Methods on the cusp of profoundly impacting their field, areas in which methodological developments are needed and updates on some of last year's picks for Methods to Watch: here is our (subjective) selection for this year.

Induced pluripotency

Methods to reprogram somatic cells to pluripotency have improved and will improve further; more biological studies of these cells are forthcoming.

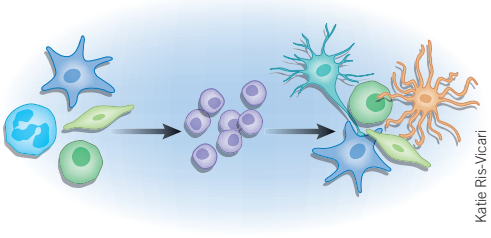
When, a year ago, we picked induced pluripotent (iPS) stem cells as an area worth watching, it had only recently been demonstrated that the basic approach—expressing a defined set of factors in somatic cells to render them pluripotent—worked in human.

The potential of this system, for understanding early development, as a research model for disease, or even in future applications in the clinic, was apparent, but several questions remained.

There has since been progress in many directions, in work from several labs. By starting with different cell types, or by using small molecules, the efficiency of reprogramming has been improved up to 100-fold and has allowed iPS cells to be generated without one or more of the reprogramming factors. Screens for small molecules that can improve the results even further will doubtless continue.

The range of cell types that have been rendered pluripotent has also increased and now includes pancreatic beta cells, neural stem cells and human keratinocytes, among others. Human iPS cells have in addition been generated by reprogramming somatic cells from individuals affected with genetic disease. And recently, transient expression of the reprogramming factors has been used to generate mouse iPS cells, circumventing problems that can result from viral integration into the genome.

In addition to further technical improvement, continued studies of iPS stem cell biology, whether at the level of gene expression, epigenetics or differentiation, will be critical for harnessing their full potential. This is still an area worth watching, we bet. **Natalie de Souza**



Katie Ris-Vicari

Reprogrammed iPS cells are pluripotent.

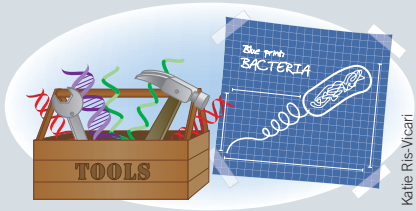
Synthetic life

After constructing a synthetic genome, the challenge is to prove its functionality.

A major long-term goal of synthetic biology is to design a living organism with a minimal, redundancy-free genome, custom made for certain functions. The short-term challenge lies in assembling a whole genome, nonessential genes and all, from raw chemicals.

In 2008, technical breakthroughs were achieved for genome assembly. J. Craig Venter and colleagues used an *in vitro* recombination strategy to recombine oligonucleotide cassettes of 24 kb into larger modules and then moved to yeast for the final recombination steps to obtain the 582.9 kb genome of *Mycoplasma genitalium* (*Science* **319**, 1215–1220; 2008). Similarly, the group led by Mitsuhiro Itaya assembled the 134.5 kb genome of rice chloroplasts with an *in vivo* recombination strategy in which domino clones of 4–6 kb are assembled in *Bacillus subtilis* (*Nat. Methods* **5**, 41–43; 2008).

Testing these synthetic genomes for functionality will be the next step on the path to synthetic life. The Venter group had shown previously that they can swap the entire natural genome of *M. mycoides* for that of *M. capricolum,* and they are now looking to transplant the synthetic *M. genitalium* genome into *M. capriolum*—an endeavor not without technical challenges. It remains to be seen whether the synthetic genome assembled in yeast, and consequently not protected against bacterial restriction nucleases, will replicate and indeed encode a living bacterium. Another aspect that will need optimizing is codon usage. The genomic fragments should be nontoxic for the host within which they assemble. The completed genome, however, has to be transplanted into a final recipient that will translate the genetic code into functional proteins.



Katie Ris-Vicari

Assembling life from synthetic parts.

Understandably, this prospect of custom-building life raises concerns and, like any technology, it can evoke horror scenarios, but it also holds tremendous promise for both understanding biology and harnessing its power for technology and medicine. **Nicole Rusk**

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