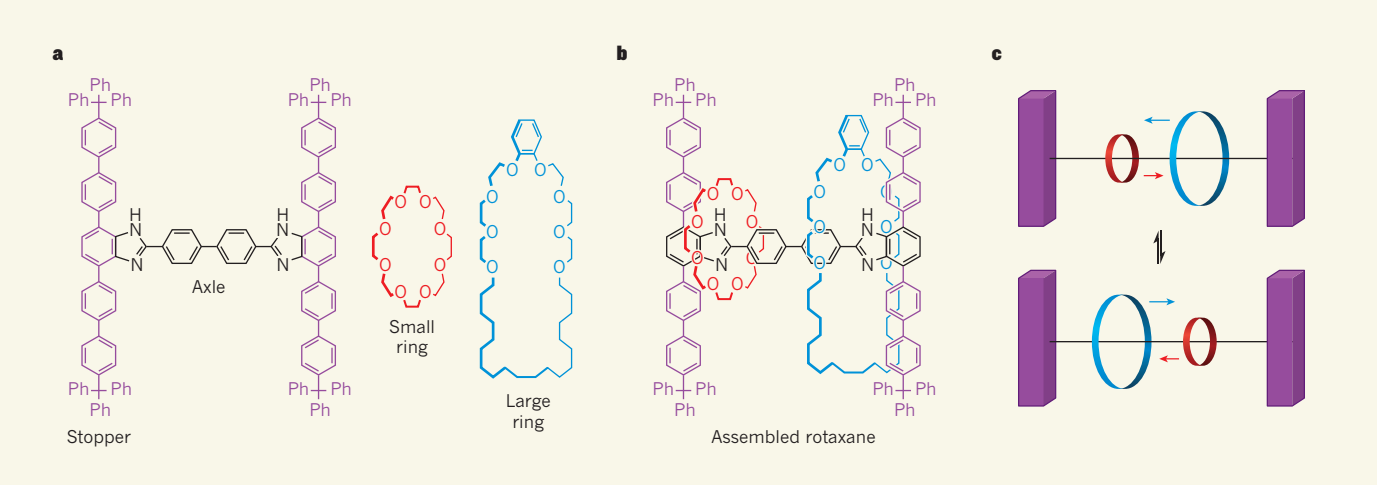

Figure 1 | Ring-through-ring shuttling of a rotaxane. **a**, **b**, Zhu *et al.*[7] report a molecule known as a rotaxane that consists of two rings, one much larger than the other, threaded on to an axle. Large groups, known as stoppers, at the ends of the axle prevent the rings from slipping off (Ph, phenyl group). **c**, The authors find that the rings can slip past each other to exchange their positions on the axle. Shuttling takes place by means of the smaller ring passing through the larger one.

mole — a considerable amount, but not as high as might have been expected.

The two-ringed rotaxane is remarkably simple compared with some of the synthetic molecular machines that have been produced so far. It might therefore seem surprising that this is the first time that a ring-through-ring shuttling process has been observed. However, to achieve their breakthrough, Zhu and colleagues had to bring together several key structural features.

First, the dramatic difference in the size of the rings is important for enabling shuttling to occur. Indeed, the authors produced another rotaxane analogue in which the larger ring was 12 atoms smaller and found that no ring-through-ring shuttling occurs, even at elevated temperatures.

Second, when large rings are used as components of rotaxanes, the stoppers on the ends of the axle must be extremely large to prevent the rings from slipping off. This demand can complicate the synthesis of rotaxanes because larger stoppers often cause problems with solubility, and their use typically adds further steps to an already complex synthetic route. Zhu *et al.* overcame these issues by using simple T-shaped stoppers that they had developed previously to make porous materials (known as metal–organic frameworks) that incorporate rotaxanes[8].

Such structural issues highlight a limitation of the newly identified dynamic process: if rotaxane structures that show ring-through-ring shuttling must be so contrived, will it be possible to use ring-through-ring shuttling to develop molecular machines? It is to be hoped that the answer is 'yes', because ring-through-ring shuttling could bring an extra dimension to rotaxane-based switches. A potential application suggested by the authors is molecular-level weaving, in which ring-through-ring shuttling controls the entanglement of molecular threads — essentially, a small ring is used to pull a molecular chain through a larger ring, akin to threading a macroscopic needle.

Multi-ring rotaxanes could potentially also be used for information storage, in which data are encoded by the order of the rings on the axle. Before now, there was no major advantage to this approach compared with storing data in simpler molecules, because the ring order was fixed at the time of synthesis[6]. Zhu and colleagues' work opens up the possibility of using external stimuli to order and reorder the rings, and therefore of writing and rewriting any encoded information. ■

Steve Goldup *is in the School of Chemistry, University of Southampton, Southampton SO17 1BJ, UK.*
e-mail: s.goldup@soton.ac.uk

1. Erbas-Cakmak, S., Leigh, D. A., McTernan, C. T. & Nussbaumer, A. L. *Chem. Rev.* **115**, 10081–10206 (2015).
2. Bissell, R. A., Córdova, E., Kaifer, A. E & Stoddart, J. F. *Nature* **369**, 133–137 (1994).
3. Serreli, V., Lee, C.-F., Kay, E. R. & Leigh, D. A. *Nature* **445**, 523–527 (2007).
4. Cheng, C. *et al. Nature Nanotechnol.* **10**, 547–553 (2015).
5. Lewandowski, B. *et al. Science* **339**, 189–193 (2013).
6. Lewis, J. E. M., Winn, J., Cera, L. & Goldup, S. M. *J. Am. Chem. Soc.* **138**, 16329–16336 (2016).
7. Zhu, K., Baggi, G. & Loeb, S. J. *Nature Chem.* https://doi.org/10.1038/s41557-018-0040-9 (2018).
8. Zhu, K., O'Keefe, C. A., Vukotic, V. N., Schurko, R. W. & Loeb, S. J. *Nature Chem.* **7**, 514–519 (2015).

This article was published online on 30 April 2018.

MEDICAL RESEARCH

Life of a liver awaiting transplantation

People waiting for a liver transplant can die before an organ is found, or, if one is available but of poor quality, there is a risk of transplant failure. A machine that preserves livers might offer a way forward. SEE ARTICLE P.50

STEFAN SCHNEEBERGER

The standard approach for handling donated livers before transplantation is storing them on ice. On page 50, Nasralla *et al.*[1] report the results of a clinical trial that compared two organ storage methods. More than 200 people who received a liver transplant were randomly allocated either a donor liver that had been stored on ice or one preserved with the aid of a machine that perfuses the organ at body temperature (37 °C) with oxygenated blood containing nutrients (Fig. 1). The latter method is called normothermic machine perfusion (NMP), and this technique enables organ function to be monitored outside the body before transplantation.

The concept of machine perfusion of an organ awaiting transplantation is not new. Indeed, machine-assisted perfusion was in use before cold storage became the method of choice owing to its simplicity and reproducibility[2]. However, interest in revisiting perfusion

as a transplant approach has been gaining momentum.

The main outcome monitored in the latest trial was the post-transplantation level of the enzyme aspartate transaminase in patients' blood. This measurement is commonly used to assess liver damage and to estimate the risk of transplant failure. The authors found that the use of NMP was associated with less liver damage than that found in livers preserved on ice. Moreover, preservation by NMP reduced the number of organs that were discarded as unsuitable for transplantation compared with livers preserved on ice, and was associated with a better blood-flow profile in the recipient.

The liver's bile ducts can be a point of vulnerability for transplant success, and whether NMP has a positive effect on the viability of these ducts might only be revealed after long-term monitoring. It could therefore be premature to assert that NMP technology has been shown to be a more effective and suitable method for organ storage until additional studies can fully determine the long-term effect of the NMP approach. But it is also fair to say that Nasralla and colleagues' work makes a convincing case for NMP's superiority. Moreover, mimicking the normal conditions for an organ outside the body is a persuasive idea. This clinical trial represents a milestone by directly comparing ice and NMP storage approaches. It could pave the way for the clinical application of NMP and drive a research push in this area.

Organ storage on ice slows the liver's metabolism, and can result in tissue damage by decreasing levels of the energy-storage molecule ATP. The alterations result in accumulation of harmful reactive oxygen species, damage to mitochondrial organelles, and trigger an inflammatory response when blood flow is restored to the transplanted organ[3]. NMP probably boosts transplant success through mimicking the normal conditions for the organ and enabling ATP replenishment. Such effects would eventually limit the generation of reactive oxygen species and cell damage.

Although Nasralla and colleagues' study is convincing regarding the clinical impact of NMP, it does not clarify the underlying molecular events. Factors including organ architecture and cellular composition will need to be explored in detail to determine the length of preservation times that can be safely used. Other clinical trials of machine-assisted organ perfusion are under way, testing a range of temperatures and conditions[4]. NMP has been performed successfully for 48 hours before transplantation in porcine livers[5]. The median duration of NMP in Nasralla and colleagues' study was around 9 hours.

Pioneering advances in surgical techniques, immunosuppressive drug treatment and patient care have made organ transplantation the standard treatment for chronic organ failure. Yet three fundamental limitations remain: organ shortages; a decline in the quality of donor organs[6]; and restrictions on the time permitted for handling and transporting organs. The use of NMP has the potential to increase the number of organs available for transplantation, and could lessen the need to rapidly transplant an organ after its removal from the donor's body, enabling more time for assessing the liver.

Nevertheless, NMP poses certain challenges. It might be straightforward to set up the machine, prepare the organ for perfusion and do basic technical problem-solving, but substantial training and experience in using this method will be required before it can be routinely used in the clinic. Furthermore, the travel and care plan for an NMP organ is more complex than that for shipment on ice because extra steps are needed in the clinical routine. Standardized protocols and reporting methods need to be established to enable this procedure to advance in a controlled fashion. The sharing of information by medical professionals using NMP could help clinicians gain the collective experience necessary to minimize procedural risks.

Perhaps the greatest advance from this technology is that it might provide proof of principle that organs can survive when a machine helps to mimic the conditions organs encounter in the human body. The human liver itself then becomes like a patient. It is perfused, monitored and fed by a machine. If it performs well, it is transplanted immediately; if not, it might undergo treatment, modification or repair before transplantation.

The routine clinical use of NMP might boost interest and investment in finding new ways to treat, regenerate and recreate organs that are supported outside the body. The ability to preserve an organ under close-to-normal conditions could be instrumental in advancing not only liver transplantation, but also liver surgery and organ care. Tissue engineering, like transplantation, works towards the goal of providing human organs suitable for transplantation. As NMP offers the potential to modify and monitor an organ, the methods used in both fields might start to merge. This idea is fascinating, because not only would this change many aspects of transplantation, but it might also eventually close the gap between the two technologies. ■

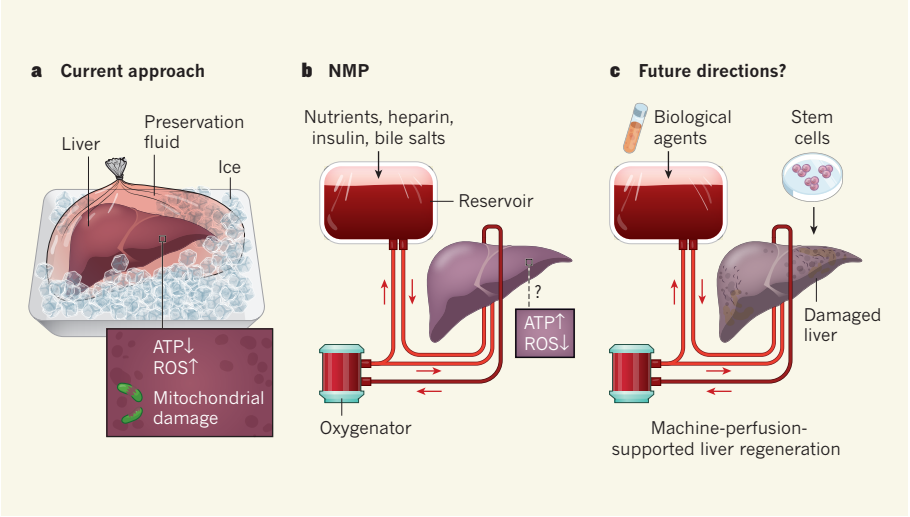

Figure 1 | Supporting the human liver outside the body. Nasralla *et al.*[1] report a clinical trial that compared methods of liver storage before transplantation. **a**, In the current standard approach, livers are stored on ice in preservation fluid. However, this can lead to a decrease in levels of the energy-storage molecule ATP, an increase in harmful reactive oxygen species (ROS) and damage to mitochondrial cellular organelles when blood flow returns after transplantation[3]. **b**, In an approach termed normothermic machine perfusion (NMP), donated livers are maintained at body temperature (37 °C) by a machine. This device pumps the liver's deoxygenated blood (dark red) through the machine, and then returns oxygenated blood (light red) containing nutrients and essential factors such as bile salts, heparin and insulin to the liver. On the basis of analyses of enzyme levels (not shown), the authors found that NMP results in less liver damage than that incurred when livers are stored on ice. This might be because perfusion results in higher ATP levels and fewer ROS compared with ice storage. **c**, Machine-based organ perfusion could perhaps be adapted to repair liver damage before transplantation. Such an approach might require the addition of biological agents such as growth factors, or the introduction of stem cells.

Stefan Schneeberger *is in the Department of Visceral, Transplant and Thoracic Surgery, Innsbruck Medical University, 6020 Innsbruck, Austria.*
e-mail: stefan.schneeberger@i-med.ac.at

1. Nasralla, D. *et al. Nature* **557**, 50–56 (2018).
2. Clark, E. A., Terasaki, P. I., Opelz, G. & Mickey, M. R. *N. Engl. J. Med.* **291**, 1099–1102 (1974).
3. Eltzschig, H. K. & Eckle, T. *Nature Med.* **17**, 1391–1401 (2011).
4. Verhoeven, C. J. *et al. J. Hepatol.* **61**, 672–684 (2014).
5. Vogel, T. *et al. PLoS ONE* **12**, e0188494 (2017).
6. Orman, E. S. *et al. Liver Transplant.* **19**, 59–68 (2013).

This article was published online on 18 April 2018.