between conventional hard metals[5]. Pan *et al.* accomplish this suppression by cutting a deep, narrow notch around the circumference of a cylindrical glass bar, and compressing it in the direction of its axis (see Fig. 1a of the paper). The central region of the bar near the notch undergoes extensive plastic deformation, during which shear bands are suppressed by the constraints exerted by the outer parts of the bar. The authors then cut out the central part and deformed the unconstrained sample under tension or compression. Remarkably, the resulting material exhibits properties similar to those of conventional crystalline metals: it undergoes work hardening and does not form shear bands.

The mechanism responsible for this hardening, however, is far from conventional. To explain why, let's consider the ground states of crystals and glasses. A crystal in its undeformed ground state has the lowest possible flow stress (a measure of the force needed to sustain plastic deformation). The introduction of dislocations during deformation costs energy, and their entanglement raises the flow stress[3]. A glass in its ground state, however, has the highest possible flow stress because it has the lowest number of STZs. Deformation of this state costs energy, but through shear-induced dilatation introduces new STZs that lower the flow stress (see ref. 6, for example).

All glasses are in non-equilibrium states. When they are heated (annealed) to a temperature at which their atoms can move, the process tightens up their atomic packing and lowers their energies towards a ground state[7]. This process is called structural relaxation, or ageing, and it changes the properties of glasses[8]. For example, it can increase the density by a few tenths of a per cent; raise the elastic stiffness by a few per cent; increase viscosity by many orders of magnitude; and sometimes cause ductile glasses to become brittle.

Reversal of this ageing process is called rejuvenation, and can be achieved in several ways. The simplest is to heat a glass until it becomes a liquid again, and then rapidly cool it[1]. Another approach is to 'shake up' the structure, for example by ion irradiation[9] or plastic deformation[10]. By heavily deforming samples of metallic glasses under constrained conditions, Pan *et al.* raise the energies of the glasses far above the energy of the ground state, rejuvenating them and loading them up with STZs. When the authors then deform them under the less-constrained conditions of a tensile or compressive test, structural relaxation sets in: the atomic packing increases and the volume introduced by the earlier deformation disappears; the number of STZs drops, causing the flow stress to increase; and work hardening is achieved.

The practical implications of this work are clear: if metallic glasses can be treated so that the threat of shear-band failure is greatly reduced, then they can be more fully exploited for structural applications. However, this will require the development of methods for rejuvenating large volumes of metallic glasses — Pan and colleagues' rejuvenated samples are only 3 millimetres long and 1.5 mm in diameter. Large-scale rejuvenation will require the deformation of large quantities of alloys under constrained conditions, which could be achieved using methods such as confined cold rolling[10] or equal-channel angular extrusion[11].

The authors' rejuvenation technique might also advance glass science. Because glasses are not in equilibrium, their properties depend on the processing path by which a particular state is reached. For example, in their experiments, Pan *et al.* measured the heat of relaxation of their glasses (a measure of the glasses' internal energy) after rejuvenation and after various stages of subsequent deformation. It would be interesting to know how the structure and other properties of their glasses compare with those of glasses that have the same heats of relaxation, but which were obtained by the cooling of melted material and annealing. In other words, what makes the authors' rejuvenation technique attractive is that it opens up many more paths for exploring the complex relationship between structure and properties in glasses.

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1. Schroers, J. *Adv. Mater.* **22**, 1566–1597 (2010).
2. Pan, J., Ivanov, Yu. P., Zhou, W. H., Li, Y. & Greer, A. L. *Nature* **578**, 559–562 (2020).
3. Kocks, U. F. & Mecking, H. *Prog. Mater. Sci.* **48**, 171–273 (2003).
4. Jensen, K. E., Weitz, D. A. & Spaepen, F. *Phys. Rev. E* **90**, 042305 (2014).
5. Donohue, A., Spaepen, F., Hoagland, R. G. & Misra, A. *Appl. Phys. Lett.* **91**, 241905 (2007).
6. de Hey, P., Sietsma, J. & van den Beukel, A. *Acta Mater.* **46**, 5873–5882 (1998).
7. Battezzati, L., Riontino, G., Baricco, M., Lucci, A. & Marino, F. *J. Non-Cryst. Solids* **61–62**, 877–822 (1984).
8. Egami, T. *Ann. NY Acad. Sci.* **371**, 238–251 (1981).
9. Magagnosc, D. J. *et al. Acta Mater.* **74**, 165–182 (2014).
10. Chen, H. S. *Appl. Phys. Lett.* **29**, 328 (1976).
11. Segal, V. M. *Mater. Sci. Eng. A* **271**, 322–333 (1999).

In retrospect

Turning connective tissue into neurons for 10 years

Giacomo Masserdotti & Magdalena Götz

A method for directly converting connective-tissue cells into neurons opened up a new branch of research into cell-based therapies and called into question long-held beliefs about how development affects a cell's identity.

Our bodies rely on specialized cell types: brain cells compute information, red blood cells bind oxygen, and so on. Because almost all our cells have identical DNA, different patterns of gene and protein expression are needed to define these cell types. The selection and maintenance of these expression cascades were once thought to be irreversible after development. Over time, it emerged that cell identity could be changed, but it was often assumed that a cell could be converted into another cell type only if the two had a similar developmental origin. Ten years ago, Vierbuchen *et al.*[1] overthrew this idea, by showing that connective-tissue cells called fibroblasts could be converted into functional neurons — which have a very different developmental origin — if they were engineered to express just three extra transcription factors.

This achievement was built on almost a century of visionary experiments in manipulating cell identity. In 1927, Hans Spemann showed that it was possible to change the fate of cells in a salamander embryo. The embryologist grafted 'organizer' cells (which drive early development of the body plan) from a donor embryo into a host embryo[2], triggering the formation of a second embryo from the host cells. In 1962, the biologist John Gurdon showed that development can also be returned to the start[3] — the nucleus of an adult cell can reacquire a state similar to that of cells in the earliest stages of development, and in this state it can give rise to an entire embryo.

In the 1980s, it became clear that cells can also be directly converted from one specialized cell type to another (Fig. 1a). The first example[4] was the conversion of fibroblasts into muscle cells by inducing the cells to express the transcription factor MyoD. Some

years later, a different transcription factor was used to turn non-neuronal cells of the brain called glia into neurons *in vitro*[5]. The first demonstration that this type of conversion could also occur *in vivo* in mice[6] opened up a potential new branch of therapy based on converting reactive glia into new neurons after brain insults or neurodegeneration[7].

In vitro, a wealth of other conversions was documented[8], but all involved either reversion to an embryonic state[9] or transformation into another cell type from within the same 'germ layer'. Germ layers are the three layers of embryonic tissue (endoderm, mesoderm and ectoderm), which give rise to different organs and cell types. For instance, the gut tube and liver derive from the endoderm; muscle and connective tissue from the mesoderm; and neural tissue and skin from the ectoderm.

It was assumed that cells could be converted only to other cell types from the same germ layer, owing to their closely related developmental origins. This dogma was shattered by Vierbuchen and colleagues, who converted mesoderm-derived fibroblasts from mice into functional neurons by co-expressing the three transcription factors Brn2, Ascl1 and Myt1l in the fibroblasts (Fig. 1b). By showing that developmental barriers are not an unsurmountable hurdle to cell-type conversion, the paper had a tremendous impact.

First, it sparked a wave of interest in direct reprogramming to produce neurons. All of a sudden, fibroblasts — which are relatively easy to isolate from mouse embryos and are easy to grow *in vitro* — could be converted into a cell type of great therapeutic interest. The year after the paper's publication, human fibroblasts were directly converted into neurons[10], although this required more transcription factors than were needed for the conversion of mouse cells. It was only a few more years before transcription-factor cocktails had been defined to generate diverse neuronal subtypes[11–13].

In 2015, it emerged that the 'induced neurons' produced using Vierbuchen and colleagues' method retain their cellular age — if the fibroblasts come from a 60-year-old donor, the reprogrammed neurons show a corresponding cellular age[14]. Thus, direct neuronal reprogramming is well suited for obtaining neurons to study age-related neurodegenerative diseases such as Alzheimer's disease, Huntington's disease or motor neuron disease[15,16].

Beyond these key impacts on translational research, the paper raised questions about how developmental origin affects the maintenance of cell identity. For instance, the work called into question whether sharing a germ layer would always ease direct reprogramming between cell types. The answer is no: skin cells, derived from the ectoderm, cannot be readily converted to neurons[17] (Fig. 1c). Moreover, neurons can switch between subtypes only during development[18]. These findings called for reconsideration of models of cell-identity maintenance. Perhaps, instead of depending on developmental origin, the key factors in how easily cell types can interconvert relate to similarities and differences in gene regulation between the mature cell types[19].

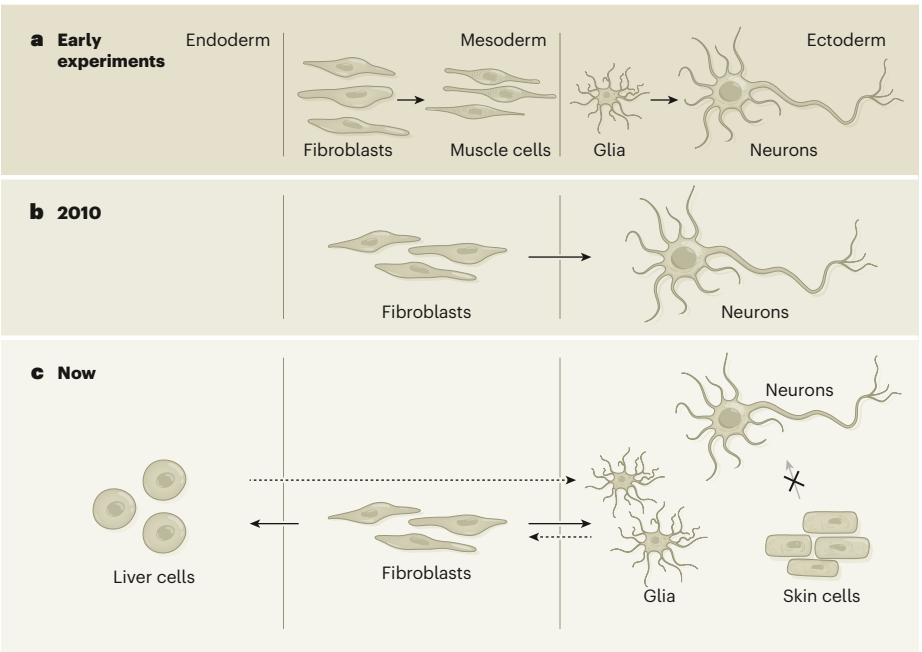

Figure 1 | Breaking developmental barriers using direct reprogramming. Three early embryonic tissues called the germ layers (endoderm, mesoderm and ectoderm) give rise to all the body's different cell types. **a**, Early experiments in cell reprogramming revealed that cells called fibroblasts can be converted into muscle cells *in vitro* through forced expression of one transcription factor[4], and that glia (non-neuronal brain cells) can be converted into neurons by another transcription factor[5]. It was assumed that these conversions were possible only because the cell types had a shared developmental origin: fibroblasts and muscle both arise from the mesoderm; glia and neurons from the ectoderm. **b**, In 2010, however, Vierbuchen *et al.*[1] demonstrated that co-expression of three transcription factors could induce fibroblasts to become neurons. **c**, The discovery led to many insights into cell identity. More conversions have been achieved[8] (examples indicated by arrows). We now know that cells cannot be converted into every cell type from within the same germ layer (skin cells cannot become neurons[17], for instance). We can also hypothesize about other conversions that might be possible (dashed arrows) using different cocktails of transcription factors.

If this is the case, it should be possible to ascertain rules for interconverting cell types by altering specific gene-regulation parameters. However, no systematic studies to explore the potential of a given starter cell type to convert into different target cells have yet been carried out. This means that it is not yet possible to identify common rules for reprogramming — or, conversely, for the maintenance of identity. Filling this gap is now an important task.

The ease of direct programming hints at the fragility of the mechanisms that maintain cell fate. So what keeps cells stable over decades? Researchers are starting to investigate the mechanisms (passive and active) that regulate expression of the transcription factors involved in switches of cell type, and to ask whether long-lived cells are more difficult to convert because they have developed more-elaborate fate-maintenance mechanisms. This could also be the reason that human cells are much harder to convert into other cell types than are mouse cells.

The identification of these mechanisms would not only be a conceptual breakthrough, but would also help to overcome conditions in which cell identity becomes altered as cells deteriorate during ageing. For example, proteins that repress gene expression are involved in maintaining some aspects of cell identity in mature neurons[20]. However, little is known about whether or how these factors are depleted in ageing and neurodegeneration, and whether the loss of cell identity is a key contributor to ageing-related diseases.

Direct reprogramming has revolutionized the concept of what defines a cell type, and has allowed us to explore fascinating questions about development. It has also triggered a revolution in disease modelling. That this has taken place in just one decade is testament to the impact of Vierbuchen and colleagues' discovery.

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1. Vierbuchen, T. *et al. Nature* **463**, 1035–1041 (2010).
2. Mangold, O. & Spemann, H. *Wilhelm Roux Arch. Entwickl. Mech. Org.* **111**, 341–422 (1927).
3. Gurdon, J. B. *J. Embryol. Exp. Morphol.* **10**, 622–640 (1962).
4. Davis, R. L., Weintraub, H. & Lassar, A. B. *Cell* **51**, 987–1000 (1987).
5. Heins, N. *et al. Nature Neurosci.* **5**, 308–315 (2002).
6. Buffo, A. *et al. Proc. Natl Acad. Sci. USA* **102**, 18183–18188 (2005).
7. Barker, R. A., Götz, M. & Parmar, M. *Nature* **557**, 329–334 (2018).
8. Xu, J., Du, Y. & Deng, H. *Cell Stem Cell* **16**, 119–134 (2015).
9. Takahashi, K. & Yamanaka, S. *Cell* **126**, 663–676 (2006).
10. Pang, Z. P. *et al. Nature* **476**, 220–223 (2011).
11. Caiazzo, M. *et al. Nature* **476**, 224–227 (2011).
12. Son, E. Y. *et al. Cell Stem Cell* **9**, 205–218 (2011).
13. Victor, M. B. *et al. Neuron* **84**, 311–323 (2014).
14. Mertens, J. *et al. Cell Stem Cell* **17**, 705–718 (2015).
15. Hu, W. *et al. Cell Stem Cell* **17**, 204–212 (2015).
16. Victor, M. B. *et al. Nature Neurosci.* **21**, 341–352 (2018).
17. Wapinski, O. L. *et al. Cell* **155**, 621–635 (2013).
18. Rouaux, C. & Arlotta, P. *Nature Cell Biol.* **15**, 214–221 (2013).
19. Gascon, S., Masserdotti, G., Russo, G. L. & Götz, M. *Cell Stem Cell* **21**, 18–34 (2017).
20. von Schimmelmann, M. *et al. Nature Neurosci.* **19**, 1321–1330 (2016).

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Nuclear physics

Nuclear force probed at short distances

Alexandra Gade

The dense soup of matter in the core of neutron stars is hard to model, but particle-accelerator experiments in which energetic electrons scatter off atomic nuclei could help to explore this high-density regime. **See p.540**

Modelling the fundamental strong force between protons and neutrons — collectively called nucleons — is tricky. But on page 540, Schmidt and collaborators[1] demonstrate a way to explore these interactions in atomic nuclei, and compare experimental measurements against calculations that use various models of the strong nuclear interaction. They do so at the shortest inter-nucleon distances yet probed, by poking nucleon pairs using high-energy electrons and focusing on a previously unexplored regime of short-distance, high-momentum interactions in a nucleus.

Quantum chromodynamics (QCD) is the fundamental theory of the strong interaction, one of the four forces in nature. In that theory, the nucleon–nucleon (*NN*) interaction that binds protons and neutrons into atomic nuclei is largely determined by the underlying dynamics of quarks and gluons (quarks being the elementary particles that combine to form protons, neutrons and other, less stable particles; gluons are the carriers of the strong force that 'glues' the quarks together).

However, because the unwieldy nature of QCD makes it impossible to model atomic nuclei computationally, we still lack a truly quantitative understanding of the *NN* force from QCD. Instead, modellers have resorted to approximations known as effective *NN* interactions for use in models of nuclear properties[2,3]. These treat nucleons as point-like objects. Some effective interactions are phenomenological — they are based on experimental data obtained by scattering nucleons from each other[3]. Others[2] are derived from first principles and exploit symmetries manifested in QCD.

Because of the way they were developed, we can be fairly confident that the effective *NN* interactions accurately represent the actual interactions at typical inter-nucleon distances in nuclei, but not necessarily at the tiny distances that are relevant, for example, when describing the high-density cores of neutron stars. We know that the *NN* interaction is attractive down to about 1 femtometre (10^{-15} metres). At smaller distances, very strong repulsion sets in[2,3]. In atomic nuclei, nucleons consequently position themselves close enough to take advantage of the attraction, but shy away from the notoriously hard core of their neighbours at the shortest distances.

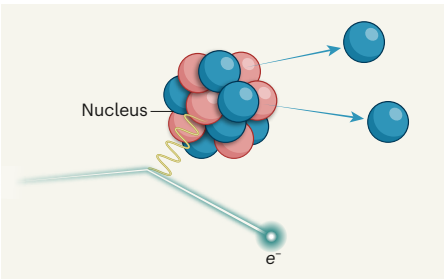

Figure 1 | High-energy electron scattering probes the strong nuclear interaction. Schmidt *et al.*[1] studied nuclear reactions in which high-energy electrons (e^-) scattered off systems of nucleons (protons and neutrons; blue and pink, respectively), and in which high-momentum protons were liberated. The resulting data were used to investigate the interactions that occur between nucleons separated by very small distances, and to show that current models of nucleon–nucleon interactions might be valid at these short distances.

For the description of most nuclear properties, nucleons can be approximated as independent particles subjected to a mean field created by the other nucleons. But about 20% of the time[4], as a result of density fluctuations in nuclei, two nucleons come close enough to form a short-range correlated pair that defies the mean-field description. According to Heisenberg's uncertainty principle, such large local density fluctuations are associated with large fluctuations in momentum[5].

Schmidt and collaborators have now tested the details of effective theories of the nuclear force — that is, theories based on effective *NN* interactions — using the particle detector system known as the CEBAF Large Acceptance Spectrometer (CLAS) at the Thomas Jefferson National Accelerator Facility in Newport News, Virginia. They scattered energetic electrons off pairs of nucleons that were separated by very small distances (and which have characteristically high momenta) in nuclei to study the *NN* repulsion, and used the data to test the accuracy of effective *NN* interactions at these distances. Their work pushes the investigation of such pairs to the highest momenta yet attained.

In optics, the resolving power of an instrument is the smallest distance at which two closely spaced objects can be separated. This distance is typically proportional to the wavelength of light used: the smaller the wavelength, the better the resolving power. In nuclear physics, to resolve nucleons in a nucleus, a resolution of about 1 fm is required. The high-energy electron scattering used by Schmidt *et al.* achieves this resolution because high-energy electrons have a tiny wavelength (the de Broglie wavelength) and a high momentum, which they impart to the nucleon systems being studied.

From data taken using the CLAS detector, Schmidt and collaborators picked out reactions in which a scattered high-energy electron (e,e', where e is the incoming electron and e' is the scattered electron) liberated a proton (p) from a target nucleus (A); these reactions are described as A($e,e'p$) events. More specifically, the authors selected scattering reactions in which a property of the liberated proton known as the missing momentum was measured to be more than 400 megaelectronvolts per c (where c is the speed of light). For the high-energy conditions studied, this missing momentum is approximately equal to the initial momentum of the struck proton inside the nucleus.