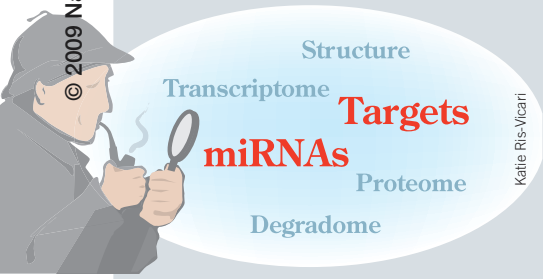
Experimental micro-matchmaking

Although microRNA target predictions are continually improving, high-throughput validation of direct interaction is still needed.

The small but biologically extremely influential microRNAs were again under intense scrutiny in 2008. A microRNA exerts its control by binding to the 3′ UTR of a target mRNA and prevents its translation, either by promoting mRNA degradation or by hindering the translation process.

To understand their true biological significance, the large pool of microRNAs must be matched to the even larger pool of mRNAs in a cell. Computational target predictions are notoriously error prone, and last year we called for methods to do large-scale wet-lab validation of microRNA targets predicted *in silico*. In this regard, 2008 brought several successful efforts. The groups of Nikolaus Rajewsky and David Bartel independently decided to wed proteomics and molecular biology techniques and used quantitative mass spectrometry to assess fluctuations in protein levels at proteome scale in cells with altered levels of a specific microRNA (*Nature* **455**, 58–63; 2008, *Nature* **455**, 64–71; 2008). Because the end result of regulation by a microRNA is always a reduction in protein, the targets should be identifiable with a quantitative, proteome-wide screen.



More help arrives to predict matches for miRNAs.

Another system-wide approach to tackle the microRNA-target matching question is degradome sequencing, introduced by the groups of Pamela Green (*Nat. Biotechnol.* **26**, 941–946; 2008) and Michael Axtell (*Curr. Biol.* **18**, 758–762; 2008) in plants. Here the researchers sequenced products of microRNA-mediated mRNA decay and used the resulting sequence signatures to identify the microRNA. This strategy was very successful in plants, where the match between microRNA and target is perfect; it remains to be seen how easily it can be adapted to organisms with less perfect matches.

In the meantime, the computational experts incorporated the increasing amount of experimental data into new algorithms for target prediction. One example is mirWIP, a program from the group of Victor Ambros that incorporates information from a large data set of microRNA-associated mRNAs—identified by immunoprecipitation of the RNA-induced silencing complex—to predict miRNA targets in *Caenorhabditis elegans* (*Nat. Methods* **5**, 813–819; 2008).

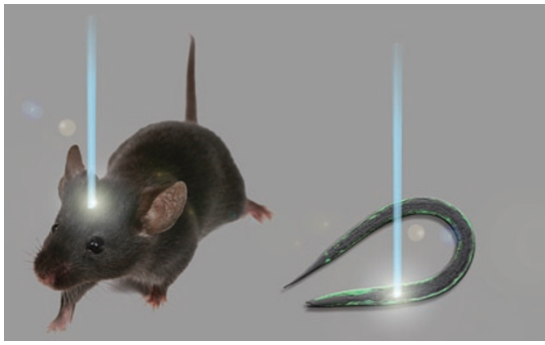
All these system-wide efforts will improve the quality of target prediction and will provide good candidates for experimental validation—a high-throughput wet-lab technique is still needed. Stay tuned. **Nicole Rusk**

Controlling cell function with light

The use of light for active cellular control rather than just passive observation continues to make headway.

We were confident that light-based techniques for manipulating cell function, one of our nominees as a "method to watch" last year, would see further development and increased use in the year that followed. This confidence was well placed.

More and more investigators discovered the usefulness of the light-activated bacterial channel channelrhodopsin-2 (ChR2) for neuronal stimulation. ChR2 has proven to be well suited for mapping neuronal circuits in brain slices and *in vivo*, and now the use of ChR2 is quickly expanding to include behavioral studies.



Light can now be used to control cellular function and behavior in mice as well as worms.

Mice expressing ChR2 in the somatosensory cortex, for example, could be trained to detect brief trains of light-stimulated action potentials in ChR2-expressing neurons (*Nature* **451**, 61–64; 2008), and in zebrafish, it was shown that a light-triggered single action potential in a somatosensory neuron could evoke an escape behavior (*Curr. Biol.* **18**, 1133–1137; 2008).

Although use of ChR2 in the clinic is still a long way off, there was even progress on this front. Transduction of rat spinal neurons with ChR2 after spinal cord injury, followed by photostimulation, resulted in recovery of respiratory function that was retained after photostimulation ceased (*J. Neurosci.* **28**, 11862–11870; 2008). Likewise, ChR2 expression in retinal neurons restored light sensitivity to animals with retinal degeneration (*Nat. Neurosci.* **11**, 667–675; 2008).

All the action in the past year wasn't restricted to ChR2, though. Other light-based methods for regulating cell function saw substantial advances as well. There were improvements in the speed and flexibility with which light could be directed to defined regions in biological samples, thus improving methods for light-based uncaging of bioactive compounds. In addition, many new light-activated compounds were added to the arsenal at biologists' disposal. This included not only classical small-molecule caged compounds but a growing array of light-sensitive, protein-based tools that can be genetically targeted. Although the use of light for observation will never be overshadowed by its power to manipulate cell function, the latter use is certainly coming into its own. **Daniel Evanko**

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