be excluded as possible companions.

Stars that are less luminous than main-sequence K-type stars are not massive enough to feed a white dwarf until it reaches the Chandrasekhar mass, so they, too, are not plausible candidates. What's more, because the impact of the supernova ejecta would not make a putative companion less luminous than it was before the explosion, a companion more luminous than a type-K star, if it existed, should have been seen in the images. Because no companion has been detected by their search, Schaefer and Pagnotta conclude that the progenitor of the system that left behind SNR 0509–67.5 was a pair of white dwarfs that merged and exploded as a supernova. This conclusion seems sound.

As a follow-up to the present study, the authors have examined other type Ia supernova remnants in the Large Magellanic Cloud (personal communication). They can exclude, as progenitors for the supernovae that produced these remnants, systems involving companion stars that are at an evolutionary stage beyond the main-sequence phase. An investigation[4] of the remnant of type Ia supernova SN 1572, which was first observed by Tycho Brahe in 1572, ruled out a red-giant companion. It also ruled out the very luminous objects that are predicted by hydrodynamic simulations[5] of the impact of the supernova ejecta on a companion star, and it pointed to a subgiant star as the companion. A later study[6] confirmed that identification, although the issue is still debated[7].

On the basis of comparisons between hydrodynamic simulations[8] and supernova data, red giants (and supergiants) are unlikely candidates for the companion stars of type Ia supernovae. The impact of the supernova ejecta on a red-giant companion — which could form a system (called symbiotic) in which the white dwarf accretes mass from the stellar wind of its companion, a recurrent nova (a repeatedly bursting star) or some other kind of system with the white dwarf — would produce a bump in the ultraviolet–optical light emission of the supernova at its very early stages. But, so far, this bump has never been seen in any type Ia supernova. Failure to detect this signature would suffice to rule out red-giant companions. However, in a number of type Ia supernovae, such as supernova SN 2006X (ref. 9), the detection of narrow spectral features, associated with sodium moving away from the supernova site at about only 50 kilometres per second, indicates that recurrent novae could be progenitors of at least some type Ia supernovae. This slow-moving sodium would probably come from matter ejected from the system before the white-dwarf explosion. But it could also come from other sources.

A recent theoretical study[10] has shown that the double-degenerate route should produce subluminous type Ia supernovae, which are dimmer than their typical counterparts. And the single-degenerate path has been successful[11] in explaining observations of standard type Ia supernovae. All in all, it seems that neither the single-degenerate nor the double-degenerate hypothesis for type Ia supernovae can currently be rejected. What seems clear from Schaefer and Pagnotta's results[3] is that the double-degenerate progenitor path does work in some cases — for SNR 0509–67.5 at least. ■

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ANGELMAN SYNDROME

Drugs to awaken a paternal gene

Mutations in the maternal copy of the *UBE3A* gene cause a neurodevelopmental disorder known as Angelman syndrome. Drugs that activate the normally silenced paternal copy of this gene may be of therapeutic value. SEE LETTER P.185

ARTHUR L. BEAUDET

Angelman syndrome is characterized by intellectual disability, epilepsy, impaired coordination and a characteristic joyful demeanour. Most commonly, it is caused by a deletion of five to six megabases of DNA from chromosome 15, although 'loss-of-function' mutations, or other abnormalities, in the maternal copy of the *UBE3A* gene also result in Angelman syndrome. In all cases, the outcome is very low expression levels of the enzyme UBE3A in neurons.

UBE3A is one of a handful of human genes that are subject to genomic imprinting, whereby either the maternal or the paternal copy of a gene is active, with the other copy remaining silent. In the case of *UBE3A*, only the maternal copy is active in neurons. So a child develops Angelman syndrome if they inherit mutant *UBE3A* from their mother. Indeed, in all cases of the disorder, the paternal copy of *UBE3A* is normal. On page 185 of this issue, Huang *et al.*[1] use drug screening to identify compounds that activate the paternal copy of *UBE3A* in a mouse model of Angelman syndrome*.

Inherited neurological disabilities in children are notoriously resistant to treatment. For some disorders that are characterized by overt abnormalities in the brain (for example, holoprosencephaly, lissencephaly and agenesis of the corpus callosum), the prospects for major interventions after birth remain gloomy. But there may be more room for optimism in conditions in which the brain architecture and function seem quite normal in early infancy — for example, as in fragile X syndrome, Rett syndrome, Angelman syndrome and Prader–Willi syndrome. In these cases, one could hope that the disorder might be cured by restoring normal gene expression.

Other than gene therapy, or perhaps gene correction or recovery of function of a mutant protein, a potential strategy for treating some disorders might be activating the alternative copy of a mutant gene or a gene related to it. For instance, activating the expression of fetal haemoglobin has been a long-term goal for the treatment of sickle-cell anaemia and β-thalassaemia. For many disorders involving genomic imprinting, activating the silenced copy of the gene on the related chromosome may correct the defects associated with the mutant gene.

Mice are useful models for testing whether postnatal restoration of gene expression can overcome the pathological features of a disease. A mouse model of Rett syndrome has, for instance, been tested[2] in this way, with favourable results. Angelman syndrome seems another viable candidate disorder for such treatment, because the brain anatomy in this condition seems normal at birth, and some electrophysiological abnormalities can be reversed in cultured cells[3].

*This article and the paper[1] under discussion were published online on 21 December 2011.

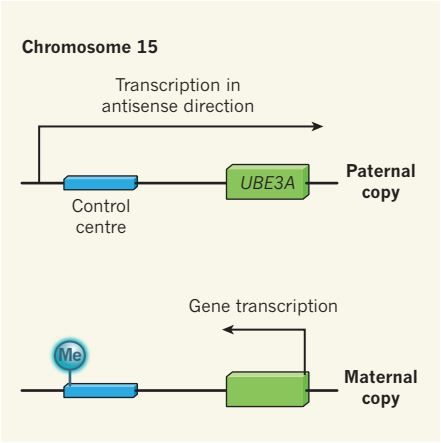

Figure 1 | Differential regulation of maternal and paternal *UBE3A*. Of the two copies of the *UBE3A* gene, only the maternal copy is expressed in neurons, with the paternal copy being silenced by genomic imprinting. Specifically, expression of paternal *UBE3A* is inhibited by transcription in the antisense direction of a long sequence that includes not only this gene but also the control centre that regulates its expression. In the equivalent maternal chromosome, the sequence encoding the control centre is methylated (Me) and so is not expressed. This inhibits transcription in the antisense direction and allows expression of *UBE3A*. Huang *et al.*[1] identify drugs that can activate expression of paternal *UBE3A*. Such drugs could be useful for treating Angelman syndrome, a disorder in which maternal *UBE3A* expression is absent or very low.

To search for compounds that could activate the silent paternal copy of *UBE3A*, Huang *et al.*[1] used a mouse model that had an altered copy of *UBE3A*, isolating cortical neurons from the brains of the animals shortly before birth. The mice were engineered so that their neurons expressed a fluorescently tagged version of UBE3A in response to drugs that activated the paternal copy of its gene. The screen focused on drugs already approved for human use — so that a future clinical trial might be undertaken more readily — and it identified 16 inhibitors of topoisomerase enzymes that were positive in the assay.

The authors focused on topotecan, the most active of the compounds. When they infused the drug into the lateral-ventricle region of the brains of living mice for two weeks, they found that the paternal copy of *UBE3A* was activated throughout the brain. Remarkably, a brief exposure to the drug also gave persistent *UBE3A* activation in spinal-cord neurons for at least 12 weeks after the termination of treatment.

Silencing of the paternal copy of *UBE3A* is probably mediated by an 'antisense' RNA transcript encompassing *UBE3A* on the paternal chromosome (but transcribed in the opposite direction to the gene sequence). Expression of this transcript is regulated by an imprinting control centre on the maternal chromosome (Fig. 1). The sequence functioning as the control centre, together with its promoter region, is methylated on the maternal chromosome, suppressing transcription in the antisense direction, which would silence the maternal *UBE3A*. The equivalent control centre on the paternal chromosome is unmethylated, allowing transcription of the antisense sequence and so silencing the paternal *UBE3A*. Huang *et al.* demonstrate that topotecan causes minimal change in methylation of the imprinting control centre on the paternal chromosome, but somehow still reduces expression of the antisense transcript for *UBE3A*, as well as for other paternally expressed genes that are part of the same transcript.

Reduced expression of paternally expressed genes is a potential drawback. If the 5–6-megabase deletion of chromosome 15 is inherited from the father, the child will develop Prader–Willi syndrome, because the deletion includes the genes involved in this disorder. Therefore, treatment with drugs such as topotecan could convert cells that have a molecular status characteristic of Angelman syndrome into cells with a Prader–Willi molecular status. Clearly, it would be preferable to reduce expression of the *UBE3A* antisense transcript while leaving expression of the other paternally expressed genes intact. But it is reasonable to hope that, after treatment with a topoisomerase inhibitor, cells would express a mixture of maternal and paternal transcripts — a situation that might greatly improve the symptoms of Angelman syndrome without causing notable symptoms of Prader–Willi syndrome. Of course, such treatment could also alter the expression of other genes across the genome, with unknown consequences. On all counts, a sequence-specific knock-down of the antisense transcript seems preferable.

An obvious question is how quickly a topoisomerase inhibitor could be prescribed for patients with Angelman syndrome. It is noteworthy that Huang and colleagues did not demonstrate any reversal of the symptoms in their mouse model, and so this is the next step before proceeding further in this direction.

Other issues concern risk–benefit assessments and regulatory processes. In the United States, topotecan has been injected into the cerebrospinal fluid of adults with neoplastic meningitis[4]. So at least in that country, a physician could theoretically inject topotecan into the cerebrospinal fluid of a patient with Angelman syndrome as a compassionate, off-label use of the drug. However, this seems quite risky in the absence of additional safety and dosage information in children. Presumably, the youngest infants would benefit most from the treatment, because normal brain development could then start as early as possible rather than being delayed by some years.

Systematic trials would require a regulatory process for investigating new drugs, and that would take at least a few months. Because the symptoms of Angelman syndrome are quite severe, and as there are no effective treatments

50 Years Ago

On December 19 Lord Mills announced in the House of Lords that the Government, after considering the question of decimal coinage … thought real advantage would follow from adopting a decimal currency. In view of the widespread use of accounting and other monetary machinery, the transitional cost would be substantial, but could be limited by choice of the size of the new units and careful timing of the change-over.
From *Nature* 13 January 1962

100 Years Ago

Mr. E. C. Snow, in his paper entitled "The Intensity of Natural Selection in Man" … has set himself to answer the following question: Has heavy infantile mortality any selective value or tendency to eliminate the more sickly and to spare the hardier children? Of the data available for the investigation of this problem, the most satisfactory are derived from the annual volumes of Prussian statistics … Thirty rural districts in Prussia were taken, and all the children in them born in the year 1881 were considered. It was ascertained for each district how many of these children died in the first two years of life and how many in the next eight … If the infantile mortality tends to weed out the weaker children, then in those districts in which the mortality among the children born in 1881 was highest in the years 1881 and 1882 it should tend to be lowest in the years 1883–90, since stronger children less likely to succumb to the ailments of childhood would have survived their first two years … We are of the opinion that, on the whole, the author is justified in saying: "Natural selection in the form of a selective death-rate is strongly operative in man in the earlier years of life."
From *Nature* 11 January 1912

for the disorder, the risk–benefit ratio may be viewed as quite favourable for giving topotecan to patients on an experimental basis. The infrastructure for a clinical trial is already in place, because clinical trials (albeit unsuccessful ones) using other drugs for treating Angelman syndrome have already been conducted[5]. Moreover, it is feasible to diagnose almost all cases of Angelman syndrome at birth or even *in utero*[6], so all that is needed is development of a successful treatment. If topoisomerase inhibitors can indeed reverse disabilities associated with Angelman syndrome, Huang and co-workers' data[1] may lead to clinical trials before too long. ■

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APPLIED PHYSICS

Nanowire electronics comes of age

Three-dimensional nanowire-like electronic devices are gaining ground over conventional planar technology. They may be the means to improve the performance of the electronic circuitry of the future.

TOMÁS PALACIOS

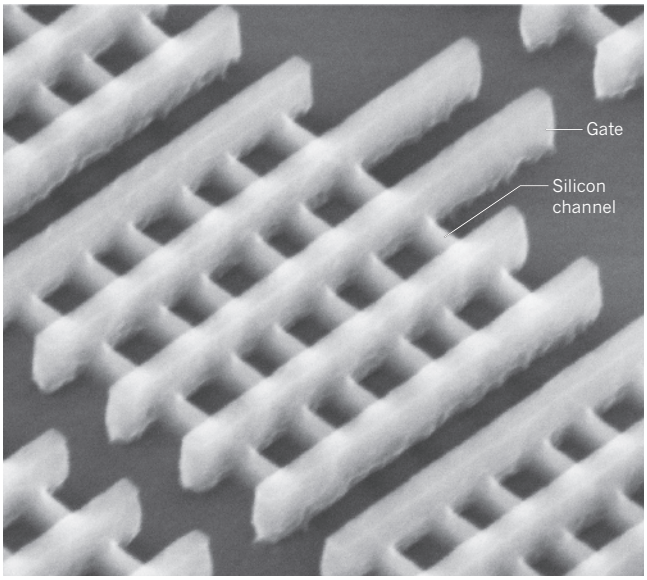
For many years, semiconductor nanowires have offered the prospect of enabling the next generation of electronic devices. But despite this promise, and some exciting preliminary developments[1,2], nanowire electronics has been hampered by technological limitations. It is extremely challenging to develop a nanowire-based fabrication technology for transistors — the building blocks of electronics — that is compatible with the requirements of future microprocessors. Writing in *Applied Physics Letters*, Dhara and co-workers[3] describe a simple technique that may change the way nanowire-based transistors are made.

Transistors are electric switches. In field-effect transistors, which are ubiquitous in modern electronic circuitry, the flow of current between two metal electrodes (source and drain) is controlled by a voltage applied to a third electrode called the gate. The current typically flows through a two-dimensional planar region called the channel. However, the performance of the device could be greatly improved by the use of a three-dimensional nanowire-based channel, in which the gate electrode is wrapped around the channel.

To make their nanowire wrap-gate transistors, Dhara *et al.*[3] first sandwiched a layer of indium arsenide nanowires between two layers of a polymer film that changes its structure when exposed to an electron beam. Next, the authors selectively removed some of the polymer film by exposing it to the electron beam of a lithography system. This procedure made the nanowires — which are horizontal and constitute the transistors' channels — free-standing and ready for subsequent fabrication of the drain and source electrodes as well as the wrap-gate.

The transistor fabrication technology developed by Dhara and colleagues is much simpler than that traditionally pursued for wrap-gate nanowire transistors, which typically involves several lithography steps as well as chemical-etching procedures. In addition, with the authors' technology, the devices have a tenfold larger electron mobility than that previously reported[4] for horizontal wrap-gate nanowire devices.

In spite of the beautiful simplicity of Dhara and co-workers' technique, their work does not solve the second challenge for nanowire electronics, which is how to integrate the billions of closely packed nanowire devices that will potentially be needed in future microprocessors. But the past year has witnessed several breakthroughs that overcome this problem. In combination with the authors' technology[3], these advances may take nanowire research in fresh directions and bring nanowire devices closer to the market.



INTEL

Figure 1 | Tri-gate transistors. This scanning electron micrograph shows an intermediate step in the fabrication of Intel's high-performance 22-nm transistors, each of which is made of multiple parallel, nanowire-like silicon channels, or fins. The electrical conductivity of the channels is controlled by a voltage applied to 22-nm-long gate electrodes, which are oriented perpendicularly to the channels. In this technology, only three sides (top, left and right) of the channels are in contact with the gate electrodes. For further improvements in performance, a technology such as the one developed by Dhara *et al.*[3], which consists of gate electrodes that wrap around the entire channel, is necessary.

One way to integrate billions of nanowire transistors on the same chip is to relax the nanowire's geometry: instead of free-standing nanowires, one side of the nanowire can be made to touch the surface of an underlying substrate. Last year, Intel announced[5] that its future microprocessors will incorporate transistors in which nanowire-like channels have three sides in contact with 22-nanometre-long gate electrodes, to improve the control of the transistors' current over that of two-dimensional planar devices. These tri-gate devices (Fig. 1) are effectively rectangular nanowires that have one side attached to the substrate. Although their geometry is slightly different from that of prototypical, free-standing nanowire devices, their operating principle is similar. This innovative geometry allows such nanowire-like devices to be made with a technology that is compatible with that used in the microelectronics industry.