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Twenty-Five Years of Biotech Trends

Mostly Boom, Some Busts as the Industry Comes of Age

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What have been the most important developments in biotechnology over the last quarter-century? If you ask 29 experts, as I did for this article, you're sure to get 29 different answers.

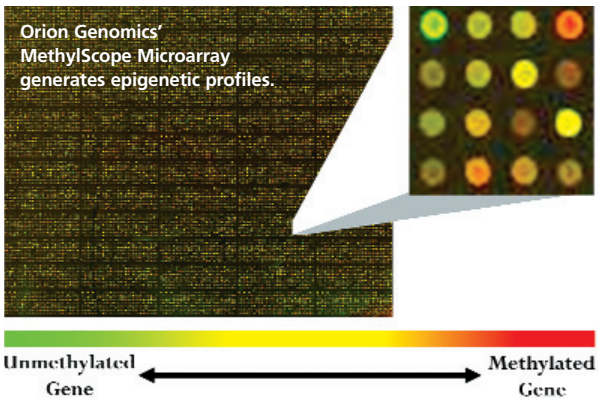
The first thing that struck me about the responders was their optimism. Although it's tempting to present the views of this many experts in terms of "boom" and "bust," most experts preferred to accentuate the positive. Among those who mentioned failures, almost every one was qualified with something along the lines of "but it may be too early to tell."

Genomic science has rapidly advanced over the past two decades. For example, microarray profiling vividly shows how gene expression has been altered in a disease state. Serono

Optimism in biotech is nothing short of amazing given, as Andy Strayer, Pharm.D., vp for clinical operations at **PPD** (www.ppdi.com), notes, only one in ten biotech companies is profitable. But while the failures have been many and prominent, the perception is that success far outweighs failure.

Admittedly, that generalization is difficult to prove. Biobusiness' boom and bust cycles more or less track parallel peaks and troughs for biology itself, which has generated dozens of technologies that are gorgeous in concept, but exasperating in their commercial realization. Remember antisense?

John Thompson, senior vp of corporate development at **Invitrogen**



(www.invitrogen.com), describes the last 25 years in biotech as "a time of dynamic growth and unparalleled discovery," particularly in the fundamental understanding of how life works through such agents as DNA, genes, proteins, and cells.

The *Scientific American* special issue on biotechnology in 1980, and the March 1980 *Time* cover story on interferon caused Crawford Brown, Ph.D., CEO of **Eden Biodesign** (www.edenbiodesign.com), to change academic course from chemical engineering to microbiology. During these 25 years Dr. Brown notes that biotech's "sky-high" hopes to cure cancer (not to mention the common cold) are still elusive.

"Even today, as noted in the joint *Financial Times/Scientific American* supplement on stem cells distributed during the BIO meeting, that cycle of hype and hope continues." Although Dr. Brown believes that many of the promises of stem cell research are likely "false hopes," he predicts that "real medical and economic benefits" will come, but they could take decades.

Not everyone is so pessimistic. Michael Goldberg, general partner with Mohr Davidow Ventures (Menlo Park, CA), quotes Nobel prizewinning Prof. Paul Berg (Stanford): "Human embryonic stem cells will have a greater impact on human medicine and reduction of suffering than recombinant DNA."

Goldberg notes that **Geron** (www.geron.com) will soon begin clinical trials of the first human embryonic stem cell therapy, based on the work of Hans Keirstead, Ph.D., a neurobiologist at the University of California (Irvine).

Interleukin-2, which *Fortune* featured on its cover in 1985, was touted as "the next interferon" and a possible cancer cure but, according to Goldberg, was "a giant bust." He believes that gene therapy may be heading down the same road of long-on-promise, short on results.

Mario Elhers, M.D., Ph.D., CMO at **Pacific Biometrics** (www. pacbio.com), weighed in with several observations. What's in, he says, are pharmacogenomics, biomarkers, companion diagnostics, blockbuster protein drugs, theranostics, fully humanized monoclonal antibodies, RNAi, protein therapeutics, and structure-guided drug design. What's out: antisense, gene therapy, ex vivo cell therapies, cancer vaccines, high throughput screening against non-validated drug targets.

What's passed: "The era of every university professor with an idea getting $10 million to start a new biotech company. Also gone from the scene are prominent startup IPOs, naive biotech investors, and innovative early-stage R&D within big pharma."

According to Ivor Royston, M.D., Forward Ventures (San Diego), "The most significant change in biotechnology over the past 25 years has been the shift from the era of gene discovery and cloning to an era of functional genomics and systems biology."

Dr. Royston explains that in the late 1970s and early 1980s, biotechnology's major breakthrough was recombinant DNA, which led to replacement treatments like EPO, G-CSF, insulin, and human growth hormone. Today's blockbuster bio-drugs, which represent a greater understanding of biochemical disease pathways, include Gleevec, Tarceva, Avastin, Herceptin, Erbitux, and Rituxan.

"Gene-based medicine is the biggest change in biotech," says Ron Woznow, Ph.D., president of the Canadian Gene Cure Foundation (Vancouver, BC).

"Biotech is more focused today on developing healthcare products and services rather than new platform technologies. However, the transition to gene-based medicine, which depends on these innovations, will be delayed by social, legal, and ethical issues relating to privacy and who should benefit from the exploitation of the human genome."

"When they were discovered in 1975, monoclonal antibodies (Mabs) were a promising scientific tool but impractical therapies," observes Alejandro Aruffo, Ph.D., vp of global pharmaceutical development at the **Abbott Bioresearch Center** (www.abbott.com). "Now these agents are changing millions of lives."

Mabs, according to Dr. Aruffo, offer the best hope for patients with cancer, autoimmune diseases, and cardiovascular disease, as well as for new or emerging diseases like SARS, HIV, and other infectious diseases.

The most significant change for David Hale, president of **CancerVax** (www.cancervax.com), is the emergence of targeted therapeutics. "Just look at how we treat cancer today, by pumping the patient full of toxins. The approval of monoclonal antibodies like Herceptin and Rituxan in the 90s and the more recent approval of kinase inhibitors, such as Gleevec and Tarceva, have launched a specifically targeted attack on cancer.

"From cancer vaccines like Provenge and Canvaxin to angiogenesis drugs that starve tumors, the biotech industry is showing no signs of slowing down."

Our experts' views on genomics were mixed. Nate Lakey, CEO at **Orion Genomics** (www.oriongenomics.com), muses that it's still an open question if the gene-to-target model presumed to operate in the post-genomics age will generate the anticipated numbers of new drugs.

Many firms whose business models were based on DNA sequences as a means of uncovering drug targets to find novel drug classes have changed their businesses. Some are now diagnostics companies, while others have licensed molecules or purchased companies outright. "These firms were forced to become product companies," he adds.

Lakey also thinks the promise of cDNA sequencing (expressed sequencing tags) was not met. "ESTs underrepresent genes in genome by about 50%," he says, "and it's the wrong half as far as new drug discovery is concerned."

Not everyone is down on the genome, though. One consequence of human gene sequencing is expected to be personalized medicine and "targeted" therapies (which include a molecular diagnostic). The question is: Can the cost structure of pharmaceutical development and manufacturing support this idea? Some people think so.

"Across several disease areas, there is a great need for targeted therapeutics for patient subsets," stated Stuart Peltz, Ph.D., president and CEO of **PTC Therapeutics** (www.ptcbio.com).

Changing Business Climate

Is the goal of starting a biotech company, going public, and getting rich in the process, a dream whose time has come and gone? Dale Pfost, Ph.D., CEO of **Acuity Pharmaceuticals** (www.acuitypharma.com), believes so. Now, according to Dr. Pfost, entrepreneurs are grooming their organizations for acquisition, almost from the beginning. "More than 90% of bio-entrepreneurs envision this trade-sale scenario," says Dr. Pfost.

He cites as reasons the high cost of existing as a publicly traded company and a shift in economic models. "Future IPO cycles may change this view somewhat, but the old days are definitely gone."

Brenda Gavin, managing partner at Quaker BioVentures (Philadelphia), believes that public investors have become more sophisticated in their product development time line expectations. "Most investors today know they are in for a long haul—as a result there are fewer stock run-ups based on spurious data."

At the same time Gavin acknowledges that trade-sale exits are now much more likely than IPOs, with startups more likely to practice "capital efficiency" than in the past.

"Venture capitalists now want to know how companies are going to get through clinical trials for the least amount of capital possible," she notes. "We are much less inclined to build up large management teams or be interested in the broad-based, multiple product, multiple technology companies.

"This means focus on one or two products and a greater dependence on outsourcing to CROs and consultants, and for venture firms keeping tighter reins on cash through tranched financings—only investing the money when significant milestones are met."

Barbara Schilberg, CEO of **BioAdvance** (www.bioadvance. com), agrees. "The end game has changed in the growth of biotech companies. Startups can no longer sell a dream, as they did in the 80s and 90s." Schilberg also likes personalized medicine. "That's where biotech will shine."

Bioreactor technology has played a significant role in the slow, steady improvement in volumentric productivity for cell culture. New Brunswick Scientific

As Erica Fawell, Ph.D., president of Medical Arts & Ventures (San Francisco), points out, biotech companies who adopted FIPCO (fully integrated pharmaceutical company) business plans found themselves without products to sell.

"Biotech needs to reclaim its original position as a risk-taking R&D machine focused on innovation. Only in this way can biotech continue to meet its original goal and mission, helping to introduce effective drugs at affordable prices."

Due to stagnating internal innovation and the looming peak of patent expirations in 2005 and 2006, Big Pharma is seeking more alliances and acquisitions with small biotech companies, notes Matthew Hudes, managing partner at Deloitte Life Sciences (San Francisco).

"The number of Big Pharma-biotech alliances increased from 69 in 1993 to 502 in 2004," says Hudes, "Moreover, the total value of new alliances involving biotech companies has grown significantly from $6 billion in 1999 to $11 billion in 2004."

In addition, biotechnology companies large and small are increasingly focusing on "in-licensing." Almost 20% of small biotech companies recently surveyed by Deloitte plan to predominantly in-license with opportunistic selling of the commercial rights to products, or out-licensing, and only a little more than one-third plan to continue on the traditional path of predominantly out-licensing to larger firms.

More than 70% of small biotech companies plan to increase the number of alliances they form over the next three years.

Regulatory and Legal

It's easy to forget how advances on the legal and regulatory fronts have transformed disparate biological, chemical, and informational disciplines into what we know today as biotechnology. Luckily, regulatory and legal experts are quick to remind us.

What started the ball rolling was the 1980 case, *Diamond v. Chakabarty*, in which the U.S. Supreme Court ruled that living organisms could be protected by patents. The development, says Douglas Robinson, an attorney and partner in the Washington, D.C. firm Banner & Witcoff, forms the legal underpinning of the entire biotech industry.

"Before then, some living tissues were patentable, some not," notes Robinson, which led to the uncertainty that years of work might simply be copied by a competitor. Tomorrow's *Diamond* case, according to Robinson, may involve the patenting of human tissues, or even of human beings.

Estelle Tsevdos, Ph.D., and Donna Praiss, lawyers with the New York firm of Hunton & Williams, note that once it became apparent that biotech's technology base was patentable, capital and financial investment in new companies and research mushroomed.

"The *Chakrabarty* decision marked the foundation and the beginning of the biotechnology industry," says Dr. Tsevdos. "Recognizing the incentive to obtain exclusionary rights in genetic research, the inevitable stampede to the U.S. Patent and Trademark Office began."

Apparently, 1980 was a very good year for biotech. Claire Philpott, a partner at Lane Powell (Portland, OR), believes the 1980 Bayh-Dole Act, which mandates that universities and research institutions transfer federally funded discoveries to the commercial sector, was a significant triumph for biotech commercialization.

Philpott also credits computing power with the ability to complete complex biological projects, for example the human genome project, adding that "the emergence of bioethics in the 1990s is the third change to shape the biotech industry.

When the public application of new technologies clashes with long-held moral beliefs, questions are raised about how organizations should structure clinical trials or whether they should pursue certain areas of research."

John W. Ryan, an attorney with Washington, D.C. law firm Crowell & Moring, notes that in 1980 Stanford University was issued U.S. patent 4,237,224, which covered a method for replicating a biologically functional DNA by introducing desired exogenous genetic material into microorganisms.

U.S. patent 4,736,866, issued to Harvard College, covers a mouse whose germ cells and somatic cells were genetically engineered to include an activated oncogene, making the mouse more susceptible to cancer.

Pamela Williamson Joyce, vp of regulatory affairs and quality assurance at **Serono** (www.serono. com), cites legal/regulatory changes such as the 1997 FDA Modernization Act for helping to push drugs through the regulatory process. Williamson Joyce also credits electronic regulatory submissions as the enabling technology for putting the drug approval process on a set timetable.

Tools of the Trade

The winner of the "greatest technology" award for the past 25 years has got to be cell culture, which predates the biotech industry by many decades (millennia, if you include Sumerian beer brewing).

While cell culture basics existed long ago, it took tens of thousands of biologists, geneticists, and chemical engineers to perfect fermentation systems that increased volumetric capacity for recombinant proteins at least tenfold in the past decade, and 30-fold since biotechnology's inception.

Runners-up for top technology could fill the pages of this magazine, but PCR is at the top of nearly everyone's list. "The use of PCR for high-speed parallel sequencing has enabled the evolution of all genomics tools in play today," says Patrick Lucy, business leader for microbial pharmaceuticals at **Dowpharma** (www.dowpharma.com).

Lucy's biggest bust, which he mentions with a big qualifier, is the Human Genome Project. "Everyone said the Genome Project would help us identify drugs, but that hasn't happened. That day will come eventually, but it's been slow in arriving."

William L. Warren, partner and co-chair of the life sciences practice group at Sutherland Asbill & Brennan (Atlanta), gives the nod to PCR (and gene amplification in general), rapid genetic sequencing that allowed completion of the human genome project two years ahead of schedule, and embryonic stem cells.

The last 25 years have been the age of tools and instrumentation, which, according to Michael Crawford, marketing director at **High Throughput Genomics** (www.htgenomics.com), have provided a higher return on investment than any pharmaceutical or diagnostic.

Technological tool advances have fueled biotechnology research into a wide range of interesting areas that might lead to new therapeutics and diagnostics. Among them: PCR, gene sequencing, automated liquid handling, protein analysis (GCMS), real-time cell analysis, sample-preparation methods, and, most importantly, high-speed computing.

Companies that were blips on the radar screen in the early '80s are now powerful corporate entities: **Applied Biosystems/ Celera, Invitrogen, Affymetrix,** and **Qiagen.** Established tools companies have also prospered in the tools space: **Beckman Coulter, GE Healthcare** (formerly Amersham), **PerkinElmer, Thermo,** and **Agilent**.

As for busts, Crawford points out that genome sequencing has not produced one new drug, and SNP analysis has not resulted in one new lead compound.

Gary Skuse, Ph.D., director of bioinformatics at the Rochester Institute of Technology, says parallel technologies like automated DNA sequencing, 2-D gel analysis software, and microarrays have enabled biology to evolve from a hypothesis-driven discipline to a data-driven activity, which in turn helps generate newer, more relevant hypotheses.

Bioprocessing

Modularly designed production-scale fermentors and bioreactors have shortened time to market by reducing the six to nine-month design and fabrication time for bioreactors to as little as 12 weeks. **New Brunswick Scientific** (www. nbsc.com) pioneered this idea in 2002, which was pointed out by Mike Sattan, marketing director.

Jerold Martin, senior vp at **Pall** (www.pall.com), believes that large-scale production of recombinant proteins and monoclonal antibodies would not be possible without the concomitant development of process-scale manufacturing technologies based on filtration, particularly tangential flow microfiltration for separation of bacterial and mammalian cells from fermenter and bioreactor harvest fluids. As for busts, Martin identified attempts to develop mouse monoclonals as therapeutics.

Analytical mass spectrometry, particularly in-gel digest of proteins with subsequent MALDI-TOF analysis, has now become an everyday tool. "Today, every academic and pharmaceutical organization has a mass spectrometry core facility, which proves that it has become a cornerstone method in biotechnology," says Elena Chernokalskaya, Ph.D., director of technology development at **Millipore** (www.millipore.com).

Ger Brophy, Ph.D., who heads product acquisition and licensing for GE Healthcare (www.ge.com), observes that since technologies become obsolete rather quickly, it's important for vendor companies to offer platform technologies and integrated instrumentation that better address customer workflow requirements.

Dr. Brophy also notes that advances like personalized medicine will require a new level of genetic diagnostics before symptoms occur. "We still have a ways to go, but we're getting closer to the broad-based population screening at the front end of disease," he says.

The most significant change from a bioprocess perspective over the past 25 years has been the impact of disposable technology, according to Dr. Brown. "When I began my career in the 80s at Wellcome (now **GSK's Biopharmaceuticals Centre of Excellence**), there were teams of around 12 staff who worked fulltime washing out, cleaning, prepping and sterilizing the flasks used for vaccine development and licensed product manufacture.

"Today we have disposable flasks and tubing, and we will soon have fully disposable fermenters, presterilized for single use." GEN