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Prospects and problems in biotechnology

Julian Davies

Many commercially important products have been made from microorganisms for thousands of years (Table 1) and biotechnology, in the form of food and beverage production, must rank as one of the oldest industries (1). In more recent times, industry has capitalised on the ability of microorganisms to produce pharmacologically – active compounds such as antibiotics, which combined with techniques for large scale fermentation and extraction had led to the development of the antibiotic industry. This represents one of the best examples of advanced methods of organism manipulation leading to controlled growth and production. Thus biotechnology is not a new field; the recent excitement in this area comes from the application of modern concepts and experimental developments in molecular genetics and biochemistry. New methods for the manipulation of microorganisms *in vivo* and *in vitro* have provided scientists with a variety of methods to (a) improve the yield of a known product from a microorganism or (b) to use microorganisms as cellular factories to produce large amounts of rare (mostly human) proteins. As examples of the latter, it is now possible to produce highly purified human growth hormone, insulin, interferons and other proteins in microorganisms, in gram amounts (2). Previously, these materials were not available in amounts sufficient for extensive pharmacological testing and therapeutic application. The *prospects* for the new applications of biotechnology are enormous and much has been written about the things that can and will be done (3).

Table 1: Products of biotechnology

Organism	Product
Saccharomyces cerevisiae	bread, wine
Lactobacillus sp.	yoghurt
Penicillium roquefortii	blue cheese
Clostridium acetobutylicum	acetone/butanol
Aspergillus niger	citric acid
Corynebacterium glutamicum	lysine
Bacillus sp.	proteases
Penicillium chrysogenum	penicillin
Streptomyces griseus	streptomycin

The many predictions presented the first *problem* of biotechnology since, in terms of the organisms to be manipulated, products to be made, and the time taken to accomplish them, the goals were overly-optimistic. This led to expectations in the scientific and business world that have generally been disappointed; an unfortunate situation because the "new" biotechnology will succeed given sufficient time. The main predictions in the beginning came largely from the over-optimism of the press, and that same press is now criticising the failure of biotechnology to come up with dramatic cancer cures and new energy sources. The introduction of new human therapeutic agents takes much time, largely because of governmental regulatory processes that have to be followed to ensure efficacity and safety. For most new drugs, from discovery to sale may take as long as 10–20 years. Human interferon was cloned and produced in bacteria in 1980 and will probably be on the market for some indications in 1984–85; this is probably close to the lower limit in terms of time for new drug registration. Human insulin made in bacteria has taken about the same length of time from cloning to market (4). One must also to be clear about the "so-called" large amounts of money invested in biotechnology. Apart from internal efforts of the giant pharmaceutical and chemical companies the investment has not been as large as most people seem to imagine, especially when one realises that the yearly research budget of a medium sized pharmaceutical company may far exceed the value of some of the biotechnology companies! Too much was expected, too soon, from a relatively small investment.

However the prospects remain bright. The technical possibilities in the application of recombinant DNA technology to the production of bio-

logical products for commercial use are realistic, but it is neither useful nor practical to set time scales for developments. To give one very good example, alcohol production from biomass has been considered one of the primary goals for the biotechnology industry (5). What could be simpler? Organisms such as yeasts give good sugar-alcohol conversion rates; yeasts grow well on simple substrates on the large scale and the fermentation technology is largely established. The production of alcohol in Brazil has been mentioned often as a model of what can be done. However, this is a government subsidised programme and a convenient, easily *metabolised* carbohydrate source is readily available in the country. Even under these circumstances the programme is clearly not a commercial or industrial success and its future is in jeopardy.

The production of large amounts of fuel and feedstock alcohol from biomass in Europe and the U.S., without heavy government subsidy is unlikely in the short term. Fossil fuel reserves are still available and prices are remaining firm; in economic terms alone, alcohol production cannot compete. However, should fossil fuel sources become limiting, the expensive development of biomass fermentation would be warranted to provide replacement fuel, not because it would be cheaper, but because it would be the best available alternative especially in view of the controversy surrounding nuclear power generation. Table 2 indicates some of the difficulties to be anticipated in developing industrial processes for alcohol production from biomass using recombination organisms. In the West Indies, a good source (sugar cane) is available that is easily metabolised and limited transport would be necessary. However, the engineering problems are still considerable; the removal of alcohol requires energy and the most efficient microorganism has yet to be found. The use of thermophilic strains has often been suggested, but this would impose an additional set of engineering problems. The production of alcohol from biomass is a complex metabolic situation – it is not like making interferon in bacteria. The metabolism of the chosen industrial organism has to be channeled into alcohol production without dissipating metabolic energy into other products. As more complex lignocellulose-carbohydrate sources are considered (such as wood or corn wastes) additional microbiological and environmental complications will be encountered since most microorganisms metabolise these sources very poorly; pretreatment of the biomass will add to the overall cost. The engineering of a recombinant microorganism capable of breaking complex carbohydrates into simple sugars and thence into alcohol, at high efficiency and in the presence of substantial contaminants such as lignin, will be a formidable task. It will be done, but only when there is a need for it.

Thus we can see a pattern in recent developments in biotechnology – provided that we concentrate on "simple" cloning – the manipulation of eukaryotic genes with prokaryotic expression systems – the accomplishments have been impressive. Over one hundred eukaryotic genes have been cloned in bacteria and a number of them have been expressed and developed to a stage where their commercial application can be foreseen in the near future (Table 3). However, because of the need for appropriate registration, commercial gains from these products have been slower than expected. By contrast, complex cloning-expression for such ap-

Table 2: Production of alcohol from biomass – problems to be solved

1. Requirement for mixed cultures for combination of degradative enzymes
2. Inhibitory action of lignin and other components of biomass
3. Requirement for metabolic channeling in organism
4. Inhibitory action of alcohol
5. Cost of biomass and its transport
6. Process engineering – alcohol removal – energy requirements

Table 3: Some eukaryotic genes cloned in microorganisms

Gene	Application
Interferons	antiviral, anti-tumour agents
Insulin	antidiabetic
Growth Hormones	human congenital defects animal growth promotant
Urokinase Plasminogen activator	anti-blood clotting agents
Foot & Mouth disease virus antigens Hepatitis B antigens Rabies virus antigens	vaccines
Histocompatibility antigens	diagnostic reagents

plications as antibiotics, alcohol, and chemical feedstocks is still being developed and until the appropriate host-vector systems are available and the background biochemistry sufficiently well understood, we cannot expect dramatic changes in the industrial production of such products in the near future. The situation with respect to plant genetic engineering is probably even more long term.

In addition to problems associated with over-optimistic predictions of the commercial development and application of the "new" biotechnology industry, there are a whole host of scientific problems that are much more interesting and challenging. Although the cloning process has been developed technically to a fine art to enable genes to be found in large chromosomal "libraries" using the knowledge of limited polypeptide or nucleotide sequences (6), there exist difficulties associated with the expression, secretion and purification of the required product. Simply put, why is it that foreign gene expression in a microorganism such as *E. coli* occasionally fails? Why are there difficulties in transcription, translation, processing, etc.? Table 4 lists some of the technical difficulties encountered in attempts to obtain the efficient expression of eukaryotic genes in microorganisms. There is a variety of solutions to these problem situations. For example, if a particular eukaryotic gene has codon usage pattern incompatible for the tRNA complement of the needed host microorganism, the gene (or parts of it) can be synthesized replacing the "true" codons with those more appropriate to the host in question. This does not appear to be a major problem for *E. coli* since several eukaryotic genes containing (apparently) rare *E. coli* codons can be expressed at high level. However, rare codons may slow down translation and thereby influence secretion, proteolysis, folding, etc. The most obvious example of codon usage difficulties would be likely to apply when the yeast *Saccharomyces cerevisiae* is used as the host microorganism (7). However, yeast as a host vector system is still in a relatively early stage of development compared to *E. coli* and with the success of high level gene expression in *E. coli*, yeast expression systems do not appear to offer many advantages for eukaryotic protein production at the moment.

Table 4: Some potential problems in gene cloning and expression in microorganisms

Cloning:	Finding the gene, rare sequence, rare messenger RNA, uncharacterized protein
Expression:	Transcriptional loop-back, nucleases, ineffective codon usage, lethal protein
Processing:	Proteases, insolubility
Activity:	Lack of post-translational modification, co-factor requirements

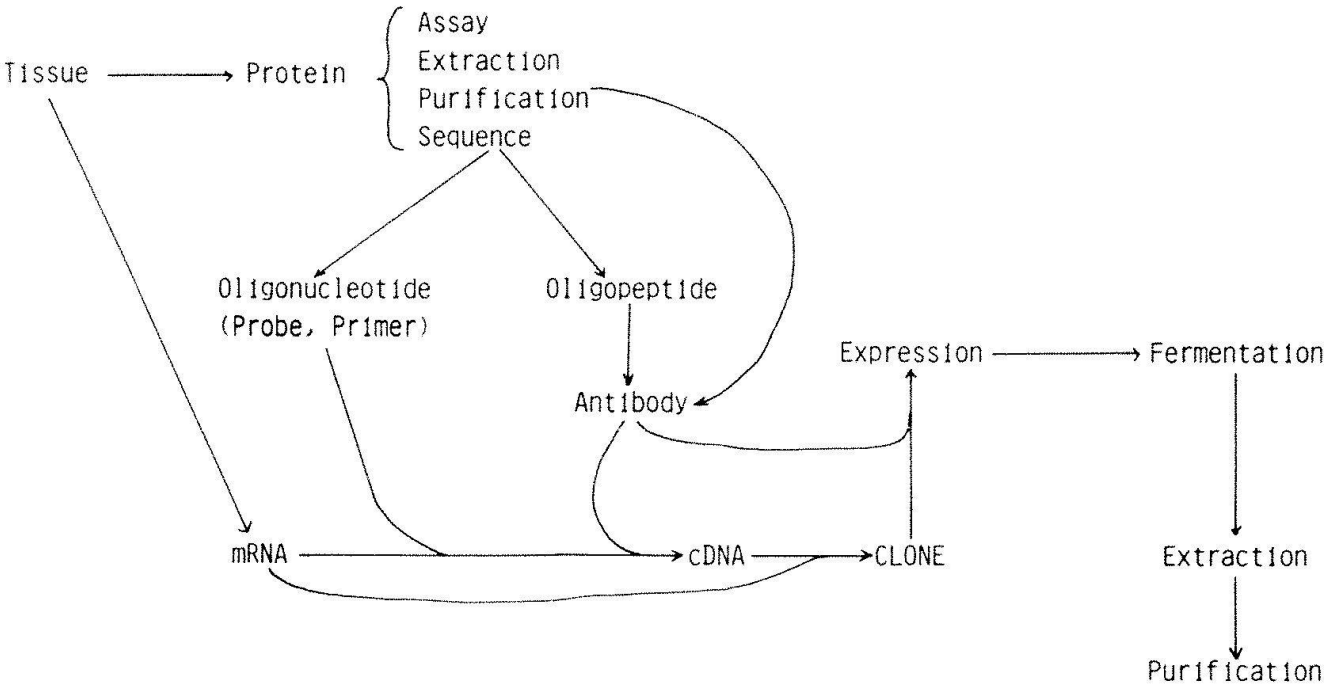

Figure 1. An outline of the steps involved in the cloning, expression and processing of a mammalian gene and its product.

On the other hand, mammalian cell expression systems (8) may prove to be effective alternatives especially when post translational modifications have been identified as critical for the activity of a given protein. Modifications such as glycosylation and amidation do not seem to be common in bacteria or yeast and in fact do not seem to be essential, since at least for β-interferon the non-glycosylated form appears to retain full anti-viral and anti-proliferative activity (9). The difficulties may come when blood proteins are to be made (such as clotting factors) or when the antigenic and protective activity of a viral coat protein is dependent on appropriate post-translational modification. A substantial amount of work on the development of expression vectors and large scale culture with cheap medium components will be needed before we can expect the practical, commercial realisation of protein production in mammalian cells.

Thus, in spite of the fact that gene cloning has become almost a by-word, continued development and innovation will be necessary to guarantee the success of recombinant DNA techniques in the commercial production of human proteins. As a final thought we must not forget that protein chemistry is the beginning and end of all recombinant DNA procedures (Figure 1). Knowledge of protein sequence and biological activity is necessary at the start of every project. The development of methods to release and purify mammalian proteins made in large amounts from microbes, in fully active but non-toxic or non-immunogenic forms will remain a priority as a prospect and a problem for all biotechnology industries.

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