differentiate into mature white blood cells. Furthermore, treatment with AG-221 prolonged the survival of mice transplanted with the AML cells.

It remains to be seen whether these effects will be recapitulated in humans. However, preliminary results[10] from early-phase clinical trials of AG-221 suggest that the drug provides a therapeutic benefit in some people with *IDH2*-mutant AML. It is less clear whether it will have a similar effect on people who have solid tumours that harbour *IDH* mutations. In an ongoing phase I clinical trial to test a drug called AG-120 that inhibits mutant IDH1, interim analysis shows that the drug frequently stabilizes the disease in patients with solid tumours, but rarely causes tumour regression (see go.nature.com/2ngnxji).

Mutant IDH proteins are inherently tractable as therapeutic targets because their abnormal function can be inhibited. But restoring the activity of an inactivated enzyme such as TET2 is more difficult. The effect of TET2 loss is to increase DNA methylation, and there is evidence that some *TET2*-mutant blood cancers are hypersensitive to drugs that inhibit DNA methylation[11]. However, it is not clear whether this reflects a true therapeutic vulnerability of cells that lack TET2, or whether some other feature of these cancers is responsible for this sensitivity.

In the second study, Shih *et al.*[4] compared the effects of preventing DNA hypermethylation induced by genetic loss of *TET2* and restoring TET2 activity by inhibiting mutant IDH2 in AML. The authors generated mice that harboured mutations in either *Idh2* or *Tet2*, in combination with mutations in another gene, *Flt3*, which encodes a receptor tyrosine kinase protein (an enzyme that activates signalling pathways that promote the proliferation of blood-cell progenitors). Activating mutations in *FLT3* are common in AML. In mice, a *Flt3* mutation combined with either a *Tet2* mutation or an *Idh* mutation leads to AML.

The authors transplanted the leukaemic cells from their mutant mice into wild-type recipient animals to model conditions in patients, in whom both normal and leukaemic blood cells circulate. They then treated the recipient mice with either AG-221 or a drug called 5-azacytidine (5-Aza), which inhibits DNA methylation. Treatment of mice harbouring *Tet2*- and *Flt3*-mutant AML cells with 5-Aza decreased the level of DNA methylation and induced differentiation of the leukaemic cells — as did AG-221 treatment of mice harbouring *Idh2*- and *Flt3*-mutant AML cells. However, neither treatment significantly reduced the percentage of circulating blood cells that were derived from the donor mice, suggesting that neither killed a significant portion of the mutant cells.

Shih and colleagues next treated their *Tet2*- and *Flt3*-mutant mice with the FLT3 inhibitor AC-220 and 5-Aza, either alone or in combination, and treated their *Idh2*- and *Flt3*-mutant mice with AC-220 and AG-221, again either alone or together. Both combination treatments resulted in more-profound responses and increased the reversal of DNA hypermethylation more effectively than the single treatments. Tellingly, the combination therapies dramatically reduced the percentage of circulating cells that were derived from the donor mice, suggesting that two-pronged therapies that target both epigenetic dysregulation and kinase signalling can induce potent antileukaemic responses.

Together, the two current studies provide a valuable proof-of-concept that targeting epigenetic dysregulation could be an effective therapeutic strategy in AML. However, they also suggest that such approaches will not be sufficient to eradicate disease. Instead, Shih and colleagues' data indicate that the key to a cure might lie in dual-pronged therapies. Their work provides a compelling rationale for clinical trials of combined epigenetic- and kinase-targeted therapies.

Finally, it was unexpected that these combination therapies would kill AML cells, and this raises an interesting question: how do epigenetic dysregulation and proliferation-promoting signals interact in AML? Further studies will be required to rule out the possibility that inhibition of FLT3 signalling simply potentiates the effects of AG-221 and 5-Aza. However, if that is not what happens, then these findings suggest that there is a greater interplay between these (seemingly) functionally distinct pathways than is currently appreciated. A more thorough mechanistic understanding of how these pathways cooperate to promote leukaemia has the potential to uncover exciting new strategies to treat AML. ■

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PLANETARY SCIENCE

Reckless orbiting in the Solar System

Planets and most asteroids revolve around the Sun in the same direction. But an asteroid that shares Jupiter's orbit has been revolving in the opposite direction for about a million years. SEE LETTER P.687

HELENA MORAIS & FATHI NAMOUNI

The Solar System formed in a disk of gas and dust whose constituents revolved around the Sun in the same direction. In the final stages of planetary formation, trillions of bodies were expelled beyond the reach of the planets, forming a relatively thin disk of debris. The Galaxy's tidal forces then modified this structure into a spherical shell known as the Oort cloud that remains gravitationally bound to the Sun. This shell is located more than 10,000 times farther from the Sun than Jupiter is, and shelters objects that orbit the Sun in the direction opposite (retrograde) to that of planetary motion. On page 687, Wiegert *et al.*[1] report the discovery of the first object that shares the orbit of a planet but revolves in the retrograde direction.

Thousands of objects called Trojan asteroids populate Jupiter's orbit, revolving around the Sun in the same direction as the planet (prograde). These objects sit near Lagrange points, which form an equilateral triangle with the Sun and Jupiter. Whereas Trojan asteroids have stable orbits, other prograde asteroids can enter a transient co-orbital state for several thousand years[2], in which they have the same orbital period as a planet. Co-orbital states can take many shapes, depending on the asteroid's motion in space. These shapes include tadpoles, horseshoes, quasi-satellites — in which the asteroid stays close to the planet for many orbital periods — and combinations thereof (Fig. 1a).

The dynamics of most small bodies in the

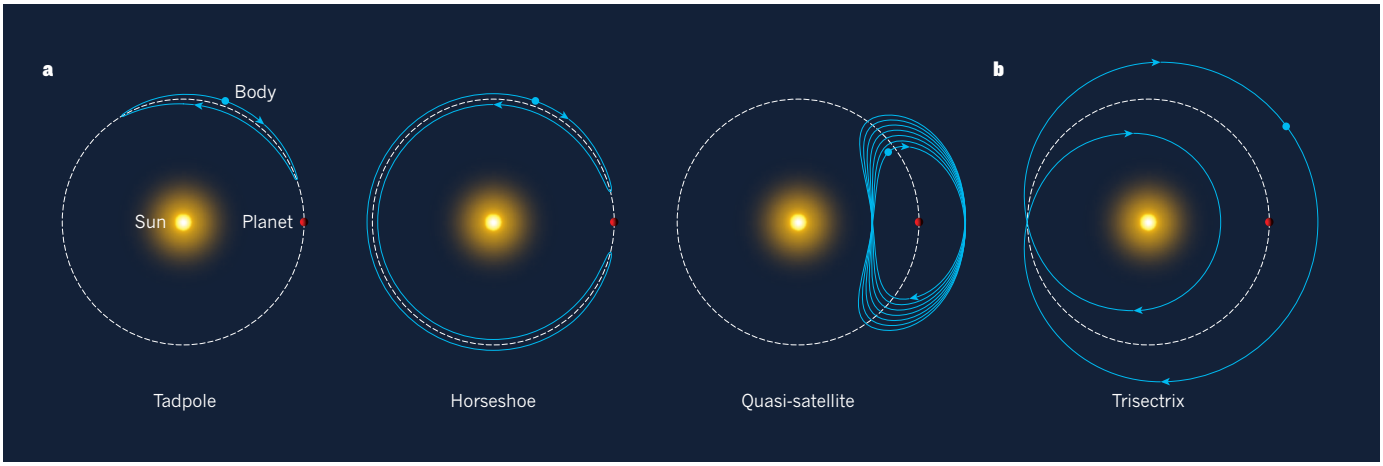

Figure 1 | Co-orbital states. As small bodies travel through the Solar System, they can enter co-orbital states, in which they have the same orbital period as a planet. **a,** Co-orbital bodies that orbit the Sun in the same direction as a planet can follow trajectories (blue curves with arrows) that, from the perspective of the planet, look like tadpoles, horseshoes or 'quasi-satellites'. The white circle represents the orbit of the planet around the Sun. The tadpole and horseshoe shapes arise because the planet's gravitational attraction alters the body's orbital path — the body goes through a cycle of catching up with the planet and falling behind, seeming to change direction from the perspective of the planet. The quasi-satellite shape results from the two orbits having different eccentricities. When viewed from the planet, the body seems to loop around it. **b,** Wiegert *et al.*[1] have discovered the first co-orbital body that orbits the Sun in the opposite direction to a planet. When viewed from the planet, the body's orbit takes the shape of a type of curve called a trisectrix.

Solar System are complex, making it difficult to identify their source. Objects called Centaurs exhibit a 'random walk' in the outer Solar System because they have close encounters with the giant planets, and this limits their orbital stability to a few million years[3,4]. Centaurs can evolve into short-period comets, collide with the Sun or a planet, or be ejected from the Solar System. Most Centaurs orbit in the general direction of planetary motion, pointing to an origin in the Kuiper belt — a reservoir of remnants from the Solar System's formation that is situated beyond Neptune's orbit.

Other small bodies called Halley family comets (HFCs) typically have high orbital inclinations with respect to Earth's orbital plane. They are named after their most famous member, Halley's comet, which has a retrograde orbit and reaches perihelion — its closest approach to the Sun — roughly every 75 years. The source of HFCs is a matter of debate, however. Given their wide range of inclinations, HFCs could have evolved from long-period comets originating in the Oort cloud. Alternatively, they might have evolved from Centaurs[5], or maybe they emerged from a hitherto undetected reservoir of high-inclination orbits beyond Neptune[6]. Small bodies that have orbits similar to HFCs but that lack cometary activity are known as Damocloids[7].

Wiegert and colleagues study the object 2015 BZ_{509}, which was detected[8] in January 2015 using the Panoramic Survey Telescope and Rapid Response System (Pan-STARRS) in Hawaii. Wiegert *et al.* use additional observations from the Large Binocular Telescope in Arizona to improve the accuracy of the parameters that describe the object's orbit. They show that 2015 BZ_{509} is in the 1:1 retrograde resonance with Jupiter. This means that the object is co-orbital (the ratio of its orbital period to that of Jupiter is 1:1) and that the two bodies exert regular, periodic gravitational influences on one another (orbital resonance).

When viewed from the perspective of Jupiter, the orbit of 2015 BZ_{509} takes the shape of a type of curve called a trisectrix (Fig. 1b). Such an orbit would be stable indefinitely if the asteroid's motion around the Sun were influenced only by Jupiter[9]. The authors confirm that 2015 BZ_{509} has long-term stability, having been in its current state for about a million years. This stability is a unique feature of retrograde resonances — even though 2015 BZ_{509} passes Jupiter every six years (twice per orbit), the duration of the encounters is much shorter than if the object were on a prograde orbit.

The authors also discuss the nature and origin of 2015 BZ_{509}. Such small bodies in orbit around the Sun can be either rocky or icy, depending on whether they formed in the inner or outer Solar System. If icy bodies pass close to the Sun, they can become comets, but rocky or icy bodies that do not show signs of cometary activity are loosely said to be asteroids. Wiegert *et al.* observe 2015 BZ_{509} when it is near perihelion, about three times farther from the Sun than Earth is. They detect no signs of cometary activity, which suggests that the object would be classified as an asteroid. It is likely to be a Damocloid that was captured in the 1:1 (co-orbital) retrograde resonance with Jupiter.

However, 2015 BZ_{509} is not the only known retrograde asteroid in resonance: 2006 BZ_8 and 2008 SO_{218} are currently in the 2:5 and 1:2 retrograde resonances with Jupiter, respectively, and 2009 QY_6 is in the 2:3 retrograde resonance with Saturn[10]. Indeed, 2006 BZ_8 could even enter the 1:1 retrograde resonance with Saturn in the future[10]. Simulations have shown that capture in resonance is more likely for objects that have retrograde orbits than for those that have prograde orbits[11].

Resonances extend the lifetimes of objects on planet-crossing orbits by protecting them from disruptive close encounters with planets[4,5,11]. The particularly long lifetime of 2015 BZ_{509} on its retrograde orbit, in the same region of space as the largest planet in the Solar System, makes it arguably the most intriguing small body in this region. Further studies are needed to confirm how this mysterious object arrived at its present configuration. ■

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