now shows that Q system–based MARCM can be used with GAL4-MARCM to independently mark and manipulate two populations of cells and study their cell-cell interactions.

Using this 'coupled MARCM' approach, they traced lineages and studied cell division patterns of neuroblasts in the fly olfactory system and of cellular populations of the wing imaginal disc. They show that combining these two binary systems into logic gates creates a whole battery of new expression patterns that can help gain genetic access to specific cells.

Without a doubt, one of the major powers of the GAL4 system is its ability to manipulate many cell types through thousands of *GAL4* lines generated by the fly community over the years. Similarly, the broader community should now be encouraged to generate large numbers of *QF* lines with different expression patterns. A current limitation of the Q system is the inability to generate ubiquitously expressing *QF* transgenic flies, a hurdle that Luo hopes will soon be overcome.

Albeit with some differences, the Q system also works in mammalian cells. Future work is needed to make this tool conducive for mouse transgenesis, and it will be equally interesting to know if it can be applied to worms or zebrafish. Luo is optimistic that researchers will not be discouraged by the high number of transgenes required for some of the Q system applications—eight for coupled MARCM. "If it can do things uniquely, people will overcome their high energy barrier and delve into it," he adds with confidence.

Erika Pastrana

RESEARCH PAPERS
Potter, C.J. *et al.* The Q system: a repressible binary system for transgene expression, lineage tracing, and mosaic analysis. *Cell* **141**, 536–548 (2010).

some way primed for reprogramming. What is more, any such early event in the induced cells is clearly not sufficient because continued expression of the reprogramming factors is required during this period.

The researchers also realized that they could not trace the origin of a subset of iPSC colonies. They saw these arise, in an as-yet-undefined manner, at 4–8 days after induction of the cells. As this is the time period when the initially formed colonies undergo compaction, it is possible that these 'satellites' arise from cells that detach from other colonies. This underscores the fact that changes in reprogramming efficiency, typically measured as the number of iPSC colonies per number of starting cells, could artifactually report other changes in the cultures, either in cellular properties or in the way that the cells are handled.

Sometimes you can learn a lot by just taking a look, but it is fair to say that imaging the reprogramming process has raised more questions than it has answered. They are fascinating questions, though, and will undoubtedly seed more detailed and targeted studies. Live imaging is catching on in many different domains of stem cell research and will surely continue to enable scientists to both ask and answer questions about these most dynamic and interesting of cells.

Natalie de Souza

RESEARCH PAPERS
Smith, Z.D. *et al.* Dynamic single-cell imaging of direct reprogramming reveals an early specifying event. *Nat. Biotechnol.* **5**, 521–526 (2010).

NEWS IN BRIEF

GENOMICS

The splicing code, decoded

For many years, researchers have attempted to define the combinatorial rules that control alternative splicing. Barash *et al.* now report a code, implemented in a web tool, that predicts tissue-specific alternative splicing with high accuracy. To construct the algorithm, they analyzed a large amount of data profiling alternatively spliced exons in diverse mouse tissues, known RNA binding sites and sequence motifs, exon-intron organization characteristics, evolutionary conservation and RNA fold structure.
Barash, Y. *et al. Nature* **465**, 53–59 (2010).

STEM CELLS

Making mechanosensitive sensory hair cells

Damage to mechanosensitive sensory hair cells found in the mammalian inner ear can result in permanent hearing loss and balance problems because these cells do not regenerate. Oshima *et al.* report a protocol to generate such cells, which could eventually be used in therapies. Starting with embryonic stem cells and induced pluripotent stem cells, they identified conditions for differentiation into hair cell–like cells that exhibited characteristic hair cell morphologies and were responsive to mechanical stimulations.
Oshima, K. *et al. Cell* **141**, 704–716 (2010).

NEUROSCIENCE

A bold application of optogenetics

Functional magnetic resonance imaging measures brain activity by detecting blood oxygenation level–dependent (BOLD) signals. For a long time, the link between BOLD signals and neural firing has been hard to demonstrate. Using optogenetic tools to excite specific sets of neurons, Lee *et al.* now show that neuronal activity elicits BOLD signals. The unification of these two powerful methods will open new possibilities for mapping large-scale neural circuits in the brains of live animals.
Lee, J.H. *et al. Nature* **465**, 788–792 (2010).

BIOSENSORS

Digital ELISA

The enzyme-linked immunosorbent assay, ELISA, is not sensitive enough to detect proteins found in very low concentrations in biological samples. Rissin *et al.* describe a 'digital ELISA', which can be used to detect proteins in serum at concentrations as low as 10^{-15} M. Using an on-bead ELISA format, they capture proteins of interest and distribute the beads into femtoliter-volume well arrays, where they image them by fluorescence microscopy. The percentage of fluorescent beads is proportional to the concentration of the protein in the sample.
Rissin, D.M. *et al. Nat. Biotechnol.* **28**, 595–599 (2010).

BIOPHYSICS

High-throughput single-molecule force spectroscopy

Typical single-molecule force spectroscopy procedures require substantial time and effort to acquire multiple measurements. Halvorsen and Wong describe a centrifuge force microscope in which the instrument components and sample—consisting of thousands of beads bound to a coverslip via a DNA tether and receptor-antigen pair—are on a rotating arm. Centrifugal force pulls the beads from the surface, and visualizing the rupture events yields thousands of parallel measurements of receptor unbinding.
Halvorsen, K. & Wong, W.P. *Biophys. J.* **98**, L53–L55 (2010).