Introduction

30 Years at the Heart of Biotechnology

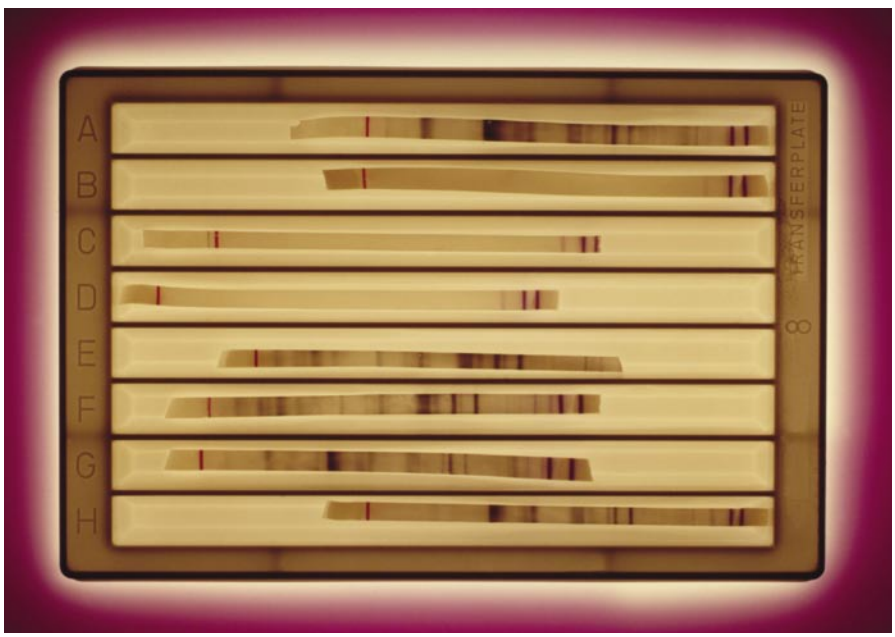
by Cheryl Scott, senior technical editor

Recombinant DNA technology is the vital basis of the modern biotechnology industry. In a very real sense, the genetically engineered organisms that synthesize the complex molecules we call biotech products can be considered to be the unsung "proletariat" of bioprocessing. It all began about 30 years ago, with the advent of DNA cloning technology (**1**). In 1975, scientists and others met at California's Asilomar conference center to discuss the ramifications of their work — and how it should be regulated. By the 1980s, an industry was born out of the possibilities being realized through genetic engineering.

The industry matured over the ensuing decade, with both science and regulations becoming more sophisticated. Analytical methods improved, genomes were explored and mapped, and our experience with recombinant DNA grew. After 25 years, the now-legendary Asilomar conference was bookended by a repeat performance, during which the most general agreement turned out to be that the related issues were a lot more complicated than they ever were or anyone could have imagined before (**2**). And at that meeting, we were talking mainly about the ethical issues. Never mind the practical logistics of making things work.

What I most noticed at that second Asilomar meeting, myself, was that there wasn't a lot of industry participation. Maybe that's because the bioprocessing industry was busy with its own growing pains — in particular, the looming capacity crisis and an explosion of options in analytical methods and expression systems. Transgenic technology still flounders in the shadow of ethical issues and public perception problems. Fermentation and cell culture still dominate. And since 2000, the production yields they offer have risen to rival what transgenics so proudly touted back in the late 1990s.

Mammalian cell culture, in particular, has seen great advancement over the past five years. What once was considered an impressive titer (1 g/L) is now pretty much the baseline. This progress is primarily attributable to the work of our specialists in cell line engineering. With this latest installment to our supplement series, *BioProcess International* salutes those responsible for these amazing developments.



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Powerful Producers

Our main focus here is on mammalian cell lines because they are where the most dramatic advancements have been seen. Although the driving forces have been manufacturing capacity and transgenic competition, new and improved tools for analysis and screening have been the primary enablers of progress. You'll see many of them mentioned in these pages.

Genetic engineering itself remains a fairly simple procedure — I did it myself once in the lab section of a "biotech for journalists" short course years ago. Mix bits of one organism (me, in that case) with another (we used bacteria), add the appropriate enzymes, then heat and cool with precision and bingo. I had a tiny batch of part-me, mostly *E. coli* organisms in a pipette tip. As long as you have the appropriate ingredients, the power is in the precision.

That's also the case on the industrial scale — to an extreme, of course — and it's more so every day. The better your information is, the higher the level of precision you can operate on. Bioinformatics and genomic/proteomic research have provided us with an amazing amount of very good, very useful information. Thus cell line engineers may go forth as modern magicians — even if you compare their work with that of their recent forebearers.

Culture Media History

I enjoyed your article on "Developments in Media for Culturing Cells" (*BPI* 3(6, supplement) June 2005; 16–27). I think including a history of cell culture developments was also very useful and should appeal to many readers. I know I find the history fascinating. But there were a few possible mistakes in the history I would like to point out.

First: Carrel and Baker developed the D-flask in 1923. It was round and had a canted neck ("D" stood for its diameter). Earle developed the T-flask in the late 1940s ("T" stands for total area).

Second: Fisher did not develop CMRL 1066. He did develop V-605 and V-614 in the late 1940s. V-614 was the first commercially available medium, but it has not been available or used since the 1950s — mainly because it contained only two sugars and 12 amino acids. The first medium of any significance was M199, which was developed at CMRL (Connaught Medical Research Laboratories) and published in 1950 by Morgan et al. That medium was used to grow polio viruses at CMRL in 1954 for production of the first polio vaccine. I think that was done serum free. M199 is still widely used today. CMRL 1066 was developed from its formulation some years later.

Third: Maniatis et al. and the others did not develop cell fusion techniques in 1978. Cell fusion was being done routinely in the 1960s using Sendai virus — and later PEG (polyethylene glycol) — to make hybrid cells between species. That was the technique Kohler and Milstein used in 1975 to create hybridomas.

I do not mean to be picky because your article was very informative and interesting, but I thought you would want the information.

John A. Ryan, PhD
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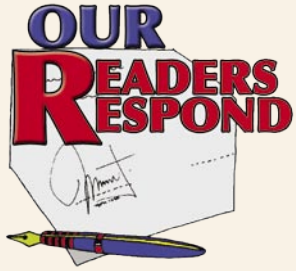

A Continuing Education

A journalist is only as good as her sources. As such, she should never fear correction — from her editor, publisher, or readers. In my case, especially the readers and authors. Everything I know about biotechnology, I learned from you. And I have a special love for science history. These are more than anecdotes; they're the giants whose shoulders you stand on! So thanks for keeping me on my toes.

Cheryl Scott

You'll notice that the final article in this supplement's line-up is not about genetic engineering, but rather cell line adaptation. It addresses an issue that came up when we were working on last year's special issue about culture media (see the "Our Readers Respond" box). As serum-free, protein-free, and animal-product–free media have grown in popularity, we've wondered about cell lines that were previously "employed" to make biotech products using older, serum-containing media. How are those old processes updated? Even newly developed manufacturing processes usually require adapting cells to grow in chemically defined media. It is a very basic form of cell line "engineering" — that is, directing the process of natural selection.

One thing I've learned in putting the current supplement together is that even the modern, ultra-high-tech version of cell line engineering that's going on in bioprocess companies around the world today is not so different from that of years past. No one can pick up a specific genetic sequence (with, say, a set of nanoscale tweezers) and insert it precisely into an exact portion of a given chromosome in a cell. There is a random aspect to the genetic engineer's work. Thus screening is both vitally important and rapidly improving on its own. Along with new gene promoters and suppressors, genomic and proteomic information, and enzymes for precisely cleaving and fusing nucleic acids, high-throughput screening is a major tool in the modern genetic engineer's laboratory.

Get the Picture

This special issue is like the highlight reel shown during half-time of a soccer game on TV. Things are moving fast in the discipline of cell line engineering, and the results are far from final. Our authors have managed to point out the goals scored so far — with some interpretive commentary along the way — while conveying a sense of the strategies involved. Most of these people are involved in the game themselves, and some are here to report their own successes.

As we explored in our most recent supplement, *The Bio Process* (March 2006), cell line engineering is but the first step in a long process of development toward manufacturing a biotech product for the global market. We thought it made sense, after such a broad overview as that was, to get down into the fine details of bioprocessing. And why not start at the beginning? We'd love to hear from you: Which area should we focus on next? Shall we proceed chronologically through the development process? Or is another area seeing such dramatic progress as cell line engineering — and so worthy of immediate attention?

While you mull that over, we'll step back again and look at the business of manufacturing. Look for a special issue on outsourced unit operations in September, then an examination of the rising importance of PAT and other analytical technologies under the risk-based regulatory paradigm in November. And just like the science and technology we cover, we hope to offer a few surprises along the way. Stay tuned!

References

1 *Biotechnology at 25: The Founders.* http://bancroft.berkeley.edu/Exhibits/Biotech/25.html.

2 Barinaga M. Asilomar Revisited: Lessons for Today? *Science* 287(5458) 2000: 1584–1585; www.biotech-info.net/asilomar_revisited.html.