The cryo-EM structures show that closure of the VFT domain brings the cysteine-rich stalk and the 7TM domain of each subunit in the dimer closer together (Fig. 1), with the 7TM domains rotating, such that one of the α-helices (known as TM6) of each mGlu5 monomer forms a new interface between the two monomers. It is worth noting that the 7TM domains in the full-length receptors were reconstituted in different media (a nanodisc of lipids or a micelle of detergents) for each structure, and this might have influenced the relative orientation and proximity of the 7TM domains within the dimer. However, the authors carried out crosslinking experiments that provide more evidence of the structural changes proposed to occur on receptor activation, and further support comes from previously published studies[5–7] of other class C GPCRs.

Koehl *et al.* also carried out experiments to examine the effects of mutations to mGlu5 on its activation mechanism. Their results suggest that an interaction between the cysteine-rich stalk and a region of the 7TM domain known as the second extracellular loop (ECL2) governs activation by agonists that bind to the VFT domain, but not activation by agonists that bind to the 7TM domain. The conformation of this loop modelled by the authors is similar to that observed in the X-ray structure[8] of the 7TM domain of the related mGlu1 receptor in complex with an inhibitor. ECL2 is known to influence activation states in other GPCRs[9], but Koehl and colleagues' study provides the first indication that it also has a key role in mediating interdomain communication in class C GPCRs. However, the relatively low resolution of the new structures prohibits meaningful comparisons of the interactions between ECL2 and the cysteine-rich stalk in the inactive and active conformations of mGlu5. Whether these regions constitute targets suitable for drug discovery also remains an open question.

The resolution of the 7TM domains in both conformations is also insufficient to visualize the small-molecule inhibitors or activators that were used in the purification and reconstitution of the agonist-free and agonist-bound receptor structures, respectively. It remains to be seen how the structures of binding pockets in the 7TM domain change in the presence of inhibitors or activators. Indeed, the resolution of the 7TM domains is lower than those previously obtained[10–12] for structures of the 7TM domains of mGlu5 bound to inhibitors. The structure of receptors in complex with an intracellular effector (such as a G protein) will be required to stabilize, and therefore visualize at high resolution, active 7TM conformations, and to understand how allosteric modulators binding to the 7TM domain alter the activation states, to enable the structure-guided design of drugs that target glutamate receptors.

Koehl and colleagues' structures reveal the large-scale conformational changes that occur in a dimeric, full-length, class C GPCR when an agonist binds to the N terminus. The strategies used to stabilize full-length proteins will inform efforts to obtain the structures of other class C GPCRs, including receptors for ions and the inhibitory neurotransmitter GABA, as well as for receptors involved in taste. An appreciation of how these dimeric, multidomain receptors are organized should inform our understanding of how receptor complexes composed of two or more different class C GPCRs, or from different GPCR classes, are formed and activated. These structures might also guide future protein engineering of class C GPCRs to enable the identification of pockets that can be targeted by drugs, and might ultimately open up avenues of research for structure-guided drug discovery. ■

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BIOTECHNOLOGY

On the road to a gene drive in mammals

A method for making a version of a gene more likely to be inherited than normal, generating what is called a gene drive, might be used to control insect populations. It has now been reported to work in mammals, too. SEE LETTER P.105

BRUCE R. CONKLIN

When Gregor Mendel tracked pea-plant characteristics over successive generations in the nineteenth century[1], his landmark study revealed key insights into the fundamental mechanisms governing genetic inheritance. Mendel observed consistent patterns of inheritance that corresponded to each descendant receiving one of the two maternal copies of a gene affecting the characteristic and one of the two paternal copies of this gene. In this typical scenario of genetic inheritance, both maternal copies of a gene have an equal probability of being inherited, as do both paternal copies.

However, inheritance does not always proceed so fairly, and in some cases the odds of a particular copy of a gene being transmitted to the next generation can be heavily skewed. One natural example is that of 'jumping genes', which are inherited in a non-Mendelian pattern[2]. Genetic-engineering approaches are being developed to manipulate the inheritance pattern of a gene copy such that it will spread through a population more rapidly than would be expected by normal Mendelian inheritance, generating what is called a gene drive and leading to super-Mendelian inheritance[3,4]. This process generates what is called a gene drive. So far, gene drives have been mainly engineered in insects. Grunwald *et al.*[5] report on page 105 a method for generating a gene drive in mice, offering an option to use this approach in mammals.

Gene drives developed in insects might provide a way to alter mosquito populations to decrease the probability that they transmit diseases such as malaria or dengue fever[3,4]. For example, a gene drive that affects mosquito fertility could be used to specifically eliminate a species of malaria-transmitting mosquito[4], allowing its ecological niche to be filled by other mosquito species that cannot harbour the malaria-causing parasite. Alternatively, gene drives can be designed[6] to confer widespread, species-specific resistance to infection by this parasite, for instance by using a gene drive to spread sequences that encode antimalarial antibodies so that mosquitoes are no longer infected by the parasite[7].

The technology needed for gene drives has been greatly accelerated in insects by harnessing a gene-editing technique called CRISPR[3,4,6]. This system relies on the insects being engineered to express the enzyme Cas9 and a guide RNA that provides gene-targeting specificity. Cas9 generates a cut in a genomic DNA sequence that matches the guide RNA sequence (Fig. 1). If the guided cut generates

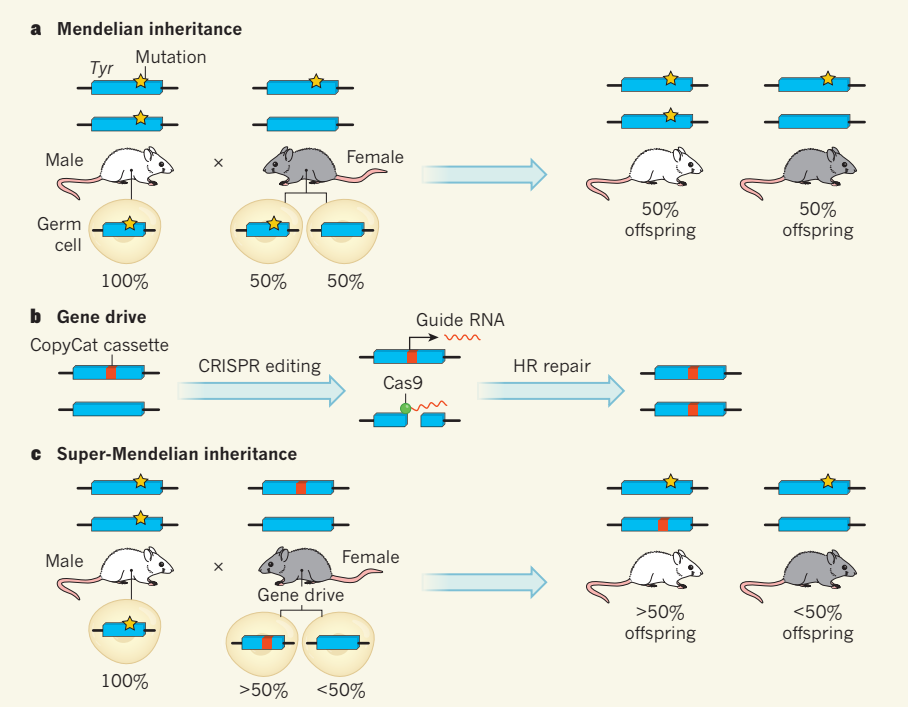

Figure 1 | Engineering super-Mendelian inheritance in mice. **a**, If mice have a mutation in both copies of their *Tyr* gene, their coat is white, but if one copy of *Tyr* is functional, their coat is grey. Coat colour can therefore be used to track the inheritance of versions of this gene. In the normal pattern of genetic inheritance, termed Mendelian inheritance, both parental copies of a gene have an equal probability of being included in reproductive cells called germ cells, which are passed to the next generation. Therefore, in a cross between a parent that has two mutant copies of *Tyr* and a parent with one mutant copy and one wild-type copy, the predicted Mendelian inheritance pattern is that half the offspring will have two mutant copies of *Tyr* and half will have one mutant and one wild-type copy. **b**, Grunwald *et al.*[5] used a genetic-engineering approach termed CRISPR to alter the pattern of genetic inheritance in mice, generating what is called a gene drive. They inserted a sequence called a CopyCat cassette into *Tyr* at a location that prevents *Tyr* from encoding a functional protein. This cassette encodes a CRISPR component called a guide RNA that enables another CRISPR component, the protein Cas9, to specifically cut the wild-type copy of *Tyr*. The authors found that, in the reproductive tissues of female mice, such a cut is repaired by a process called homologous recombination (HR), which uses the copy of *Tyr* containing the CopyCat cassette as a template, and so results in a cell that contains two copies of *Tyr* that have this cassette. **c**, The authors observed that using such a Cas9-mediated gene drive resulted in more than half of the germ cells containing the CopyCat cassette, rather than the 50% expected. This causes a manipulated pattern of gene inheritance, termed super-Mendelian.

a double-stranded DNA break in one copy of a gene, this break can be repaired by a process called homologous recombination, in which the undamaged chromosome containing a sequence that matches that in the region of the DNA break is used as a repair template.

A DNA sequence needed for the gene drive, called a cassette, which encodes CRISPR machinery, can be engineered and inserted into a chosen site in a host chromosome. The cassette encodes components needed to initiate a targeted Cas9-mediated DNA break on the sister chromosome. Successful repair of this break by homologous recombination using the chromosome that contains the cassette results in both the maternal and paternal sister chromosomes having identical copies of this cassette (a state called homozygosity). The cassette can be engineered to deliver additional DNA sequences, and such gene editing results in cells that are homozygous for any desired gene on the cassette. Achieving this effect consistently in the reproductive cells (germ cells) would ensure that all offspring receive the cassette, rather than just half the offspring as expected by Mendelian patterns of inheritance. If a gene drive works efficiently in rapidly reproducing populations such as insects, it would be predicted that an entire population could be manipulated to carry the desired gene on the cassette.

Gene drives have flourished in mosquito studies that have adapted the genetic-engineering tools developed in the fruit fly *Drosophila melanogaster*. Gene drives engineered in mosquitoes can be stably transmitted over many generations through a process that uses a form of high-fidelity homologous recombination that is remarkably efficient in the mosquito reproductive tissues (the germ line)[4,6]. However, it has been difficult to apply these approaches in mammals, which have evolved independently from insects for more than 700 million years.

But now, Grunwald and colleagues have developed a CRISPR-based gene drive for mice. They engineered animals to express Cas9 and a cassette they called CopyCat, which encoded a guide RNA that targets a sequence in the gene *Tyr* (Fig. 1). CopyCat was inserted into the *Tyr* sequence at a position that ensured that the guide RNA wouldn't target the copy of *Tyr* in which the cassette was inserted.

Tyr encodes an enzyme called tyrosinase, which affects mouse coat colour. This enabled the frequency of genetic modification of the gene to be tracked over generations by monitoring coat colour and using DNA-sequence analysis to assess the transmission of the CopyCat cassette. The authors tested the effect of different genetic elements called promoters that affect Cas9 expression patterns. If Cas9 was expressed ubiquitously and continuously, the Cas9-mediated cut site in *Tyr* had a high level of DNA damage, which arose from a DNA-repair process called non-homologous end joining (NHEJ). When the authors limited Cas9 expression to the male germ line, they also observed high rates of DNA damage caused by NHEJ. However, the gene drive worked successfully when Cas9 was expressed specifically in the female germ line, and, in this context, the Cas9 cuts of the *Tyr* sequence were repaired by homologous recombination. The transmission rates of the CopyCat element to the next generation in female mice were greater than the 50% transmission that would be expected for standard Mendelian inheritance. The maximum efficiency of this CRISPR editing was a 72% success rate in copying the CopyCat cassette.

The reason for the sex-specific differences in homologous recombination and NHEJ that the authors observed is unknown. But it could be a major impediment for using mammalian gene drives because NHEJ damages the guide-RNA recognition site and therefore blocks the ability to transmit the gene drive. Male and female germ-cell development is substantially different, so further investigation will be needed to learn whether efficient homologous recombination occurs in the male germ line when the timing or pattern of Cas9 expression is altered. Nevertheless, Grunwald and colleagues' work is an important proof-of-concept that will surely be followed by modifications that might lead to improvements in future mammalian gene drives.

If gene drives become efficient in mammals, one possible way in which they might be used is to tackle pests or disease-causing agents. The eradication of invasive rodents from islands can bring about a dramatic recovery of native ecosystems, but achieving this eradication using current pest-control methods requires Herculean efforts[8]. A mammalian gene drive might provide a powerful alternative. However, eradication is not the desired outcome if a disease-harbouring species is native to a region but has a key role in supporting ecosystem balance[9,10]. Native species can harbour organisms, such as the bacterium that causes plague, that are responsible for deadly human diseases. A gene

drive engineered to express an antibody to block an infectious agent would protect people from animal-transmitted disease and maintain native species that are essential[9,10] to the ecosystem.

Another possible application of mammalian gene drives is to speed the generation of animal models of disease, because it can be challenging to breed a mouse that has specific combinations of mutations in several genes.

Because gene drives have the potential to alter an entire species, appropriate regulation of this technology is a major concern. Only the most intractable and major health challenges should be considered for possible interventions using gene drives. Any proposed genetic change should be tested to minimize the chances of unintended consequences to the species or the ecosystem. This challenge is particularly daunting for highly mobile species such as the mosquito, which can fly long distances and across national boundaries. Certainly, the use of a gene drive for mosquito-borne diseases such as malaria warrants international efforts that proceed using careful planning and monitoring, and with the engagement of local communities. Nevertheless, it should be remembered that even the best-planned efforts can have unexpected outcomes. A mammalian gene drive might offer a more attractive test case than an insect one for pest eradication or infectious-disease control, because wild mammalian populations can be more easily restricted to a geographic region than can insect populations.

More than 150 years after Mendel's work illuminated one way in which genetic inheritance can be governed, a powerful tool has emerged to manipulate inheritance in mammals. It seems certain that the promise of continual improvements in gene drives will be matched with even more discussion of how to move forward. The development of this technique to generate a mammalian gene drive is another milestone in this exciting area of research. ■

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QUANTUM PHYSICS

A traffic jam of light

A technique that harnesses energy loss has been used to produce a phase of matter in which particles of light are locked in place. This opens a path to realizing previously unseen exotic phases of matter. SEE ARTICLE P.51

KADEN R. A. HAZZARD

When light passes through matter, it slows down. Light can even be brought to a standstill when it travels through carefully designed matter. One way in which this occurs is when the velocity of individual particles of light (photons) in a material is zero. Another, more intriguing, way is when photons, which normally pass through each other unimpeded, are made to repel each other. If the repulsion is strong enough, the photons are unable to move, and the light is frozen in place. On page 51, Ma *et al.*[1] report that such a phase of matter, known as a Mott insulator, can be produced by exploiting energy loss in a system in which photons move through an array of superconducting circuits.

A wide variety of experiments aim to engineer large quantum systems for use in computation and high-precision sensing, and to design materials that have unprecedented properties. These experiments often treat dissipation — the loss of energy or, more generally, information about a system — as anathema to producing large quantum systems. The reason is that tiny perturbations, including dissipation, often destroy quantum effects in systems of more than a few particles. Great care is therefore taken to minimize dissipation.

However, when dissipation is carefully engineered, it can also be a resource, and its utility for realizing exotic quantum matter is beginning to be harnessed[2–8]. One common way to use dissipation to produce unusual quantum states is to lower the temperature of a material. This can be accomplished by immersing the material in a coolant to extract energy. Just as cars on a motorway can go from a high-energy, smoothly flowing state to a jammed state by dissipating energy into heat and sound, quantum systems can go from a relatively hot initial state to a cold, jammed state by dissipating energy into photons.

Ma and colleagues used a more sophisticated method to dissipate energy from superconducting circuits, which are similar to ordinary circuits, but have some elements replaced by superconducting wires. The authors used a chain of eight superconducting

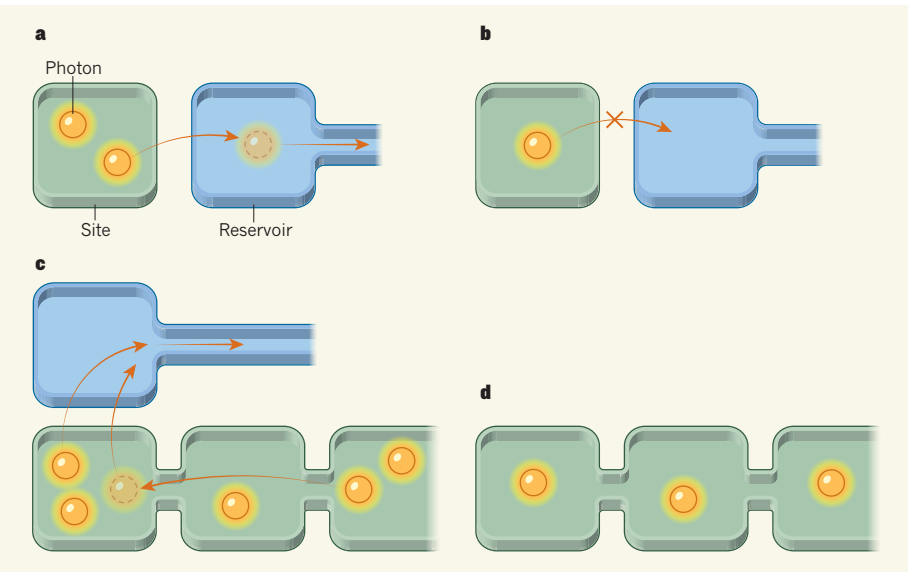

Figure 1 | Production of a Mott insulator. Ma *et al.*[1] report a technique for organizing particles of light (photons) into a phase of matter called a Mott insulator. **a**, The method uses superconducting circuits that can be thought of as sites that photons can occupy. If there are two photons on a site, one photon can move between the site and a 'reservoir', and then will be rapidly lost to the outside world. **b**, If there is a single photon on a site, it will not move to the reservoir. **c**, Coupling the end of a chain of sites to a reservoir forces the end site to be occupied by a single photon. If any of the other sites are occupied by two photons, one of the photons will move through the chain until it reaches the end site and then be lost to the reservoir. **d**, The end result of this process is a Mott insulator, a simple picture of which is a state that has exactly one photon per site.