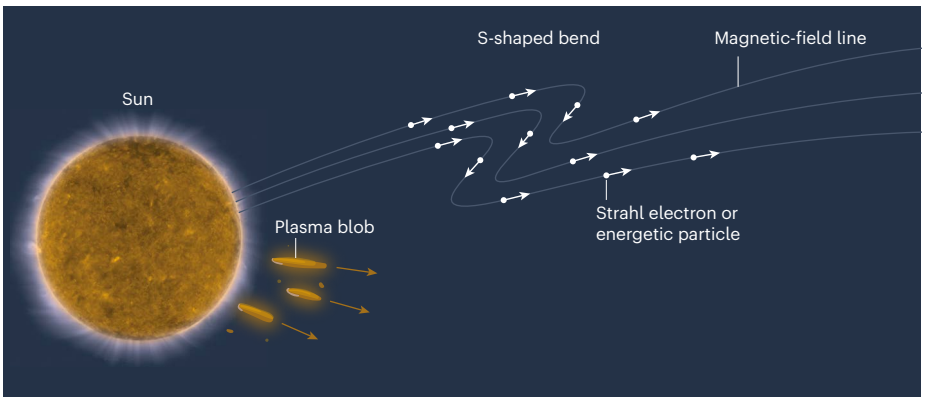

Figure 1 | The near-Sun environment. The Sun's outermost atmosphere generates an outflow of plasma particles (ions and electrons) called the solar wind. 'Strahl' electrons and energetic particles in the wind stream along the Sun's magnetic-field lines. Four papers[3–6] report observations from the Parker Solar Probe (PSP), which is currently in orbit around the Sun. The PSP data suggest that the field lines contain S-shaped bends and that the Sun releases blobs of plasma that form part of the young solar wind. The ultraviolet-light image of the Sun was taken by NASA's Solar Dynamics Observatory on the day that the PSP made its first close encounter with the Sun.

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