to hepatocytes (known as hepatotoxicity) caused by AAV2 alone. Because low levels of HAdV and human herpesvirus 6B (HHV-6B) were detected in the liver in most cases, the authors speculate that these viruses might enable AAV2 replication, leading to damage to hepatocytes.

In the third paper, Servellita *et al.*[4] (page 574) report similar findings from the United States. They detect AAV2 in 13 of 14 cases, compared with only 4 of 113 controls. All 14 cases also tested positive for HAdV. In the 13 children infected with AAV2, the authors found co-infection with a 'helper' virus that might promote AAV2 replication — either Epstein–Barr virus (EBV) or HHV-6. Thus, most of the cases had a triple infection (AAV2, HAdV and either EBV or HHV-6). The fact that these authors examined only children who were infected with HAdV might explain why they detected more concomitant viral infections than did the other groups.

All three studies make the same observation of AAV2 in children with unexplained acute hepatitis. That the studies took place on two continents adds to their value, given the global nature of the outbreak (Fig. 1). However, a note of caution is needed — these studies were all conducted retrospectively, rather than being gold-standard prospective trials, in which subjects are selected for study, with data being subsequently collected over time. The case numbers are relatively small, and the number of liver samples even smaller. The studies report limited clinical information (such as ethnic background, whether the children were born by caesarean section and whether they could have been exposed to viruses during day care), which is needed to reveal potential factors or co-factors in disease development. Such data would be essential to exclude the possibility that AAV2 is a harmless bystander.

Direct evidence for how AAV2 might cause hepatitis is limited. Ho and co-workers' genetic and histological analyses imply that the disease is rooted in abnormal immune responses, rather than in a hepatotoxic role for AAV2. Morfopoulou and colleagues provide support for this conclusion, finding that liver samples were enriched in adaptive immune cells and immune-related proteins, but contained no detectable HAdV or AAV2 proteins, or viral particles.

Further evidence for the idea that this rash of cases is immune-related comes from gene-therapy trials. AAV is perhaps the most commonly used viral vector for delivering genes to people for gene therapy[9]. Hepatotoxicity has been observed in trials that involve AAV-based approaches, but it is rare, and generally not fatal[9]. If AAV2 directly caused hepatitis, one would expect more cases to have been reported.

Going forward, in-depth immunological analyses will be eagerly awaited. In addition, analysis of any direct toxic effects of AAV2 on liver cells — using 3D cultures called liver organoids, for instance — will be needed to understand how AAV2 infection (with or without helper viruses) might affect hepatocyte metabolism and viability[9]. This distinction between immune-mediated and hepatotoxic effects is highly relevant, because it will dictate whether this disease should be managed through immunosuppression or directed antiviral drugs.

The three studies cannot rule out the possibility that COVID-19 is a contributory factor, because the timing of the hepatitis outbreak meant that antibodies against the SARS-CoV-2 virus were prevalent in all groups. The children often reported symptoms of viral infection, including fever and gastrointestinal problems, suggesting that a SARS-CoV-2 reservoir might be present in the intestine or in bile-duct cells called cholangiocytes (these cells express high levels of the protein ACE2, which mediates infection by SARS-CoV-2)[10]. Researchers should investigate the possibility that SARS-CoV-2 proteins act as 'superantigens', triggering a powerful immune response to HAdV-F41 or AAV2 in a host whose immune system has been sensitized.

Even if a direct involvement of SARS-CoV-2 can be ruled out, the timing of the hepatitis outbreak in relation to the COVID-19 pandemic is striking. The wave of hepatitis in spring 2022 coincided with the relaxation of COVID-19 measures around the globe, and cases rapidly tailed off (although scattered new cases are still being reported). As such, the timing of the outbreak might be explained by the fact that children were suddenly exposed to a barrage of viruses after lockdowns, or had poorly trained immune systems that led to an increased susceptibility to otherwise harmless viruses.

Although the current studies report few follow-up data, the acute hepatitis apparently resolved without the need for long-term immunosuppression in most cases. Prospective, properly controlled follow-up investigations are now needed, to determine the extent to which AAV2 infection can cause, or contribute to, acute hepatitis in children. Until then, surveillance for AAV2 (and related viruses) in such cases is to be advised.

Frank Tacke is in the Department of Hepatology and Gastroenterology, Charité – Universitätsmedizin Berlin, 13353 Berlin, Germany.
e-mail: frank.tacke@charite.de

1. Alexander, E. C. & Deep, A. *JAMA Netw. Open* **5**, e2237091 (2022).
2. Ho, A. *et al. Nature* **617**, 555–563 (2023).
3. Morfopoulou, S. *et al. Nature* **617**, 564–573 (2023).
4. Servellita, V. *et al. Nature* **617**, 574–580 (2023).
5. Gutierrez Sanchez, L. H. *et al. N. Engl. J. Med.* **387**, 620–630 (2022).
6. Kelgeri, C. *et al. N. Engl. J. Med.* **387**, 611–619 (2022).
7. Karpen, S. J. *N. Engl. J. Med.* **387**, 656–657 (2022).
8. Sant'Anna, T. B. & Araujo, N. M. *Virol. J.* **19**, 173 (2022).
9. Shen, W., Liu, S. & Ou, L. *Front. Immunol.* **13**, 1001263 (2022).
10. Brevini, T. *et al. Nature* **615**, 134–142 (2023).

The author declares competing interests.

Electrochemistry

An organic catalyst for chlorine production

Thomas Turek

The industrial process for making chlorine uses a vast amount of energy globally. An organic catalyst has been developed that could form the basis of a more energy-efficient process, replacing expensive inorganic catalysts. **See p.519**

Chlorine is required for the manufacture of an enormous variety of products in the chemical industry. Most of this chlorine is made using a process called chlor-alkali electrolysis, which requires energy equivalent to about 1% of worldwide electricity production, and is therefore responsible for huge carbon dioxide emissions. Any improvement in the energy efficiency of the process would thus be of great economic and environmental importance. On page 519, Yang *et al.*[1] report an organic catalyst with extremely high activity and selectivity for chlorine production in the chlor-alkali process, which could help to reduce its energy demands.

The chlor-alkali process is carried out in a reactor known as a membrane cell, which is divided into two chambers. In the conventional process, concentrated sodium chloride solution is passed through the first chamber, where the salt's chloride ions (Cl^-) are converted to chlorine at the cell's anode.

In the second chamber, water is converted to hydrogen gas and hydroxide ions (OH^-) at the cathode. The reactions that occur in each chamber are known as half reactions. Sodium ions (Na^+) pass from the first chamber to the second through a membrane, and react with the hydroxide ions to produce sodium hydroxide. The overall process therefore converts sodium chloride and water into chlorine, hydrogen and sodium hydroxide.

An intensively studied approach for improving the energy efficiency of chlor-alkali electrolysis is to replace the hydrogen-producing half reaction with an oxygen reduction reaction (in which oxygen is converted into hydroxide ions), at least during periods when no hydrogen is needed in the chemical plant[2]. This alternative process reduces the electrical energy demand by up to 25%, and has been adopted this year by the German company Covestro on an industrial scale at its facility in Tarragona, Spain (see go.nature.com/3kjseqp). Yang *et al.* tested their catalyst using a laboratory-scale cell that carries out this modified process (Fig. 1). It should be noted, however, that hydrogen production will probably need to increase tremendously as global infrastructure for energy and industry converts to using hydrogen fuel as a replacement for fossil fuels[3]. This could mean that hydrogen-producing chlor-alkali processes will be prioritized in the future.

The only other way to improve energy efficiency is to reduce losses associated with the components of the membrane cells. The largest of these energy losses results from the electrical resistance of the membrane. Another major source of losses is ‘kinetic resistance’ to the formation of the gaseous products (particularly chlorine). Kinetic resistance arises from the fact that electrochemical reactions involve the transfer of electrons at solid electrodes. The energy losses result in an overpotential — that is, a higher voltage is needed to drive the reaction than is theoretically required.

Early industrial chlor-alkali processes used electrodes made of graphite, but this material is gradually oxidized by the oxygen that is produced as a by-product of the reaction, and therefore becomes structurally unstable. The invention of dimensionally stable anodes (DSAs) in the 1960s was a major breakthrough[4], not only for chlorine production, but also for the implementation of electrochemistry in general[5]. These anodes consist of a metallic substrate, such as titanium, coated with a mixture of two oxides: a conductive oxide of a noble metal (such as ruthenium) and a corrosion-resistant material such as titanium dioxide. This combination makes the anodes highly durable and catalytically active for chlorine production, and results in relatively low formation of the undesirable oxygen by-product.

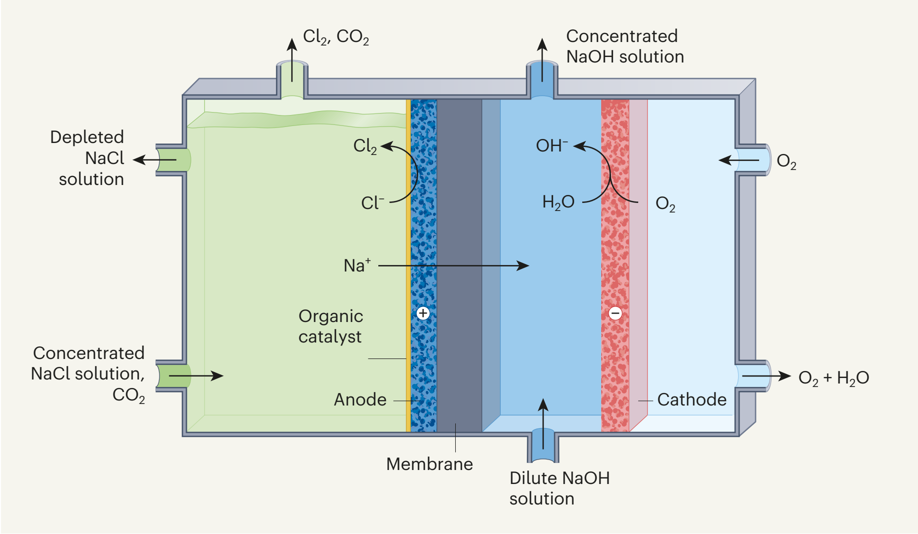

Figure 1 | Chlorine production catalysed by an organic ligand. Yang *et al.*[1] report a variant of the electrochemical chlor-alkali process for producing chlorine. The reaction occurs in a cell divided into two chambers. Concentrated sodium chloride solution containing dissolved carbon dioxide is passed through the first chamber, where the salt’s chloride ions (Cl^-) are converted to chlorine (Cl_2) at the cell’s anode. This reaction is promoted by an organic catalyst that coats the anode; CO_2 is also required for the catalytic mechanism. In the second chamber, oxygen and water (which enters the chamber as part of a dilute sodium hydroxide solution) are converted into hydroxide ions (OH^-) at the cathode. Sodium ions (Na^+) pass from the first chamber to the second through a membrane, and react with the hydroxide ions to produce sodium hydroxide. The authors report that this process has the potential to use less electrical energy than current chlor-alkali processes.

Since the advent of DSAs, no further substantial progress has been made in the development of electrodes for chlorine production. Research in the past few years has focused on suppressing oxygen formation, but always using catalysts based on noble metals[6].

Yang *et al.* are the first to demonstrate that an organic catalyst can exhibit even higher activity than noble metals in the chlor-alkali process, maintaining excellent selectivity for chlorine production with very little oxygen formation. Organic molecules that can take part in electrochemical processes are currently also being investigated intensively for energy storage in batteries[7]. An advantage of organic molecules for these applications is that many could be produced cheaply from readily available, renewable raw materials, and could greatly reduce costs.

In the current study, the authors use an organic molecule that contains an amide group (NHC=O) as the catalyst for chlorine production. They observe that catalysis occurs only in the presence of dissolved CO_2, which gives rise to an intermediate product that greatly accelerates the reaction rate. This results in a decrease in the overpotential — the authors calculate that the voltage used to drive chlorine production is about 30 millivolts less than that required for a state-of-the-art process using a DSA under industrial operating conditions. Compared with chlor-alkali cells that produce chlorine, sodium hydroxide and hydrogen, this translates to a reduction in electrical energy demand of 2–5%. This might seem small, but it would result in considerable global savings, given the scale of chlorine production. Moreover, there is room for further improvement by developing even better organic catalysts.

It should be emphasized that the calculated reduction in overpotential does not take the electrical resistance of the electrode into account. The measured voltage reduction was smaller than the overpotential reduction, which Yang *et al.* attribute to the high resistance of the organic molecules. This problem must now be solved by engineering the catalytic coating, for example by altering its thickness or porosity. Engineering the coating should also help to prevent leaching of the catalyst into the sodium chloride solution, which was observed during prolonged test runs of 450 hours.

Another potential drawback of the new catalyst is the requirement for dissolved CO_2 — this reaction component was not previously used in the chlor-alkali process, and must be separated from the chlorine product and recycled. However, it should be possible to modify industrial processes to achieve this separation without major effort. A small amount of oxygen is inevitably generated as a by-product in the reported process, but no more than in the equivalent process using a DSA. This oxygen could easily be separated from the chlorine using established methods for industrial chlorine production.

A much greater obstacle to commercialization is the need for long-term stability of the electrodes — which are typically expected to last for at least five years in industrial processes before being replaced or refurbished. Such a long lifetime is very difficult to achieve for organic molecules, especially given that the electrode is exposed to chlorine and traces of oxygen at high temperatures. Further studies of the long-term stability of the organic catalyst are therefore now required. Nevertheless, by overturning the idea that organic catalysts are less effective than metals for electrochemistry, Yang and colleagues' study opens up a new strategy in the search for cheaper and more-energy-efficient industrial processes for making chlorine.

Thomas Turek is at the Institute of Chemical and Electrochemical Process Engineering, Clausthal University of Technology, D-38678 Clausthal-Zellerfeld, Germany.
e-mail: turek@icvt.tu-clausthal.de

1. Yang, J. *et al. Nature* **617**, 519–523 (2023).
2. Roh, K., Brée, L. C., Perrey, K., Bulan, A. & Mitsos, A. *Appl. Energy* **255**, 113880 (2019).
3. Castelvecchi, D. *Nature* **611**, 440–443 (2022).
4. Beer, H. B. Improvements in or relating to electrodes for electrolysis. UK Patent GB1,147,442 (1965).
5. Trasatti, S. *Electrochim. Acta* **45**, 2377–2385 (2000).
6. Lim, T. *et al. Nature Commun.* **11**, 412 (2020).
7. Janoschka, T. *et al. Nature* **527**, 78–81 (2015).

The author declares no competing interests.

Engineering

5G enables automated control of train traffic

Toktam Mahmoodi

Key tasks for ensuring railway safety have been performed automatically using fifth-generation (5G) mobile networks. The trial forms part of a Europe-wide scheme to test the feasibility of automating transport.

The ability to drive a car can be useful when travelling abroad, but it doesn't necessarily equip a driver with the knowledge required to navigate foreign roads and follow regulations. Autonomous vehicles suffer no such culture shock, and could make it easier to get around in a foreign country. The fifth generation of mobile networks (5G) provides the sort of connectivity and flexibility needed for safe autonomous driving. Writing in *IEEE Access*, Corujo *et al.*[1] put 5G to the test of managing the control signals used in railway operations — a step towards 5G-run automation in the broader transport sector.

Connected automated transport is a focus of European research investment, as is the role that 5G will have in realizing it (see go.nature.com/3hvnnnp). 5G networks hold promise because they can be tailored to provide specialized services for a given infrastructure. This is known as network slicing[2], and widespread use of this technique was not possible with previous generations of mobile networks. The 5G infrastructure is multiplexed, which means that each network 'slice' constitutes a potentially isolated network that can be customized for a particular task. Because of this, 5G can adjust its performance dynamically, depending on the application: for example, one task might need high bandwidth, rather than fast data transfer.

Researchers have started to test the capabilities of 5G for autonomous transportation — not only in terms of cars on roads[3], but also of public-transport vehicles, such as trains. As part of this initiative, the European Commission has established several cities as 'living labs', in which it has set up 5G networks in strategic areas, such as harbours. One such project is based in Aveiro, Portugal (see go.nature.com/41hjk), where Corujo *et al.* conducted their investigation of how 5G could be used to automate the operation of railway networks. The team examined two specific use cases: controlling the barriers at railway level crossings, and providing drivers (either human or algorithmic) with crucial safety information from the crossing as a train approaches it (Fig. 1).

In the first case, the authors used the 5G network to detect incoming trains automatically and to lower barriers to stop road traffic and pedestrians, with timing aligned with global regulations. The test was done on a railway track in Aveiro that is used infrequently and only by heavy freight trains. Corujo *et al.* placed sensors on the track a few kilometres from a level crossing. When these sensors detected an incoming train, the information was transmitted to a level-crossing controller that lowered the barriers to separate the road from the tracks.

The crucial safety decisions involved in this process required the reliable, fast communication provided by 5G. Conventional level crossings are controlled and monitored by various means, including manually by station staff, and automatically through sensors that are connected to the level-crossing controller

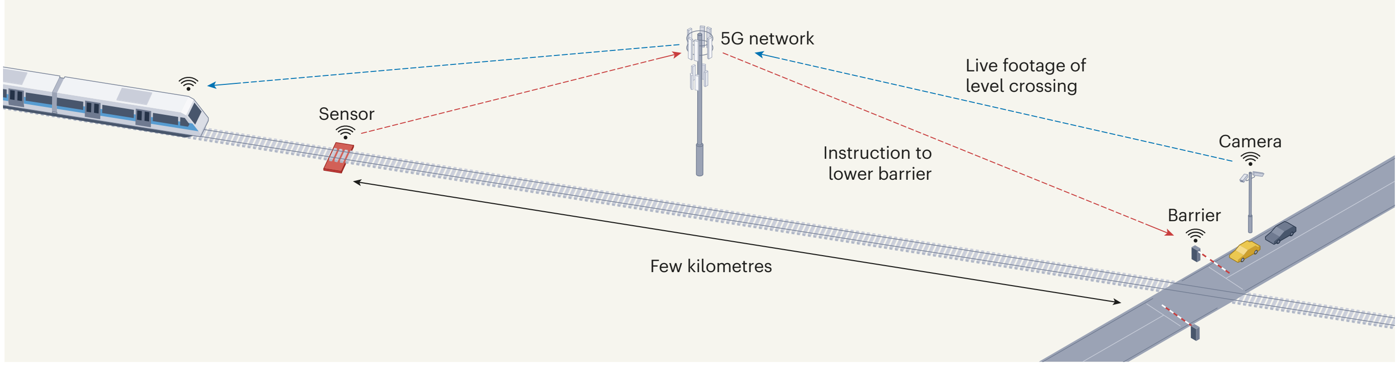

Figure 1 | Testing automation of a railway level crossing using 5G networks. Corujo *et al.*[1] tested two ways of using fifth-generation (5G) mobile networks to automate control of a level crossing on a train track in Aveiro, Portugal. In the first test, the authors detected a train using track sensors located a few kilometres from the level crossing, and transmitted the information (red arrows) to a level-crossing controller that then lowered the barriers, preventing road traffic from crossing the track. In the second test, live video footage of a level crossing was transmitted (blue arrows) to the driver as the train approached the crossing. The 5G network provided the speed and bandwidth necessary for safe automation in preliminary tests conducted in a controlled laboratory environment, and showed potential for similar success in the real-world setting.