effect of large impacting bodies releasing enough energy to blast parts of the atmosphere away. There is evidence for both processes in noble-gas isotopic ratios on Mars.

In the absence of CO_2, Chevrier *et al.* suggest[2] that other greenhouse gases promoted warmth. One candidate is methane; but methane is decomposed by ultraviolet sunlight, so a methane source comparable to Earth's biosphere would be needed to warm Mars above freezing. Another possibility is sulphur dioxide (SO_2), which, judging by the bulk chemistry of martian meteorites, could have been released from martian volcanoes in amounts similar to or exceeding their water emission. But SO_2 is soluble, and could have acted only as a 'lever' to raise temperatures to near freezing, making it easier for perturbations, such as asteroid or comet impacts, to cause temporary wet climates. Such impacts would have flash-heated the surface and released water, producing rain and erosion. Irrespective of any long-term greenhouse effect, the conclusion seems unavoidable that Mars was warmed transiently by many impacts early in its history[5].

A pivotal assumption made by Chevrier *et al.* is that the clays were formed in equilibrium with the atmosphere. But if the clays were formed in isolation from the atmosphere, beneath the surface, their thermodynamics might be of little relevance. Smectites are found in martian meteorites (Fig. 1) that formed in the subsurface when small amounts of saline waters infiltrated basalt[6]. Generally, suitable subsurface environments include long-lived hydrothermal systems that result from impacts on ice-rich ground; indeed, on Earth, smectites are characteristic of some hydrothermal systems in impact craters[7].

A further unresolved problem is that sulphates are found on Mars in places that range from young deposits around the planet's northern cap[8] to the ancient Meridiani outcrops[9], which are thought to be more than 3.7 billion years old. The stratigraphy of sulphate-rich deposits in an enormous chasm, Juventae Chasma, suggests that some of those deposits are similarly ancient[10]. The interpretation of Chevrier and colleagues' findings could therefore be more complicated than a geochemical history of an early age of clays succeeded by a sulphate era.

The history of recent Mars exploration shows that observations on the ground can completely overturn ideas inferred from orbit. Gusev Crater was chosen as a landing site for NASA's Spirit rover because it was interpreted from above as a lakebed. But what the rover found was a largely basaltic surface, rather than fluvial sediments. Meridiani Planum was selected for NASA's Opportunity rover because orbital data showed abundant haematite. But surface minerals there proved to be even richer in sedimentary sulphates.

Only a complete picture on the ground can provide confidence about the early environment of Mars, and whether it was ever conducive to life. Two rovers, NASA's Mars Science Laboratory rover and the European Space Agency's ExoMars, planned for launch in 2009 and 2013, respectively, might supply the answers — if targeted to the clays and sulphates of the planet. ■

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SYNTHETIC BIOLOGY

Designs for life

Philip Ball

The genome of one bacterium has been successfully replaced with that of a different bacterium, transforming one species into another. This development is a harbinger of whole-genome engineering for practical ends.

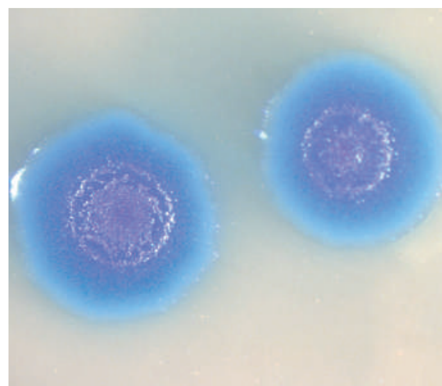
If your computer doesn't do the things you want, give it a new operating system. As they describe in *Science*[1], Carole Lartigue and colleagues at the J. Craig Venter Institute in Rockville, Maryland, have now demonstrated that the same idea will work for living cells*.

In an innovation that presages the dawn of organisms redesigned from scratch, the authors report the transplantation of an entire genome between species. They have moved the genome from one bacterium, *Mycoplasma mycoides*, to another, *Mycoplasma capricolum*, and have shown that the recipient cells can be 'booted up' with the new genome — in effect, a transplant that converts one species into another.

This is likely to be a curtain-raiser for the replacement of an organism's genome with a wholly synthetic one, made by DNA-synthesis technology. The team at the Venter Institute hopes to identify the 'minimal' *Mycoplasma* genome: the smallest subset of genes that will sustain a viable organism[2]. The group currently has a patent application for a minimal bacterial genome of 381 genes identified in *Mycoplasma genitalium*, the remainder of the organism's 485 protein-coding genes having been culled as non-essential.

This stripped-down genome would provide a 'chassis' on which organisms with new functions might be designed by combining it with genes from other organisms — for example, those encoding cellulase and hydrogenase enzymes, for making cells that respectively break down plant matter and generate hydrogen.

Mycoplasma genitalium is a candidate platform for this kind of designer-genome synthetic biology because of its exceptionally small genome[2]. But it has drawbacks, particularly a relatively slow growth rate and a requirement for complex growth media: it is a parasite of the primate genital tract, and is not naturally 'competent' on its own. Moreover, its genetic proof-reading mechanisms are sloppy, giving it a rapid rate of mutation and evolution. The goat pathogens *M. mycoides* and *M. capricolum* are somewhat faster-growing, dividing in less than two hours.



J. CRAIG VENTER INST.

Figure 1 | Genome swap. Colonies of the transformed bacteria (about 1 mm across).

Incorporation of foreign DNA into cells happens naturally, for example when viruses transfer DNA between bacteria. And in biotechnology, artificial plasmids (circular strands of DNA) a few kilobases big are routinely transferred into microorganisms using techniques such as electroporation to get them across cell walls. In these cases, the plasmids and host-cell chromosomes coexist and replicate independently. It has remained unclear to what extent transfected DNA can cause a genuine phenotypic change in the host cells — that is, a full transformation in a species' characteristics. Two years ago, Itaya *et al.*[3] transferred almost an entire genome of the photosynthetic bacterium *Synechocystis* PCC6803 into the bacterium *Bacillus subtilis*.

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But most of the added genes were silent and the cells remained phenotypically unaltered.

Genome transplantation in *Mycoplasma* is relatively easy because these organisms lack a bacterial cell wall, having only a lipid-bilayer membrane. Lartigue *et al.*[1] extracted the genome of *M. mycoides* by suspending the bacterial cells in agarose gel before breaking them open, then digesting the proteinaceous material with proteinase enzymes. This process leaves circular chromosomes, virtually devoid of protein and protected from shear stress by the agarose encasement. This genetic material was transferred to *M. capricolum* cells in the presence of polyethylene glycol, a compound known to cause fusion of eukaryotic cells (those with genomes contained in a separate organelle, the nucleus). Lartigue *et al.* speculate that some *M. capricolum* cells may have fused around the naked *M. mycoides* genomes.

The researchers did not need to remove the recipient's DNA before adding that of the donor; instead, they added an antibiotic-resistance gene to the *M. mycoides* donor genome. With two genomes already present, no replication was needed before the recipient cells could divide: one daughter cell had the DNA of *M. capricolum*, the other that of *M. mycoides*. But in the presence of the antibiotic, only the latter survived. Some *M. capricolum* colonies did develop in the transplanted cells after about ten days, perhaps because their genomes recombined with the antibiotic-resistant *M. mycoides*. But most of the cells, and all of those that formed in the first few days, seemed to be both genotypically and phenotypically *M. mycoides* (Fig. 1), as assessed by means of specific antibodies and proteomic analysis.

The main question raised by this achievement is how much difference a transplant will tolerate. That is, how much reprogramming is possible? The DNA sequences of *M. mycoides* and *M. capricolum* are only about 76% the same, and so it was by no means obvious that the molecular machinery of one would be able to operate on the genome of the other.

Yet synthetic biology seems likely to make possible many new cell functions, not by whole-genome transplants but by fusing existing ones. When John Glass, a member of the Venter Institute's team, presented the transplant results at a recent symposium on the merging of synthetic biology and nanotechnology[4], he also described the institute's work on genome fusion (further comments on matters arising from the symposium appeared in last week's issue of *Nature*[5]).

One target is to develop a species of anaerobic *Clostridium* bacterium that will digest plant cellulose into ethanol, thus generating a fuel from biomass. Cellulose is difficult to break down — which is why trees remain standing for so long — but it can be done by *Clostridium cellulolyticum*. However, this creates glucose. *Clostridium acetobutylicum*, meanwhile, makes butanol and other alcohols, but not from cellulose. So a combination of genes from both organisms might do the trick. For such applications, it remains to be seen whether custom-built vehicles or hybrids will win the race. ■

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MOLECULAR MEDICINE

Entry granted

Edouard M. Cantin and John J. Rossi

The inability to efficiently deliver small interfering RNAs to target organs hinders their therapeutic application. So a demonstration of siRNA delivery to a notoriously difficult organ — the brain — is very exciting indeed.

The process of RNA interference (RNAi) uses small RNA triggers to decrease gene expression in a sequence-specific manner. In most applications, a small interfering RNA (siRNA) sequence — 21–23 nucleotides long — silences a target messenger RNA with a complementary sequence by either directing site-specific cleavage or inhibiting its translation into a protein[1,2]. This technique is a powerful and versatile tool for inhibiting gene expression, and has elicited a great deal of interest in harnessing it to treat human disease. Although during the past two years several significant findings have enabled systemic delivery of siRNAs to various tissues and organs[1], one tissue that has been difficult to target from the periphery is the brain; this is because traversing the blood–brain barrier poses a great challenge. On page 39 of this issue, Kumar *et al.*[3] describe a method to meet this challenge.

The junctions between the endothelial cells that line the brain capillaries prevent the passage of most molecules[4]. Chemically modified liposomes conjugated to monoclonal antibodies raised against epidermal growth factor can penetrate the mouse brain, as can neuropeptides, but these approaches do not directly target neurons[4].

Similarly, viral vectors can be designed to express short hairpin-structured RNA sequences, which, once expressed, are processed to siRNAs. Such vectors have been used to introduce siRNAs directly into the brain tissue using the neurosurgical method of stereotaxis; thus, it has been shown that a decrease in the transcription of certain genes alleviates symptoms of neuronal diseases[5,6]. But direct injection within the cranium (the protective upper portion of the skull) is invasive, and systemic delivery of brain-targeting agents is a highly desirable alternative.

Kumar *et al.*[3] exploited the fact that neurotropic viruses — such as the rabies virus — that preferentially infect the nervous system can penetrate the brain. The rabies virus achieves this through glycoproteins on its lipid envelope. To test whether rabies viral glycoprotein (RVG) could promote transport of a non-rabies viral vector to the brain, the authors used the technique of pseudotyping, whereby an envelope glycoprotein from a specific virus is used to confer tropism for specific cell types to a viral

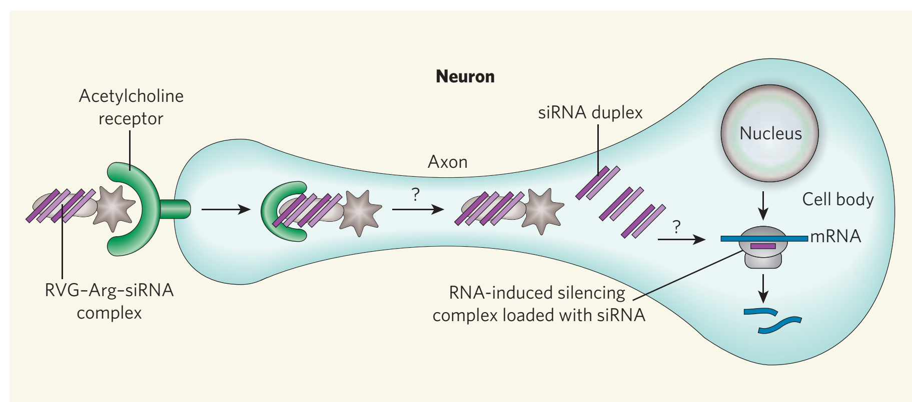

Figure 1 | Binding and uptake of peptide-conjugated siRNA by neuronal cells[3]. After binding to the acetylcholine receptor, the RVG–Arg–siRNA complex is internalized. It is then transported along the axonal process to the cell body, where siRNAs are released and incorporated into the RNA-induced silencing complex. Targeted cleavage of an mRNA sequence follows. The mechanisms of siRNA complex release from the acetylcholine receptor and its transport along the axon are not fully understood.

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