The Scientist

Volume 23 | Issue 12 | Page 41

The ten most exciting tools to hit the life sciences this year.

It's been a tough year for every industry, and the life sciences are no exception. Yet companies and academic laboratories across the globe have developed innumerable new products designed to take your research to the next level. But with many lab budgets tighter than last year, which technologies are worth the investment?

That's why, for the second year in a row, we have gathered a panel of expert judges to pick the year's best innovations to hit the life sciences market in the past year. This year's winners run the gamut from imaging, genomics, and other tools that stunningly capture both intracellular and extracellular processes. Our judges—Steven Wiley, Jean Wang, Shawn Levy, and David Piston—are all known for pushing the technical boundaries, and have collectively published more than 600 academic papers.

It may have been a tough year for industry in general, but it was a great one for life science innovation.

Judge Bios

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Cell culture in 3D

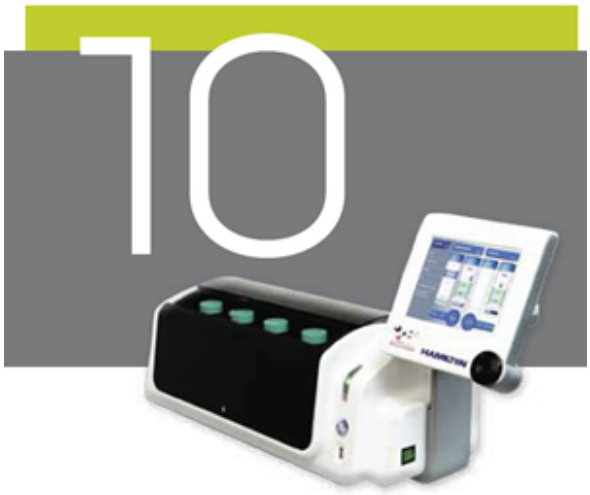


Image courtesy of Amy Schneck

The Benchtop BioLevitator, which combines an incubator and a centrifuge into a single unit, is one of the first 3D cell culture systems.

"This is a completely new kind of technology," says Amy Schneck, assistant product manager of the Hamilton Company, which developed the instrument. Besides creating a 3D culture, which is closer to an in vivo environment, the BioLevitator also allows researchers to grow more cells in less time relative to 2D culture, Schneck adds. Global Cell Solutions, a partner company, developed a unique microcarrier—a matrix lined with proteins—that facilitates cell growth on the 3D surface.

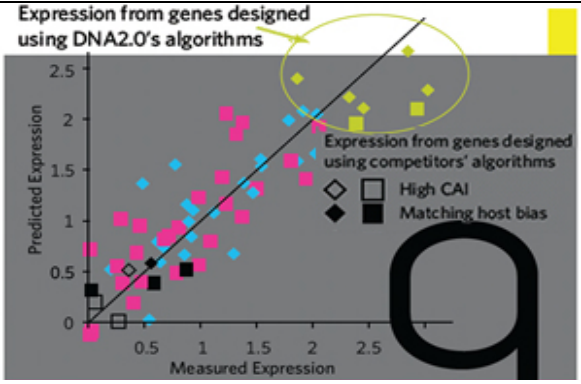
The BioLevitator can grow four cell culture tubes at once and also contains internal magnets that keep cells suspended and homogenous. Multiple protein coatings support different cell lines. During the culture, each tube is monitored for carbon dioxide, temperature, cell density, and pH. When cultures are complete, all data can be transferred to a computer for analysis using the BioLevitator's USB port.

At $35,000, this compact, multipurposed instrument is also environmentally friendly because it works more efficiently than 2D systems, reducing the use of harsh chemicals and labware required for other instruments. As a result, Hamilton estimates that the 3D system can cut annual costs by 60 percent when culturing 40 million Chinese hamster ovary cells per week. The BioLevitator will be available in December 2009.

LEVY: The benchtop size and microprocessor-controlled and -monitored environment, coupled with innovative use of magnetic fields to maintain cells in suspension, makes the BioLevitator an innovative product in a very traditional field.

WILEY: This is a compact unit to greatly simplify microcarrier-based cell culture, which is usually a very complex system to implement. This should allow high-density culturing of anchorage-dependent cell lines, which are usually more physiologically relevant than anchorage-independent ones.

New recipe for protein expression



Synthetic genes are considered the most cost-efficient, timely, and flexible tool for achieving high levels of protein expression, a fundamental component of modern biotechnology research. But since different codons can produce the same amino acid, scientists have innumerable combinations to choose from

Image Courtesy of Claes Gustafsson, DNA2.0

when encoding a protein. And some combinations produce better results than others. Typically, researchers use anecdotal evidence to pick which set of codons will optimize protein expression, with hit-or-miss results. Now, scientists from the California-based company DNA2.0 have developed new design algorithms to predict the best set of codons to use based on actual gene characteristics. The system, described in the September issue of *PLoS ONE*, (4(9): e7002), produces protein expression up to 10 times better than previous approaches, says Mark Welch, the director of gene design for DNA2.0.

The team designed, synthesized, and expressed varied sets of genes encoding two different proteins (a DNA polymerase and a single-chain antibody) and, based on which codons produced the most protein, developed a design principle to predict the gene combinations that optimize protein expression.

The company made their *E. coli* algorithm free when they published it in *PLoS ONE*, but their yeast algorithm will cost up to $25,000 per year for use on an infinite number of genes, says Claes Gustafsson, the company's vice president of sales and marketing. The price of already-made algorithms for other species varies depending on the size of the requesting institution and number of genes that need to be synthesized. The company can also develop algorithms for new hosts from scratch, but the process can take up to a year and cost between $100,000 and $250,000. The technology is still so new, Gustafsson says, that "the exact business plan is still up in the air."

PISTON: **This is another important milestone towards the use of fully synthetic genes, especially for protein engineering applications.**

WILEY: **Very nice! Definitely innovative thinking going on here.**

New measure of metabolism

Image Courtesy of Steve Chomicz

Invented by Seahorse Bioscience in Massachusetts, the XF96 Analyzer is the first instrument that can measure the two major energy pathways in cells—mitochondrial respiration and glycolysis—providing a comprehensive picture of cellular metabolism and how that process goes awry in disease. "Before this instrument, we could never do the magnitude or complexity of experiments," says Steve Chomicz, vice president of sales & marketing at Seahorse Bioscience.

Prior to the XF96 Extracellular Analyzer, scientists relied on the Clark electrode technology for measuring cellular oxygen consumption, a time-consuming technique that provided minimal information. Now in just 35 to 90 minutes, the XF Analyzer can measure oxygen consumption—an indicator of mitochondrial respiration—as well as extracellular acidification, which is a byproduct of

glycolysis. After isolating a small volume of cells in a microplate, the instrument can measure the change in dissolved oxygen and pH levels using optical biosensors. With the instrument's 96 wells, researchers can test the effects of up to four drugs on cellular metabolism, elucidating the bioenergetics of the cell. Currently selling for $100,000 to $200,000, the machine was first released to users in January 2009, and now boasts more than 400 clients worldwide.

WILEY: I want one!

PISTON: This is a great example of how the reduced volumes made possible with microfluidic principles can increase both signal-to-noise and temporal resolution.

New sequence capture tool

Scientists have a plethora of invaluable genomic data—3 billion base pairs' worth—but no way to use it. The genome has been too large and cluttered for researchers to fully analyze the information. Now HybSelect, launched by the Germany-based company febit in March, uses DNA microarrays to narrow in on regions of the genome that play an important role in a particular disease. The technology has already been used to study cancer, multiple sclerosis, Alzheimer's, and diabetes.

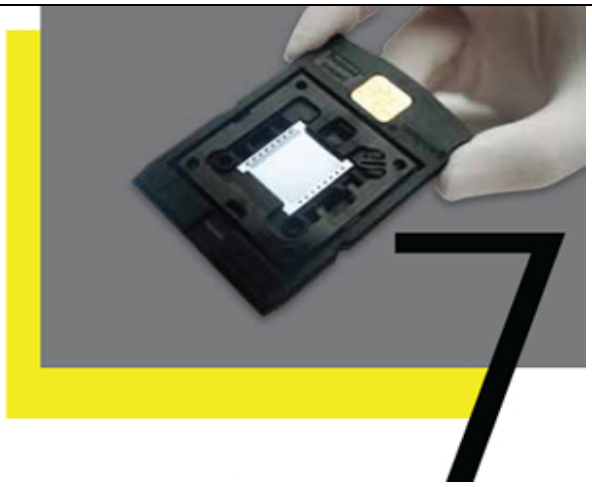


Image Courtesy of Eva Sterzel, Febit

"It lets us dissect a large genome and isolate the juicy bits that can be used to research diseases," says Peer Stähler, febit's chief scientific officer and a former microbiologist at the Max Planck Institute for Brain Research.

Researchers interested in isolating specific DNA sequences have two options: they can either send their samples to febit or buy the HybSelect technology themselves. Samples isolated at febit are sent back to researchers with tips on how to best sequence the genes. In case researchers don't have access to sequencing equipment, the company also offers next-generation sequencing, the whole process taking just 2 weeks and costing as little as $10,000 (for a pilot study), says Stähler. Labs interested in cutting down shipping time can also purchase a Geniom RT Analyzer, the company's all-in-one microarray processing and analysis instrument, and Geniom Biochip, which contains the HybSelect application, for $150,000. The machine is relatively small (55.7 x 90.7 x 66.5 cm; 110 kg) and can process up to 16 samples a day.

WANG: The idea of sequence capture is not new, but the technological development is new and will improve the capacity and efficiency of deep sequencing.

LEVY: The ever-increasing output of DNA sequencing technologies, the successes of genome-wide association studies, and the appreciation of how rare variants contribute to disease and phenotype all illustrate the need for efficient and cost-effective methods to capture genomic regions of interest for further characterization.

All-in-one microscopes

Image Courtesy of Olympus

This year saw the introduction of two new all-in-one microscope systems from Olympus: the FluoView FV10i, the world's first self-contained confocal microscope, which can be used for creating 3D views of a specimen, and the FSX100, a self-contained fluorescence and brightfield microscope, the first of its kind commercially available in the United States. Both systems combine the illumination systems, microscopes, movable stages, and cameras all into a simple little box.

"They don't look like anything that is typical for scientists," says Mark Clymer, a product manager for Olympus. The fact that they are self-contained means they "can be installed just about anywhere." Furthermore, he adds, these systems hold a particular advantage "for fluorescence imaging, which is typically done in dark rooms, [as] it can be done in the laboratories [with] the lights on."

Video courtesy of Olympus

The FSX100 costs $55,000, and the FluoView FV10i runs $147,000 for the oil-based model and $167,000 for the water immersion version, optimal for live cell imaging.

In addition, both microscopes are completely "software driven," meaning they are extremely logical and can be easily navigated, even by first-time users. "Someone could sit down and really without any guidance can generate publication-quality images in minutes," Clymer says, making these microscopes particularly useful in multiuser facilities.

PISTON: **Such a simple yet powerful microscope system will expand the use and development of fluorescent protein technology to labs with little or no imaging experience.**

WILEY: **Very innovative, but will it find a use?**

Zinc fingers create knockout rat

Image Courtesy of the Medical College of Wisconsin and Sigma Aldrich

Sigma-Aldrich took the bronze in last year's competition for their CompoZr zinc finger nuclease (ZFN) service, which initiates double-strand DNA breaks at specific sites to knock out even a single base pair. This year the company follows up with the first fruit of that platform—the knockout rat.

"We all knew how well CompoZr worked in cell lines, and the natural extension was to use that in vivo," says Edward Weinstein, director of the company's Sigma Advanced Genetic Engineering (SAGE) Labs.

This year, Medical College of Wisconsin researchers used custom zinc-finger nucleases from Sigma to create the first targeted knockout rats, some of which glowed green with the expression of a fluorescent protein, such as GFP. Now rodents beyond mice can be developed into models of specific human diseases.

Dave Smoller, president of Sigma's research biotech business unit, says that Sigma can make custom zinc finger nucleases for $25,000–$35,000, but that as different proteins are validated and "put on the shelf," the price could come down for some commonly targeted genes. Weinstein said that SAGE Labs aims to sell rat models of human diseases for "a reasonable price," but declined to be more specific, and will take orders for custom knockout rats. SAGE has already inked a deal with the Michael J. Fox Foundation to create a panel of five different knockout rats that lack genes implicated in Parkinson's disease.

WILEY: This advancement shows the real power of the ZFN technology. Gene knockouts have proven to be revolutionary in understanding gene function, but have been mostly restricted to mice and simpler model organisms. ZFN technology provides a new approach for making knockouts in a greater variety of organisms.

LEVY: Beyond transgenics, ZFN have numerous applications in basic research, agriculture, and possibly medical therapeutics.

A camera that quantifies

Image Courtesy of Photometrics

Measuring and comparing the level of fluorescence emanating from proteins, capturing co-localization events at membranes, and depicting viral entry are the bread and butter of cell biologists, who often measure these phenomena using electron-multiplying charge-coupled device (EMCCD) cameras. But these devices spit out figures in units of measurement that are essentially arbitrary, dependent on gain settings that can vary from camera to camera or over time. This means that imaging data is basically irreproducible within and across labs.

The Evolve camera, however, makes imaging data quantifiable and reproducible by measuring images in units of photoelectrons, which result when photons from fluorescent proteins or reflected light hit the camera's sensors. This overlays detailed images with quantitative, standardized data on how many photoelectrons were captured per pixel.

"What we want is for scientists to realize the value of this and start using that unit of measure," says Deepak Sharma, senior product manager at Photometrics, which released the camera at the end of February.

Sharma won't say exactly how many Evolves Photometrics has sold so far, but says that the number sold this year is "not in the thousands yet." Sharma says that the cost of a new Evolve varies according to geography, but that it is "comparable" to EM cameras with a similar CCD, which can go for upwards of $30,000. "We feel that in 4 or 5 years this is going to have changed the direction of imaging science—standardized it."

WANG: Imagine a world where researchers could reproduce their imaging experiments and more directly compare their data. Just think of the scientific advances we could make if studies were more quantitative and verifiable. And consider the new insights we could derive from being able to integrate data from different experiments.

WILEY: I think this is a great development for quantitative imaging. If supported by software, it could force all cameras to follow.

Manipulate cells using light

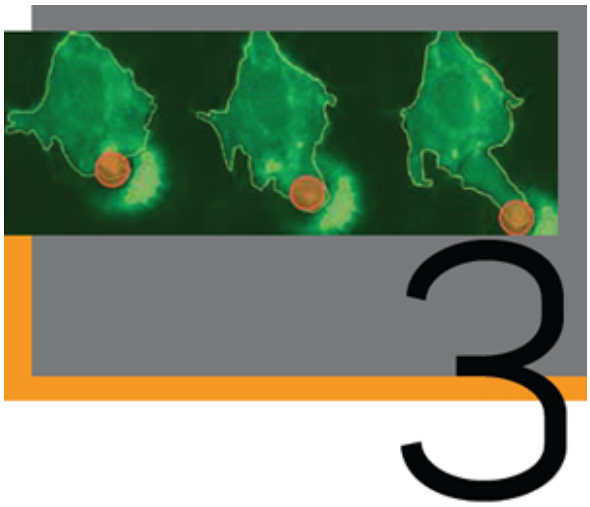


Image by Anselm Levskaya

There's an ever-growing armament of tools for tagging proteins to watch cellular events unfold, but until recently, researchers lacked ways to experimentally manipulate those events with the same molecular-level precision. A handful of genetically encoded light-sensitive systems have now been reported that do just that, but most require a heavy dose of protein engineering (see this issue's Lab Tools).

Wendell Lim and his colleagues at the University of California, San Francisco, may have found a solution. Normally, the light-sensitive plant protein phytochrome and its binding partner, phytochrome interaction factor (PIF), link up and translocate to the nucleus in response to red light; infrared light breaks the bond. The researchers modified the genes so that the pair, when activated, instead moved to the cell membrane. They then linked PIF to a cytoskeletal protein. Spatially targeted pulses of red light flipped on PIF, which in turn activated the cytoskeletal protein, reshaping the cell (*Nature*, 461:997–1001, 2009).

Phytochrome "converts light into a protein-protein interaction," says Lim. Researchers can link PIF to any number of proteins, potentially making the system applicable to a broader array of cell processes than other light-controlled systems, he adds.

The group submitted the mutant phytochrome and PIF plasmids to Addgene, a nonprofit plasmid repository that facilitates distribution of plasmids among the scientific community. Researchers can request the plasmids for about $65 each.

WILEY: **Because the system is genetically encoded, modular (works with any pair of proteins), reversible, and uses nontoxic wavelengths of light, it is likely to have an extremely high impact.**

LEVY: **This data may offer an unprecedented ability to control protein interaction and localization**

in the cell.

Quick pathogen ID

Image Courtesy of Abbott Laboratories

When facing an outbreak of an unknown, deadly pathogen, any delay costs lives. So in the 1990s, during a government-run meeting on biodefense, David Ecker was disappointed by the best ideas being offered for pathogen detection. “They were talking about the Gram stain,” Ecker recalls.

At the time Ecker, at Ibis Biosciences, had been using mass spectrometry to test drug candidates for their ability to bind to RNA, by comparing the atomic weight of a bound RNA to an unbound (lighter) molecule. He figured, why not use the tool to identify genomes based on their different weights? “If we could measure a small molecule sticking to a nucleic acid, I could just measure a nucleic acid.”

The trick was to design PCR primers for conserved areas in a viral or bacterial genome, making them universal for an entire class of pathogens. The part of the genome sandwiched by the primers and amplified by PCR would be variable enough to distinguish a particular strain and subtype within each class of pathogen.

While it hasn’t been approved for clinical trials or diagnostics yet, the machine is being used for testing basic mutation rates in viruses, forensics, and other applications, including being used by the U.S. Navy and Centers for Disease Control and Prevention to identify the new H1N1 virus.

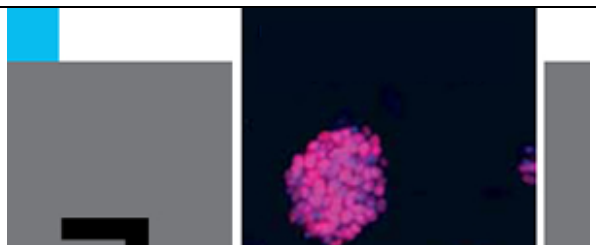
After their acquisition by Abbott Laboratories late last year, Ibis and Abbott engineers designed a sleeker version of the machine called the PLEX-ID, which the *Wall Street Journal* dubbed the Innovation of the Year. The tool costs more than $100,000, and $30–$40 per sample.

PISTON: This automated molecular “canary” combines genetics, robotics, spectroscopy, and informatics to greatly accelerate the identification of unknown diseases, and early detection is always important.

WANG: High-throughput detection of infectious agents is a timely development in light of the continuous threats from pandemic agents.

Pluripotency from proteins

This year’s most exciting innovation, announced in April, circumvents the complications that come with the most common technique for reprogramming cells to an embryonic-like state.



For the first time, Sheng Ding of Scripps Research Institute in La Jolla, Calif., and his colleagues induced pluripotency in mouse embryonic fibroblast cells using only proteins, avoiding genetic modification altogether.

Protein-induced pluripotent stem cell colonies express endogenous nanog (immunostained in red). *Image Courtesy of Hongyan Zhou*

"The iPS cell technology was really a breakthrough discovery, but genetic modification [poses] tremendous hurdles for practical applications," including the potential to cause diseases such as cancer, says Ding.

The team struggled with the idea for nearly 2 years before finding the right conditions and the perfect combination of ingredients, which included the protein form of Shinya Yamanaka's four transcription factors, as well as a histone deacetylase inhibitor known to enhance reprogramming efficiency (*Cell Stem Cell*, 4(5):381-84, 2009).

San Diego–based Fate Therapeutics, of which Ding is a founder, holds the exclusive license for the protein-induced stem cell technology and the specialized cells derived from it. The technology—which could consist of the solution of proteins with validated protocols or the pluripotent cells themselves—is not commercially available yet, but is being developed "in association with partners," says Fate CFO Scott Wolchko.

Wolchko declined to comment on the cost other than to say that it will depend on "the ultimate application of the technology," with the most basic applications such as toxicology testing and the development of reagents at the low end of the price scale, and more advanced drug development and cell therapy applications costing a bit more.

WANG: This study not only overcomes the danger of using transgenes to generate iPS cells, but its result also suggests, to my amazement, that pluripotency, once induced, can be self-propagated without the continuous supply of the exogenous recombinant proteins.

PISTON: Since there is still disagreement about the genetic profile of iPSCs, an alternative derivation of them that preserves their functionality will create new useful cell lines and also lead to better understanding of these cells.

Judge Profiles

JEAN Y.J. WANG, based at the University of California, San Diego, is a distinguished professor in medicine, the chair of the biomedical sciences graduate program, and the associate director of basic research at the Moores UCSD Cancer Center. In studying the functions of cancer genes, her laboratory employs biochemistry, cell biology, molecular biology, mouse genetic models and high-throughput technologies, to elucidate the functional interactions of oncogenes and tumor suppressors in the regulation of differentiation and cell death.

DAVID PISTON is a professor of molecular physiology & biophysics at Vanderbilt University. He is the director of the Vanderbilt Biophotonics Institute, as well as the co-director for biomedical application of Vanderbilt's Advanced Computer Center for Research and Education (ACCRE). His lab uses quantitative fluorescence microscopy to study living cells and tissues, and he established an in vivo molecular imaging center at Vanderbilt.

H. STEVEN WILEY is the lead biologist at the Environmental Molecular Sciences Laboratory (EMSL) at Pacific Northwest National Laboratory, where he uses cell imaging, computational biology and high-throughput proteomics to understand cell communication. His work combines the techniques

of molecular and cellular biology with both biochemical and optical assays, and uses the results to construct computer models of the cellular processes. He sits on the editorial board of *The Scientist*, where he is also a columnist.

SHAWN LEVY is faculty investigator at the HudsonAlpha Institute for Biotechnology. Prior to joining HudsonAlpha, Levy was an assistant professor of biomedical informatics and molecular physiology and biophysics at Vanderbilt University Medical Center. His research interests include technology and methods development in high-density gene expression profiling, genotyping, structural and functional genomics, and the development of bioinformatic tools for the integration of clinical and molecular data from diverse technology platforms.