For Lansdorp these results argue against the immortal strand hypothesis. "There is no obvious fixed pattern of sister chromatid segregation," he explains. Instead, he wants to pursue his previously suggested 'silent sister hypothesis', which proposes that non-random segregation of perhaps a few chromosomes could help regulate gene expression and cell fate in adult stem and progenitor cells.

To accumulate evidence for this hypothesis, Lansdorp and his team want to tackle the proposed function of the asymmetric segregation. They plan to design chromosome-specific probes to follow specific sister chromatids and relate their segregation pattern to cell fate. In addition, the scientists want to correlate allele-specific gene expression with chromatid segregation in single cells to confirm the existence of "active" and "silent" sisters. Of course, getting enough material for high-throughput sequencing from single cells is not without its technical challenges and will necessitate the development of sensitive amplification methods.

Once functional evidence for the 'silent sister hypothesis' mounts, Lansdorp believes that studies into the mechanism will also follow. He acknowledges that at present he and his colleagues can only speculate about the mechanism. "In reality we don't have a clue," he says very candidly, adding that different epigenetic marks at the centromeres of the sister chromatids may lead to asymmetric nucleation of microtubules, making a distinction between the active and the silent sister.

Identifying the roles of the sisters could transform how we think about development and stem cell biology.

Nicole Rusk

RESEARCH PAPERS
Falconer, E. *et al.* Identification of sister chromatids by DNA template strand sequences. *Nature* **463**, 93–97 (2010).

go up as we include more cell types," he adds.

And as next-generation sequencing becomes more accessible, others can use Repli-Seq to analyze their cells of interest—other human cell types or cells from other species; all one needs is a reference genome. For a lower-resolution, more cost-effective analysis to look at just early versus late replication, for example, barcoding could be used, enabling analysis in a single lane of sequencing, suggests Hansen, adding: "We think now we can get the basic profiles of the main S-phase fractions in 1–2 lanes of sequencing."

An important advantage of Repli-Seq that will permit analysis of numerous cell populations, including rare ones, is the lower number of cells required—about 2,000 per replication time fraction. Such amounts can be obtained from a tissue sample, and eventually Hansen and Stamatoyannopoulos aim to examine entire lineages. These data might one day be among the reference information for many cell lines; for now the group is negotiating to upload their material into the University of California Santa Cruz Genome Browser, with much more data yet to come.

Irene Kaganman

RESEARCH PAPERS
Hansen, R.S. *et al.* Sequencing newly replicated DNA reveals widespread plasticity in human replication timing. *Proc. Natl. Acad. Sci. USA* **107**, 139–144 (2010).

NEWS IN BRIEF

MICROSCOPY

High-temperature, single-molecule imaging

It is a challenge to image single molecules at temperatures higher than 37 °C because the index-matching fluids used in conjunction with high-numerical-aperture lenses can transfer heat to the lens, causing damage. This has been a limitation for single-molecule sequencing-by-synthesis, preventing the use of thermophilic polymerases. Schwartz *et al.* now describe tiny TiO_2 colloidal lenses that have a high refractive index and are capable of single-molecule imaging at 70 °C, which should improve the efficiency of single-molecule sequencing.

Schwartz, J.J. *et al. Nat. Nanotechnol.* **5**, 127–132 (2010).

SPECTROSCOPY

NMR for membrane-anchored proteins

Membrane-anchored proteins, consisting of a soluble domain and a lipid anchor, are difficult to study by solution NMR spectroscopy without removing the anchor, thus precluding study of its structural role. Valentine *et al.* now report the use of reverse-micelle technology to obtain high-resolution NMR solution structures for two myristoylated proteins. A surfactant shell, through which the lipid extends, encloses an aqueous solution in which the protein is encapsulated, and the whole assembly is solvated in a low-viscosity liquid ideal for NMR spectroscopy.

Valentine, K.G. *et al. Structure* **18**, 9–16 (2010).

IMAGING AND VISUALIZATION

Detecting Fe-S clusters

Proteins containing Fe-S clusters have many essential biological functions, but not much is known about Fe-S cluster metabolism and its role in disease, owing to a lack of tools for imaging Fe-S clusters. Hoff *et al.* now describe a fluorescent probe to detect Fe-S clusters, based on the complementation of two Venus fluorescent protein fragments when glutaredoxin 2 dimerizes upon coordinating a 2Fe-2S cluster. This approach can be used to image Fe-S cluster proteins in both bacterial and mammalian cells.

Hoff, K.G. *et al. Chem. Biol.* **16**, 1299–1308 (2009).

CHEMICAL BIOLOGY

Controlled condensation in cells

Controlling chemical synthesis inside cells is a challenge, owing to problems with biocompatibility and selectivity. Liang *et al.* now report the condensation reaction of 2-cyanobenzothiazole and D-cysteine, which occurs under mild conditions and can take place in living cells under the control of pH, disulfide reduction or enzymatic cleavage. It is promising for use in *in vivo* molecular imaging applications.

Liang, G. *et al. Nat. Chem.* **2**, 54–60 (2010).

CELL BIOLOGY

Delivery with vertical silicon nanowires

Shalek *et al.* demonstrate that DNA, proteins, peptides and small molecules can be delivered into mammalian cells via vertical silicon nanowire arrays. When these nanowires impale the cell membrane, they release their 'cargo' into the cytosol; in all cases shown the introduced molecules carry out their intended functions. No chemical modification or packaging of the delivery agent is needed, and the cells grow and divide normally for several weeks.

Shalek, A.K. *et al. Proc. Natl. Acad. Sci. USA* **107**, 1870–1875 (2010).