to use amphotericin B routinely throughout an individual's life? As new therapeutic approaches are developed for all people with cystic fibrosis, they might also help people who have other lung conditions that have similar disease characteristics. ■

David N. Sheppard *is in the School of Physiology, Pharmacology and Neuroscience, University of Bristol, Bristol BS8 1TD, UK.*
Anthony P. Davis *is in the School of Chemistry, University of Bristol, Bristol BS8 4LN, UK.*
e-mails: d.n.sheppard@bristol.ac.uk; anthony.davis@bristol.ac.uk

1. Ratjen, F. *et al. Nature Rev. Dis. Primers* **1**, 15010 (2015).
2. Muraglia, K. A. *et al. Nature* **567**, 405–408 (2019).
3. Davies, J. C. *et al. N. Engl. J. Med.* **379**, 1599–1611 (2018).
4. Keating, D. *et al. N. Engl. J. Med.* **379**, 1612–1620 (2018).
5. Mall, M. A. & Galietta, L. J. V. *J. Cystic Fibros.* **14**, 561–570 (2015).
6. Shen, B., Li, X., Wang, F., Yao, X. & Yang, D. *PLoS ONE* **7**, e34694 (2012).
7. Li, H. *et al. Nature Chem.* **8**, 24–32 (2016).
8. Stoltz, D. A., Meyerholz, D. K. & Welsh, M. J. *N. Engl. J. Med.* **372**, 351–362 (2015).
9. Quinton, P. M. *Am. J. Physiol. Cell Physiol.* **299**, C1222–C1233 (2010).
10. Anderson, T. M. *et al. Nature Chem. Biol.* **10**, 400–406 (2014).
11. Cioffi, A. G., Hou, J., Grillo, A. S., Diaz, K. A. & Burke, M. D. *J. Am. Chem. Soc.* **137**, 10096–10099 (2015).
12. Grillo, A. S. *et al. Science* **356**, 608–616 (2017).
13. Diamond, J. M. *Nature* **300**, 683–685 (1982).

D.N.S. declares competing financial interests.
See go.nature.com/2siykfi for details.

This article was published online on 13 March 2019.

BIOCATALYSIS

Enzymes trapped and zapped

Many enzymes cooperate with other proteins and small molecules to function. A strategy that mimics the confinement of such cooperative partners in cells might allow these enzymes to be used in applications outside biological systems.

ALISON NARAYAN

Nature precisely controls thousands of chemical reactions in every cell. Many of these form complex chains of reactions, analogous to a falling line of dominoes: when an enzyme triggers the first reaction of a chain, the other reactions are triggered in sequence. Such reaction cascades can be difficult to recreate outside living systems. Even when the same catalysts are used as those that evolved in nature, it is frequently not possible to achieve the naturally occurring reaction rates when cascades are carried out in a test tube. Writing in *Angewandte Chemie*, Megarity *et al.*[1] report a solution to this problem that mimics a naturally occurring strategy for promoting efficiency: the co-localization of cooperating catalysts.

The use of enzymes to catalyse reactions offers an alternative to using conventional catalysts, and can greatly improve the sustainability, safety and cost of chemical processes[2]. The advantages are amplified when multiple chemical reactions can be conducted sequentially in a single reaction vessel, analogous to the way in which reaction cascades occur in a cell. These advantages drive scientists to design improved platforms for enzymatic reactions, despite the difficulty of reconstituting multienzyme cascade processes outside cells[3].

Biological reactions often require electrons to be shuttled to the catalyst, using several protein and small-molecule carriers that are co-localized in cells. Several strategies can facilitate this electron shuttling in cells, including the engineering of high-affinity interactions between partners in the shuttling pathway[4]. Such interactions can be realized at protein–protein interfaces[5], by the binding of small molecules in enzyme active sites[6] and by compartmentalizing reactants within individual organelles[7]. Combinations of these three approaches are used in cells to form nanoscale reactors, which accelerate reactions compared with the analogous processes occurring freely in solution[8].

Megarity *et al.* envisaged mimicking this natural process by trapping enzymes in synthetic nanoreactors on the surface of a plentiful source of electrons, thus facilitating the electron transport required to power biocatalytic reactions. Researchers from the same group as the current authors had previously reported[9] that an enzyme called ferredoxin–$NADP^+$ reductase (FNR) binds tightly to the pores of electrodes made of indium tin oxide (ITO). In natural systems, FNR accepts two electrons from a protein partner called ferredoxin. The interaction between an electrode and FNR mimics the electrostatics of the ferredoxin–FNR protein–protein interaction. More specifically, the negatively charged surface of the electrode mimics the negatively charged patch of ferredoxin that forms an interface with a positively charged surface of FNR (Fig. 1a).

FNR uses the electrons it receives from ferredoxin to chemically reduce a small molecule known as $NADP^+$ — a cofactor that acts as an electron shuttle. The reduced form of the

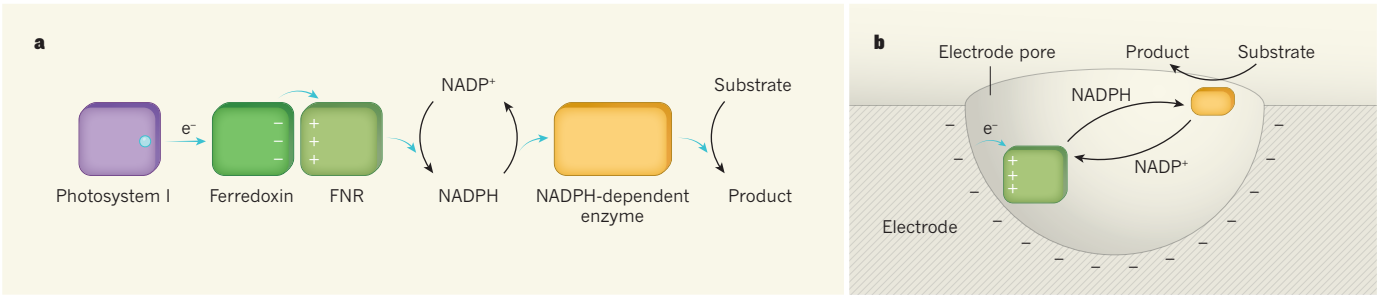

Figure 1 | Enzymatic electron-shuttling processes. a, In photosynthetic systems, a protein complex called photosystem I transfers electrons (e^-) to the ferredoxin protein. Ferredoxin passes electrons to an enzyme called ferredoxin–$NADP^+$ reductase (FNR), to which it binds tightly because a negatively charged region on its surface interacts with a positively charged region on FNR. FNR uses the electrons it receives from ferredoxin to chemically reduce a cofactor, $NADP^+$. The reduced form of the cofactor, NADPH, then transports electrons to an NADPH-dependent enzyme, which uses them to catalyse the transformation of a substrate to a product. **b**, Megarity *et al.*[1] have trapped FNR and NADPH-dependent enzymes in the pores of an electrode, which acts as a plentiful source of electrons. When the system is immersed in a solution of NADPH, electrons flow from the electrode through the cascade of reactions, allowing NADPH-dependent enzymes to be used effectively outside biological systems.

© 2019 Springer Nature Limited. All rights reserved.

cofactor, NADPH, can then transport electrons to the next enzyme in a cascade (Fig. 1a). ITO electrodes provide a high localized concentration of electrons, and Megarity *et al.* anticipated that they could augment the natural FNR system by replacing ferredoxin with a nanoporous ITO surface that would co-entrap FNR with a partner enzyme that performs the final step in a cascade (Fig. 1b).

To demonstrate this concept, the authors first established that FNR and a second enzyme (alcohol dehydrogenase; ADH) can be co-entrapped in the disordered pores of ITO electrodes. When both FNR and ADH were adsorbed onto the electrode and placed in a solution containing $NADP^+$ and a substrate for ADH, the authors observed the formation of a reaction product. They also observed an electric current, the size of which depended on the amount of FNR present, indicating that FNR-mediated electron shuttling was occurring.

Megarity *et al.* found that the enzyme-loaded electrode could be reused by rinsing it thoroughly with water and then plunging it into a fresh solution of the reaction substrate. This not only demonstrated the robustness of their set-up, but also showed that both FNR and ADH become tightly bound within the electrode pores. By contrast, the authors found that $NADP^+$ is mostly not retained in the pores, and must be added to the reaction solution to restore a high reaction rate.

The authors' system simplifies electron transport and accelerates the rate of cofactor regeneration for cascades initiated by the transfer of electrons to FNR. The researchers estimate that this nanoconfinement strategy leads to a local concentration of 1.6 millimolar — about 1,000 times higher than solution concentrations — for each catalytic component in a pore, which reduces the distance required for the cofactor to travel between FNR and ADH compared with the distance required if the reaction is performed purely in solution. As a result, the overall rate of product formation is increased. Megarity and colleagues calculate that each 'minimal catalytic unit' in the reaction — the smallest number of enzyme molecules and cofactors needed for a reaction to occur; in this case, one FNR, one ADH and one NADPH — can produce about 125 molecules of product each second, which is a feat for a cascade involving a series of electron transfers.

Encouragingly, the authors show that three other NADPH-dependent enzymes can be used in place of ADH in their system to catalyse a variety of reduction reactions. This indicates that the nanoconfinement approach could have broad utility for NADPH-dependent biocatalytic transformations — although the observed reaction kinetics for each enzyme were different. Further work is required to define the full scope of NADPH-dependent enzymes and classes of enzyme powered by non-NADPH cofactors that are compatible with this strategy.

For example, testing reductase enzymes other than FNR in the authors' system will reveal whether porous electrodes can generally act as a source of electrons for proteins in electron-shuttling pathways, and whether this strategy can be used to recycle cofactors other than NADPH. Many classes of enzyme rely on electron transport, and a general strategy that would allow them to be used effectively in reactions outside biological systems could dramatically improve the scalability of such reactions. It could also facilitate the study of enzymes for which the electron-supplying partners are unknown.

Megarity and colleagues' work explores the nanoconfinement of two enzymes. One could also imagine packing additional enzymes into electrode pores to increase the efficiency of more-complex multi-enzyme cascades. The use of a synthetic compartmentalization system could thus find application in the enzymatic production of both the simple 'commodity' chemicals produced at large scales for the chemical industry, and structurally complex molecules, such as pharmaceutical agents. ■

Alison Narayan *is in the Department of Chemistry, Life Sciences Institute, University of Michigan, Ann Arbor, Michigan 48109, USA.*
e-mail: arhardin@umich.edu

1. Megarity, C. F. *et al. Angew. Chem. Int. Edn* https://doi.org/10.1002/anie.201814370 (2019).
2. Sheldon, R. A. & Woodley, J. M. *Chem. Rev.* **118**, 801–838 (2018).
3. Ricca, E., Brucher, B. & Schrittwieser, J. H. *Adv. Synth. Catal.* **353**, 2239–2262 (2011).
4. Li, Y. & Cirino, P. C. *Biotechnol. Bioeng.* **111**, 1273–1287 (2014).
5. Roy, A. *et al. J. Am. Chem. Soc.* **136**, 17343–17349 (2014).
6. Munro, A. W. & McLean, K. J. in *Encyclopedia of Biophysics* (ed. Roberts, G. C. K.) 601–605 (Springer, 2013).
7. Cardoso, A. R. *et al. Free Radical Biol. Med.* **52**, 2201–2208 (2012).
8. Avalos, J. L., Fink, G. R. & Stephanopoulos, G. *Nature Biotechnol.* **31**, 335–341 (2013).
9. Siritanaratkul, B. *et al. Chem. Sci.* **8**, 4579–4586 (2017).

This article was published online on 8 March 2019.

ASTRONOMY

X-ray chimneys in the Galactic Centre

X-ray observations of the Galactic Centre have uncovered chimney-like structures filled with hot plasma. The discovery might reveal how energy is transported from this central region to far-off locations. SEE LETTER P.347

MASHA CHERNYAKOVA

The centre of our Galaxy hosts a supermassive black hole that currently emits electromagnetic radiation extremely weakly, but could have been much more active in the past. Observations of γ-rays have revealed two huge structures known as Fermi bubbles located above and below the Galactic plane[1]. These bubbles are filled with highly energetic particles moving at close to the speed of light, which were released from the Galactic Centre a few million years ago. On page 347, Ponti *et al.*[2] report X-ray observations that reveal chimney-like structures connecting the region around the Galactic Centre to the Fermi bubbles.

The authors used more than 750 hours of X-ray observations made by the space-based XMM-Newton and Chandra telescopes to obtain the first detailed X-ray map of the central region of our Galaxy, an area of around 300 × 500 parsecs. (For comparison, the distance from Earth to the Galactic Centre is about 8,000 parsecs.) This map reveals two elongated, quasi-linear structures, each about 160 parsecs in length, above and below the supermassive black hole at the centre of the Milky Way (Fig. 1). Ponti *et al.* name these two structures the northern and southern Galactic Centre chimneys.

Previous X-ray and radio observations revealed two smaller lobes of outflowing matter, at a scale of about 15 parsecs, located above and below the Galactic plane[3,4]. The chimney structures connect these lobes to the Fermi bubbles, which start from about 100 parsecs above the Galactic plane and occupy a huge region approaching the size of the Galaxy itself.

The similarities between the northern and southern chimneys suggest that they have a common origin, most probably connected to the Galactic Centre. The chimneys seem to be well confined in the direction along the Galactic plane and have sharp edges at their vertical extents. Both are filled with a hot plasma (at a temperature of about 8 million kelvin) and have a total luminosity about a million times greater than that of the Sun.

The observed temperature and luminosity are consistent with the idea that the plasma in the chimneys is heated by energy released during the explosion of massive stars concentrated

© 2019 Springer Nature Limited. All rights reserved.