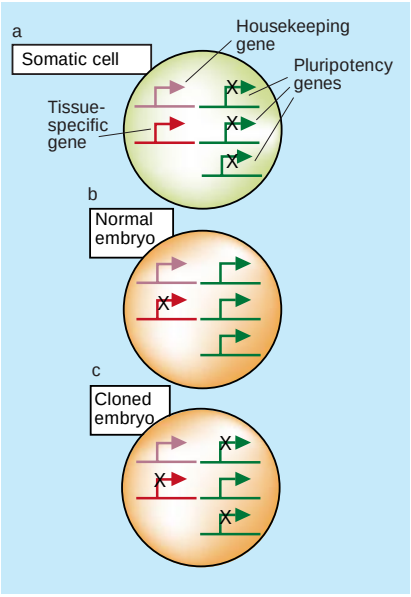

Figure 1 **Why is cloning inefficient? The figure shows gene expression in specialized (somatic) tissues, normal embryos and cloned embryos. Housekeeping genes are needed for activities common to all cells; tissue-specific genes are activated only in particular somatic cells; and 'pluripotency' genes are expressed in embryonic cells that generate a wide range of tissue types.** a, **A somatic cell (such as a cumulus cell), with an active housekeeping gene and tissue-specific gene and three inactive pluripotency genes.** b, **In normal embryos, the housekeeping and pluripotency genes are expressed; the tissue-specific gene is repressed.** c, **As shown in the new studies[1,2], after cloning with the nucleus from a cumulus cell, gene activity is not reset correctly in many cloned embryos; in this example, whereas the housekeeping gene is expressed and the tissue-specific gene is silenced, only one of the pluripotency genes is reactivated.**

stage at which the authors studied them.)

Bortvin *et al.*[2] also used embryonic stem (ES) cells, which express the 11 'pluripotency genes', for cloning, and found that expression continued in the cloned embryos. They argue that this might explain why ES-cell-derived clones are more likely to develop to term than cumulus-derived clones. What about genes that are normally expressed in somatic tissues and silent in early embryos? Bortvin *et al.* examined three such genes, and found that all were silenced in cloned embryos — perhaps implying that silencing is more efficient than reactivation. However, another study[5] suggests that cloned embryos do retain some memory of the differentiated cells from which they were derived, in that a tissue-specific gene remained active, so this issue probably needs further investigation.

Several studies[6–8] have now shown altered gene-expression profiles in cloned embryos, including amphibians. But these recent experiments[1,2] that look at pluripotency genes have taken our understanding further. They link gene-expression defects to defects in early development, and they provide good gene candidates with which to examine the precise mechanisms of reprogramming.

Why is reprogramming so difficult? The answer is probably that, once cells have differentiated into specific types, the silencing of unwanted gene expression is very tightly controlled, involving many reinforcing mechanisms. For instance, the modification of DNA with methyl groups (methylation) is commonly associated with gene silencing, as is the methylation of the histone proteins that bundle DNA into a compact form (chromatin) in the nucleus. These 'marking' mechanisms are likely to be connected in a way that makes the silent state very stable. Conversely, gene expression is often associated with histone acetylation.

It would be interesting to find out whether and how such marks can be reprogrammed, particularly on the genes studied by Boiani *et al.*[1] and Bortvin *et al.*[2]. The early embryo can certainly reset the chromatin modifications characteristic of the male and female gametes from which it was formed[9,10]. In terms of cloned embryos, so far only genome-wide chromatin reprogramming has been studied[10]. But it seems that, for the most part, the somatic patterns of histone methylation and acetylation are reset very inefficiently (although in a few embryos these marks look relatively normal, and are associated with a higher rate of successful development to a crucial stage, the blastocyst stage). So chromatin modifications might indeed provide a mechanistic explanation for the difficulties in reactivating silent genes, and silencing active ones. Efficient reprogramming might require enzymes that remove acetyl groups from histones and methyl groups from DNA or histones (although DNA and histone 'demethylases' — if they exist at all — are still elusive[11]).

Whatever the arguments for and against cloning, its study is already providing insight into the biology of cell differentiation, the extent to which cells can have many different fates, and the factors involved in reprogramming. With patience, this line of research should lead to more efficient and safer applications of reprogramming technologies in medicine. ■

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Condensed-matter physics

Thermopower to the people

Cronin B. Vining

The larger-than-expected thermally generated voltage seen in a layered-oxide material — which may prove useful in power generation or cooling — is now attributed to the spins of moving charges.

Thermocouples generate a voltage in a temperature gradient. This is known as 'thermopower', or the Seebeck effect, after its discoverer Thomas Johann Seebeck. These devices have found a range of applications, from cooling devices for seats in luxury automobiles to power supplies for spacecraft (including the Voyager missions; Fig. 1, overleaf). Metallic thermocouples generate relatively small voltages, but semiconductor thermocouples produce much larger voltages and can convert heat directly to electricity or generate cooling from an electrical input. Two different groups have reported semiconductor thermoelectric materials that are about twice as efficient as any previously known[1,2], achieved by carefully controlling the composition and structure of the materials on the atomic scale. But an entirely different approach to high thermopower uses magnetic cobalt oxides — layered materials that combine the thermopower of semiconductors with the electrical conductivity of metals. On page 425 of this issue, Wang *et al.*[3] account for their extraordinarily high thermopower.

These cobalt oxides ($Na_xCo_2O_4$) were first considered as thermoelectric materials by Terasaki *et al.*[4] and have a variety of unusual properties. They are ionically bonded (unlike the classic semiconductor thermoelectric materials, which are covalently bonded), and can be doped with varying numbers of sodium atoms to achieve the desired properties. At room temperature, their thermopower is as much as ten times larger than might be expected, much larger than is typical of metals.

At the same time, $Na_xCo_2O_4$ has some unusual magnetic properties. At low

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Figure 1 **Powerful heat. In 1822, the Estonian–German physicist Thomas Johann Seebeck (inset) discovered that if heat is applied across the junction of two wires, a current is generated. Seebeck called the effect 'thermomagnetism' (a term later replaced by the more accurate 'thermoelectricity'). It is the basis of thermocouples — devices used for cooling, and for power generation such as in the Voyager mission to Jupiter and Saturn, seen here at its launch in 1977.**

temperatures it is an antiferromagnet, which means that there are 'spins' in the material that take on a particular kind of order. Unlike most magnets, the spins in $Na_xCo_2O_4$ are not fixed to specific atoms within the lattice but instead are free to move about the crystal. When these spins move, they carry some energy with them — and by doing so, contribute to the thermopower of the material. This doesn't happen in an ordinary metal, or in an ordinary magnet, because there the spins don't move.

The moving spins — or, more technically, spin entropy — are thought to be behind the enhanced thermopower of cobalt oxides. If this is the case, the thermopower should be suppressed if a magnetic field is applied in the plane of the layered-oxide material, blocking the motion of the spins. Wang *et al.*[3] have shown, quite unambiguously, that this is indeed what happens (Fig. 4 on page 427): they offer a textbook-quality illustration of quantitative agreement between their experimental results and a remarkably simple (and classic) interpretation of the spin contribution to the thermopower, an agreement that holds over a wide range of temperatures and magnetic fields. There are already reports that $Na_xCo_2O_4$ has thermoelectric properties comparable to the best known thermoelectric materials[5,6] at temperatures near 1,000 K. Perhaps understanding the role that spin has to play in the thermopower of these oxides will enable further progress to be made. ■

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Alzheimer's disease

Mental plaque removal

Bart De Strooper and James Woodgett

Lithium, already used to treat psychiatric disorders, has been found to reduce amyloid-peptide production in a mouse model of Alzheimer's disease. The implication is that lithium's target molecule helps to generate the peptides.

Studies of people with Alzheimer's disease have revealed several notable changes in the brain, including the build-up of protein deposits known as amyloid plaques outside nerve cells, and the accumulation of so-called neurofibrillary tangles inside the cells. Should treatments for this disease target the plaques or the tangles? On page 435 of this issue, Phiel and co-workers[1] propose the idea of tackling both with a single drug — one that inhibits the enzyme glycogen synthase kinase-3 (GSK-3).

This enzyme is an evolutionarily conserved serine/threonine kinase that, in response to cellular signalling events, modifies the functions of a variety of proteins by specifically adding phosphate groups to the amino acids serine or threonine[2]. It is one of the candidates for producing excessive phosphorylation of the tau protein — and 'hyperphosphorylated' tau is the main component of the neuronal tangles seen in patients with Alzheimer's disease. The precise effects of these tangles are unknown, and indeed it remains a matter of debate whether the phosphorylation of tau by GSK-3 *in vivo* harms[3] or protects[4] neurons. Nonetheless, the accumulation of tangles does correlate with progression of the disease.

So, too, does the build-up of amyloid plaques. One of the major components of these plaques is a small peptide known as amyloid-β (Aβ) peptide, which is produced from a longer protein — the amyloid precursor protein (APP) — that sits in neuronal membranes. APP is precisely snipped in two places to generate Aβ. The first cleavage is carried out by an enzyme called β-secretase, or by metalloprotease enzymes[5]. This cleavage generates a membrane-bound fragment of APP (the carboxy-terminal fragment), which is then severed by the γ-secretase complex. The Aβ peptide is thereby produced, and is shed from the neuronal surface (Fig. 1). The prevalent hypothesis is that Aβ peptides, congregating outside nerve cells in the brain, are the main trigger for the neuronal degeneration characteristic of Alzheimer's disease[6].

The past decade has seen strong investment in the development of drugs that tackle the deposition of amyloid plaques, using various approaches[7]. On the other side of the coin, the idea of using GSK-3 inhibitors to prevent the build-up of tangles has been around for some time (although validation of this strategy has been problematic, mainly because there are still no good animal models of tangle accumulation, but also because of the question marks over the importance of the *in vivo* phosphorylation of tau by GSK-3). Phiel *et al.*[1] now add an interesting twist to the issue. They find that lithium and kenpaullone — two structurally unrelated inhibitors of GSK-3 — interfere with the production of Aβ peptides in cell culture. This has been found previously for lithium and with different cells[8], but Phiel *et al.* go further