and colleagues' determination of the equation of state for a unitary Fermi gas represents an outstanding example of quantum simulation, providing valuable qualitative and quantitative information on a regime for which a comprehensive theoretical description is inevitably difficult. In the long run, their technique might be generalized to all other cold atomic systems and become a useful tool with which to probe thermodynamic properties and thus search for exotic quantum states of matter. ■

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REGENERATIVE MEDICINE

Cell reprogramming gets direct

Cory R. Nicholas and Arnold R. Kriegstein

In a feat of biological wizardry, one type of differentiated cell has been directly converted into another, completely distinct type. Notably, the approach does not require a stem-cell intermediate stage.

Barriers to transdifferentiation — the direct conversion or reprogramming of one cell type into another — are falling fast. On page 1035 of this issue, Vierbuchen *et al.*[1] maintain the pace of this research by describing a potential innovation for generating disease-specific and patient-specific tissues of the central nervous system (CNS) that does not rely on stem cells. The route to possible regenerative-medicine-based treatment of CNS disorders such as epilepsy, stroke and Parkinson's disease may have taken another unexpected turn.

In 2006, the ability to reprogram fibroblasts, a type of cell found in connective tissue throughout the body, to embryonic-like stem cells (called induced pluripotent stem, iPS, cells)[2] was a breakthrough: it cleared the way to create disease- and patient-specific stem cells and sidestepped the thorny ethical issues associated with embryonic stem (ES) cells from human embryos. Disease-specific iPS cells, derived from patients with specific genetic disorders, such as some cases of amyotrophic lateral sclerosis (Lou Gehrig's disease), are already being used to study disease mechanisms and to search for new drug targets. Patient-specific iPS cells hold the promise of replacement-cell therapy without the risk of immune rejection. But such are the developments in cell transdifferentiation[1,3] that one might ask if stem cells will be dispensable in the quest for regenerative medicine.

It was once thought that cells are irreversibly instructed to become specific cell types in the body. We now know that this is not the case. Reprogramming of cell fates began with work in the 1960s that harnessed the ability of the oocyte (egg) to instruct differentiated adult cell nuclei to revert to an undifferentiated state. This process, called somatic-cell nuclear transfer (SCNT)[4], can result in an embryo and ES cells with the genetic make-up of the adult cell. Similarly, fusing ES cells with adult cells can convert the adult cell nucleus to an undifferentiated state[5] (Fig. 1). But the clinical relevance has remained doubtful: human SCNT has not yet succeeded, and cell fusion results in tetraploidy, a clinically unacceptable duplication of nuclear material.

The 2006 paper[2] boosted the reprogramming field with the discovery that adult fibroblasts can be induced to undergo a dramatic cell-fate reversal to an undifferentiated iPS cell state through the transient expression of four master-regulatory genes that encode transcription factors. The iPS cell approach has unquestionable clinical relevance. But adult cells must first be completely de-differentiated to an ES-cell-like state, and then subsequently re-differentiated to an adult cell type of interest — a time-consuming and inefficient detour (Fig. 1).

This detour raised the question of whether cell reprogramming could be optimized by directly inducing other adult cell fates without complete de-differentiation. Transdifferentiation of mammalian cells took a knock when reports of lineage reprogramming turned out to represent cell fusion[6]. But other studies suggested that conversion of one cell type to another could be achieved by activation of a few core factors[7]. An especially notable advance was the 2008 discovery[3] that transient activation of three transcription factors induced the direct reprogramming of pancreatic exocrine cells into insulin-producing endocrine cells with robust (20%) efficiency. In this and most other studies, however, reprogramming occurred only between closely related cell lineages.

This is where Vierbuchen and colleagues[1] come in. Beginning with a set of 19 candidate genes that encode transcription factors involved in neuronal development or function, they eventually found that a combination of only three factors was sufficient to convert fibroblasts into neurons (Fig. 1). The fibroblasts were derived from mouse embryos and newborn or adult tail-tips of 'reporter' mice engineered to express a green fluorescent marker when the gene for the protein tau was turned on. Because

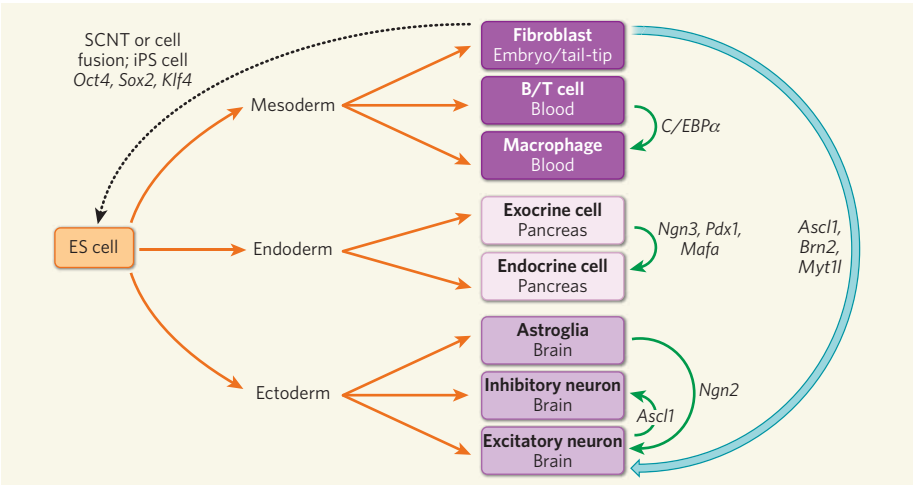

Figure 1 | Indirect and direct routes to cell-lineage reprogramming. The indirect routes involve reprogramming of a variety of adult cell types from different lineages to produce a de-differentiated embryonic stem (ES) cell state. Indirect routes (dotted arrow) include somatic-cell nuclear transfer (SCNT) or cell fusion, or creation of induced pluripotent stem (iPS) cells by the introduction of genes such as *Oct4*. But the de-differentiated cells must then be re-differentiated to adult cell types along the respective mesodermal, endodermal or ectodermal lineages. Vierbuchen *et al.*[1] demonstrate that a direct route can be taken (blue arrow): by inducing lineage-specific transcription factors encoded by genes including *Ascl1*, *Brn2* and *Myt1l*, they show that fibroblasts can be directly converted into distantly related cortical excitatory neurons. This is an advance over the intra-lineage conversion achieved between cells of the blood, pancreas or brain by induction of the other genes noted. Intra-lineage conversion studies not shown include fibroblast to macrophage and fibroblast to muscle cell by *PU.1* and *MyoD*, respectively.

the *Tau* gene is specifically expressed in neurons, cells that had converted into neurons could be easily identified. Vierbuchen *et al.* observed that, when they introduced all 19 genes together, some of the fibroblasts turned green. These presumptive neurons were called induced neuronal (iN) cells.

Fewer genes were then tested, and eventually a combination of only five of them — *Brn2*, *Myt1l*, *Zic1*, *Olig2* and *Ascl1* — was shown to be enough to convert fibroblasts to neurons in 12 days of culture. These iN cells expressed a variety of neuronal markers and were capable of firing action potentials, a basic function of neurons. Furthermore, when cultured with mouse neural cells, the iN cells received both excitatory and inhibitory synaptic connections from the mouse neurons, and were able to form functional synapses with each other.

Vierbuchen *et al.*[1] found that they could further reduce the pool of transforming genes to *Ascl1*, *Brn2* and either *Myt1l* or *Zic1*, increasing the efficiency of conversion by two- to threefold, up to around 20%. *Ascl1* alone was able to produce cells with immature neuronal features, but co-infection with *Brn2* and *Myt1l* was required to produce cells with more mature neuronal features. Surprisingly, most of the iN cells resemble excitatory cortical neurons of the forebrain — they express a protein called TBR1, and they mostly form excitatory synapses.

Why this should be so is a mystery, especially given the role of *Ascl1* in the developing brain. *Ascl1* encodes a transcription factor that is expressed by progenitor cells in the inhibitory neuron lineage[8] that does not express TBR1. Furthermore, forced expression of *Ascl1* in excitatory cortical neuron progenitor cells is sufficient to induce them to express inhibitory neuronal cell markers[9]. It is unclear how to reconcile this observation with the role of *Ascl1* in producing excitatory iN neurons. Interestingly, a previous study showed that forced expression of *Neurog2* (*Ngn2*), a gene encoding a transcription factor required for the development of excitatory neurons, can induce TBR1 expression and excitatory neuron conversion from astroglia[10].

Multipotent precursor cells of neural crest ectodermal origin have been isolated from rodent and human skin[11]; they have yielded neural cells, although most of them seemed to be peripheral glia or non-functional neurons. Vierbuchen and colleagues' approach, by contrast, generated functional excitatory neurons of the CNS. If their approach could be modified to produce large numbers of neurons, including other types, such as inhibitory neurons that produce the neurotransmitter γ-aminobutyric acid (GABA) or dopamine-producing neurons, it could alter strategies for regenerative medicine.

However, there are obstacles to be overcome. Importantly, it must be shown that iN reprogramming has been established after silencing the expression of the three exogenous transcription factors to confirm that an intrinsic and stable conversion of cell fate has occurred. This would also pave the way for safe, transient and non-viral reprogramming methods similar to those used in iPS cell production[12]. Moreover, it remains to be seen whether adult human fibroblasts from a skin biopsy, or alternative accessible cell types such as blood cells, could be efficiently converted into functional neurons. Only mouse fibroblasts were used by Vierbuchen *et al.*, and the authors did not determine the functionality of the iN cells derived from adult mouse fibroblasts.

In addition, transplantation experiments will be necessary to see whether iN cells can integrate into the brain and ameliorate disease in animal models. A way of expanding cell numbers is also required. As many as millions of cells might be needed for therapeutic applications in humans; unlike iPS cells, there is no current step for expanding iN cell number. This same limitation, by contrast, may give iN cells an advantage over iPS cells, because they are unlikely to form tumours in the way that pluripotent stem cells can.

Nonetheless, we have an exciting prospect. If iN conversion is possible with human cells, it could be quickly applied to the creation of disease-specific neurons for disease modelling and drug discovery, and to understanding the genetic and epigenetic mechanisms that determine cell fate. The question is no longer whether cell fates can be substantially manipulated without reversion to an undifferentiated pluripotent state. Rather, it is how many different cell types can now be generated by activating distinct combinations of lineage-specific factors. ■

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CLIMATE CHANGE

Tropical cyclones in the mix

Ryan L. Sriver

What was responsible for the unusual climatic conditions that prevailed during the early Pliocene, 5 million to 3 million years ago? Modelling studies point to intense tropical-cyclone activity as a possible answer.

During the early Pliocene, many factors that affect climate were similar to those of today, including the positions of the continents, the intensity of sunlight and the atmospheric concentrations of carbon dioxide[1]. But at this time, 5 million to 3 million years ago, the global mean temperature was about 4 °C warmer; and surface conditions in the tropical oceans resembled a permanent El Niño, marked by anomalously warm temperatures in the eastern tropical Pacific. Currently, El Niño events are intermittent, occurring roughly every 3–8 years, and can alter temperature and precipitation patterns worldwide.

On page 1066 of this issue, Fedorov *et al.*[2] propose that increased tropical-cyclone activity was a key contributor to the climate of the early Pliocene, part of a positive-feedback mechanism that maintained warmth with permanent El Niño-like conditions. These results may provide clues to understanding not only the climate of the early Pliocene, but also the nature of future climate change in a greenhouse world.

Much attention has been focused on understanding how the frequency and intensity of tropical cyclones might alter in response to changes in Earth's climate. However, it now seems that these events do not just passively respond to climate change. Rather, there is mounting evidence that tropical cyclones have an active role in the dynamics of the climate system, primarily as a source of vertical mixing in the ocean[3–6]. This mixing contributes to maintaining the large-scale ocean circulation[7] that transports heat around the globe. Thus, tropical cyclones may be closely tied to global temperature patterns through feedbacks associated with vertical ocean mixing and transport. These feedbacks may help in understanding past climate paradoxes in which conditions were demonstrably different from those of today. But such conditions are difficult to simulate in the current generation of climate models, which do not typically include feedbacks from tropical cyclones.

Fedorov *et al.*[2] show how tropical cyclones may have contributed to the climate of the early Pliocene. Using a multifaceted modelling approach, they demonstrate that the large-scale atmospheric conditions could have favoured widespread cyclone activity, with the global frequency of events being almost double that of the present day. This increased activity would have led to more of the vertical ocean mixing