

including drug-resistant strains. Notably, the chimaeras showed low toxicity in mice.

It might be expected that the chimaeras would target LptD, but when Luther and colleagues tested for interacting partners, they found evidence of BamA targeting. The authors analysed strains of *K. pneumoniae* that showed resistance to the chimaeras. They found that resistant strains carried mutations in several genes, including *bamA* and genes responsible for LPS modification. Reintroduction of the wild-type *bamA* gene into the resistant strains led to increased sensitivity to the chimaera, indicating that BamA has a role in the antibiotic's mechanism of action.

Direct chimaera–BamA binding was confirmed with *in vitro* assays in which the authors fluorescently labelled the chimaeras and monitored changes in fluorescence that indicate binding to a large protein such as BamA. As with darobactin, NMR experiments suggested that chimaera binding stabilizes BamA in a potentially inactive conformation, consistent with direct BamA targeting. However, when the bacteria were treated directly with the chimaeras, both the outer and inner membranes were rapidly permeabilized; this suggests that the compounds might act directly on the membrane. The results raise the possibility that the chimaeras act in a similar way to polymyxins, with binding to BamA strengthening their membrane targeting.

In the third study, Hart *et al.*<sup>7</sup> identified a compound, MRL-494, that had similar antibiotic potency against both wild-type *E. coli* and a mutant defective in outer-membrane integrity and efflux mechanisms, suggesting that this antibiotic might not need to penetrate the cell to exert its activity. *In vitro*, MRL-494 exhibited moderate potency against Gram-negative pathogens, including *K. pneumoniae* and *P. aeruginosa*. The efficacy of MRL-494 in animal models remains to be tested.

The authors showed that treatment of *E. coli* with the compound resulted in decreased abundance of OMPs in the outer membrane, indicating BamA as a possible target. In support of this possibility, Hart *et al.* identified a *bamA* mutation that confers resistance to MRL-494 in *E. coli*. They showed that, whereas MRL-494 inhibited normal folding of a model OMP in *E. coli* cells expressing wild-type *bamA*, it had less effect on the resistant cells. The researchers found that MRL-494 stabilizes BamA against heat-induced protein aggregation in cells, suggesting an interaction between the two. However, MRL-494 stabilizes the resistant *bamA* mutant to a similar extent. Furthermore, MRL-494 displays similar potency against Gram-positive bacteria, which lack BamA. Therefore, in Gram-negative bacteria, MRL-494 might inhibit BamA directly or might target the outer membrane and affect BamA function indirectly.

Together, these studies describe new antibiotics that are active against difficult-to-treat Gram-negative bacteria. Given the compounds' size and chemistry, they are likely to act at the cell surface, bypassing the need to breach the permeability barrier. Imai *et al.* provided compelling evidence that BamA is the target of darobactin, including a putative binding site, to be confirmed by demonstrating

**“These studies describe new antibiotics that are active against difficult-to-treat Gram-negative bacteria.”**

reduced binding to resistant mutants. The chimaeric compounds both seem to bind BamA and LPS. But, as is also the case for MRL-494, further experiments will be required to determine whether their activity is caused by direct effects on BamA.

Future research to identify specific BamA binding sites for any of the compounds, and to examine the mechanism by which antibiotic binding impairs BamA activity, would provide a platform for further antibiotic development. Such research might also shed light on how BamA mediates the insertion and folding of OMPs, which is poorly understood.

Darobactin and MRL-494 are initial lead

compounds, and medicinal-chemistry efforts could yield more-potent and effective analogues. Preclinical studies aimed at determining their toxicity in animal models will also be important. Luther and colleagues' chimaeras are at a more advanced stage of development, because, as the authors show, they have potent *in vivo* activity as well as favourable toxicity, pharmacokinetics and pharmacodynamics in animal models. The future looks promising for this newly discovered class of antibiotic.

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1. World Health Organization. *Global Priority List of Antibiotic-Resistant Bacteria to Guide Research, Discovery, and Development of New Antibiotics* (WHO, 2017).
2. Nikaido, H. *Microbiol. Mol. Biol. Rev.* **67**, 593–656 (2003).
3. Li, X.-Z. & Nikaido, H. *Drugs* **64**, 159–204 (2004).
4. Munita, J. M. & Arias, C. A. *Microbiol. Spectr.* **4**, VMBF-0016-2015 (2016).
5. Imai, Y. *et al. Nature* **576**, 459–464 (2019).
6. Luther, A. *et al. Nature* **576**, 452–458 (2019).
7. Hart, E. M. *et al. Proc. Natl Acad. Sci. USA* **116**, 21748–21757 (2019).
8. Konovalova, A., Kahne, D. E. & Silhavy, T. J. *Annu. Rev. Microbiol.* **71**, 539–556 (2017).
9. Storek, K. M. *et al. Proc. Natl Acad. Sci. USA* **115**, 3692–3697 (2018).
10. Srinivas, N. *et al. Science* **327**, 1010–1013 (2010).
11. Mares, J., Kumaran, S., Gobbo, M. & Zerbe, O. *J. Biol. Chem.* **284**, 11498–11506 (2009).
12. Li, J. *et al. Lancet Infect. Dis.* **6**, 589–601 (2006).

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### Condensed-matter physics

## Magnetic and topological order united in a crystal

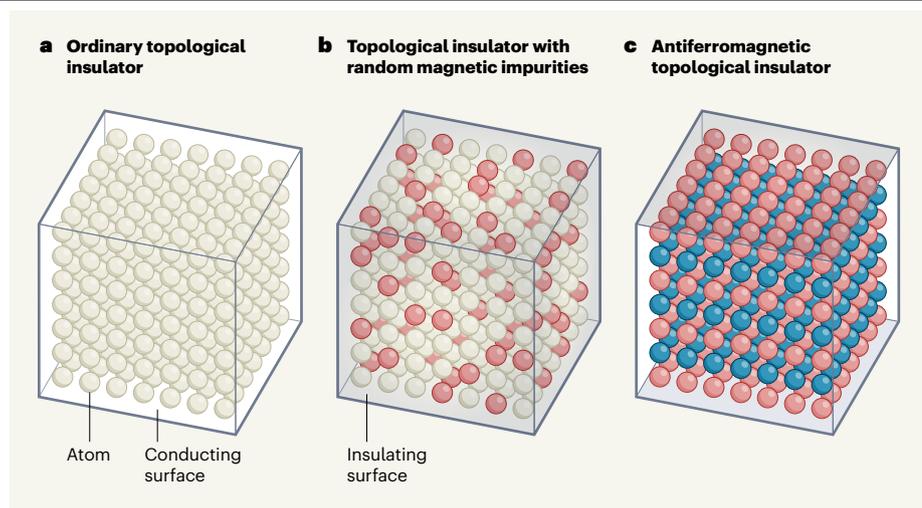
Roger S. K. Mong & Joel E. Moore

A material that has electrically conducting surfaces has been found to show, when cooled, a type of magnetic ordering that reduces conduction at the surfaces. Such remarkable behaviour could have practical applications. **See p.416 & p.423**

An ordered arrangement of magnetic moments in a material normally prevents the formation of another kind of electronic order associated with an exotic state of matter known as a topological insulator. But Otrokov *et al.*<sup>1</sup> (page 416) and Rienks *et al.*<sup>2</sup> (page 423) report that manganese bismuth telluride integrates these two types of electronic behaviour. The complex layered structure of alternating magnetic and topologically non-trivial regions in this material leads to an intriguing and potentially technologically useful interplay between magnetic and topological order.

One of the earliest descriptions of electronic order in solids was of ferromagnetism,

the existence of which was reported in natural minerals in Greece and China more than 2,000 years ago. In a simple ferromagnet, microscopic magnetic moments, arising predominantly from the spin (intrinsic angular momentum) of a material's electrons, align in the same direction, leading to an overall macroscopic magnetic moment. The concept of antiferromagnetism, in which spins align in alternating directions and the average magnetic moment is zero, was developed only in the 1930s. These two kinds of magnetic order are viewed theoretically as breaking time-reversal symmetry: when the direction of time is reversed, the pattern of spins



**Figure 1 | A new spin on topological insulators.** **a**, In an ordinary topological insulator, the atoms are unmagnetized (beige), the interior is electrically insulating and all of the surfaces are conducting. **b**, When random magnetic impurities (red) are introduced, all of the surfaces become insulating. Rienks *et al.*<sup>2</sup> present evidence that magnetic manganese atoms sit in random locations when added to bismuth selenide, but separate into layers when added to bismuth telluride (not shown). **c**, If the electron spins (intrinsic angular momenta) of atoms form a pattern that alternates between layers (illustrated by the red and blue atoms), an antiferromagnetic topological insulator forms. This has both conducting and insulating surfaces; whether a particular surface is conducting or insulating depends on its orientation relative to the magnetic structure. Here, the top and bottom surfaces are insulating, and the others are conducting. Otrokov *et al.*<sup>1</sup> present evidence for such an antiferromagnetic topological insulator.

is changed. Time reversal acts by reversing velocities (a bit like running a movie backwards) as well as by reversing the direction of angular momenta, including spins.

However, unbroken time-reversal symmetry is required to produce topological insulators, which have been a tremendously active area of study<sup>3,4</sup>. Topological insulators have an electrically insulating interior, but a conducting surface. The property that sets them apart from ordinary insulators is that their surfaces cannot be made to have a simple insulating state as long as time-reversal symmetry is unbroken. This makes topological insulators ideal platforms for generating excitations known as Majorana zero modes, which are the basis for a topological approach to quantum computing<sup>5</sup>.

The two current papers demonstrate that crystalline manganese bismuth telluride manages to combine these seemingly incompatible magnetic and topological orders. When cooled, the material becomes magnetic, and yet displays a kind of topological insulating behaviour. Unlike an ordinary topological insulator, for which every surface is conducting, such an antiferromagnetic topological insulator has surfaces that are conducting or insulating, depending on how the specific surface cuts through the alternating pattern of spins<sup>6</sup> (Fig. 1).

Manganese bismuth telluride can be viewed as a stack of magnetic manganese telluride layers that are separated by layers of a benchmark topological insulator, bismuth telluride<sup>7</sup>. Indeed, a thin-film version of this material was produced earlier this year by alternately growing single layers of manganese telluride and

bismuth telluride<sup>8</sup>. The current work shows that crystalline manganese bismuth telluride integrates two of the most actively studied kinds of order: topological insulating behaviour and single-layer magnetism, as seen in monolayer ferromagnets, such as chromium triiodide<sup>9</sup>.

The key feature of the antiferromagnetism in manganese bismuth telluride is that it can retain a modified version of time-reversal symmetry. In an antiferromagnet, the flipping of spins associated with time reversal changes the pattern of alternating spins. However, the combined transformation of first flipping the spins and then shifting the position of the pattern by a unit cell (the smallest repeating unit of a crystal lattice) can leave the pattern unchanged.

Consider adding such antiferromagnetism to a topological insulator. The conducting surfaces of the topological insulator are susceptible to externally applied or intrinsic magnetic fields, because such fields break time-reversal symmetry. Depending on how an antiferromagnetic pattern ends at a surface, the surface can have alternating spins akin to those in a 2D antiferromagnet, uniform spins similar to those in a 2D ferromagnet or a more complicated spin configuration. Consequently, what happens to the surface conduction of the material depends on how these surfaces cut the magnetic order (Fig. 1).

Otrokov *et al.* carried out numerical simulations in conjunction with various experimental probes of manganese bismuth telluride. On the basis of the results, they argue that the material has both an antiferromagnetic order and

a band inversion (whereby the usual ordering of electron energy bands is flipped), which is a signal of a topological insulator. The authors used a method known as X-ray magnetic circular dichroism to confirm the magnetic ordering experimentally.

In addition, these authors used a technique called angle-resolved photoemission spectroscopy to study the electronic structure at the material's surface. They observed that a structure in the surface electron bands, known as a Dirac cone, is modified near and below the temperature at which the material becomes antiferromagnetic. This Dirac cone is the distinguishing feature of the surface of a topological insulator, and its disappearance is a sign that the surface has been converted from conducting to insulating.

Rienks *et al.* carried out detailed studies of the atomic and electronic structure of bismuth telluride to which varying amounts of manganese had been added through a process called doping. They found that a small amount of doping (about 6% manganese) turns the topological insulator into a ferromagnet (as opposed to the antiferromagnet seen by Otrokov *et al.*). Rienks and colleagues also observed a tendency of doped bismuth telluride to form septuple layers, similar to those in crystalline manganese bismuth telluride, but separated by standard, quintuple layers of bismuth telluride. In addition, they studied manganese-doped bismuth selenide, which might have been expected to behave in the same way as its telluride counterpart, given that these compounds are similar topological insulators.

Rienks *et al.* found that manganese added to bismuth selenide does not have as strong a tendency to form layers as it does in bismuth telluride, and they showed that this structural difference has consequences for the magnetic structure and surface electrons. The telluride compound has a gap in energy between surface electron bands and has a magnetization that is perpendicular to the plane of the surface. By contrast, the selenide compound does not have this gap and has in-plane magnetization. The energy gap in the telluride compound disappears when the temperature is raised above the magnetic transition temperature. This connection between the energy gap and magnetism has been challenging to observe in other materials and samples.

A notable requirement for an antiferromagnetic topological insulator is that whether a surface has gaps (insulating) or does not (conducting) depends on the surface termination of the 3D crystal. This difference could be seen by producing other surfaces, or by looking at steps on a surface using scanning tunnelling microscopy. The combination of magnetic and topological behaviour observed in the current papers could lead to new spin-based electronic devices, because the topological aspects

might, for example, improve how materials transport spin currents. There is an overlap in potential applications with a topological phenomenon called the quantum anomalous Hall effect (QAHE), which is generated using magnetic impurities in thin films of topological insulators<sup>10,11</sup>. Steps on the surface of an antiferromagnetic topological insulator produce the same perfectly conducting edge channels as in the QAHE.

The fact that manganese bismuth telluride is intrinsically magnetic, rather than having its magnetism result from randomly located impurities, as in current QAHE materials, could be advantageous. Key questions remain about how the magnetism varies between different samples of this material. In particular, it seems that both the magnetic transition temperature and the nature of the magnetic ordering between planes could vary, and that an applied magnetic field might be used to switch this ordering. At a more fundamental level, antiferromagnetic topological insulators are predicted to support, without applied electric or magnetic fields, a quantized electromagnetic response (one that comes in discrete units), known as axion electrodynamics<sup>6</sup>. The current papers show

how the synthesis and theory of crystals that have various symmetries combine to reveal important types of electronic order.

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- Otrokov, M. M. *et al.* *Nature* **576**, 416–422 (2019).
- Rienks, E. D. L. *et al.* *Nature* **576**, 423–428 (2019).
- Hasan, M. Z. & Kane, C. L. *Rev. Mod. Phys.* **82**, 3045–3067 (2010).
- Moore, J. E. *Nature* **464**, 194–198 (2010).
- Fu, L. & Kane, C. L. *Phys. Rev. Lett.* **100**, 096407 (2008).
- Mong, R. S. K., Essin, A. M. & Moore, J. E. *Phys. Rev. B* **81**, 245209 (2010).
- Chen, Y. L. *et al.* *Science* **325**, 178–181 (2009).
- Gong, Y. *et al.* *Chinese Phys. Lett.* **36**, 076801 (2019).
- Huang, B. *et al.* *Nature* **546**, 270–273 (2017).
- Chang, C.-Z. *et al.* *Science* **340**, 167–170 (2013).
- Tokura, Y., Yasuda, K. & Tsukazaki, A. *Nature Rev. Phys.* **1**, 126–143 (2019).

remarkably successful at treating leukaemia.

Despite the immense potential of this strategy, the use of ACT is currently limited because the modified T cells that are transferred back to a person with cancer can be short-lived, and are often unable to overcome a tumour's ability to hinder their function. When naive T cells recognize a disease-causing agent or a tumour cell, they proliferate to form short-lived tumour-killing (that is, cytotoxic) CD8 T cells (also known as effector cells) that kill these infected or malignant cells (Fig. 1). If the infection or the tumour cells are eliminated, most of these CD8 T cells die, but a small population remains in the form of long-lived memory T cells, which are self-renewing and can generate cytotoxic CD8 T cells if the same infection or malignancy is encountered again<sup>3</sup>.

However, if the infection or tumour cannot be eliminated, the cytotoxic T cells progressively lose their function (a process termed exhaustion). The ideal population of T cells for use in ACT would infiltrate tumours and accumulate in substantial numbers while retaining cytotoxic function and the capacity for self-renewal<sup>2</sup>. Yet the differentiation of T cells into cytotoxic CD8 T cells impairs successful retention of the potential to form long-lived memory cells. This raises the question of whether a strategy can be found to induce both of these beneficial traits in T cells used for ACT. It has been speculated that, in the unforgiving tumour microenvironment, CD8 T cells would need to have a robust metabolism to sustain the nutritional and energetic requirements needed for survival and to retain their antitumour activity<sup>4</sup>.

Wei *et al.* used the CRISPR–Cas9 gene-editing technology to disrupt more than 3,000 genes associated with metabolism in T cells, to test their functions in a mouse model of antitumour ACT. The authors identified more than 200 genes that have a striking ability to affect the persistence and function of the CD8 T cells transferred into tumour-bearing mice. The disruption of many genes had a negative effect on the ability of the cells to persist and thus accumulate in tumours, but the disruption of four genes resulted in a much higher than normal number of T cells infiltrating the tumours.

At the top of this list is the gene that encodes the enzyme REGNASE-1. Its deletion in CD8 T cells caused 2,000 times more of these cells to accumulate in tumours than did CD8 T cells that expressed REGNASE-1. This enzyme binds to and degrades RNA, and influences immune responses<sup>5–7</sup>, but its role in the antitumour function of CD8 T cells had not been explored. CD8 T cells that lacked REGNASE-1 were better than wild-type CD8 T cells at fighting two types of tumour in mice: an aggressive skin cancer called melanoma and a blood cancer termed acute lymphocytic leukaemia. The REGNASE-1-deficient CD8 T cells proliferated at a similar rate to

### Medical research

# Antitumour T cells stand the test of time

Miguel Reina-Campos & Ananda W. Goldrath

Enhancing antitumour immune responses has revolutionized cancer treatment, yet some hurdles impede this approach. The discovery of a way to boost the lifespan and function of antitumour immune cells removes a key obstacle. **See p.471**

Immune cells called cytotoxic CD8 T cells can directly kill tumours and are key weapons mobilized in many immunotherapy approaches used in the clinic. However, the cells' activity can be thwarted by the ability of tumours to create harsh microenvironments, recruit immunoregulatory cells and induce inhibitory signals that hamper T-cell function, accumulation and tumour infiltration. On page 471, Wei *et al.*<sup>1</sup> report that depletion of the protein REGNASE-1 extends the survival of antitumour CD8 T cells and enhances their function, enabling the cells to fight cancer more effectively.

The development of anticancer clinical strategies that use immune cells has profoundly improved the treatment of certain malignancies. The delivery of T cells that can specifically target tumours is used in

an approach called adoptive T-cell therapy (ACT), which relies on T cells that have been taken from a person's blood or tumour. These cells are stimulated in the laboratory to cause them to divide and to increase the number of

**“This study offers a strong incentive to investigate the use of combinatorial approaches.”**

antitumour T cells, and, in some cases, they are modified to enhance their ability to eliminate cancer cells<sup>2</sup>. For example, T cells can be engineered to express a receptor, called a chimaeric antigen receptor (CAR-T), that specifically targets tumours, and such cells are