need to be open to the possibility that methyl groups could be just about anywhere." To follow up on this hypothesis, the Church team is working on high-throughput methods for allele-specific methylation.

The Zhang and Gao groups, in contrast, focused mostly on CpG islands, partly because those are the regions with higher methylation, and partly because they are clearly defined and thus present a stable set of targets. They compared the methylation patterns in all CpG islands on two chromosomes in iPSCs and human embryonic stem cells (hESCs). To their surprise, the researchers noted that only 10% of the regions show a difference in methylation between the cell lines. For Zhang, this underscores the advantages of a targeted strategy over genome-wide sequencing. "Full methylome sequencing is not cost-effective," he concludes, "because 90% of your data will not give you too much information."

As Church's and Li's teams, Zhang and his colleagues saw decreased promoter methylation and increased gene body methylation in highly expressed genes. In addition, they observed that the methylation patterns of iPSCs and hESCs differ. Zhang describes their findings: "iPSCs tend to be more methylated… and this could be causing an extra effort to do the re-differentiation." To assess this difference in more detail, Zhang plans to look at the methylation state in 'clean' iPSCs, that is, cells free of inducing factors, and their intermediate and fully differentiated descendents.

With these techniques, the role of the fifth base is becoming a lot more prominent.

Nicole Rusk

RESEARCH PAPERS

Ball, M.P. *et al.* Targeted and genome-scale strategies reveal gene-body methylation signatures in human cells. *Nat. Biotechnol.* **27**, 361–368 (2009).

Deng, J. *et al.* Targeted bisulfite sequencing reveals changes in DNA methylation associated with nuclear reprogramming. *Nat. Biotechnol.* **27**, 353–360 (2009)

sequences, like DNase I–hypersensitive sites and putative enhancers. Coding regions, in contrast, were significantly underrepresented. "When we first saw this, we were upset," says Margulies, "but then we realized that it underscores that the algorithm is picking up things that are not encoded in the primary sequence, since we know that in coding regions the primary sequence is important."

Might the effect that a sequence change has on structural profiles be a way to identify functional changes in noncoding regions of the genome? Possibly, says Margulies, although the experiments are still in progress. Notably, when the researchers examined single-nucleotide polymorphisms from the PhenCode project that are known to have associated phenotypes, and compared them with a set of neutral single-nucleotide polymorphisms, they found that the phenotype-causing variants are significantly more likely to produce large structural changes in the DNA.

Whether this approach will have predictive value for identifying functional noncoding variants remains to be seen, but the prospect is certainly exciting. And, as Margulies emphasizes, there may be still other informative ways of looking at DNA, "a living molecule, not just a sequence of letters," after all.

Natalie de Souza

RESEARCH PAPERS

Parker, S.C.J. *et al.* Local DNA topography correlates with functional noncoding regions of the human genome. *Science* advance online publication (12 March 2009).

NEWS IN BRIEF

STEM CELLS

Human induced pluripotent stem cells with a clean genome

Reprogramming of differentiated cells to induced pluripotent stem cells was initially achieved using integrating viruses to deliver the reprogramming factors. This can cause abnormalities in the cells and is undesirable particularly for therapeutic applications. Yu *et al.* now reprogram human fibroblasts using the oriP/EBNA1 vector to deliver the reprogramming factors. This vector forms a stable episome and is lost from cells in the absence of drug selection.

Yu, J. *et al. Science* advance online publication (26 March 2009).

PROTEOMICS

Finding inhibitors with ABPP

Activity-based protein profiling (ABPP), which uses reactive chemical probes to target enzyme active sites, can be used to elucidate the function of uncharacterized enzymes. Bachovchin *et al.* now adapt ABPP to a competitive inhibitor screen using fluorescence polarization, which monitors the apparent size of a fluorophore-tagged activity-based probe (whether it binds to the enzyme or not). This allows them to screen very large compound libraries, unlike the previous gel-based readout.

Bachovchin, D.A. *et al. Nat. Biotechnol.* **27**, 387–394 (2009).

GENOMICS

Inherited transcriptional errors

Mutations that are passed on to daughter cells are usually caused by changes in the DNA sequence. Errors in transcription, leading to mutation in the RNA, are as short lived as the RNA itself and thought to have no impact on the heritable phenotype. Gordon *et al.* now show with a bistable *lac* operon that the molecular noise caused by transcriptional errors can trigger a positive feedback loop that results in a heritable phenotypic difference in genetically identical cells in the same environment.

Gordon, A.J.E. *et al. PLoS Biol.* **7**, e1000044 (2009).

PROTEIN BIOCHEMISTRY

Reverse micelles for nuclear magnetic resonance

Membrane proteins are notoriously difficult to study with nuclear magnetic resonance spectroscopy owing to their need to be solubilized in large detergent micelles, which prevents rapid molecular tumbling needed for optimal data collection via triple-resonance experiments. Kielec *et al.* now use reverse micelles, a micelle that has flipped its orientation in a low-viscosity organic solvent, and thus facilitates fast molecular tumbling, to investigate the structure of a potassium channel.

Kielec, J.M. *et al. Structure* **17**, 345–351 (2009).

MICROSCOPY

Ultrastable AFM

Instrumental drift in atomic force microscopy (AFM) is a critical problem that limits imaging resolution. Sharper tips and high-sensitivity detection methods can improve resolution, but rapid scanning is still required to minimize instrumental drift. King *et al.* now describe a different solution to stabilize the AFM stage: they scatter laser light off the apex of the AFM tip to create a local frame of reference. This permits them to control the position of the AFM tip with high precision, allowing them to scan slowly, improving imaging resolution.

King, G.M. *et al. Nano Lett.* **9**, 1451–1456 (2009).