Based on a biophysical model built to describe the flows, the researchers postulated that myosin II might generate the pressure at the rear of the lamellipodium that drives forward flow. Indeed, treatment with blebbistatin, an inhibitor of myosin II activity, resulted in a depletion of large particles at the leading edge of the cell. "The fact that the particle distribution was reversed in blebbistatin, which is what we expected, gave us a lot of confidence that we are actually measuring fluid flow with this approach," says Keren. Notably, although blebbistatin treatment slows down the movement of fish keratocytes, it does not halt them completely. At least in the *in vitro* context, therefore, and at least for this cell type, fluid flow is not essential for movement.

Fish keratocytes are among the fastest moving cells. They are involved in wound healing and migrate in a sheet at the surface of the animal. It is possible, as Keren speculates, that the fluid flow seen *in vitro* may also exist at the leading edge of the sheet *in vivo*. It will be of interest to extend this approach to other motile cell types, but this is likely not to be trivial. The measurement requires approximately one minute for particle equilibration within the lamellipodium, so it requires steady movement of the cells over this time frame.

"We study a very simple and probably idealized *in vitro* system for cell movement," says Keren, "but it allows us to show that you can measure and model fluid flow in the moving cell. So for the first time, you can see what the fluid is doing."

Natalie de Souza

RESEARCH PAPERS

Keren, K. *et al.* Intracellular fluid flow in rapidly moving cells. *Nat. Cell Biol.* **11**, 1219–1224 (2009).

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is the short read length. Other next-generation sequencing platforms have used paired-end reads, short reads from either end of a longer molecule, to improve isoform discovery. Scientists at Helicos are currently developing a similar but distinct approach for the single-molecule sequencer.

Their strategy involves the capture of long molecules in the flowcell followed by sequencing of the initial 30 nucleotides. Then they turn off the laser, which captures the signal of the incorporated fluorophore-labeled nucleotides, and add unlabeled nucleotides to extend the strand for a defined length, after which they turn the laser back on and sequence the next 30 bases. The end result is intermittent sequence information on a long molecule that will make its characterization much easier than if it has to be assembled from short reads. Milos predicts that this strategy will, for example, be invaluable for finding long intergenic noncoding RNAs, transcripts that span the interval between exonic regions, and she adds: "I think people are very interested to learn if these are indeed true cellular RNAs."

This is just one application for single RNA molecule sequencing; it is likely that in 2010, when Helicos will make this technology available to customers, many more will become apparent.

Nicole Rusk

RESEARCH PAPERS

Ozsolak, F. *et al.* Direct RNA sequencing. *Nature* **461**, 814–818 (2009).

NEWS IN BRIEF

SYSTEMS BIOLOGY

Metabolic network in 3D

Zhang *et al.* used structural genomics to solve three-dimensional structures of the 478 proteins (120 by experiment and 358 by modeling) involved in the central metabolic network of the bacterium *Thermotoga maritima*. This comprehensive structural analysis allowed them to assign metabolic functions to the proteins and identify essential genes as well as investigate questions about the mechanism of metabolic network expansion and the evolution of protein folds.

Zhang, Y. *et al. Science* **325**, 1544–1549 (2009).

STEM CELLS

Reprogramming with OCT4

Four transcription factors, OCT4, SOX2, c-Myc and KLF4, are necessary to reprogram somatic cells into induced pluripotent stem (iPS) cells. But for clinical applications involving iPS cells, it is desirable to avoid overexpressing the oncogenes encoding c-Myc and KLF4. Now Kim *et al.* report that *OCT4* (*POU5F1*) alone is all you need to reprogram human neural stem cells into neural iPS cells that look like and behave like human embryonic stem cells.

Kim, J.B. *et al. Nature* **461**, 649–653 (2009).

CHEMICAL BIOLOGY

Inducing cell signaling

Hashiro *et al.* describe an alternative concept for inducing specific cell-signaling pathways, without requiring protein engineering: they take advantage of the fact that many proteins activate downstream signaling pathways upon localizing to the plasma membrane. By placing a synthetic ligand at the plasma membrane, they can induce translocation of the endogenous protein to the plasma membrane and subsequent activation of the downstream signaling cascade.

Hashiro, S. *et al. J. Am. Chem. Soc.* **131**, 13568–13569 (2009).

PROTEOMICS

Natural product discovery using proteomics

Nonribosomal peptide synthetases and polyketide synthetases are very large enzyme machines in microorganisms that synthesize interesting and potentially pharmacologically valuable metabolites. Bumpus *et al.* describe an assay to enrich for such high-molecular-weight proteins, identify them by mass spectrometry and use the sequence information to link gene expression to the metabolic product.

Bumpus, S.B. *et al. Nat. Biotechnol.* **27**, 951–956 (2009).

GENOMICS

Metagenomics of bug splatter

With a unique approach to sampling the diversity of species in a local environment, Kosakovsky Pond *et al.* collected biological matter (from insects, bacteria and other species) from the front bumper of a moving vehicle and subjected it to phylogenetic profiling. They built a complete pipeline for metagenomic analysis, which involved DNA sequencing of the bumper samples, quality control, sequence alignment via database matching and taxonomic assignment; all tools are available in the Galaxy platform.

Kosakovsky Pond, S. *et al. Genome Res.* advance online publication (9 October 2009).