



**Figure 1 | Slim, strong and a live wire.** **a**, The honeycomb lattice pattern of graphene explains its strength and good conductivity. Each carbon atom (green dot) uses three of its outer valence electrons to form strong covalent bonds, leaving one left over that is available for conduction. **b**, The quadratic, newtonian energy-momentum relation,  $E = p^2/2m^*$  ( $E$ , energy;  $p$ , momentum;  $m^*$ , reduced mass) is obeyed by electrons in a semiconductor. **c**, The energy-momentum relation of electrons in graphene is quite different,  $E = v|p|$  ( $v$  is the electron velocity), allowing them to be modelled as massless, relativistic particles according to the Dirac formulation of quantum mechanics.

analogue of an effect observed by Edwin H. Hall in 1879 in a macroscopic conductor. In a magnetic field, charged particles such as electrons experience a force perpendicular to their motion, causing them to move in closed circles. A magnetic field applied at right angles to the surface of a conductor will therefore deflect the electrons from their path between the terminals, establishing a voltage perpendicular to the direction of current flow. In a conventional solid, the Hall resistance (given by the ratio between the perpendicular voltage and the forwards electron current) increases smoothly as the applied magnetic field increases.

In a two-dimensional solid at low temperatures, however, quantum effects — specifically, the wave-like properties of the electrons — come into play. Only an integer number of electron wavelengths may fit into the circular orbits induced by the magnetic field, restricting the permitted electron energies to a set of discrete, quantized values. This means that in turn the Hall resistance no longer increases continuously with increasing magnetic field strength, but in a characteristic series of steps quantized in units of  $h/e^2$  (where  $h$  is Planck's constant and  $e$  the electron's charge). Since its discovery in 1980, this quantum Hall effect has had a profound impact on semiconductor research, with two Nobel Prizes in Physics — those of 1985 and 1998 — being awarded for work on it.

Both Novoselov *et al.*<sup>2</sup> and Zhang *et al.*<sup>3</sup> observed quantized steps in the Hall resistance of graphene — a result that highlights the exemplary quality of their samples. The exact numerical values at which the resistance steps occurred were, however, found to be shifted by one-half of a unit from those expected for non-relativistic electrons. The relativistic

theory provides an explanation: just as Dirac's original theory explained why electrons have an intrinsic angular momentum, known as spin, the effective Dirac theory for graphene endows electrons with an additional 'pseudospin'. When an electron completes a circle in an applied magnetic field, its pseudospin rotates by  $360^\circ$ . As is the case for real spin, such a rotation introduces a  $180^\circ$  phase shift in the electron wave, so an additional half wavelength must fit in the circumference of the circle, changing the pattern of allowed energies. The pattern of the observed steps<sup>2,3</sup> in the Hall resistance fits with this picture perfectly, providing convincing evidence for graphene's Dirac electronic structure.

The electrical conductivity of graphene at zero magnetic field, with a minimum value at low temperature that is close to  $4e^2/h$  for several different samples<sup>2</sup>, raises interesting

questions. Such a 'universal' minimum conductivity is in itself reasonable; how to explain the precise value, however, is an open question. Away from the minimum, the conductivity varies linearly with electron density — expected for newtonian electrons, but surprising for relativistic electrons. Finding answers to these remaining riddles will be essential for realizing the potential of graphene-based electronics. So it's time for theorists to sharpen their pencils. ■

Charles L. Kane is in the Department of Physics and Astronomy, University of Pennsylvania, 209 S. 33rd Street, Philadelphia, Pennsylvania 10104, USA.  
e-mail: kane@physics.upenn.edu

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## MICROBIOLOGY

# RAMP resistance

Angus Buckling and Michael Brockhurst

**There is an urgent need for new antimicrobial agents because antibiotic resistance has become so prevalent. But a promising class of such agents, known as RAMPs, may suffer from the same problem.**

In a report published in *Proceedings of the Royal Society*, Perron *et al.*<sup>1</sup> demonstrate experimentally that bacteria can readily evolve resistance to a group of proteins called ribosomally encoded antimicrobial peptides (RAMPs). RAMPs are produced by animals, plants, fungi and bacteria as part of their natural defence against microbial attack<sup>2–4</sup>, and are being developed as antibiotics. But because bacterial resistance to chemotherapeutic RAMPs could confer resistance to the battery of innate human RAMPs<sup>4</sup>, the worrying prospect is that widespread use of these agents may compromise our natural defence against bacteria.

With the emergence of bacteria that are resistant to 'last resort' antibiotics such as vancomycin<sup>5</sup>, there is a desperate need to identify new antimicrobial agents. RAMPs may be just such agents. They are a diverse group of proteins, and their mode of action varies considerably, but a common feature is their positive charge. This allows them to bind to the negatively charged membranes of bacteria. The effectiveness of a variety of RAMPs in clinical trials<sup>2,3</sup>, and the recent discovery of fungus-derived RAMPs that can be produced in large yields<sup>3</sup>, suggest RAMPs could be in widespread clinical use within the next few years.

The potential advantages of RAMPs are the apparent difficulty that bacteria face in evolving resistance to them, and the fact that resistance to conventional antibiotics does not seem to confer resistance to RAMPs<sup>2</sup>. Bacteria have

obviously encountered RAMPs in one form or another for millions of years, yet widespread resistance is rare. Furthermore, previous experimental tests suggest that the evolution of resistance does not readily occur<sup>6,7</sup>.

However, resistance evolution is all about the level of exposure. Although bacteria had been exposed to natural antibiotics such as penicillin and streptomycin (respectively produced by the *Penicillium* mould and *Streptomyces* bacteria) for millions of years, resistance was at low levels when widespread clinical use of these drugs began in the 1940s. But after a few years of exposure to high clinical doses, resistance was widespread in many species of pathogenic bacteria.

On the basis of such logic, Perron *et al.*<sup>1</sup> attempted to experimentally induce resistance to a RAMP in two different bacterial species, *Escherichia coli* and *Pseudomonas fluorescens*. The RAMP in question, pexiganan, is a synthetic analogue of a RAMP derived from toads (magainin) that has been modified for use as a chemotherapeutic agent. The authors exposed bacteria to slowly increasing concentrations of the drug for 600 generations (a few months in the lab), unlike previous work where drug concentrations were kept constant, and populations were allowed to evolve for no more than 200 generations<sup>6,7</sup>. The results were astounding: 22 out of 24 populations of bacteria had developed resistance to the drug.

The ability of bacteria to evolve resistance to

antibiotics does not necessarily mean that resistance will become a widespread problem. Antibiotic resistance often compromises the bacteria in other ways — for example, by reducing their growth rate<sup>8</sup>. This means that antibiotic-sensitive bacteria will outcompete the resistant forms when neither is exposed to the antibiotic. Perron *et al.*<sup>1</sup> investigated this possibility, and indeed found a 'cost' of antibiotic resistance: in the absence of the antibiotic, resistant bacteria took longer to start reproducing than control bacteria, although once they had got going, their replication rate was unaffected.

Unfortunately, bacteria have other tricks up their sleeves. In addition to adapting to antibiotics, they can also adapt to antibiotic resistance. There have been numerous cases of bacteria with antibiotic resistance developing mutations in other parts of their genome that compensate for the associated costs<sup>8,9</sup>. These adaptations are sometimes so specific that the growth rate of bacteria can decrease if the genetic changes conferring antibiotic resistance are replaced with the original sensitive form of the gene after compensatory adaptation has occurred<sup>9</sup>.

Why should bacterial resistance to RAMPs cause more concern than resistance to other antibiotics? The major problem will be if resistance to chemotherapeutic RAMPs also confers resistance to naturally occurring RAMPs in humans and other organisms. Bacteria that are normally dealt with unnoticed by our innate immune system may then cause serious infections. Large-scale use of chemotherapeutic RAMPs may ultimately help pathogenic bacteria colonize parts of animals and plants that were previously off limits to them.

This perspective may be overstating the case for concern. Humans alone produce a highly diverse arsenal of RAMPs, which are also thought to be constantly evolving new ways of targeting bacteria<sup>1</sup>; and RAMPs constitute only one part of our natural immunity. Furthermore, RAMP resistance, where observed, is often specific to a small range of RAMPs<sup>4</sup>. There are exceptions, however. A variety of bacteria, including *Staphylococcus aureus* — famed for methicillin resistance — and the opportunistic pathogen *Pseudomonas aeruginosa* have evolved a degree of generalized RAMP resistance by increasing the amount of positively charged protein in their membranes. The consequence may be to reduce the binding efficiency of the positively charged RAMPs<sup>10</sup>.

As Perron *et al.*<sup>1</sup>, and others<sup>2-4</sup>, emphasize, RAMPs are likely to make a major contribution to human health and agriculture. But given the prospect of resistance, extra caution is necessary in developing and using them. ■ Angus Buckling is in the Department of Zoology, University of Oxford, Oxford OX1 3PS, UK. Michael Brockhurst is at ISEM, Université de Montpellier II, 34095 Montpellier, France. e-mail: angus.buckling@zoology.oxford.ac.uk

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## SEISMOLOGY

# The start of something big?

Rachel Abercrombie

**Can we predict the final size of an earthquake from observations of its first few seconds? An extensive study of earthquakes around the Pacific Rim seems to indicate that we can — but uncertainties remain.**

How does a seismic fault, initially essentially immobile, start to slip at speeds of metres per second as an earthquake rupture front runs along it at speeds of up to 3 kilometres per second? Does the eventual size of an earthquake depend on the nature of this process? Or do all earthquakes begin in the same way, with the extent of rupture determined by conditions along the fault? Such fundamental questions get seismologists talking, because knowing how earthquakes begin is an essential part of understanding and modelling the dynamics of earthquake rupture, and may allow an earthquake's course to be predicted. Research until now has been inconclusive, but results described by Olson and Allen (page 212 of this issue)<sup>1</sup> imply that the final magnitude of an

earthquake depends at least partially on what happens in its first few seconds. This timescale is equivalent to less than a tenth of the duration of the larger earthquakes in their study.

Research into the onset of earthquakes large and small has found that they often begin with small-amplitude shaking<sup>2</sup>. The interpretation of these initial 'sub-events' remains controversial. One model has it that a small, isolated sub-event triggers a larger fault patch, which itself triggers further fault patches, and so on as long as sufficient energy is available. In this 'cascade' model, the beginning of a large earthquake is no different from the beginning of a small earthquake: therefore, predicting the final magnitude from the first few seconds is impossible. An alternative model is that the small



**Figure 1 | Finding fault.** A view of the Lavic Lake seismic fault in California. The Hector Mine earthquake, one of those considered by Olson and Allen<sup>1</sup> in their study of the initial waves of Pacific Rim earthquakes, occurred along this fault line on 16 October 1999.

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