to bind and activate the APC. So, Cdc14 can be viewed as an 'anti-Cdk1' phosphatase, directly reversing Cdk1's phosphorylation of key targets. Once Sic1 has accumulated and the APC is activated by Cdh1, cells can inactivate their mitotic CDKs and exit mitosis.

Amon and colleagues[1] and Shou *et al.*[2] have now tackled the problem of how Cdc14 is controlled. They began by investigating where Cdc14 is found during the cell cycle, and, using immunolocalization, made the remarkable discovery that Cdc14 is dramatically relocalized within the nucleus. During the G1 and S phases, Cdc14 is found in the nucleolus — a sub-compartment within the nucleus. Then, just as the cells enter anaphase, Cdc14 spreads to the entire nucleus and also, to some extent, the cytoplasm. This is the first report of regulated localization to the nucleolus as a regulatory mechanism, and the authors suggest that Cdc14 is activated by release from nucleolar sequestration, allowing it to associate with its substrates.

This is a beautiful hypothesis. But the great tragedy of science, as noted by Thomas Huxley, is the slaying of a beautiful hypothesis by an ugly fact. So, in this case, are the supporting facts as attractive as the model? To find out, the two groups looked at what might anchor Cdc14 to the nucleolus. Using a protein-interaction screen they found that Cdc14 binds to a protein called Cfi1 (also known as Net1), the localization of which precisely overlaps with the pattern of Cdc14 in the nucleolus. Unlike Cdc14, however, Cfi1 remains in the nucleolus during anaphase. Cfi1 shares a stretch of sequence with a known phosphatase regulator called Reg1, indicating that it might, perhaps, regulate Cdc14 (ref. 1).

Genetic results indicate that, in fact, Cfi1 inhibits Cdc14, possibly by directly affecting its phosphatase activity. The authors first reasoned that, if Cfi1 is the anchor, when it is removed from cells Cdc14 should be released. And this is just what they found — in *cfi1* deletion mutants, Cdc14 was no longer localized to the nucleolus[1,2]. Amon and colleagues further found that the *cfi1* mutants behaved like cells overproducing Cdc14. Such cells have problems entering S-phase because, in order for them to do so, Sic1 must be phosphorylated and destroyed. But the overproduced Cdc14 partially reverses this phosphorylation, delaying destruction of Sic1. Overproduction of Cfi1, by contrast, is lethal. Cells arrest late in mitosis and have elongated spindles — similar to *cdc14* mutants. The toxic effects of Cdc14 overproduction can be overcome by simultaneously overproducing Cfi1 (ref. 1).

Amon and colleagues also found that when Cfi1 is overproduced in normal cells, Cdc14 is not sequestered in the nucleolus; instead, it is found with Cfi1 throughout the cell. This indicates that, when levels of Cfi1 are high, its binding sites in the nucleolus become saturated and it can inhibit the dispersed Cdc14 as well. Shou *et al.*[2] found that recombinant Cfi1 could reduce Cdc14's phosphatase activity *in vitro*. So, Cfi1 may be a multifunctional inhibitor, working both by sequestering Cdc14 in the nucleolus and by interfering with it biochemically.

But why do cells use nucleolar sequestration — as opposed to the commonly observed cytoplasmic localization — to regulate Cdc14? Perhaps Cdc14 has substrates in both the cytoplasm and the nucleus, leaving the nucleolus as the only place where it does not normally function. Whatever the reason, nucleolar sequestration is likely to be a general regulatory mechanism. In fact, reporting in *Nature Cell Biology*, Weber *et al.*[12] show that the tumour-suppressor protein $p19^{Arf}$ activates p53 by sequestering a p53 inhibitor, Mdm2, in the nucleolus. Arf mutants that bind Mdm2 but do not localize to the nucleolus are biologically inactive. Although there is no evidence that this is regulated sequestration, it is clearly a similar mechanism. So, the nucleolus, which has always been viewed as a factory for the production of ribosomes, is now taking on the appearance of a resort — a nice, quiet place to visit and get away from it all. □

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April fool The News and Views article "Millennium bug" by R. S. Siew – published on 1 April (*Nature* **398,** 376; 1999) – was, we can confirm, an April fool. Most of the references, such as the citation of Sisir, C. and Lainnellim, K. *Silico* (in press) on the crucial Y2K mutation, are figments of the author's backward thinking. G. K. Chesterton, cited as having published a paper in *Protista* in 1997, in fact died in 1936, and as far as we are aware did no research in this field. □

Daedalus

Theological chemistry

The most convincing evidence for religious belief is subjective. Many people claim to sense the presence of God, to be able to communicate with Him in prayer, or receive comfort from Him in trouble. But to others, praying simply feels like talking into a dead telephone. Even devout believers sometimes suffer 'the dark night of the soul' when the divine presence cannot be sensed.

One theory is that the religious sense is chemical. Many primitive religions use psychotropic drugs and hallucinogens in their rituals. Nitrous oxide, ether and LSD have also been claimed to open the user's mind to higher reality. Daedalus disagrees. Such intoxicants, he reckons, merely stir up noise and nonsense inside the brain. He wants to get past the 'earthquake, wind and fire' to reach the 'still, small voice' of the authentic spiritual experience.

So he plans to conduct brain scans on monks and nuns at prayer, to identify the active region of the brain. Successful prayers and 'dark night' failures should show different patterns. With very good luck, an NMR scan might even be able to identify the molecule metabolized in a successful religious experience.

Another way of identifying it depends on Daedalus's theory of last week, that the spirit world shares the 3 K temperature of the cosmic microwave background, and that spiritually important molecules radiate spontaneously into that world. The black-body peak at 3 K is at 310 GHz, a frequency band in which molecular rotational and librational resonances occur. Isotopically substituted molecules with shifted resonances should therefore be spiritually less effective. By synthesizing candidate substances enriched with ^{2}H, ^{13}C or ^{15}N, and injecting them into the test monks and nuns, the crucial religious metabolite could be identified. People in whom it is richly present will be believers, those without it will be hard-boiled materialists. A simple tablet or injection will then enable the latter to feel religious experience for themselves.

Daedalus's 'Theological Prozac' will at last open the private, subjective claims of religion and mysticism to scientific study. It will make spiritual experiences freely accessible and reproducible, allowing them to be classified and their implications understood. With luck, the resulting illumination will bestow spiritual comfort on the users, unaccompanied by the stern orthodox convictions attached to it by the more doctrinal aspects of religion.

David Jones