two regulatory elements that are known to affect gene silencing: a 'promoter', which lies before the start of the protein-coding portion of the gene, and a large intron (a gene segment that is transcribed into RNA, but is deleted from the transcript before the final RNA is translated into protein). To study the expression of *var* genes, Voss *et al.*[1] used an artificial marker gene as a proxy for the *var* gene. The expression of this gene, called *dhfr* (for dihydrofolate reductase), was put under the control of a *var* gene promoter (*upsC*). Parasites in which the *dhfr* marker gene was activated were selected by culturing the cells with an antifolate drug. Parasites in which the gene was active were resistant to the drug, whereas parasites with a silent *dhfr* gene died.

Although the artificial gene was present on a plasmid — a small extra circle of DNA — it behaved like the parasite's own (endogenous) *var* genes, occasionally switching on and off spontaneously. The most interesting result, however, was that the activation of the *upsC–dhfr* gene-construct silenced the previously active endogenous *var* genes. The artificial gene seemed to become an authentic member of the *var* gene family, able to compete with the other members to be the actively transcribed gene. Thus, the active *upsC* promoter seems to be sufficient to silence expression by competing *var* genes. Dzikowski *et al.*[3] have obtained similar results with different artificial *var* gene-constructs.

There is still controversy about the role of the enigmatic *var* gene intron in silencing. This intron is present in all *var* genes and contains a promoter yielding large amounts of RNA transcripts that are not translated into protein. Previous reports concluded that the intron is essential for allelic exclusion to occur[4–6]. But Voss *et al.*[1] found that the absence of the intron did not affect either the ability to switch genes or the ability to keep the inactivated gene completely silent. The intron only decreased the rate at which the silent gene was activated and also seemed to limit the activity of neighbouring genes (a 'boundary effect'). However, Voss and colleagues' artificial gene-construct[1] also contains a second promoter; this drives the expression of a blasticidin resistance gene that was used to introduce the *upsC–dhfr* construct into the *Plasmodium* cells. It is therefore possible that this second promoter can replace the intron promoter to allow complete silencing of the *upsC* promoter. That would explain why Voss *et al.*[1] could dispense with the intron, whereas other groups[3–6] could not.

Voss *et al.* argue that regulation of *var* gene expression is relatively simple (Fig. 2). In their model, the *upsC* promoter recruits proteins that keep the *var* gene silent[7]. The gene can be activated by moving to a unique location in the nucleus[8]. This 'expression spot' can accommodate only a single active gene promoter, explaining how all the other *var* gene promoters are kept silent.

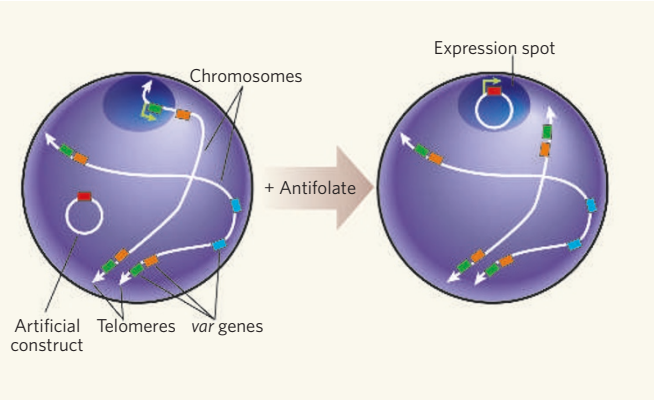

Figure 2 | A model for the regulation of *var* genes in the *Plasmodium* nucleus. Voss *et al.*[1] propose that a *var* gene (here represented by the artificial gene in a plasmid) is activated by moving to an 'expression spot' where it displaces the previously active endogenous *var* gene. Both active and inactive *var* genes are found at the nuclear periphery[8]. (Modified from ref. 1.)

Voss and colleagues' model for regulating *var* gene expression is similar to that proposed for the control of another parasite gene family, the *vsg* genes that encode the variant surface glycoproteins of African trypanosomes, the parasites responsible for sleeping sickness. Trypanosome *vsg* genes are expressed from about 20 expression sites at the ends of chromosomes (telomeres), only one of which is fully active at a time. When the trypanosome is forced to express two sites (by selection for drug resistance markers), the stressed organism can survive only by rapidly switching between the sites. The two switching expression sites were found to be very close together in the nucleus[9], indicating the existence of a unique activation area, subsequently characterized[10] as the 'expression site body'.

Although this simple model can explain allelic exclusion in the parasite gene families studied, the control of another well-studied gene family, the odorant receptor genes in mammals, involves an additional step[11]. The receptor gene family is riddled with 'pseudogenes', and the cell is able to select against expression of these faulty genes. This must mean that there is a feedback in the system: if the activated gene cannot produce a functional gene product, it is switched off and another gene is activated until a functional one is found. Such a feedback is clearly absent in *Plasmodium*, as the artificial gene introduced by Voss *et al.*[1] in the *var* gene family does not encode a functional PfEMP1.

Even for parasites, the expression-site-body model leaves many questions unanswered, as has been stated before[12]. What is the nature of the unique site? How do *var* gene promoters get in there, and how does another family member displace them? How are promoters activated in the expression site body? These questions can now be tackled, because the *var* gene family of *Plasmodium* is experimentally more tractable than trypanosomes' *vsg* gene expression sites. Voss and colleagues' experiments[1] used a single marked *var* gene promoter present in multiple copies in the cell. As procedures to introduce genes into *Plasmodium* improve[13], more precise experiments can be done using two *var* genes, each marked with a different selectable marker, and present in a single copy in the transfected cell. This should make it possible to determine how allelic exclusion works at the molecular level. ■

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CORRECTIONS

The News & Views article "Extinctions: A message from the frogs" by Andrew R. Blaustein and Andy Dobson (*Nature* **439,** 143–144; 2006) stated that the mountain pine beetle *Dendroctonus ponderosae* transmits pine blister rust (*Cronartium ribicola*). In fact, the beetles are not a vector for the rust, but they preferentially attack trees already infected with the fungus.

In "Materials science: Colloids get complex" by Alfons van Blaaderen (*Nature* **439,** 545–546; 2006), parts **d** and **e** of Figure 1 were reversed. The caption and attribution of **d** belong to image **e** in the figure, and vice versa.

In "Physiology: Plants on a different scale" by Lars O. Hedin (*Nature* **439,** 399–400; 2006), reference 15 contained several errors. The correct reference is Yoda, K., Kira, T., Ogawa, H. & Hozumi, K. *J. Biol. Osaka City Univ.* **14,** 107–129 (1963).