国家双语教学示范课程配套教材

生物技术制药（双语教材）

Biotechnological Pharmaceutics

主编 姜 和 蔡家利 朱建伟

科学出版社

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内 容 简 介

本教材根据近年国内外生物技术制药的技术发展概况，结合国内生物医药产业发展概况，以中英文双语编写而成。本教材系统地介绍了生物技术制药的基本原理、方法和实际案例以及质量控制与管理。全书共八章：生物技术制药概论、生物技术药物制备工艺、生物技术药物制剂学、生物技术药物生产的质量控制、基因工程药物、抗体药物、生物技术疫苗、核酸药物。

本教材可作为高等院校药学、制药工程、生物工程、生物技术及生物科学等专业本科生教材，有助于学生了解生物技术药物专业知识，同时熟悉专业英语，有助于跟踪迅速发展的生物医药产业前沿。本教材也可作为生物医药专业教师、科研人员、研究生及产业界人士的参考书。

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前　言

生物技术制药作为国家双语教学示范课程已经多年，我们经过多年的教学经验积累，策划编写一本适应本科教学的双语教材。经过近三年的反复讨论，教材几经易稿，终于要与读者见面了，编者心中不免有些忐忑，因为毕竟这是一本教材，不是科技著作。著作可以任意表达作者的思想和创新，而教材是要教给学生基础的知识、共识的定律、普遍接受的理论……这不是一件容易的事情，尤其是对我们这样的从国外回来的科研工作者，要尽量避免把自己的偏爱和局部知识扔给学生。在这样的前提下，写一本生物制药的教材，具有一定的挑战性。除此之外，生物医药产业本身就在高速发展，新的生物药物品种每年飞速增长，特别是抗体药物和基因工程药物发展迅速。未来威胁人类健康的重大疾病，特别是感染性疾病、癌症以及新出现的疾病主要依靠生物药物进行防治，如艾滋病、乙型肝炎、肝癌、肺癌等。从完稿到现在，我们发现又出现了很多重要的科研成果、科学进展可以写进去，但时间有限，只能作为下一版的修订内容。

本教材具有一定的前瞻性和代表性，希望读者在学习过程中一定要带着批判的眼光，结合其他科技论文和教材来学习。但是，至少本教材是一本新颖的教材，可以帮助学生打开生物医药产业的窗户，发现21世纪生物医药产业的发展前景，树立对生物医药产业的信心和希望。也希望授课教师把本教材作为一个蓝本，授课时带入自己的知识、观点和心得，这样才能真正发挥教材的作用，最大限度地让学生受益。

本教材的各章节，邀请了各个领域的专家（opinion leaders）参与编写，力争做到具有专业代表性和国际水准，但也难免因作者的书写习惯和教学科研背景的差异，不能完全满足每个读者的需求。我们也希望通过这本教材，引出更多更好的著作和教材，百花齐放；激起业内专家们更多的讨论和批评，真正达到抛砖引玉的效果。我们非常欢迎业内专家和广大读者提出宝贵的建议和意见，以便在使用本书时和以后的修改时参考；也欢迎更多的专家加入到我们的作者队伍中来，把教材编得更好。

本教材已获得重庆理工大学2013年校级规划教材资助。美籍华裔生物医药专家江华先生、朱聿文先生 (Mr. Charles Y. Zhu) 和 David Nellis 先生对本教材进行了仔细阅读与修改，在此特别致谢！

姜　和

2016年4月于重庆

Introduction

The biotechnological pharmaceutics has been our bilingual model course for years. We wanted to compile a bilingual textbook in this subject based on our previous teaching experience. After repeated discussions and revisions in the past three years, the final version of this book is about to be published, but authors of the book still have concerns. Textbooks are not scientific works, because common theory and basic concept should be taught to students by textbooks, while the authors are not supposed to express whatever creativity in their minds. It's not easy for textbook authors, as scientific researchers like us; we should try hard not to express our preference or bias to students during teaching. Besides, with the fast development of biotechnological pharmaceutics, especially in antibody-based drug and gene tech-based drug, which makes it even harder to compile a textbook. Contagion, cancer and new diseases, such as AIDS, hepatitis B, liver cancer and lung cancer, need to be treated with biotechnological pharmaceutics. Upon the finish time of this book, new research breakthroughs had been made; we'll add these new research data in the second edition due to the limited time. For this book, readers should have their own thought in the learning process, read with critique and think with creativity. This book is novel, so we hope this book can broaden readers' mind in biotechnological pharmaceutics, and we also hope teachers to use this textbook only as a directory note. Teachers' own perspectives and opinions should be expressed while teaching, and only in this way this textbook can benefit students.

Opinion leaders in many fields participated in compiling this textbook in every chapter, so we tried to set a high professional standard, and nevertheless it's impossible to meet every need from readers due to the different educational background and writing style of authors. This textbook is supposed to stimulate discussions by experts in the related fields, and critiques are very much appreciated so that we can make a better improvement and adjustment in next edition. New writers are also welcome to join us in compiling our next textbook.

This textbook was supported by the Planned Textbook Fund of Chongqing University of Technology in 2013. Many thanks to Messrs. Hua Jiang, Charles Y. Zhu and David Nellis for helping us revise and proofread this textbook.

He Jiang

April 2016 in Chongqing

目　录

Contents

第一章 生物技术制药概论

Chapter 1 Introduction of Biopharmaceuticals

1 生物技术制药基本概念

1 Basic Concept of Biotech Drugs

随着科技的进步，人类正日益感受到生物技术给生活带来的巨大变化，特别是生物技术药物对人类健康的影响。到2011年3月，有超过300个生物技术药物在美国或欧洲赢得了市场许可，全球生物技术药物市场有920亿美元的份额。至此，生物技术药物已不容人类忽视。

生物技术系指利用“生物体（含动物、植物及微生物）”来生产有用的物质或改良生物的特性，以降低成本及创新物种的科学技术。联合国条文对于生物多样性的生物技术的定义是：任何一种用生物系统、活体及其衍生体上制造、修饰有特殊用途的产品或工序的应用技术。换而言之，生命科学的技术进步用于商业化生产就是生物技术。

早期的生物技术，可追溯至远古时代。古埃及人利用酵母菌酿酒。之后，无论是传统式利用微生物发酵技术来发酵食品，或是发酵生产抗生素等，都是生物技术成功利用的例子。对于现代生物技术，在20世纪50年代DNA结构的发现以来，分子生物学急速发展，对传统的生物技术进行了一次大革命。例如利用基因克隆技术，将胰岛素（insulin）克隆到大肠

With the development of human society, more and more people feel the great influence of biotechnology on our daily lives, especially of the impact on human health by biotechnology medicine. There are more than 300 biotechnology drugs received market permission in USA or Europe until March 2011. The global market of biotechnology drugs is estimated as approximately $92 billion US dollars. Nowadays the significance of biotechnology drugs are recognized by more and more people.

Biotechnology: Biotechnology is a field of applied biology that involves the use of living organisms and bioprocesses in engineering, technology, medicine and other fields related to bio-products.The United Nations Convention on Biological Diversity defines biotechnology as “Any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use.” In other term “Application of scientific and technical advances in life science to develop commercial products” is biotechnology.

Early biotechnology can be traced back to ancient times. Ancient Egypt people used the *Yeast Saccharomyces* to make wine. Then whether traditional microbial fermentation technology was used in food fermentation, or the production of antibiotics by fermentation, are examples of the use of biotechnology. For modern biotechnology, since the discovery of DNA structure in the 1950’s, molecular biology development developed rapidly, and the traditional biotechnology get a great revolution. Such as the use of cloning technology, the insulin (insulin) cloned into *Escherichia coli*. It has opened up a path of modern biotechnology.

杆菌中生产。这开启了现代生物技术学之工业价值。

生物技术所含的主要技术范畴有：基因工程、细胞工程、酶工程、发酵工程及生化工程。基因工程是生物技术的核心和关键，是主导技术。

It contains the main technical areas: genetic engineering, cell engineering, enzyme engineering, fermentation engineering, and bio-engineering. Genetic engineering is the key of biotechnology and the dominant technology.

生物技术药物 系指应用基因工程、细胞工程、蛋白质工程等生物技术制备微生物、细胞及各种动物和人源的组织和液体等生物材料，用于人类疾病的预防、治疗和诊断的药物。现代的生物技术药物是指运用生物技术制备的医学药物。它们包括蛋白质药物（含抗体），治疗或在活体内诊断用核酸药物（含 DNA、RNA、反义寡核苷酸），以及运用其他方式（非直接）从天然非基因生物源中提取制备的产品。

Biotechnology drug or biotechnology medicine is defined here as "any pharmaceutical product used for a therapeutic or in vivo diagnostic purpose, which is produced in full or in part by either traditional or modern biotechnological means". Biopharmaceutical refers to medical drugs produced using biotechnology. They are proteins (including antibodies), nucleic acids (DNA, RNA or antisense oligonucleotides) used for therapeutic or in vivo diagnostic purposes, and are produced by means other than direct extraction from a native (non-engineered) biological source.

生物药物 生物技术药物与天然生化药物、微生物药物、海洋药物和生物制品一起归类为生物药物。

Biological Drugs: the biological technique medicine, biochemical medicine, microbial medicine, marine drugs and biological products are classified as biological drugs.

生物技术制药 系指利用基因工程技术、细胞工程技术、微生物工程技术、酶工程技术、蛋白质工程技术、分子生物学技术等研究和开发药物，用来诊断、治疗和预防疾病的发生。现在，全世界生物制药技术的产业化已进入投资收获期，生物技术已应用和渗透到医药、保健食品和日化产品等各个领域，尤其在新药研究、开发、生产和改造传统制药工业中得到日益广泛的应用，生物制药产业已成为最活跃、进展最快的产业之一。

Biotech Drugs: it was used of genetic engineering and cell engineering, microbiological engineering, enzyme engineering, protein engineering, molecular biological technology to research and develop drugs, which used to diagnose, treat and prevent the occurrence of diseases. Now, the world bio-pharmaceuticals technology industry has entered a period of investment gains, biotechnology drugs and penetrated into medicine, health food and cosmetic products in various fields, especially in drug research, development, production and transformation has been widely used in the traditional pharmaceutical industry, bio-pharmaceutical industry has become one of the most active and fastest-development industries.

生物药物工业在全球的规模以超过 15% 的年增长率迅猛发展。它

Biopharmaceutical industry has been rapidly expanding with over 15% increased annual revenue worldwide including China. The rate of increase is higher

的增长率远高于整个制药工业的4%～5%增长率（Global 2008）。自从第一个重组蛋白胰岛素于20世纪80年代初期上市以来，已有100多个重组蛋白和单克隆抗体，以及300多个非重组生物产品包括疫苗和血液制品被美国食物和药物管理局（FDA）批准（www.fda.gov；Rader, 2010）。生物药物产品是运用现代生物技术生产的供体内诊断的临床诊断试剂、预防疾病用的疫苗以及治疗用的药品。生物药物是相对比较新的也比较复杂的大分子实体，一般由生物系统例如微生物、哺乳动物细胞、植物和动物体内生产。DNA重组技术和杂交瘤技术被用来构建生物系统生产：①重组的天然蛋白质（人生长激素、细胞因子、胰岛素等）；②天然蛋白质和生物系统的衍生物（蛋白突变体，类病毒颗粒疫苗，癌细胞疫苗，免疫毒素，抗体片段融合蛋白等）；③用作疫苗或基因治疗的带有基因或遗传信息的病毒和质粒载体，或小分子干扰核糖核酸；④用于体内诊断和治疗用的单克隆抗体。2008年1月到2011年6月，美国FDA批准了18个由微生物、动物细胞及动物体内生产的重组蛋白生物药物，以及9个从天然来源的产品，如人体血液、组织、癌细胞、减毒病毒和细菌生产的疫苗或治疗产品。18个重组蛋白中有12个是来自哺乳类细胞系统，3个来自大肠杆菌，另外3个来自昆虫病毒、酵母菌和转基因山羊。

than the overall pharmaceutical industry growth rate, 4%-5% (Global 2008). Since the approval of insulin, the first recombinant protein on market in early 1980s, there have been over 100 new recombinant protein and monoclonal antibody (MAb) entities, and more than 300 non-recombinant biopharmaceuticals including vaccines and blood products approved by U. S. Food and Drug Administration (FDA) (www.fda.gov; Rader, 2010). Biopharmaceutical products or biopharmaceuticals are clinical reagents, vaccines, and drugs produced using modern biotechnology for *in vivo* diagnostics, prophylaxis, and therapy. This type of molecules is relatively new and large complex in structure, manufactured in living systems, such as micro-organisms, mammalian cells, plants, or animals. Recombinant DNA and hybridoma technologies have been used to engineer biological system to produce ① recombinant forms of natural proteins (human growth humor, cytokines, insulin, etc.); ② derivatives of natural proteins and living systems (protein muteins, virus-like particle vaccines, cancer cell vaccines, immunotoxins, IgG fusion proteins, etc.); ③ viral and plasmid vectors and small interfering RNAs that carry genetic information for vaccination or gene-therapy; ④ *in vivo* diagnostic and therapeutic monoclonal antibodies aiming on a target in a living system. Of the 27 latest (Jan. 2008-June 2011) FDA approved biopharmaceutical entities, 18 are recombinant proteins manufactured using cells, organisms, or animals. The other 9 are vaccines and therapeutics manufactured from natural product sources such as human plasma, tissue, cancer cells, attenuated virus, and bacteria. Among the 18 recombinant products, 12 are produced using mammalian expression systems, 3 are produced by *Escherichia coli* (*E. coli*), and the remaining 3 are produced by baculovirus, yeast, and transgenic goats.

2 生物技术制药发展简史

2 History of Biopharmaceutical Industries

人类利用生物技术或者说生物体或细胞生产自己所需要产物的历史悠久，从一万年前开始，人类就利用对特定植物的耕种和指定动物的畜牧以获取稳定的粮食来源，保证人类生存和社会发展的需要。约六千年前人类又学会利用发酵技术酿酒和制作面包，以此提供美味的食材。约两千年前人类用豆腐和浆糊上的霉菌治疗伤口出血和痈疮。公元4世纪，葛洪著《肘后良方》也有用海藻酒治疗瘿病（地方性甲状腺肿）的记载。神农是中国最早的将生物材料作为治疗药物的应用者，如用羊靥治疗甲状腺肿，用紫河车（胎盘）作强壮剂。1578年明代李时珍在《本草纲目》中所载药物1892种，除植物外，还有动物药444种。1673年荷兰人列文虎克用自己制造的显微镜观察到了被他称为“小动物”的微生物世界，至此人类开始认识和确证了微生物的存在。1797年英国人琴纳首创用牛痘预防天花。随后，法国人巴斯德研制鸡霍乱、炭疽和狂犬疫苗成功，并且他还实验证明了有机物质发酵和腐败是由微生物引起的，而酒类变质是因污染了杂菌所致，还发明了沿用至今的巴氏消毒法。在19世纪最后20年间，德国学者郭霍分离培养出一大批传染病的致病菌，包括炭疽芽孢杆菌、伤寒沙门菌、结核分枝杆菌、霍乱弧菌、白喉棒状杆菌、葡萄球菌、破伤风梭菌、脑膜炎奈瑟菌、鼠疫耶氏菌、肉毒梭菌、痢疾志

The history of human using technology or living body to product what they need goes back long ago. About 10,000 years ago, human cultivated special plants and special animals to get stable foodstuff origin, which guaranteed human animation and requirement of society progress. About 6,000 years ago, human study to using fermentation technology to get wine and bread as good taste food. About 2,000 years ago, human used bean curd and mold living on paste to cure blooding and ulcerative. A Chinese medical book named *Zhou Hou Liang Fang* recorded that a Chinese man, Ge Hong, used a marine swine to cure endemic goiter in AD 4 Century, Chinese man Sheng Nong was the first original biomaterial user as therapeutic medicine. For example, he used glandula thyreoidea of sheep to cure deroncus; goiter, and he used Zhi Chehe (placenta) as invigorator. A famous Chinese ancient doctor, Li, Shizheng, recorded a large number of medicine in his book *Ben Cao Gang Mu*. There were 1892 drugs, including 444 animal medicine except plant medicine, in the book. Dutchman Leeuwenhoek used the microscope produced by himself to observe the microbiological world in 1673. Human began to realize the existence of microbiology. Englishman Jenna creatively used bovine smallpox to prevent smallpox in 1797. Then Frenchman Pasteur successfully carried out research on and obtained chicken cholera vaccine, anthrax vaccine, rabies vaccine. Pasteur proved the causes of organic matter fermentation and that their degeneration was reduced by microbial, and whoopee water deteriorating was caused by mixed bacterium. Pasteur invented the pasteurization, an effective way to kill bacteria, which has been used till today. In the last 20 years of the 19th centunry, German scholar Robert Koch isolated the culture of infective pathogenic bacteria, including *Spore-Forming*, *Eberth Ella typhi*, *mycobacterium tuberculosis*, *Bacillus comma*, *Corynebacterium diphtheria*, *staphylococci*, *Clostridium tetani*, *Diplococcus intracellularis*, *Yersinia pestis*, *Clostridium botulinum*, and *Shigella dysenteriae*. The technology of brewing wine