



Figure 2 | Dammed lake. The first glacial lake in the area of the southern North Sea existed from around 450,000 to 400,000 years ago. This was dammed to the north by the extension of continental ice from Scandinavia to eastern England and central western Europe, and to the south by a band of higher land, the Weald-Artois anticlinal ridge, stretching from south-east England to northern France. The rivers entering the lake (white arrows) and the overspill at the Dover Strait into the Channel (red arrow) are shown. It was probably this overspill that initiated the first flood identified by Gupta *et al.*¹. (Map modified, with permission, from ref. 6.)

a gently upfolding ridge of bedrock, has been a point of discussion for more than a century. The consensus now is that its formation was initiated some 450,000 years ago during the first major extension of a continental ice sheet into lowland central Europe and Britain^{2,5}. The ice advanced across the emergent North Sea floor from southern Scandinavia, blocking rivers flowing northwards into the Atlantic Ocean and causing an immense glacial lake to develop in front of it, dammed by higher ground to the south and fed by the drainage of much of Western Europe (Fig. 2).

The lowest point of this dam, which was about 30 m above today's sea level⁶, stood where the Strait of Dover now lies. Once this 30-km-wide bedrock barrier was overtopped some time around 425,000 years ago, the overflow quickly became torrential. The water would initially have followed existing stream valleys into the Northern Palaeovalley, but the deluge would quickly have overwhelmed these valleys, with the turbulent waters causing dramatic deepening and enlargement. This, in all probability, was the first flood identified by Gupta and colleagues¹.

It is no exaggeration to say that this first Channel flood was probably — on the basis of comparison of the landforms it sculpted with those formed by the Lake Missoula megaflood in the northwestern United States^{4,7} — one of the largest ever identified. But although the Channel flood was only of comparable proportions to the Missoula flood, it had more profound long-term geographical consequences.

After the draining of the North Sea lake that resulted from this flood, the Thames and the Scheldt were realigned through the newly formed Dover Strait into the Channel river; the Rhine and Meuse, however, returned to the North Sea after the glaciers withdrew^{5,6}. Their diversion to the south was delayed by another 200,000 years until, during a second period of

central Netherlands and again dammed a lake in the southern North Sea⁸. This time, the level of the lake's water remained close to present sea levels, and its southern margin was not at the Dover Strait, but at a ridge further north. This was either an outcrop of bedrock, or possibly a barrier formed from moraine deposited during the previous glaciation.

The failure of this weaker barrier would have been immediate and catastrophic, and almost certainly released a vast volume of water that surged through the Dover Strait and thundered on into the Northern Palaeovalley. This event was probably the second and devastating flood so convincingly demonstrated by Gupta and colleagues¹. By ensuring that the Dover Strait gap was greatly enlarged — almost to its present

form — this single event finally sealed Britain's fate; during periods of high sea level, it would henceforth be an island. And during intervals of low sea level, such as the last glaciation, the Channel river would carry effectively half the drainage of western Europe to the Atlantic Ocean^{2,3,9}.

As Gupta *et al.* conclude¹, the implications of such significant palaeogeographical changes for plant and animal (including human) migration are manifold, culminating in the impoverishment of the British biota during the last and current interglacials, but also providing a land-bridge during glacial periods. In addition, the almost instantaneous release of huge volumes of freshwater into the Atlantic Ocean could have triggered changes in ocean circulation which might, in turn, have affected the climate of the whole North Atlantic region¹⁰. Britain's island story began here. ■

Philip Gibbard is in the Department of Geography, University of Cambridge, Downing Place, Cambridge CB2 3EN, UK.

e-mail: plg1@cam.ac.uk

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STEM CELLS

The magic brew

Janet Rossant

Researchers have engineered embryonic stem-like cells from normal mouse skin cells. If this method can be translated to humans, patient-specific stem cells could be made without the use of donated eggs or embryos.

Two reports in this issue^{1,2} and one elsewhere³ describe a seemingly simple method for changing differentiated adult cells into pluripotent stem cells. The 'gold-standard' test for pluripotency is the ability of a cell to contribute extensively to all adult cell types, including the germ line. The cells generated by these authors pass this test. The researchers introduced four gene-transcription factors into fibroblast cells originating from mouse skin, and specifically selected those cells that, in response to these factors, expressed genes indicative of a pluripo-

to isolate cell lines that resembled mouse embryonic stem (ES) cells, but when they injected these cells into early embryos, the cells differentiated into all normal adult cell types.

A previous study⁴ had shown that differentiated adult cells could be transformed into pluripotent cells when fused with ES cells. This hinted that factors found in ES cells might be essential to conferring pluripotency on other cells. However, the transcriptional profiles, modifications to chromatin (complexes of DNA and histone proteins) and DNA methyl-

those of adult cells, indicating that pluripotency is probably under complex layers of control. It was, therefore, a surprise when Takahashi and Yamanaka⁵ reported last year that they could produce cell lines with some of the properties of ES cells by introducing just four transcription factors associated with pluripotency — Oct3/4, Sox2, c-Myc and Klf4 — into mouse skin fibroblasts, and then selecting cells that expressed a marker of pluripotency, *Fbx15*, in response to these factors. These cells were called induced pluripotent stem (iPS) cells.

However, the generated iPS cells differed from ES cells in their gene-expression and DNA-methylation patterns. And when these cells were injected into normal mouse blastocysts (70–100-cell embryos), no live chimaeras — animals carrying cells throughout their bodies from both the original blastocyst and from iPS cells — were born.

Yamanaka and colleagues¹, as well as Wernig *et al.*² and Maherali *et al.*³, surmised that if selection of iPS cells were based on the expression of genes that are more essential for pluripotency than *Fbx15*, this might improve the generation of truly pluripotent reprogrammed cells. They derived embryonic or adult fibroblasts that were engineered to express drug-selectable markers under the control of one or other of the two best-studied genes crucial for pluripotency — *Nanog* and *Pou5f1* (Fig. 1). After introducing the four factors (Oct3/4, Sox2, c-Myc and Klf4) by the technique of retroviral transfection, cells were subjected to drug selection. All three groups could derive stable cell lines. In terms of transcriptional, imprinting (expression of alleles predetermined by the parent from which they originated) and chromatin-modification profiles, these were essentially identical to ES cells. Maherali *et al.*³ also report appropriate reactivation of the inactivated X chromosome in a female iPS cell line, and all authors present images of chimaeric mice, as well as evidence of germline transmission of the genetic content of iPS cells.

But questions remain about the exact sequence of molecular events that leads to this dramatic reprogramming, and whether additional changes, beyond the expression of the four transcription factors, are involved. The process of reprogramming is slow — colonies take up to 20 days to develop into real ES-like cells, and their frequency is quite low. Is this because only a few cells happen to express the right combination or levels of the four factors because of the random integrations of the retroviruses? Or are there additional events, perhaps associated with retroviral insertion, that are required for full transformation?

Continued expression of the four external factors may not be needed for the maintenance of iPS cells; in fact, these cells seem to show low-level expression of these factors. Maherali *et al.*³ directly tested the requirement for continued expression of Oct3/4 and found that it was dispensable for iPS survival. Such tests

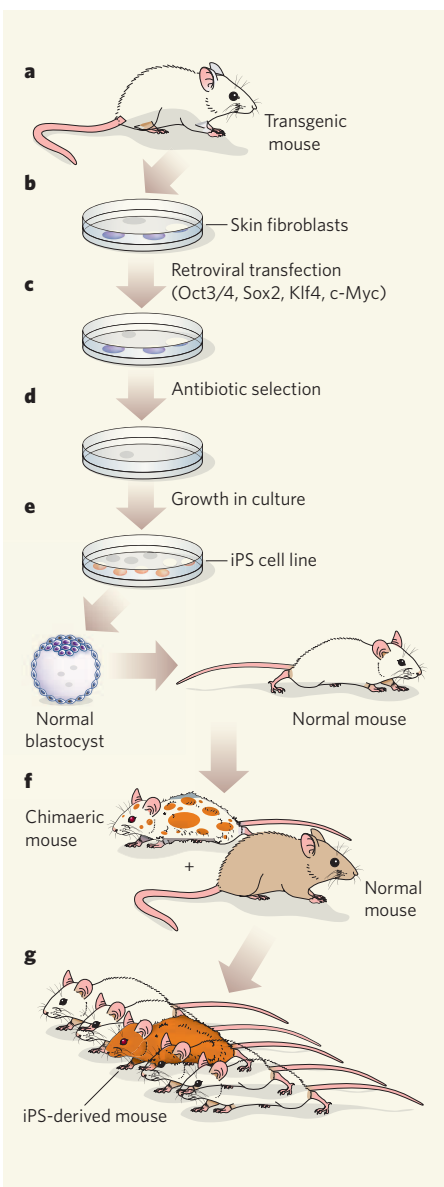


Figure 1 | Generating induced pluripotent stem cells. a, To turn adult skin fibroblasts into embryonic stem cells, researchers generated mice that carried a drug-selectable marker conferring resistance to either neomycin² or puromycin^{1,3}. Resistance to these antibiotics was linked to expression of either *Pou5f1* (ref. 2) or *Nanog* (refs 1,3), which are markers of pluripotency. b, The authors then isolated fibroblasts from these genetically modified mice and, c, introduced genes for four transcription factors — Oct3/4, Sox2, Klf4 and c-Myc — into these cells by retroviral transfection. d, The transfected cells were subjected to appropriate drug selection. Cells that did not express the gene for drug resistance — that is, *Pou5f1* or *Nanog* — died. e, Thus, rare colonies that resembled embryonic stem cells were isolated, and expanded into stable induced pluripotent stem (iPS)-cell lines. f, When injected into blastocysts of normal mice, iPS cells could contribute to all cell types of the body, including the germ line. g, When the chimaeric animals resulting from these blastocysts were crossed with normal mice, this led either to the birth of live offspring carrying the genetic content of an iPS cell¹ or to

Side effects of generating stem cells in this way are also problematic. Yamanaka *et al.*¹ found that 20% of the iPS-derived offspring developed tumours, presumably related to the activation of one of the transfected genes, *c-myc*. Some iPS-cell chimaeras have also developed tumours (R. Jaenisch, personal communication).

In addition, it is not known whether the same set of factors can reprogramme other, more specialized cell types. Clearly, the current methodology is more of a proof-of-principle than a fully rationalized series of molecular events that leads to reproducible reprogramming of adult cells. But it is an exciting proof-of-principle nonetheless. Multipotent progenitor cell lines — cells that can give rise to several, but not all, other cell types — have been developed from an increasing number of different fetal and adult sources; but none of these consistently shows the full pluripotency possessed by ES cells or these new iPS cells.

From proof-of-principle in mice to application in humans is still a leap. But since the publication of these studies online, media commentaries have focused on this possibility. The pluripotent nature of human ES cells holds enormous potential for future cell-based therapies for degenerative diseases and traumatic injuries. Use of human embryos to derive such cells remains controversial in many jurisdictions. The possibility of making cell lines with all of the properties of ES cells directly from non-controversial adult sources such as skin holds obvious appeal. It could also be a powerful way of making patient-specific stem cells to provide tissue-matched cells for therapy, and a source of cells for research into the pathogenesis of complex diseases.

Until now, the proposed method to make patient-specific ES-cell lines has been somatic-cell nuclear transfer (SCNT), or cloning. This involves reprogramming DNA from an adult cell by transplanting it into the cytoplasmic environment of an unfertilized egg⁶ — or, more recently, of a newly fertilized egg⁷. ES cells derived through SCNT have been generated in mice, albeit at a fairly low frequency. In humans, the first reported success⁸ from Woo Suk Hwang's group in South Korea is probably a parthenogenetic ES cell derived from a blastocyst, where the egg is activated without the sperm⁹; later claims by this group were found to be fraudulent. Descriptions of the generation of SCNT-derived primate ES cells at a recent stem-cell meeting in Cairns, Australia, indicate that it might be possible to derive human ES-cell lines using a similar method. However, it is still not clear whether human ES cells can be made at any reasonable frequency after SCNT. An efficient way of directly reprogramming adult cells, which also avoids the controversial use of donated eggs or embryos, would clearly be technically advantageous.

Will the same magic brew of molecular fac-

groups will certainly be rushing to test this. But translation from proof-of-principle to any therapy has many challenges. First, human cells would have to be given a built-in drug-selectable pluripotent marker by some efficient means. Second, potentially cancer-causing factors such as c-Myc must be avoided. Third, factors would need to be introduced by a method other than retroviral transfection; retroviruses can cause activation of cancer-causing genes and are therefore risky. Transient gene expression by direct introduction of membrane-permeable transcription factors into cells might be one way to achieve this, and screens for small molecules that can replace the gene products would also be useful. Despite these challenges, direct reprogramming of adult cells is clearly the way of the future, and promises to open up new frontiers in human biology and future therapy. ■

Janet Rossant is in the Program in Developmental and Stem Cell Biology, Hospital for Sick Children Research Institute, and the Department of Medical Genetics and Microbiology, University of Toronto, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada.

e-mail: janet.rossant@sickkids.ca

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QUANTUM MECHANICS

Interference in the matter

Markus Kindermann

Like any particle, electrons are also waves that can interfere with each other. Remarkably, this interference can even happen between electrons from different sources that have never physically interacted.

That electrons are waves can be conclusively demonstrated by sending them through two parallel slits, and observing the interference patterns between them that result as they diffract. Such double-slit experiments led a recent ranking of the most beautiful experiments in the history of physics¹. They were first performed with electrons in free space², but similar experiments performed later showed that the wave character also extends to electrons in small metallic conductors at very low temperatures³. Neder *et al.*⁴, whose results appear on page 333 of this issue, have moved on to a next level: they have demonstrated compellingly that electron waves can interfere even if they originate from independent sources.

The statement that classical electromagnetic waves always add up ('superpose') no matter where they come from is quite intuitive, and typically taken for granted. The waves emitted by different light sources are thus able to interfere. This interference can even be observed for sources that are incoherent, or out of phase, through a phenomenon known as the Hanbury Brown–Twiss effect⁵.

The same assertion made of electron waves is less obvious. The natural inclination is to describe each electron by its own matter wave that is independent of the waves associated with other electrons. And electrons with different origins are, one might think, evidently different.

flawed. All electrons are intrinsically identical, and there is nothing besides their state at any particular moment that distinguishes two electrons (or any two elementary particles of the same kind) from each other. This is one of the fundamental postulates of quantum mechanics, and it follows that all electrons in the Universe are described by the same matter wave that invisibly connects them.

This strange fact has profound consequences. One of these is the phenomenon of

'anti-bunching': electrons tend to avoid getting too close to each other in space. Anti-bunching has been demonstrated with electrons in free space⁶ and in electrical conductors^{7,8}. But Neder and colleagues' painstaking demonstration of the interference of electron waves from independent sources⁴ beautifully shows the fundamental mechanism underlying the anti-bunching phenomenon.

Quantum interference experiments in electrical conductors are typically performed³ by splitting an electron beam from one source into two parts that propagate along different paths and merge again at a 'drain' (Fig. 1a). The phase difference between the two waves at the drain depends, through the so-called Aharonov–Bohm effect, on the magnetic flux between the two paths, which in turn is determined by the magnetic field in the area the two paths enclose. By tuning the magnetic flux, one can thus adjust the relative phases of the waves, and dictate whether the electron wave interferes constructively (if the peaks of the waves from each path arrive at the drain at around the same time) or destructively (if a peak and a trough arrive simultaneously). The electrical current at the drain accordingly oscillates as a function of the magnetic flux.

Neder *et al.*⁴ have performed a similar experiment, but with two electron sources and drains (Fig. 1b). Their cleverly engineered interferometer, following a proposal by Samuelsson *et al.*⁹, splits the source electron beams such that every emitted electron can reach both drain contacts, but the two parts of any one source wave cannot interfere with each other. Ordinary 'one-particle' interference is thus ruled out: at the drain contact, interference can take place only between waves originating from different sources.

As these sources are independent, the two waves should be emitted with random and uncorrelated phases. All effects of wave interference on the mean current in each of the

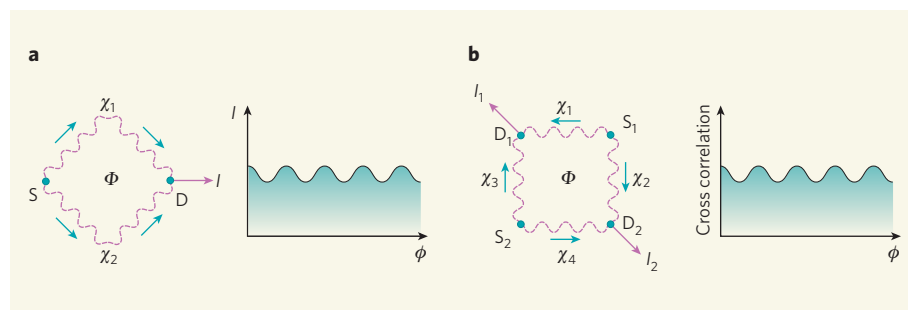


Figure 1 | One- and two-particle interferometers. **a**, In a single-electron interferometer, electrons enter from source S and choose between two paths to the drain contact D. The electron wave acquires different phases, χ_1 and χ_2 , as it propagates along the two paths. In the presence of a magnetic flux, Φ , between the electron paths, the phase difference $\chi_1 - \chi_2$ depends on Φ . The electrical current, I , into D oscillates as a function of Φ . **b**, In the two-electron interferometer demonstrated by Neder *et al.*⁴, electrons enter from two sources, S_1 and S_2 . Every electron is able to reach two drain contacts D_1 and D_2 , through which mean currents $\langle I_1 \rangle$ and $\langle I_2 \rangle$ flow. A magnetic flux, Φ , between the electron paths again influences the phases χ_1, χ_2, χ_3 and χ_4 acquired by the propagating electron waves. Interference takes place only between waves originating from different source contacts; this causes oscillations with Φ of the cross-correlations between the currents in the two drains, defined as $\langle I_1 I_2 \rangle - \langle I_1 \rangle \langle I_2 \rangle$. (For each electron to be able to reach both drains, the quantum mechanics of electron scattering requires