success (for instance, in treating irritability and aggression with atypical antipsychotics, and hyperactivity and attention deficit with stimulants); but it has not produced an agent that may be useful for treating the core symptoms — repetitive behaviours and deficits in social function and communication.

The present studies signal that, with the progress made in genomics and molecular neuroscience, autism research may be ready for translational approaches (Fig. 1). For example, rare causative mutations are being identified at fairly high rates, and knowledge of the functional consequences of such mutations may lead to an understanding of the common biological processes affected in related disorders. Studies in animals therefore seem crucial if we are to understand the neurobiological effects of such rare mutations.

Nonetheless, researchers have mixed feelings about the value of animal models of neurodevelopmental and neuropsychiatric disorders for drug discovery, given the previous lack of success. I think that modelling a human mutation or its equivalent in animals is a feasible approach for investigating the effect of pharmacological manipulations on the underlying biological deficits, irrespective of cross-species differences in the behavioural profiles associated with such mutations. As is evident from the present papers, at least under certain circumstances, this approach may lead to successes in the treatment of otherwise recalcitrant behaviours.

The most exciting implication of this work, however, is that by understanding the biological effects of a compound, its therapeutic effects can be extended beyond a specific single-gene disorder to heterogeneous syndromes with overlapping deficits at a biological level. In other words, although a mutation may be responsible for a few cases of, say, autism (in this case, only about 1–5% of individuals with autism spectrum disorders have fragile X syndrome), it is likely that there is a larger proportion of individuals with autism and/or intellectual disability who are 'fragile-X-like'. As such, treatments developed for fragile X syndrome may be effective for large numbers of such individuals.

But caution should be exercised when using this approach, because deviation in either direction from an optimal level of synaptic protein synthesis may lead to behavioural and cognitive problems. Evidence for this is emerging from other neurodevelopmental disorders, including tuberous sclerosis, Rett syndrome, neurofibromatosis and Phelan–McDermid syndrome[9–11]. For example, both fragile X syndrome and tuberous sclerosis are caused by single-gene mutations that ultimately affect synaptic protein synthesis, and both are associated with autism-like features and cognitive difficulties. Nonetheless, knockout in mice of *Tsc2*, one of two genes that are mutated in tuberous sclerosis, leads to diminished synaptic protein synthesis[12], in contrast to the enhanced protein synthesis seen when *Fmr1* is knocked out.

Attempts to extend the lessons learnt from single-gene disorders to more complex syndromes may therefore be tougher than expected. Consequently, information on behaviour, cognition and diagnosis alone may not be sufficient to guide the choice of treatment. In other words, to identify medications for individuals with autism, intellectual disability and related disorders, it will be essential to determine whether an individual is, for example, fragile-X-like or 'TSC-like' by using biomarkers that could be used in the clinic. The two papers are proof of principle that aligning mouse studies and human clinical trials holds promise. They also indicate that understanding single-gene-associated disease mechanisms that potentially represent final common pathways of several biological processes offers exciting opportunities for experimental therapeutics in neurodevelopmental and neuropsychiatric disorders. ■

Evdokia Anagnostou *is at the Bloorview Research Institute, Department of Pediatrics, University of Toronto, Toronto, Ontario M4G 1R8, Canada.*
e-mail: eanagnostou@hollandbloorview.ca

1. Henderson, C. *et al. Sci. Transl. Med.* **4,** 152ra128 (2012).
2. Berry-Kravis, E. M. *et al. Sci. Transl. Med.* **4,** 152ra127 (2012).
3. Hagerman, R. J. *J. Dev. Behav. Pediatr.* **27,** 63–74 (2006).
4. D'Hulst, C. & Kooy, R. F. *J. Med. Genet.* **46,** 577–584 (2009).
5. Dölen, G. & Bear, M. F. *J. Physiol. (Lond.)* **586,** 1503–1508 (2008).
6. Paluszkiewicz, S. M., Martin, B. S. & Huntsman, M. M. *Dev. Neurosci.* **33,** 349–364 (2011).
7. Isaacson, J. S. & Hille, B. *Neuron* **18,** 143–152 (1997).
8. Anagnostou, E. & Hansen, R. *Curr. Opin. Pediatr.* **23,** 621–627 (2011).
9. Ehninger, D., De Vries, P. J. & Silva, A. J. *J. Intellect. Disabil. Res.* **53,** 838–851 (2009).
10. Acosta, M. T., Gioia, G. A. & Silva, A. J. *Curr. Neurol. Neurosci. Rep.* **6,** 136–143 (2006).
11. Tropea, D. *et al. Proc. Natl Acad. Sci. USA* **106,** 2029–2034 (2009).
12. Auerbach, B. D., Osterweil, E. K. & Bear, M. F. *Nature* **480,** 63–68 (2011).

IMAGING

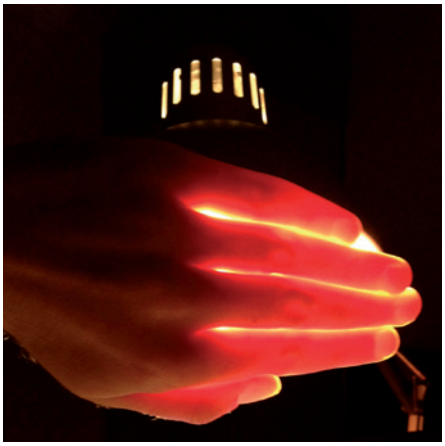
The fog clears

A technique has been developed to image a fluorescent object hiding behind a light-scattering screen without the need for a detector behind the screen. The approach could find applications in imaging biological tissue. SEE LETTER P.232

DEMETRI PSALTIS
& IOANNIS N. PAPADOPOULOS

A golfer faced with the problem of hitting a ball out of the woods after an errant shot sometimes makes a brave choice: she aims straight for the trees, swinging the club as hard as possible in the hope that the ball will bounce off the trees and miraculously emerge from the woods. On page 232 of this issue, Bertolotti *et al.*[1] describe a technique for imaging objects through light-scattering media, such as fog and human tissue, that overcomes a challenge that is in some ways similar to this one.

Consider light from a torch passing through a human hand. Information about the shapes of the bones, or even the cells, that make up the hand is thought to be encrypted in this transmitted light (Fig. 1), but a simple device such as a lens cannot be used to image the hand's interior. Numerous attempts have been made to retrieve the shapes of objects that hide behind or are within media that transmit and scatter light. Some of the photons that travel through a light-scattering medium do so without interacting with any of the medium's constituent matter. Such 'ballistic' photons exit the medium a little earlier than their non-ballistic counterparts, which bounce off the matter as they pass through the scattering medium. If the ballistic photons alone are captured in a detector, the blurring effects of scattering can be avoided[2]. However, for



D.P. & I.N.P.

Figure 1 | Seeing through. A light source placed behind a human hand emits photons that travel through the hand. Information about the hand's interior, such as its bones or cells, is encoded in the light's field but cannot be directly retrieved because it is scrambled by the scattering properties of human tissue. Bertolotti *et al.*[1] propose a method for retrieving such information.

strongly scattering media such as a human hand, ballistic light can propagate only short distances (about 1 millimetre in human tissue) without scattering. Therefore, image quality rapidly degrades as we attempt to see deeper into the tissue[3,4].

Another approach for seeing through a scattering medium is to use a technique called phase conjugation. In this method, the paths of all the photons are reversed and, as the photons travel backwards, the scattering that occurred over the course of their forward paths is undone[5–7]. We can understand how this works by returning to the golf analogy. To hit the ball out of the woods, the player would need to have memorized the exact direction in which the ball was travelling when it hit the ground. If she could then hit the ball in precisely the same direction but backwards, the ball would retrace its path and exit the woods. Unfortunately, the ball would end up at the location from which the errant shot was made, and not near the hole as the player would wish. Phase conjugation has a similar problem. A double pass through the same scattering medium gives a well-focused image of the object. However, this image forms right next to the object hiding behind the scattering medium, and thus in a position in which it cannot be observed.

In their study, Bertolotti and colleagues demonstrate that it is possible to form an image of an object hiding behind a scattering screen without the need to put a detector or a light beacon behind the screen. The authors placed a 50-micrometre-wide, two-dimensional fluorescent object at a distance of 6 mm behind a scattering screen, and shone laser light onto the screen. The light transmitted through the screen resulted in a random light pattern (speckle pattern), on the other side of the screen, that illuminated the fluorescent object. The researchers then measured the fluorescence that was generated by the object and transmitted back through the screen.

But how could they use these fluorescence measurements to form an image of the object, given that the speckle pattern illuminating the object was randomly generated by the scattering screen? The authors used fluorescence measurements of the object not only to form the image, but also as a beacon to probe the scattering medium[8,9] so as to be able to undo its blurring effect on the image. First, they made multiple measurements by adjusting the angle of illumination slightly, thereby changing the unknown speckle pattern in a predictable way. Second, they repeated their experiment many times to obtain statistical averages of the properties of the scattering screen. These measurements supplied them with the information they needed to form the image.

This technique is capable of imaging objects some distance away (6 mm in the current study) from a thin scatterer (about 3–5 μm thick for ground glass). For example, it could be used to image two-dimensional fluorescent objects in blood or other liquids surrounded by a thin scattering layer. The approach will probably be extended to three-dimensional objects and possibly to non-fluorescent objects. However, major innovation would be required to expand the technique to permit imaging of objects behind or inside thick scattering media. For now, Bertolotti and colleagues' demonstration that it is possible to see clearly a fluorescent object behind a scattering screen, beyond the ballistic spatial limit, will almost certainly intensify the search for ways to use light to see through human tissue.

What does this story suggest for our golfer who wishes to hit the ball out of the woods and direct it towards the hole? She might have to hit many balls in various directions, the equivalent of adjusting the illumination angle in the authors' experiment. She might also have to engage many friends to stand around the golf course and shout back when a ball hits them, just as fluorescent molecules send light back when photons hit them. Even after hitting all these mulligans (second-chance shots in golf), she would not know how to strike the ball in the direction of the hole. However, if she hit enough of her friends during this unusual game, she would know where her friends were standing (the image of the object). But she would still not know how to hit a single shot through the trees and towards the hole — the analogue of ballistic passage through the scattering medium. ■

Demetri Psaltis *and* **Ioannis N. Papadopoulos** *are at the Optics Laboratory, School of Engineering, École Polytechnique Fédéral de Lausanne, 1015 Lausanne, Switzerland.*
e-mail: demetri.psaltis@epfl.ch

1. Bertolotti, J. *et al. Nature* **491,** 232–234 (2012).
2. Wang, L., Ho, P., Liu, C., Zhang, G. & Alfano, R. *Science* **253,** 769–771 (1991).
3. Alex, A. *et al. J. Biomed. Opt.* **15,** 026025 (2010).
4. Helmchen, F. & Denk, W. *Nature Methods* **2,** 932–940 (2005).
5. Leith, E. N. & Upatnieks, J. *J. Opt. Soc. Am.* **56,** 523 (1966).
6. Kogelnik, H. & Pennington, K. S. *J. Opt. Soc. Am.* **58,** 273–274 (1968).
7. Agarwal, G. S., Friberg, A. T. & Wolf, E. *J. Opt. Soc. Am.* **73,** 529–537 (1983).
8. Vellekoop, I. M. & Mosk, A. P. *Opt. Lett.* **32,** 2309–2311 (2007).
9. Hsieh, C. L., Pu, Y., Grange, R., Laporte, G. & Psaltis, D. *Opt. Express* **18,** 20723–20731 (2010).

BIOCHEMISTRY

A glimpse of molecular competition

Single-molecule studies reveal how the DNA-repair protein RecA overcomes competition from another protein to bind to single-stranded DNA, and how other mediator proteins assist in this process. SEE LETTER P.274

SUSAN T. LOVETT

Chromosomes consist of two interwound DNA strands millions of base pairs in length. These long molecules inevitably suffer breakage, which can be induced by ionizing radiation, biochemicals or natural DNA processing within cells. Double-strand breaks in DNA are not normally lethal to a cell, and can be accurately repaired by a process known as homologous recombination[1,2], during which a broken DNA fragment searches for and pairs with an intact strand from another DNA molecule that carries an identical (homologous) sequence. The search process is remarkable in two respects: the homologous partner can be found even among the many millions of non-homologous segments, and the crucial base sequence can be recognized even when it is largely buried within a DNA double helix.

In all domains of life, this extraordinary search and pairing process is made possible by a class of structurally related proteins of which the RecA protein from the bacterium *Escherichia coli* is the most-studied member. To initiate the recombination process, a filament composed of many RecA molecules must form on single-stranded DNA (ssDNA). But in doing so, the protein has to compete for binding with another resident protein, the ssDNA-binding protein (SSB)[3]. On page 274 of this issue, Bell *et al.*[4] present single-molecule images of fluorescent RecA as it binds to ssDNA and extends to form a filament*. Although there have been other single-molecule studies[5–12] of RecA and of the analogous protein Rad51 from humans, this is the first study to visualize RecA binding to its natural substrate: extensively SSB-coated ssDNA. It is also the first to examine the effects of recombination 'mediators', proteins that potentiate recombination *in vivo* by aiding RecA-filament formation[13,14], particularly on SSB-coated DNA.

*This article and the paper under discussion[4] were published online on 24 October 2012.