Animal Cell Biotechnology

Volume 3

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1988

ACADEMIC PRESS

Harcourt Brace Jovanovich

ACADEMIC PRESS LIMITED
24–28 Oval Road, London NW1 7DX

United States Edition published by
ACADEMIC PRESS INC.
San Diego, CA 92101

British Library Cataloguing in Publication Data
Animal cell biotechnology.
Vol. 3
1. Cell culture
I. Spier, R. E. II. Griffiths, J. B.
(John Bryan)
591'.0724 QH585

ISBN 0-12-657553-3

Phototypeset by
Paston Press, Loddon, Norfolk
Printed by The Alden Press, Oxford

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Preface

Animal cell biotechnology is a rapidly developing and expanding subject and this means that many books on the subject are already dated on publication. When Volumes 1 and 2 of this series were published, the Editors were aware that although they provided a comprehensive introduction to the whole subject of animal cell biotechnology, the subject had progressed. The rationale for this volume is to review the advances that have been made in all facets of the subject and to make an in-depth assessment of one particular area—the bioreactor. It is felt that the number and diversity of bioreactors now commercially available for cell culture is causing confusion. The choice is so wide that many companies are delaying investment because they are spoilt for choice and lack of comparative information. In reviewing the different concepts and designs of cell reactor, one has to be cautious, because there are no bad ones, nor are there any obviously superior ones at the moment. Different products have different process requirements, varying from their biological properties to the required annual product yield. Thus, as far as possible, innovators, or investigators with a substantial experience, of a particular reactor have been asked to contribute a chapter in such a manner that comparisons can be made. An overview is added to include bioreactors not individually described, and to help the comparative process. The area of bioreactor development has been highlighted because it has moved rapidly over the past few years, there is a wide range of concepts being used, and because we hope that it will allow the more rapid evolution of one or two methods that will become the dominant culture technologies of the future.

The primary reasons for this rapid development in animal cell technology are, firstly, that it is now recognized that only animal cells can produce many of the required biomolecules in the correct configurations and with the necessary post-translational modifications, and, secondly, that developments in cellular engineering, media and bioreactor development have closed the productivity, or cost, gap with prokaryotic production systems. The fact that the use of animal cell cultures is no longer just one of the possible options but the method that has to be used, has meant a greater input of effort and

resources into its development. Monoclonal antibodies were responsible for the initial surge of investment in the early 1980s, but as this was mainly to meet the requirements of the diagnostics industry, production targets were not too difficult to achieve. Nevertheless, it was the birth of animal cell biotechnology as we now know it, increasing the scope of products from the traditional narrow confines of virus vaccines, and more recently interferon. It also proved that cell technology would lead to a multibillion-dollar industry. However, viral vaccine manufacturers, in particular, have been slow to take advantage of newly developed processes, needing the tests of time and experience to prove the reliability and consistency of such systems before moving from such safety-first techniques as roller culture. Also, the possibility of using recombinant bacteria delayed any progress in this direction for a while. Thus, the efforts of academic research laboratories in which the different aspects of cell technology continued to be developed (derivation of recombinant cell lines, serum-free media, culture reactors capable of supporting high-density growth, and more efficient purification systems) have largely been confined to the laboratory scale.

The realization that cell culture had a commercial future has overcome this hesitation, and rapid progress is now being made in two important areas. Firstly, the scope of potential products has greatly increased. In health care alone, a wide range of hormones, immunoregulators, new viral vaccines, and enzymes has been added to the classical list of vaccines, interferon and antibodies, all as a result of recombinant-DNA technology. Many of the products require 10^5–10^{11} cells per clinical dose and to be commercially viable not only does the scale of production need to be increased enormously but the cost-efficiency of the process also has to be significantly improved. Secondly, this has provided the necessary impetus and funding for many of the laboratory-scale systems to be scaled-up and used for the commercial manufacture of products, many of which are in various stages of clinical trial.

Despite the breakthrough in the use of animal cells described above, it is still only a beginning. What we now have is a range of tools, techniques, and goals. What is needed is the blending operation in order to assemble these new, but disparate, forms of expertise into a more efficient and productive *process*. The nature of the developmental work has been such that different components of the production process have been developed largely in isolation. Cell lines have been derived and selected on the basis of product expression and stability. The fact that these lines may be nutritionally extremely fastidious, or sensitive to "shear" damage in stirred tanks, was not considered. Similarly, reactors have been designed on sound engineering principles but using the most robust model cell that could be found. There is also the problem of quantifying the productivity of processes in meaningful and uniform terms, so that everyone can comprehend the performance and capability levels of the

bioreactor, and of the process as a whole. It is for these, and similar, reasons that scale-up from laboratory to industrial scale has been so slow, and why many companies have kept with the well-tried and proven methods.

When Volumes 1 and 2 were prepared, it was not intended as the beginning of a series, but as a background text to the subject. However, this intention has been overtaken by events. One cannot keep updating old chapters, because the scope of the subject is widening and some areas move faster than others. It is also essential to present publications that are balanced for the subject as a whole rather than to publish books on specialized areas of the topic. The answer, we feel, is to have an in-depth treatment of one particular aspect, but to accompany this with state-of-the-art reviews on all the other components of animal cell technology. In this volume, for reasons stated above, the bioreactor has been chosen as the special subject, and the accompanying collection of reviews on cell and product quality control, on media development and the use of growth factors, on biosensors and mixing technology, and on downstream processing, serve not only to update the reader on all these important aspects of the subject, but also as a reminder that they are all important components which have to be optimally blended together to achieve a successful process. Future volumes will follow this pattern as we can foresee the need for detailed sections on cell products, cell physiology, and product purification as these rapidly developing areas progress.

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J. B. Griffiths

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1. INTRODUCTION

As the 1980s began, animal cell culture was viewed by some in industrial and academic circles as a dying technology. Soon the molecular biologists would teach bacteria how to make interferons and even virus vaccines. Then the

ANIMAL CELL BIOTECHNOLOGY VOL. 3
ISBN 0-12-657553 3