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Animal Cell Biotechnology

Volume 3

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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.

*R. E. Spier
J. B. Griffiths*

Contents

Contributors	xiii
Preface	xv

Part I Cell Substrates

1 Safety of Recombinant Biologies: Issues and Emerging Answers

A. S. LUBINIECKI

1. Introduction	3
2. Nature of the Risks	4
3. Cell Line Characterization	5
4. Process Validation	7
5. Product Characterization	8
6. Product Quality Control Testing	9
7. Other Topics	10
8. Summary	11
References	11

2 Changing Attitudes and Actions Governing the Use of Continuous Cell Lines for the Production of Biologicals

J. C. PETRICCIANI

1. Introduction	14
2. Major Issues	17
3. WHO Activities	20
4. Summary and Conclusions	23
References	24

Part II Environmental Factors

3 Environmental Factors: Medium and Growth Factors

R. E. SPIER

1. Introduction	30
2. The Salient Background	31
3. Growth Factors and Oncogenes	36
4. The Transformation of Animal Cells in Culture	47
5. Conclusions	50
References	50

4 Immobilized Hybridomas: Oxygen Diffusion

A. D. MURDIN, N. F. KIRKBY, R. WILSON, AND
R. E. SPIER

1. Introduction	56
2. Immobilization	56
3. Mathematical Modelling	58
4. Measurement of the Metabolism of Immobilized Cells	70
5. Concluding Remarks	70
References	72

5 Sensors for the Control of Mammalian Cell Processes

O.-W. MERTEN

1. Introduction	76
2. Biochemical and Physiological Parameters	78
3. Sampling Devices, Transducers, Biosensors, and On-line Detection Systems	83
4. Applications	101
5. Conclusions	132
References	132

6 The Design of Bench-scale Reactors

N. A. DE BRUYNE

1. Introduction	142
2. Shearing and Turbulence	145
3. Revolutions Per Minute, Tip Speed, Torque, Integrated Shear Factor (ISF)	146
4. The Floating Stirrer	147
5. Continuous Culture	153
6. Methods of Oxygenation	158
7. Design Principles for BRO6	170
Acknowledgements	174
References	174

Part III Culture Systems**7 Overview of Cell Culture Systems and Their Scale-up**

J. B. GRIFFITHS

1. Introduction	179
2. Scaling-up	181
3. Conclusions	214
References	215

8 Bubble-free Reactors and Their Development for Continuous Culture with Cell Recycle

J. LEHMANN, J. VORLOP AND H. BÜNTEMEYER

1. Bubble-free Reactors—Why?	222
2. Bubble-free Aeration—How?	222
3. Perfusion in Bubble-free Reactors	229
4. Scaling-up	235
5. Conclusions	237
References	237

9 A Tubular Biological Film Reactor Concept for the Cultivation and Treatment of Mammalian Cells

H. KATINGER

1. Introduction	240
2. The Biological Film Reactor—a Concept	241
3. Experimental Testing	248
Acknowledgements	250
References	250

10 Protein Production from Mammalian Cells Grown on Glass Beads

P. C. BROWN, C. FIGUEROA,
M. A. C. COSTELLO, R. OAKLEY, AND
S. M. MACIUKAS

1. Introduction	251
2. Major Components of the Glass Bead System	253
3. Operational Considerations	255
4. Experience	257
5. Discussion	260
References	261

11 High-density Growth of Animal Cells within Cell Retention Fermenters Equipped with Membranes

W. SCHEIRER

1. Introduction	263
2. Selection of Process	264
3. Culture Principles	268
4. High-density Fermentation Systems	270
5. Conclusion	279
References	280

12 A Comparative Review of Microcarriers Available for the Growth of Anchorage-dependent Animal Cells

M. BUTLER

1. Introduction	284
2. Cell Adhesion	284
3. General Criteria for Microcarrier Design	286
4. Microcarrier Types	287
5. Choice of Microcarrier	297
6. Strategies and Costs of Microcarrier Culture Operations	298
7. Conclusions	299
References	300

13 Large-scale Fluidized-Bed, Immobilized Cultivation of Animal Cells at High Densities

P. W. RUNSTADLER AND S. R. ČERNÉK

1. Introduction	306
2. Culturing System Overview	307
3. The Fundamental Element—The Microsphere	308
4. The Fluidized-bed Bioreactor	312
5. System Performance	314
6. Culture Stability	316
7. Increase in Cell Specific Productivity	316
8. Hardware Systems	317
9. Summary	320
References	320

14 Employing a Ceramic Matrix for the Immobilization of Mammalian Cells in Culture

G. J. BERG AND B. G. D. BÖDEKER

1. The Opticell Culture System	322
2. Experiment and Results with Opticell	327
3. Conclusions	330
References	334

15 Culture of Animal Cells in Hollow-fibre Dialysis Systems

O. T. SCHÖNHERR AND P. J. T. A. VAN GELDER

- | | |
|---|-----|
| 1. Introduction | 337 |
| 2. Physical Aspects of Hollow-fibre Culture Systems | 339 |
| 3. Cell Culture in Hollow-fibre Dialysis Cartridges | 346 |
| 4. Conclusions | 353 |
| Acknowledgements | 353 |
| References | 353 |

16 Large-scale Mammalian Cell Culture Utilizing ACUSYST Technology

M. A. TYO, B. J. BULBULIAN, B. Z. MENKEN,
AND T. J. MURPHY

- | | |
|-----------------------------|-----|
| 1. Introduction | 357 |
| 2. ACUSYST Technology | 358 |
| 3. Process Control Strategy | 362 |
| 4. Specific Applications | 363 |
| 5. Conclusion | 369 |
| Acknowledgements | 370 |
| References | 370 |

17 Perfusion Culture Systems for Large-scale Pharmaceutical Production

W. R. TOLBERT, W. R. SRIGLEY, AND
C. P. PRIOR

- | | |
|----------------------------|-----|
| 1. Introduction | 374 |
| 2. Cell-Culture Technology | 374 |
| 3. Quality Control | 386 |
| 4. Regulatory Affairs | 392 |
| 5. Conclusions | 392 |
| References | 393 |

Part IV Downstream Processing

18 Downstream Processing of Animal Cell Culture Products—Recent Developments

A. ROSEVEAR AND C. LAMBE

1. Introduction	398
2. Purification	399
3. An Overview of Downstream Operations	401
4. Unique Features of Processing Animal Cell Products	403
5. Individual Unit Operations	407
6. Products of Interest	424
7. Conclusions	436
Acknowledgement	436
References	436

PART I

CELL SUBSTRATES

1

Safety of Recombinant Biologics: Issues and Emerging Answers

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1. Introduction	3
2. Nature of the Risks	4
3. Cell Line Characterization	5
4. Process Validation	7
5. Product Characterization	8
6. Product Quality Control Testing	9
7. Other Topics	10
7.1. Applicability to Other Products	10
7.2. Stability of Inserted Genes	10
7.3. Case-by-Case Analysis	10
8. Summary	11
References	11

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

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