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FINAL WORD

by Lynn C. Klotz

IS GENETIC ENGINEERING JUST ANOTHER SOUTH SEA BUBBLE?

In the early part of the eighteenth century, the British Government gave The South Sea Company a monopoly over British trade in the South Seas. British investors believed that great riches were to be had from such trade. Further rumors were circulated that England was to be given the right of free trade with Spain's colonies. These rumors, coupled with both a very positive investment climate in England at the time and some questionable actions on the part of The South Sea Company, led to incredible speculation in the trading of The South Sea Company stock. Over one period of four days, the stock was reported to have risen from £550 to £890 per share.

It is likely that many investors knew that the promises of great wealth from this trade were largely empty, and that the bubble would eventually burst. Nevertheless, they invested on the theory that they could buy low and sell high before the shake-out came. The result was that several years later the bubble burst as predicted and those caught holding the stock took a great loss. (Malkiel, Burton G. 1975. *A Random Walk Down Wall Street* (College Edition Revised). W. W. Norton & Company, Inc., New York)

We have certainly seen speculation in the stocks of genetic engineering companies. Witness the original offering of Genentech stock: offered at $35 per share, the price rose to $89 before the stock market closed on the first day. But speculation aside, the real question is whether or not there is substance behind those stocks. Is genetic engineering really a business with a future? Or is it just another South Sea Bubble?

It is my opinion that there are a large number of quantifiable, near- to medium-term business opportunities for recombinant DNA genetic engineering. Many of these are for the recombinant DNA production of *existing* products for *existing* markets. The commercial potential for such products is often easy to assess because they address markets where the numbers are known. If by recombinant DNA one can produce the product at significantly less cost, then a profit opportunity clearly exists. Furthermore, if the product is not a new human pharmaceutical, the time, expense, and risk of satisfying regulatory requirements for safety and efficacy are significantly reduced.

Before illustrating what I have just said with some specific examples, I would like to address recent investor concern about the ultimate usefulness of recombinant DNA products. Much of this concern, as I see it, centers around new human pharmaceutical products, and, in particular, interferon. Recent clinical tests on alpha and beta interferon are beginning to indicate that for some applications these interferons may not be the miracle drugs some have touted them to be. Worse yet, during 1982 four French cancer patients died during large-scale trials of interferon. But the interferon used was *not* made by recombinant DNA; instead, it was very impure interferon gathered from cells from which it is naturally produced. Finally, there are so many companies competing to produce and capture the markets for interferons, will anybody make money on such products?

Some of the "new wave" pharmaceutical products such as the interferons, lymphokines, peptide hormones, blood proteins, and effectors will indeed transform medicine, and thus will represent excellent business opportunities just as do present day pharmaceuticals. How these pharmaceuticals work, however, is just beginning to be understood. Thus it is not surprising that clinical trials sometimes produce the unexpected, and potential efficacious uses have not yet been sorted out. It is perhaps unfortunate that most of the press has emphasized these exciting but uncertain products of recombinant DNA genetic engineering. While most genetic engineering companies appear to have at least one of the new pharmaceutical products in their R&D portfolio, most also have a number of less flashy products whose use and markets are not so uncertain. Moreover, the development time for many of these products can be predicted with greater confidence.

To carry out a crude economic analysis of the opportunities presented by a few of these more mundane recombinant DNA products, I will consider the approximate costs of production by fermentation of non-protein products—metabolites, for example. For these products the cost of manufacture (fermentation plus product recovery) can vary over a wide range. At the lower end, the cost is less than $.80 per pound for citric acid and less than $1.30 per pound for lysine. At the higher end are some of the antibiotics. While the costs of manufacture of many antibiotics are held confidential by the manufacturers, one can estimate cost. For an antibiotic of low fermentation yield—in the 6 gram per liter range— such as erythromycin, the cost of manufacture is about $30 per pound, assuming the costs of fermentation and product recovery to be $1.50 per gallon of broth fermented. For penicillin, where manufacturing data are available, the cost of manufacture is about $10 per pound. Using a combination of recombinant DNA and modern biochemical engineering techniques—

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deoxyhypoxanthine. The compounds are useful in the synthesis of a predetermined sequence of RNA with T4 RNA ligase (see above). The preparation of the compounds involves reacting the pyridine salt of adenosine 5′ monophosphate with the nucleoside 5′ phosphate 2′-3′ cyclic phosphate. The product is isolated and treated with an enzyme that cleaves the 2′ phosphooxy bond to give the compound, which has the terminal phosphate group on the 3′ carbon of the nucleoside.

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cost of travel to "international" meetings in Europe and the U.S. is a great barrier to even the finest academic scientists in Japan. It is far more efficient to send young scientists to train at NIH or Cold Spring Harbor for a year than to spend the equivalent amount of money to travel to four western meetings annually.

When evaluating this policy of stationing Japanese scientists in foreign laboratories, Westerners should also note that there are laws and customs in Japan that make it nearly impossible for the Japanese to benefit from inviting foreign scientists to work and teach in their home settings. Racial pride and tradition make tenure at a major university or advancement in a Japanese research corporation an impossible goal for a westerner in Japan, further isolating the Japanese from the world scientific community. Perhaps this discrimination seems unfair, but it poses a far greater disadvantage to the Japanese than to western research efforts.

A final great myth about Japanese biotechnology that casts a spell over some industrialists is the idea that the Japanese have locked into a way of managing people that will propel them into world leadership in any innovative new technology. The Japanese have demonstrated brilliance in acquiring, developing, and refining applied biological methods, approaching and even surpassing some of the finer western efforts in selected areas of product development. But the system that efficiently builds microchips and random access memories does not necessarily foster creativity in biotechnology. In its special April issue on Japanese biotechnology, this journal will explore the Japanese industrial tradition, founded upon a system of receiving and building on the wisdom of its elders. It is a system that provides stronger rewards for loyal service than for blind achievement, a way of conducting R&D that seems to frustrate the types of young minds who have helped build the U.S. and European biotechnological base. One of the greatest challenges for the development of applied biology in Japan will be to encourage and give more autonomy to the younger scientists who have the skill and energy to pursue long-term, applications-oriented research. Success in this effort may require that some of the long-cherished Japanese management policies be abandoned for the acceptance of western methods of innovation.

It is in the common interest to explore and destroy the myths that create suspicion and inhibit collaboration between Japanese and western efforts. The long, tense history of ambivalence that has characterized relations between Japan and the major western powers must defer to the notion of world economic progress that can be achieved through collaboration in biotechnology.

—Christopher G. Edwards

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alpha-fetoprotein and carcinoembryonic antigen (CEA), shed by testicular and colorectal cancers, respectively, provide clinicians with an accurate measure of the size of a tumor. Appropriate assays are now beginning to emerge. And as Dr. Karol Sikora points out, monoclonal antibodies are also set to bring a mini-revolution in histology laboratories. "The easy detection of cancer cells in smears prepared from body secretions such as sputum and vaginal mucous could rapidly lead to automated cytological diagnosis," he writes, "thus reducing its costs and making it available to a wider range of patients" (*Nature*, 1983, **304**:97).

The greatest prize of all, of course, would be a means of fabricating "magic bullets" to destroy malignant tissue *in situ*. Researchers at Lilly Industries Ltd. in Britain have had initial success in using a CEA antibody, linked with the cytotoxic drug vindesine, to attack human colorectal tumors implanted in mice. Similar, encouraging signs have been reported elsewhere. And as Dr. Reto Obrist of the University Hospital, Basel, Switzerland, observed recently in *Trends in Pharmaceutical Sciences* (1983, **4**:375), once such an approach is thoroughly proven, there will be a double benefit. If highly toxic molecules *can* be delivered precisely where they are needed, then many potent compounds will once again be candidates for clinical use. The defeat of drug toxicity could prove to be one of the unexpected bounties from the era of the monoclonals.

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for example, computer-controlled fermentations—it should be possible to reduce the manufacturing costs of several high-priced antibiotics from the $30 per pound to the $10 per pound range. For a typical antibiotic like erythromycin (450 tons per year sales worldwide in 1974) this could represent a profit opportunity of $18 million per year.

Similarly, the manufacturing costs for many of the amino acids can be reduced substantially through recombinant DNA and biochemical engineering. For example, a $5 per pound reduction in cost for the amino acid phenylalanine (used in aspartame) is entirely reasonable to expect. Given estimates of sales for 1984 in the 2.5 million pound range, such a cost reduction would result in a profit opportunity of $12.5 million per year.

For protein products, the manufacturing cost can be expected to be higher because the yield per unit volume of fermentation broth is usually less than for non-proteins, and product purification costs will generally be higher (due in part to the delicate nature of most proteins). At the low end, production costs can be expected to range from $5 per pound to $35 per pound when yields are good and purification is not critical or problematic. When extremely high purity is required or yield problems exist, production costs could easily be 10 times greater, or $350 per pound.

The cost of production of protein products can be lowered from the high to the low ranges using recombinant DNA to increase yields and to aid in purification (by developing strains which secrete the product into the medium, for example). Such reduction in costs from several hundred dollars per pound to under a hundred dollars per pound represents significant opportunities for products in markets of even modest volumes.

I have used these simple examples of existing products to illustrate the point that it is possible to quantify real and current business opportunities for recombinant DNA genetic engineering without relying on dreams of blue-sky breakthroughs. While I believe that many of the exciting opportunities do reside in the future, with new products developed from the use of recombinant DNA technologies in agriculture, pharmaceuticals, and many other industries, the fact is that the recombinant DNA industry represents a real business opportunity right now and is not just another South Sea Bubble.