enrolled people with *BRCA* mutations have resulted in the approval of three PARP inhibitors for cancer treatment[9]. These and other successes have inspired many efforts to search for synthetically lethal genetic relationships involving commonly mutated tumour-suppressor genes such as *TP53*, *PTEN* and *RB1*. Despite the enormous potential for such efforts to yield drug targets, a challenge remains: how can researchers systematically search for synthetically lethal gene relationships? Now, functional-genomics approaches offer a way to proceed.

The CRISPR knockout data sets from Project Score and the Cancer Dependency Map were analysed by Behan *et al.* and Chan *et al.*, respectively. Both groups found that WRN, a type of helicase that can unwind DNA and is a member of the RecQ family of proteins, is essential in cancers that have a type of genomic alteration called microsatellite instability (MSI). Lieb *et al.* found a similar synthetically lethal relationship between MSI and WRN using a functional-genomics approach involving a technique called RNA interference.

MSI is a common driver of cancer progression in a range of tumour types, including colon, gastric, endometrial and ovarian cancers. It arises when errors occur in a DNA-damage repair system called DNA mismatch repair. Inactivation of a number of different genes, for example, *MLH1* and *MSH2*, can cause a deficiency in mismatch repair. Behan and Chan, and their respective colleagues, found that mutations in genes required for mismatch repair caused synthetic lethality if the gene that encoded WRN was also inhibited. They characterized this synthetic lethality using experiments that measured cellular DNA-repair defects and cell-death mechanisms in cells studied *in vitro* and *in vivo*. This discovery of a strong and specific synthetically lethal dependency represents a major step forward for efforts to develop approaches to treat cancers that have MSI.

The exact molecular mechanisms that underlie the specificity of this synthetically lethal interaction remain to be determined. For example, why does this WRN dependency occur only with tumours that have MSI, and not with tumours that have other forms of genomic instability? Interestingly, this genetic interaction is highly specific; experiments by Behan *et al.*, Chan *et al.* and Lieb *et al.* demonstrated that repression of WRN, but not repression of the four other RecQ helicases that function in the same pathways as WRN, is synthetically lethal in cancers that have deficiencies in DNA mismatch repair. Next-generation functional-genomics approaches promise higher-resolution characterization of individual genetic interactions, which could reveal not only the genes that are involved in a process, but also how those genes function to affect the cell. Such approaches should also enable scientists to elucidate the mechanisms that underlie a particular example of synthetic lethality[10,11].

WRN has both helicase activity and exonuclease activity (the ability to remove nucleotides from a strand of DNA). Behan *et al.*, Chan *et al.* and Lieb *et al.* demonstrate that the disruption of WRN's helicase activity, but not its exonuclease activity, is required for the synthetically lethal effect that they observed. There is a possibility that WRN could be targeted by small-molecule inhibitors. Further studies might enable the development of potent and specific WRN helicase inhibitors that could be tested in cancers that have MSI. These discoveries exemplify how a combined genomics and functional-genomics approach — characterizing the genetic alterations that are already present in cancer models and then assessing the effects of experimentally induced perturbations in further genes — can reveal important cancer-cell dependencies and provide a pathway towards therapeutic innovation. ■

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1. Behan, F. M. *et al. Nature* **568**, 511–516 (2019).
2. Chan, E. M. *et al. Nature* **568**, 551–556 (2019).
3. Lieb, S. *et al. eLife* https://doi.org/10.7554/eLife.43333 (2019).
4. Wang, H., La Russa, M. & Qi, L. S. *Annu. Rev. Biochem.* **85**, 227–264 (2016).
5. Komor, A. C., Badran, A. H. & Liu, D. R. *Cell* **168**, 20–36 (2017).
6. Tsherniak, A. *et al. Cell* **170**, 564–576 (2017).
7. Meyers, R. M. *et al. Nature Genet.* **49**, 1779–1784 (2017).
8. Hartman, J. L. IV, Garvik, B. & Hartwell, L. *Science* **291**, 1001–1004 (2001).
9. Ashworth, A. & Lord, C. J. *Nature Rev. Clin. Oncol.* **15**, 564–576 (2018).
10. Horlbeck, M. A. *et al. Cell* **174**, 953–967 (2018).
11. Adamson, B. *et al. Cell* **167**, 1867–1882 (2016).

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CATALYSIS

# A fresh approach to ammonia synthesis

**Ammonia is vital to society, but its manufacture is energy intensive, has a large carbon footprint and requires high initial capital outlays. An intriguing reaction now suggests that energy-efficient alternatives are possible.** SEE LETTER P.536

MÁTÉ J. BEZDEK & PAUL J. CHIRIK

Global food production requires ammonia-based fertilizers. The industrial transformation of atmospheric nitrogen gas ($N_2$, also known as dinitrogen) into ammonia ($NH_3$) is therefore essential for human life. Despite the simplicity of the molecules involved, the cleavage of the strong nitrogen–nitrogen triple bond (the N≡N bond) in dinitrogen and the concomitant formation of nitrogen–hydrogen (N–H) bonds poses a difficult challenge for catalytic chemistry, and typically involves conditions that are costly in terms of energy requirements: high reaction temperatures, high pressures or combinations of reactive reagents that are difficult to handle and energy-intensive to make. On page 536, Ashida *et al.*[1] demonstrate that a samarium compound mixed with water and combined with a molybdenum catalyst can promote ammonia synthesis from dinitrogen under ambient conditions. The work opens up avenues of research in the hunt for ammonia-making processes that operate under ambient conditions, and raises the question of what an ideal process should be.

Motivated by a looming global fertilizer shortage at the turn of the twentieth century, and later by munitions shortages (ammonia can be used to make explosives), the chemists Fritz Haber and Carl Bosch were the first to demonstrate[2] that dinitrogen could be "pulled from air" and converted to ammonia. In the modern version of the Haber–Bosch process, dinitrogen and hydrogen gas are combined over a catalyst typically based on iron to produce ammonia (Fig. 1a). Today, global ammonia production occurs at a rate of about 250–300 tonnes per minute, and provides fertilizers that support nearly 60% of the planet's population[3,4].

The modern conditions for ammonia synthesis involve temperatures greater than 400 °C and pressures of approximately 400 atmospheres, and are therefore often said to be 'harsh'. This common misconception has motivated chemists to find 'milder' alternatives that use new catalysts to lower the operating temperatures and pressures. In reality, the search for new catalysts should be inspired by the need to reduce the capital expenditure associated with building ammonia plants, and by the requirement to reduce

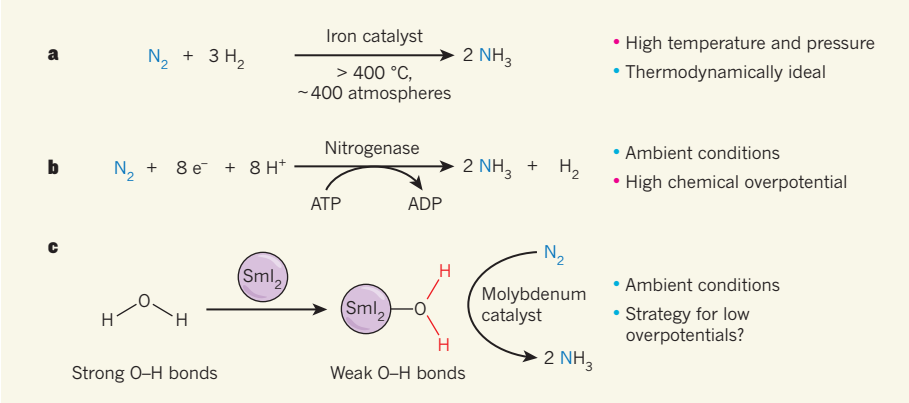


**Figure 1 | Comparison of approaches for making ammonia.** **a**, The industrial Haber–Bosch synthesis of ammonia ($NH_3$) reacts nitrogen gas ($N_2$, also known as dinitrogen) with hydrogen molecules ($H_2$), typically in the presence of an iron catalyst. The process requires high temperatures and pressures, but is thermodynamically ideal — minimal energy is wasted on side processes. **b**, Nitrogenase enzymes catalyse the reaction of dinitrogen with six electrons ($e^-$) and six protons (hydrogen ions; $H^+$) under ambient conditions to make ammonia. However, two extra electrons and protons form a molecule of $H_2$, and the conversion of ATP (the cell's fuel molecules) to ADP drives the reaction. The process therefore has a high chemical overpotential — it uses much more energy than is needed simply to drive the ammonia-forming reaction. **c**, Ashida *et al.*[1] report that a mixture of water and samarium diiodide ($SmI_2$) converts nitrogen to ammonia under ambient conditions in the presence of a molybdenum catalyst; the $SmI_2$ weakens the oxygen–hydrogen bonds in water, effectively producing hydrogen atoms (red) that react with dinitrogen. This approach might allow the development of reactions that have low overpotentials.

carbon emissions — not only from ammonia synthesis itself, but also from production of the hydrogen used in the process[5].

Chemists have turned to nature for inspiration, as they often do. The nitrogenase family of enzymes is largely responsible for the biological conversion of dinitrogen to ammonia (a process called nitrogen fixation), and is the source of nitrogen atoms in amino acids and nucleotides, the building blocks of life. Unlike the Haber–Bosch process, however, nitrogenases do not use hydrogen gas as a source of hydrogen atoms. Instead, they transfer protons (hydrogen ions; $H^+$) and electrons to each nitrogen atom to form N–H bonds (Fig. 1b). But although nitrogenases fix nitrogen at ambient temperatures, they use eight equivalents of protons and electrons per dinitrogen molecule (rather than six, the number needed according to the stoichiometry of the reaction) to provide the necessary thermodynamic driving force for fixation and for other coupled processes[6]. This use of excess hydrogen equivalents means that nitrogenases operate with a large chemical overpotential — they use much more energy than is actually needed to drive fixation[7].

Chemists have mimicked the nitrogenase reaction by adding sources of protons and electrons to metal-containing complexes that contain bound dinitrogen. For example, workers from the same group as Ashida *et al.* previously reported[8] molybdenum complexes that catalyse fixation in this way, producing up to 230 molecules of ammonia per molybdenum complex. However, the associated overpotentials are substantial (reaching nearly 300 kilocalories per mole of dinitrogen, in some cases)[9]. Viewed through this lens, the Haber–Bosch process is close to being a thermodynamically ideal process for ammonia synthesis, and is not as energetically harsh as it is sometimes claimed to be.

A challenge for catalysis researchers is to combine the best of the biological and industrial approaches to nitrogen fixation — that is, to find a process that operates near ambient temperature and pressure, has minimal chemical overpotential, and does not require a capital-intensive plant to make ammonia on a large scale. This is a big challenge, because no combination of acids (which are proton sources) and reducing agents (electron sources) has been found that provides a thermodynamic driving force for fixation on a par with that of hydrogen gas, and which is reactive enough to form N–H bonds from dinitrogen at, or near, ambient temperature.

But what would happen if, instead of functioning separately, proton and electron sources can be coaxed into working together? Ashida *et al.* have adopted this strategy, and thereby report what could be a fundamentally new approach to catalytic ammonia synthesis. They make use of a phenomenon known as coordination-induced bond weakening[10], which arises from the interplay of samarium diiodide ($SmI_2$) and water (Fig. 1c).

Water that is not in a chemical complex contains strong oxygen–hydrogen (O–H) bonds that are difficult to cleave. But when the oxygen atom in water coordinates (donates its lone pair of electrons) to $SmI_2$, the O–H bonds are weakened and the resulting mixture becomes a potent source of hydrogen atoms — effectively, an excellent source of both protons and electrons. Ashida *et al.* use this source of hydrogen atoms with a molybdenum catalyst to fix nitrogen. Considerable coordination-induced bond weakening has previously been measured in $SmI_2$–water mixtures, and used to make carbon–hydrogen bonds[11,12].

The extension of this idea to catalytic ammonia synthesis is noteworthy for two main reasons. First, it is remarkable that the molybdenum catalyst facilitates ammonia synthesis in aqueous solution, because molybdenum complexes often degrade in water. Second, the use of coordination-induced bond weakening provides a new way of fixing nitrogen under ambient conditions that avoids the use of potentially dangerous combinations of proton and electron sources — such combinations can spontaneously ignite. The authors' approach also works when ethylene glycol ($HOCH_2CH_2OH$) is used instead of water, expanding the range of hydrogen-atom sources for making ammonia by this method.

Ashida and co-workers propose a catalytic cycle for their process in which the molybdenum catalyst first coordinates to dinitrogen and cleaves the N≡N bond to form a molybdenum nitrido complex (which contains a molybdenum–nitrogen triple bond). The $SmI_2$–water mixture then delivers hydrogen-atom equivalents to this complex, ultimately producing ammonia. Forming N–H bonds with molybdenum nitrido complexes poses a considerable thermodynamic challenge, because N–H bonds are also weakened when bound to molybdenum, as noted by our group[10]; this effect is a source of chemical overpotential. The $SmI_2$ not only facilitates hydrogen-atom transfer, but also keeps the metal in a reduced form and prevents the deleterious formation of molybdenum oxide in aqueous solution.

The method reported has considerable operational challenges that currently make it impractical for synthesizing ammonia: $SmI_2$ is used in large quantities, which generates a lot of waste; separating ammonia from aqueous solutions is energetically costly; and a chemical overpotential of about 140 kcal $mol^{-1}$ remains. Nevertheless, Ashida and colleagues' work creates a playground in which chemists can explore methods for ammonia synthesis. Future research should focus on finding alternatives to $SmI_2$, based on metals that are more abundant than samarium, to promote coordination-induced bond weakening, enable N–H bond formation and lower the energetic costs of making ammonia from air and water. ■

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1. Ashida, Y., Arashiba, K., Nakajima, K. & Nishibayashi, Y. *Nature* **568**, 536–540 (2019).
2. Hager, T. *The Alchemy of Air* (Random House, 2009).
3. Schlögl, R. *Angew. Chem. Int. Edn* **42**, 2004–2008 (2003).
4. Smil, V. *Enriching the Earth: Fritz Haber, Carl Bosch, and the Transformation of World Food Production*

(MIT Press, 2001).
5. Appl, M. in *Ullmann's Encyclopedia of Industrial Chemistry 2012* Vol. 3, 139–225 (Wiley, 2012).
6. Hoffman, B. M., Dean, D. R. & Seefeldt, L. C. *Acc. Chem. Res.* **42**, 609–619 (2009).
7. Pappas, I. & Chirik, P. J. *J. Am. Chem. Soc.* **138**, 13379–13389 (2016).
8. Eizawa, A. *et al. Nature Commun.* **8**, 14874 (2017).
9. Bezdek, M. J., Pappas, I. & Chirik, P. J. *Top. Organometal. Chem.* **60**, 1–21 (2017).
10. Bezdek, M. J., Guo, S. & Chirik, P. J. *Science* **354**, 730–733 (2016).
11. Chciuk, T. V. & Flowers, R. A. II *J. Am. Chem. Soc.* **137**, 11526–11531 (2015).
12. Kolmar, S. S. & Mayer, J. M. *J. Am. Chem. Soc.* **139**, 10687–10692 (2017).

NEUROSCIENCE

# Brain implants that let you speak your mind

**A brain–computer interface device synthesizes speech using the neural signals that control lip, tongue, larynx and jaw movements, and could be a stepping stone to restoring speech function in individuals unable to speak.** SEE ARTICLE P.493

CHETHAN PANDARINATH & YAHIA H. ALI

Speaking might seem an effortless activity, but it is one of the most complex actions that we perform. It requires precise, dynamic coordination of muscles in the articulator structures of the vocal tract — the lips, tongue, larynx and jaw. When speech is disrupted as a consequence of stroke, amyotrophic lateral sclerosis or other neurological disorders, loss of the ability to communicate can be devastating. On page 493, Anumanchipalli *et al.*[1] bring us closer to a brain–computer interface (BCI) that can restore speech function.

Brain–computer interfaces aim to help people with paralysis by 'reading' their intentions directly from the brain and using that information to control external devices or move paralysed limbs. The development of BCIs for communication has been mainly focused on brain-controlled typing[2], allowing people with paralysis to type up to eight words per minute[3]. Although restoring this level of function might change the lives of people who have severe communication deficits, typing-based BCIs are unlikely to achieve the fluid communication of natural speech, which averages about 150 words per minute. Anumanchipalli *et al.* have developed an approach in which spoken sentences are produced from brain signals using deep-learning methods.

The researchers worked with five volunteers who were undergoing a procedure termed intracranial monitoring, in which electrodes are used to monitor brain activity as part of a treatment for epilepsy. The authors used a technique called high-density electrocorticography to track the activity of areas of the brain that control speech and articulator movement as the volunteers spoke several hundred sentences. To reconstruct speech, rather than transforming brain signals directly into audio signals, Anumanchipalli *et al.* used a two-stage decoding approach in which they first transformed neural signals into representations of movements of the vocal-tract articulators, and then transformed the decoded movements into spoken sentences (Fig. 1). Both of these transformations used recurrent neural networks — a type of artificial neural network that is particularly effective at processing and transforming data that have a complex temporal structure.

Learning how brain signals relate to the movements of the vocal-tract articulators was challenging, because it is difficult to measure these movements directly when working in a hospital setting with people who have epilepsy. Instead, the authors used information from a model that they had developed previously[4], which uses an artificial neural network to transform recorded speech into the movements of the vocal-tract articulators that produced it. This model is not subject-specific; rather, it was built using a large library of data collected from previous research participants[4]. By including a model to estimate vocal-tract movements from recorded speech, the authors could map brain activity onto vocal-tract movements without directly measuring the movements themselves.

Several studies have used deep-learning methods to reconstruct audio signals from brain signals (see, for example, refs 5, 6). These include an exciting BCI approach in which neural networks were used to synthesize spoken words (mostly monosyllabic) directly from brain areas that control speech[6]. By contrast, Anumanchipalli and colleagues split their decoding approach into two stages (one that decodes movements of the vocal-tract articulators and another that synthesizes speech), building on their previous observation that activity in speech-related brain areas corresponds more closely to the movements of the vocal articulators than to the acoustic signals produced during speech[4].

The authors' two-stage approach resulted in markedly less acoustic distortion than occurred with the direct decoding of acoustic

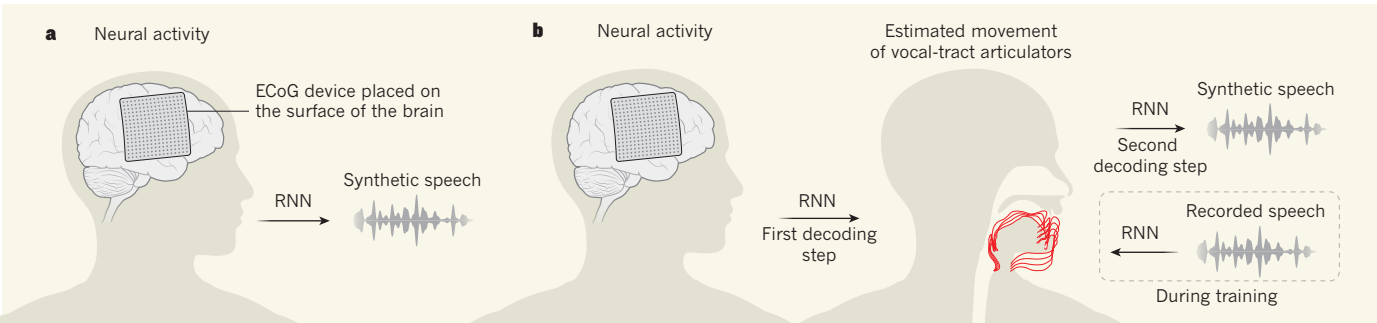


**Figure 1 | Brain–computer interfaces for speech synthesis. a**, Previous research in speech synthesis has taken the approach of monitoring neural signals in speech-related areas of the brain using an electrocorticography (ECoG) device and attempting to decode these signals directly into synthetic speech using a type of artificial neural network called a recurrent neural network (RNN). **b**, Anumanchipalli *et al.*[1] developed a different method in which RNNs are used for two steps of decoding. One of these decoding steps transforms neural signals into estimated movements of the vocal-tract articulators (red) — the anatomical structures involved in speech production (lips, tongue, larynx and jaw). For training purposes in the first decoding step, the authors needed data that related each person's vocal-tract movements to their neural activity. Because Anumanchipalli *et al.* could not measure each person's vocal-tract movements directly, they built an RNN to estimate these movements on the basis of a large library of previously collected data[4] of vocal-tract movements and speech recordings from many people. This RNN produced vocal-tract movement estimates that were sufficient to train the first decoder. The second decoding step transforms these estimated movements into synthetic speech. Anumanchipalli and colleagues' two-step decoding approach produced spoken sentences that had markedly less distortion than is obtained with a comparable direct decoding approach.