inhibitory control of DVB. This refinement improves the male's mating efficiency[7]. Hart and Hobert now show that this male-specific outgrowth of DVB occurs between days 1 and 5 of adult life. The outgrowth produces a branching neuronal architecture that, unlike many neuronal circuits in *C. elegans*, varies between individuals.

Hart and Hobert used fluorescent 'reporter' proteins to visualize DVB outgrowth and synapse formation. Their analysis reveals that outgrowth does not occur if the male does not experience copulatory activity. The authors then mimicked natural behaviours by using sophisticated genetic techniques to activate or inhibit the signalling or movement of DVB's target neuron and muscles, respectively. This shows that activity in DVB's targets stimulates the neuron's outgrowth.

What molecular pathways might mediate DVB outgrowth? Neural cell-adhesion proteins are expressed on cell surfaces in the nervous system. They have extracellular protein–protein interaction domains that can mediate communication between cells, and are thought to have a role in encoding and building the nervous system's synaptic structure[8]. Two of the best-studied proteins in this class are neurexin and neuroligin, which can interact with one another and are involved in synapse formation and regulation[9]. As such, they were natural candidates for Hart and Hobert to test.

The authors examined the roles of these proteins by combining genetic deletion or overexpression of the proteins with stimulation or suppression of activity in the circuit. These analyses led to several findings. First, neurexin is expressed in DVB and is required for DVB outgrowth. Second, the activity of neurexin is inhibited by neuroligin, which is expressed in male sex circuits and muscles. Third, neuroligin expression is suppressed by activity in the circuit, which explains why DVB outgrowth is activity dependent. Precisely how neuroligin inhibits DVB outgrowth, and whether the two proteins physically interact in this setting, remain to be determined.

Hart and Hobert's work brings together three areas of study in neuroscience: outgrowth, branching and target selection in plastic neurons; control of these processes through neuronal activity; and the function of neural cell-adhesion proteins. The value of the study therefore lies not only in the discovery of a new phenomenon, but also in the framework it provides for making more discoveries.

Analysis of *C. elegans* mutants will make it possible to identify additional molecules that affect DVB outgrowth, such as the binding partner of neurexin that stimulates outgrowth. The intracellular mechanisms that drive DVB outgrowth, and how they are controlled by interactions between neurexin and its binding partner, can then be analysed. Other questions for study include how DVB knows where to send processes, how its axonal extensions recognize appropriate synaptic targets, and precisely how circuit activity controls neuroligin expression.

Finally, Hart and Hobert found that these events occur only in males. The authors attempted to stimulate DVB outgrowth in hermaphrodites, but their results suggest that neither circuit activity nor the neurexin–neuroligin pathway are by themselves sufficient to do this. Other work[10] in *C. elegans* suggests that it is the complement of sex chromosomes (two X chromosomes in the hermaphrodite and only one in the male) in the cells of the circuit that ultimately makes them respond to sex-neutral pathways in sex-appropriate ways.

Genetic studies[9] have implicated mutations in neural cell-adhesion genes, including neurexin and neuroligin, as the bases of psychiatric disorders, partly because of the roles of these genes in neural plasticity. Progress in unravelling details of the molecular pathways underlying their activity could therefore have profound implications for understanding not only learning and memory, but also mental disorders and their sex-specific expression. ■

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1. Holtmaat, A. & Svoboda, K. *Nature Rev. Neurosci.* **10,** 647–658 (2009).
2. Hart, M. P. & Hobert, O. *Nature* **553,** 165–170 (2018).
3. Jin, Y. & Qi, Y. B. *Curr. Opin. Neurobiol.* **48,** 97–105 (2017).
4. White, J. G., Southgate, E., Thomson, J. N. & Brenner, S. *Phil. Trans. R. Soc. B* **314,** 1–340 (1986).
5. Emmons, S. W. *Phil. Trans. R. Soc. B* **370,** 20140309 (2015).
6. Jarrell, T. A. *et al. Science* **337,** 437–444 (2012).
7. LeBoeuf, B. & Garcia, L. R. *G3 Genes Genomes Genet.* **7,** 647–662 (2017).
8. Williams, M. E., de Wit, J. & Ghosh, A. *Neuron* **68,** 9–18 (2010).
9. Südhof, T. C. *Cell* **171,** 745–769 (2017).
10. Portman, D. S. *J. Neurosci. Res.* **95,** 527–538 (2017).

ORGANOMETALLIC CHEMISTRY

Dogma-breaking catalysis

The catalysts conventionally used for industrially important hydrogenation reactions are expensive and generate toxic residues. Catalysts have now been reported that might lead to cheaper, less toxic alternatives.

DOUGLAS W. STEPHAN

Reactions of hydrogen gas with organic compounds are performed on a large scale worldwide by the chemicals industry[1]. Such hydrogenation reactions are essential to the production of numerous commercial goods, including many polymers, foodstuffs and pharmaceuticals. However, a catalyst is needed to provide a thermodynamically accessible reaction pathway that allows hydrogenations to occur. Until the past decade or so, it was thought that these catalysts must derive from transition metals, but there is now a growing list of alternatives. Writing in *Nature Catalysis*, Bauer *et al.*[2] add to that list by reporting effective hydrogenation catalysts derived from alkaline-earth elements — the group of metals that includes calcium.

About 100 years ago, the chemist Paul Sabatier was the first to recognize that amorphous metals could act as catalysts to mediate the hydrogenation of organic substrates[3]. By the middle of the twentieth century, the emergence of the subdiscipline of organometallic chemistry led to the development of a wide variety of transition-metal complexes that are highly effective catalysts for these reactions[4]. Soluble transition-metal catalysts have undergone continual development to offer higher and higher reactivities. In addition, judicious changes to the ligand molecules bound to the metal atom were found to control the reactivity and selectivity of the catalytic complexes — not only the substrate selectivity, but also the stereoselectivity (the 3D geometric arrangement of atoms generated in the product). Despite these advances, most catalysts used in industrial processes are derived from the metals platinum, palladium, rhodium and ruthenium, which are expensive, toxic and rare.

The cost of the precious metals in such catalysts is not the only expense associated with their use — the removal of toxic catalyst residues from the products is also costly. This, together with increasing environmental concerns, has prompted efforts to find alternatives to conventional hydrogenation catalysts. One strategy that uses the principles of

organometallic chemistry has been to develop catalysts derived from earth-abundant, less-toxic transition metals such as iron, cobalt and nickel[5].

In the past decade or so, startling strategies for hydrogenation reactions have also been discovered. In 2006, certain molecules containing boron and phosphorus were shown to react reversibly with hydrogen[6]. It was subsequently found[7] that reactions between boron-containing molecules known as boranes and phosphorus-containing molecules called phosphines can be frustrated electronically or through steric effects (which occur when bulky chemical groups block access to certain parts of a molecule). This allows certain combinations of boranes and phosphines to chemically activate hydrogen molecules, and, in some cases, mediate the hydrogenation of many different types of compound[8,9]. Then, in 2008, a remarkable calcium-based catalyst was reported[10] for the hydrogenation of alkenes (hydrocarbons that contain carbon–carbon double bonds). Collectively, these findings provided evidence that hydrogenation can be catalysed by systems based on elements other than the transition metals, overturning 100 years of chemical dogma.

Bauer *et al.* have now broadened the range of alkaline-earth-metal derivatives that can form the basis of hydrogenation catalysts. The new catalysts are complexes with the general formula $M[N(SiMe_3)_2]_2$ (where M can be magnesium, calcium, strontium or barium; Si is silicon; and Me represents a methyl group), and can be readily prepared. The authors used them to hydrogenate substrates known as aldimines (Fig. 1).

The researchers performed 30 reactions using different reaction conditions and several aldimines. They varied the amount of catalyst used (between 2.5% and 10% molar equivalents of the reaction substrate), the pressure of hydrogen (1–12 bar) and the temperature (80–120 °C). Most of the reactions were 99% complete in times ranging from 15 minutes to 24 hours, depending on the specific substrate, catalyst and conditions.

The authors show that the hydrogenations are slower for bulkier aldimine molecules and when the carbon atom in the aldimine's imine (C=N) group is less electrophilic (attractive to negative charges). Conversely, the catalytic activity increases with the atomic size of the metal used: the magnesium catalyst is least reactive, and the calcium, strontium and barium catalysts are increasingly reactive. That said, the calcium catalyst[10] previously reported by researchers from the same group was a highly effective catalyst for aldimine hydrogenation, which suggests that the activity of the current calcium catalyst could be optimized by modifying the ligands bound to the metal atom.

Most of the aldimines tested with the catalysts had a phenyl group (a benzene ring) attached to the carbon atom in the imine. Bauer *et al.* found that the catalysts still worked when electron-withdrawing or electron-donating groups were attached to the phenyl group — something that isn't always guaranteed in chemical reactions. However, the catalysts could not hydrogenate compounds known as ketimines, which are similar to aldimines but have two groups attached to the imine carbon atom, rather than just one.

Bauer and co-workers propose a mechanism for the catalytic cycle in which the catalyst first reacts with hydrogen gas to generate a transient hydride intermediate — a process that is likely to be reversible (Fig. 1a). The aldimine inserts into the M–H bond of the hydride to generate a diamido intermediate (Fig. 1b), which then reacts with more hydrogen gas to liberate the hydrogenation product (an amine; Fig. 1c). This last step also regenerates the hydride for further catalytic cycles.

"The authors report effective hydrogenation catalysts derived from alkaline-earth elements."

The proposed mechanism might seem straightforward, but the authors note that the active form of the catalyst has not been unambiguously identified. When Bauer *et al.* reacted the calcium catalyst with hydrogen gas alone, the proposed hydride intermediate did form, but so, too, did aggregated forms of hydrides.

The researchers performed computational simulations of their reactions to cast further light on the reaction mechanism. The simulations revealed that the aggregation process probably releases energy, suggesting that a thermodynamic driving force could generate a currently undefined, catalytically active complex involving an aggregated hydride. The simulations also supported the proposed stepwise mechanism for the catalytic cycle. Finally, Bauer *et al.* used a previously reported calcium hydride complex[11] as a model of the proposed catalytic hydride intermediate, and found that it reacts with an aldimine and hydrogen gas in a way that is consistent with the proposed catalytic cycle.

Compared with industrial reactions catalysed by transition-metal complexes, Bauer and colleagues' reactions use higher amounts of catalyst and are relatively slow. Nonetheless, the findings expand the substrate scope for hydrogenation catalysts derived from abundant alkaline-earth metals, raising the possibility that low-cost and low-toxicity catalysts could one day be used for industrial applications. Work is now needed to improve the activity of such catalysts, and to find catalysts that tolerate the presence of the impurities found in industrial-grade reagents. Perhaps most crucially, the authors' work provides further evidence that the dogma that transition metals are required for hydrogenation catalysis should be firmly relegated to the false beliefs of the past. ■

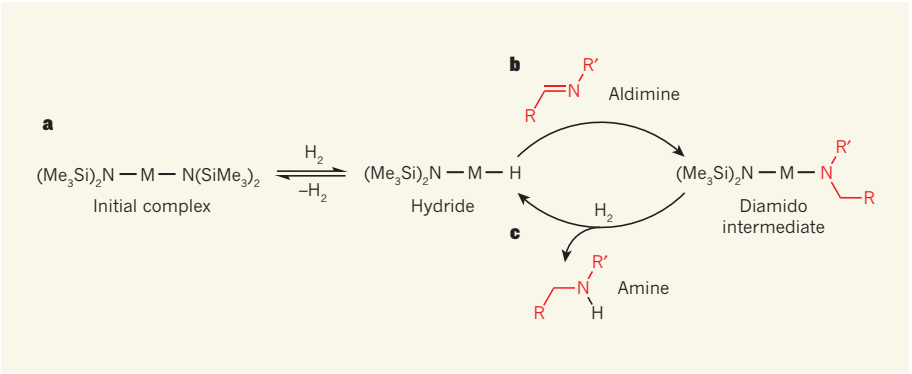

Figure 1 | Simplified hydrogenation mechanism for catalysts that contain alkaline-earth metals. Bauer *et al.*[2] report that complexes containing alkaline-earth metals catalyse the reaction of aldimine compounds with hydrogen gas (H_2), and propose the following mechanism. **a**, The initial complex reacts with H_2 — probably reversibly — to generate a transient hydride intermediate. **b**, The aldimine inserts into the M–H bond of the hydride to form a diamido intermediate. **c**, This intermediate reacts with more H_2 to liberate the hydrogenation product (an amine), regenerating the hydride for further catalytic cycles. Me, methyl; Si, silicon; M, magnesium, calcium, strontium or barium; R is typically an aromatic group, such as phenyl; R′ is *t*-butyl, isopropyl, phenyl or a mesityl (a bulky analogue of the phenyl group).

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1. de Vries, J. G. & Elsevier, C. J. (eds) *Handbook of Homogeneous Hydrogenation* (Wiley, 2006).
2. Bauer, H. *et al. Nature Catal.* http://dx.doi.org/10.1038/s41929-017-0006-0 (2018).
3. Sabatier, P. *Ind. Eng. Chem.* **18,** 1005–1008 (1926).
4. Hudlický, M. *Reductions in Organic Chemistry* 2nd edn (Am. Chem. Soc., 1996).
5. Bullock, R. M. (ed.) *Catalysis without Precious Metals*

(Wiley, 2010).
6. Welch, G. C., San Juan, R. R., Masuda, J. D. & Stephan, D. W. *Science* **314,** 1124–1126 (2006).
7. Welch, G. C. & Stephan, D. W. *J. Am. Chem. Soc.* **129,** 1880–1881 (2007).
8. Chase, P. A., Welch, G. C., Jurca, T. & Stephan, D. W. *Angew. Chem. Int. Edn* **46,** 8050–8053 (2007).
9. Stephan, D. W. & Erker, G. *Angew. Chem. Int. Edn* **54,** 6400–6441 (2015).
10. Spielmann, J., Buch, F. & Harder, S. *Angew. Chem. Int. Edn* **47,** 9434–9438 (2008).
11. Causero, A. *et al. Organometallics* **35,** 3350–3360 (2016).

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BIOTECHNOLOGY

An ode to gene edits that prevent deafness

Gene editing can prevent inherited deafness in mice by disabling a mutant version of a gene that causes hearing loss. Is this a turning point on the path towards treating some types of human deafness? SEE LETTER P.217

FYODOR URNOV

When the 32-year-old composer Ludwig van Beethoven realized that his hearing was failing, he wrote to his brothers that "as the leaves of autumn wither and fall, so has my own life become barren". Although the cause of Beethoven's deafness is unknown, there are many examples of hearing loss in later life that are linked to inherited DNA changes. Two centuries later, techniques to prevent inherited forms of deafness are finally getting closer to implementation in the clinic. On page 217, Gao *et al.*[1] report progress in using gene-editing technology to treat a mouse model of inherited deafness. Given the growing momentum in using genetic engineering for human therapy, the path needed to take this approach to the clinic is clear.

The remarkable process of sensing sound occurs in the inner ear[2]. Tiny, hair-like structures called cilia on the surface of hair cells in the cochlea respond to sound waves. Ciliary motion evokes an electrical signal because the properties of a protein assembly at the base of each cilium change when such motion occurs. The TMC1 protein is thought[3] to be part of this assembly in humans, and some *TMC1* mutations cause people to lose their hearing over time. The symptoms start in childhood, and deafness, along with associated degeneration and death of hair cells, ensues within 10 to 15 years[4].

Gao and colleagues analysed the Beethoven mouse strain, in which the animals have a *Tmc1* mutation that causes them to grow deaf over time[5]. The mouse mutation they studied matches a mutation in human *TMC1* that is also linked to progressive hearing loss[6]. The mutation is dominant, which means that even if only one of a person's two copies of the gene has the mutation, they will become deaf. The mutant copy of the gene produces a defective protein that somehow impairs cell function, even though the cell also has a wild-type copy of the gene[7].

The repair of dominant-mutation-associated deafness is a delicate matter — the mutated gene must be disabled while preserving the wild-type gene within the same cell. This is no trivial undertaking, because only one nucleotide of DNA distinguishes the two versions of the *TMC1* gene from each other (Fig. 1). One way to understand this is to imagine a duet between two people trying to sing in unison. If one person is off-key, this offender must be selectively silenced to allow the correct tune to be heard, because if both singers are stopped, the music will cease.

Gene editing is the technique of choice to rid a hair cell of the mutant version of a gene[8]. This involves using a nuclease enzyme to cut a targeted DNA sequence in the specific gene inside the living cell. The cut causes a double-strand DNA break and the repair process often results in mistakes in which nucleotides are added or lost. Such a change can alter the sequence in a way that might cause translation to prematurely arrest and thereby prevent gene expression.

The authors used the nuclease Cas9, which cuts DNA at a specific site by using a snippet

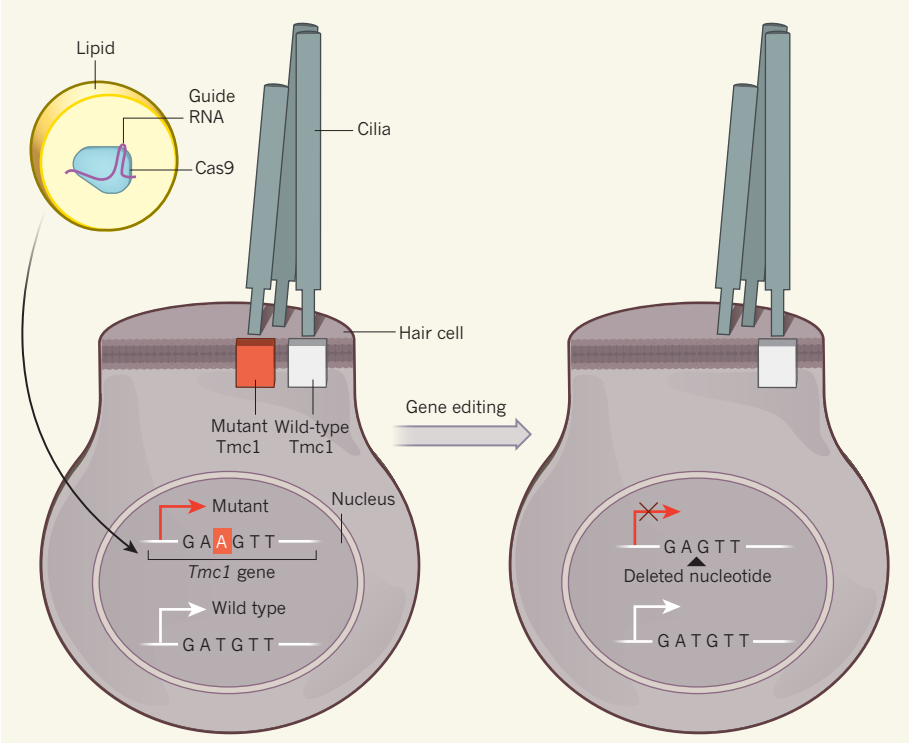

Figure 1 | Gene editing in mice can prevent inherited hearing loss. Gao *et al.*[1] investigated a mouse model of later-life deafness that is caused by a mutant version of the *Tmc1* gene. This mutation is identical to one in the human version of the gene that is linked to deafness. Hearing loss is accompanied by the death of inner-ear hair cells that sense sound using their ciliary projections. The authors injected the ears of newborn mice with gene-editing components: the nuclease enzyme Cas9 that can cut DNA, and a guide RNA that targets Cas9 to the mutant version of *Tmc1* in hair-cell nuclei. These were packaged in a lipid droplet that fuses with cells to enable the gene-editing components to enter. The mutant version of *Tmc1* has an adenine nucleotide (A, highlighted in red in the mutant nucleotide sequence) at a position that is a thymidine nucleotide (T) in the wild-type version. Gene editing selectively inactivated the mutant version of the gene through mechanisms such as nucleotide deletion. Edited cells express only the wild-type Tmc1 protein (white) and don't express the mutant version (red).