EDITED BY
PAK-LAM YU

# fermentation TECHNOLOGIES

## INDUSTRIAL APPLICATIONS

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# FERMENTATION TECHNOLOGIES: INDUSTRIAL APPLICATIONS

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# PREFACE

The past decades have witnessed remarkable progess in those technologies that service the fermentation industries. One has only to consider the recent and dramatic increase in new journals addressing biotechnological subjects to realize the extent of developments in these areas and the continued growth in stature and maturity of the fermentation industry. But is there a gap developing between fundamental scientific knowledge and its industrial applications? Has the past decade focused sufficiently on the translation of laboratory observation into industrial practice, and with what success? What lessons of the past can be carried into the next ten years of biotechnology? What are the new developments of likely industrial importance?

The International Biotechnology Conference on Fermentation Technologies: Industrial Applications provided a forum for the discussion and exchange of views on these questions within a framework of topics which covered research, fermentation, manufacturing and processing. For the efficient application of fermentation technologies in the production of traditional and recombinant products, these different stages of development need to be treated as one continuous process, that is, researchers need to look at the technologies from more than one angle. This conference brought together researchers and other professionals to exchange their knowledge and experience in the whole field of biotechnology.

The proceedings of the conference are presented in this volume in five sections: Microbial Genetics and Recombinant Products, Microbial Physiology and Biotransformations, Yeast and Animal Cell Cultures, Bioreactor Design and Biosafety, and Downstream Processing. Each section includes plenary lectures, oral and poster papers. It is hoped that this volume will help to stimulate interest in further research and development into the application of fermentation technologies for the production of commercial products.

PAK-LAM YU

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# SECTION I

# MICROBIAL GENETICS AND RECOMBINANT PRODUCTS

# BIOTECHNOLOGY AND MEDICINE: BACK TO THE FUTURE?

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At the beginning of the 90's, commercial sales of medical products developed from the applications of recombinant DNA technology total close to 2 billion US dollars worldwide. The major products are:

| Product | Application |
|---|---|
| Interferons | anti-cancer |
| Insulin | diabetes |
| Growth hormone | congenital dwarfism |
| Plasminogen activator | cardiovascular disease |
| Erythropoietin | kidney deficiency |
| Hepatitis B | vaccine |
| Antibodies | diagnostic products |
| Nucleotide sequences | |

Although this market is impressive (it developed from nothing over the past 15 years!), it is still only a fraction of the total market in products of the biotechnology industries (food, drink, agriculture, antibiotics, enzymes etc.). However, applications of genetic engineering to the latter are being studied

intensively and we can anticipate increasing use of recombinant DNA products and genetically engineered micro-organisms over the next decade.

There are two aspects of this "modern" biotechnology which are worthy of further discussion. In spite of the fact that genetic engineering has permitted enormous advances in our understanding of human biology (immune system, endocrine system, neural system, etc.) by producing the means to isolate dozens of important physiologically active proteins such as cytokines and their receptors (many of the lymphokines available are pure and in quantity at the moment and were not even known ten years ago!); we still lack understanding of many of the fundamental processes required for the cloning, expression and production of a heterologous gene.

The focus of the first genetic engineering companies was to obtain a product as soon as possible. The products were all derived from single genes and the goals were obvious to all. Thus, there was a race, essentially, which started in the late 1970's and was won when one of the companies introduced a revenue-gaining therapeutic onto the market (either directly or through a licensee). The products involved were those mentioned above and the companies comprised Amgen, Biogen, Cetus, Genentech, Genex and others.

During this period, in the race to develop a product, there were many scientific and technical problems. The problems related to difficulties in

cloning, gene expression, protein isolation and purification. These problems were usually solved by trial and error and it is to be regretted that, in the majority of instances, no attempt was made to go back to find the fundamental basis of the problem.

To give two examples: translation blocks have been encountered on many occasions during attempts at heterologous gene expression. Despite the availability of strong promoters and faithful application of the "rules" for messenger RNA attachment to ribosomes and translation initiation, gene expression was often very poor. The reason(s) for these difficulties have still not been revealed and more profound and detailed studies would clearly provide more reliable "rules" for future applications. The same is true, to a large extent, for secretion: we simply do not know enough about the molecular interactions involved in these processes. Many attempts to hook-up heterologous genes to signal peptide sequences, to obtain secretion of the desired product, ended in failure. The second example concerns protein folding: it is well known that expression of a gene in a foreign organism leads to the formation of insoluble inclusion bodies. During the "biotech race" such inclusion bodies were solubilised in a variety of different ways and then processed subsequently under oxidising conditions to reform the active nature form of the protein. There was very