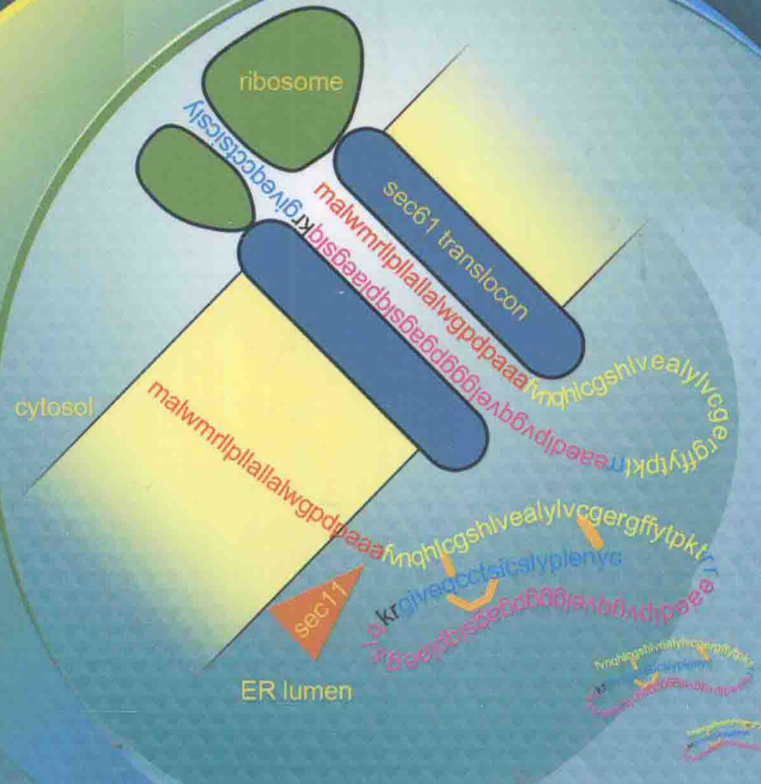
BIOLOGICS
生物药物

主编 ■ 王春晓　钦传光



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内 容 提 要

这是一本生物药物方面的英文著作，介绍了细胞因子类药物、多肽和蛋白质类药物、酶类药物、糖类药物等方面的知识。各种药物均用英文介绍，对较生僻或难懂的专业单词插入了中文解释，书末列有重点词汇表。内容生动、实用性强。本书既可作为生物或药学专业本科生、研究生的教材，也可作为相关研究人员的参考书，大众亦可从本书中汲取到保健方面的知识。

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前言
P R E F A C E

为什么有些人吃完午餐后会犯困？而有的人却感受着夜晚失眠的困扰？那么，要多补充些什么才更容易睡着呢？美味的淀粉类食物在烘烤时添加点什么物质就可以在不改变味道和外观的前提下减少90%以上的致癌物质的生成呢？人在恋爱时，身体会产生什么样的化学反应？是不是有什么物质使我们变得更聪明、更长寿呢？那些抑郁的人，他们大脑中会产生什么样的组织形态学改变？什么样的物质会变少？而我们需要采取什么样的措施，可以逆转这些变化呢？"活熊取胆汁"曾引起舆论一时的喧嚣，静下来的时候，你们是否想一探究竟，熊胆汁中到底含有何种物质，在帮助人类维持着身体的康健？哪些物质控制着伤口的愈合？在哺乳动物的胚胎发育过程中，又是缺少其中的哪种会导致俗称的"兔唇"呢？为保证"喵星人"的视力、毛发、牙齿正常，猫粮中要特别添加些什么物质呢？某些隐形眼镜的护理液的配方又跟这有什么联系呢？究竟是什么样的物质，鸟儿吃了会更勇敢、更易成长为飞行高手，鸟妈妈们要用捕食蜘蛛的方法获得并喂食给它们的小鸟呢？如果你认真地阅读过本书，心中自然就知道上述问题的答案了！

作为一本汉释英文专业读物，书中会有很多生词出现，不必担心！你们第一次见面时，它会利用它附近的空间主动告诉你它是谁。如果，你们还有再次相见的机会，而你恰巧忘了它是谁，那不妨劳动大驾，主动拜访它的永久家园——单词表，它们会排着整齐的队伍，等待着你的检阅、挑选。也许有一天，你们混得很熟，熟到它们中的很多会逐个搬家，住到属于你的精神家园——你的大脑中，短住、常住、甚至永住。

《BIOLOGICS 生物药物》是以王起振、郑新立主编的沈阳药科大学校内教材《生物药品化学》（中文版）的大部分章节骨架为纲，以生物药物的最新英文资料为内容来填充，经过精心梳理和编写而成的。本书的特点是对各种药物均用英文介绍，较生僻或难懂的专业英文单词或词组会在文字中插入相应的汉语解释，教材最后列出单词表。如此安排，既可使读者清楚地掌握专业知识，又可使读者认识更多的英语专业词汇，还可提高读者迅速阅读英文专业书刊的能力。使读者在阅读时能在较短的时间理解得更透彻，达到学英语、学专业知识的双重目的。

本书既可作为在校本科生、硕士生的教材，也可以作为药学工作者进一步钻研业务的专业参考书。此外，还可作为英文爱好者的英文科普读物。在掌握生活常识、了

解生命现象的神奇的同时，不知不觉地提高英文阅读能力。可以作为家庭保健参考书，在偶尔发现身体出现异常状况，可对照查找出身体可能缺乏、并应补充哪种生物营养物质。通过对本书的阅读，读者既可学到专业知识，又能同时掌握这部分知识的专业英语。使学习“生物药物”的本科、硕士人才，或药学工作者得到该学科的基本理论和应用价值的思维训练。

由于时间、精力及其他各种限制，我们搜集到的资料可能并不全面。另外，追求真理的路是一条渐近线。科学家们此时、彼时得到的现象或事实很可能由于现有仪器、设备的限制存在一定的片面性或偏差。因此，我们搜集到的资料本身就可能会被更新的事实所推翻。最后，笔者在细致又细致的资料搜集、整理中，难免还会有一些瑕疵或遗漏。因此，本书的不到之处，希望得到大家的谅解！同时，非常欢迎读者们为本书提出宝贵意见，因为我们知道，本书有提高的空间，而你们——校友、同行、英文和药学爱好者正是我们提高的推动力！

感谢中国药科大学吴梧桐、胡卓逸两位资深生物制药专家对本书出版过程中的建议；感谢上海海洋大学09级海洋生物制药学生李天宇、陈方乾、桂庆元同学关于生词表的建议并协助筛选生词。对于某些专业、跨专业问题，英语，德语，专业英语语言理解问题等，曾得到过美国北卡罗来纳大学医学院柯衡明教授、德国柏林夏洛特大学医学院樊华教授、中国药科大学92级校友郭新峰，沈阳药科大学校友69K药英张雁宁、75K药剂田斯文、71K药学李欢和他在脉凌医学传播公司的同事张沈伟，上海英文教育专家金益东，上海佩妍化妆品有限公司严沛总经理等专家、校友、朋友们的帮助，编者在这里一并致谢。感谢国际化创新型海洋人才培养工程085专项资金和国家海洋局海洋可再生能源专项资金（SHME2011SW02）的支持。

王春晓

2013年10月

修于美国北卡教堂山

目 录

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Chapter 1

Overview

生物药物是由活体生物合成而得，在医学上作为诊断剂、预防剂或治疗剂的制品，诸如药物、疫苗或抗毒素等，或其产品。生物药物是通过活化、扶助以及改善体内的天然调节过程来发挥预防或治疗疾病的作用。将遗传物质拼接导入活细胞培养物中，可产生更新的生物药物。

Definition of Biologics

Biologics are biologically active molecules that are used as medicines for treatment and prevention of diseases. They are also referred to as biomedical, biological, biopharmaceutical, or biotechnological products. Many new biologics are under development.

Biologics cover a wide range of medicinal (药用的，治疗的) products such as vaccines, blood and blood components, allergenics (过敏原制剂), somatic cells (体细胞), gene therapy agents, tissues, and recombinant therapeutic proteins.

The definition of biological products appeared in the U.S. Code. After several children had died due to contaminated diphtheria (白喉) antitoxin, the U.S. government enacted (通过) the Virus-Toxin Law in July 1902, in which a biological product is defined as "any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment, or cure of diseases or injuries of man." With minor revision, this definition remained the same till 1946, and was cited in section 351 of the Public Health Service (PHS) Act (《公共卫生服务法案》).

However, many of ordinary people are still unfamiliar with the term and its meaning. For example, fifteen years ago, Kevin L. Ropp asked, "Just what is a biologic, anyway?" in an article written for the magazine *FDA Consumer*. Using a simple definition from the U.S. Food and Drug Administration (FDA), Ropp noted that biological products are made from living organisms. Specifically, according to Michael Beatrice, associate director for policy coordination and public affairs in the FDA Center for Biologics Evaluation and Research (CBER) that time, "They are derived from living material-human, plant, animal, or microorganism-and they're used for the treatment, prevention, or cure of disease in humans."

The U.S. definition of biologics does not differ substantially from that used by the World Health Organization (WHO). However, WHO uses the term *biological medicines* instead, although the subject is the same. WHO's list of biological medicines includes vaccines, blood products, cell regulators, and reagents for *in vitro* diagnostic tests, and lifesaving elements in the daily practice by physicians worldwide.

However, WHO warns specifically that the quality of such essential biopharmaceutical products is the key of concern for safety due to the fact that the source of the biological materials, the manufacturing process, and the test methods may vary dramatically. The increasing complexity and sophistication of biological products and the rapid growth in this field presents considerable challenges for drug regulatory authorities and for manufacturers.

One of the most concise and useful definitions of biologics comes from the *American Heritage Stedman's Medical Dictionary*, in which the terms of *biologic* or *biological* are used interchangeably. A biologic is a "preparation, such as a drug, a vaccine, or an antitoxin, that is synthesized from living organisms or their products and used medically as a diagnostic, preventive, or therapeutic agent."

Biological medicine: What is it and how does it work?

Biological medicine is the use of therapeutic techniques and substances that activate, support and enhance the natural regulatory processes within the body. This is diametrically (完全不同，截然相反) opposed to conventional western medicine which blocks, over-rides (践踏，奔越过，不顾，不考虑), replaces natural processes, surgerily removes malfunctioning parts.

Western medicine has made spectacular advances in the past century. Restorative (有恢复健康作用的) surgical procedures and keeping people alive in emergency situations can have almost miraculous outcomes. However, modern western medicine has only recently begun to view the body in an holistic (整体) way. Interest in the emerging discipline of Psychoneuroendocrinimmunology (PNEI) finally accepts the fact that the body is not a machine that is an assembly of its constituent parts and cannot be understood using Newtonian reductionist (还原论者，简化论者) science. The body is a dynamic biological symphony, following the laws of Quantum science. It has a sophisticated capability of regulation and repair when mulfunctioning (功能失调), is better served by healing practices designed to support and strengthen (Biological Medicine) not the forceful overpowering (压倒性的) methods employed by conventional western medicine.

Brief History of a Lifesaving Biologic

To supplement the definitions and to foster (促进) an even better understanding of the value of biologics, a brief history of a particular biologic - the first vaccine which was developed to protect humans against one of the most deadly diseases in the world-will be reviewed.

By the late 18th century, smallpox (天花) was an extremely prevalent and deadly disease. In France, it was estimated that as much as 60 percent of the population developed the disease, and 20 percent died of it. In the Americas, the mortality (死亡率) rate reached 90 percent. Smallpox killed millions of people.

In 1796, Edward Jenner, a British doctor who is also a naturalist and keen observer, noticed that patients infected with cowpox were resistant to smallpox. To test his observations, Dr. Jenner inoculated a healthy subject with pus (脓) taken from a person with cowpox and then injected the healthy subject with smallpox. He demonstrated that the subject did not develop smallpox. Dr. Jenner named his discovery "vaccine," derived from the Latin term *vacca* meaning "cow", and the process "vaccination" (疫苗接种). The significance of Dr. Jenner's work was quickly recognized, and in less than 10 years, people around the world were vaccinated against smallpox.

Over the ensuing years, additional vaccines were added to the physician's toolkit (工具箱), and today the WHO lists over 20 different diseases, such as tuberculosis (肺结核) and yellow fever (黄热病), which can be either prevented or treated with vaccines.

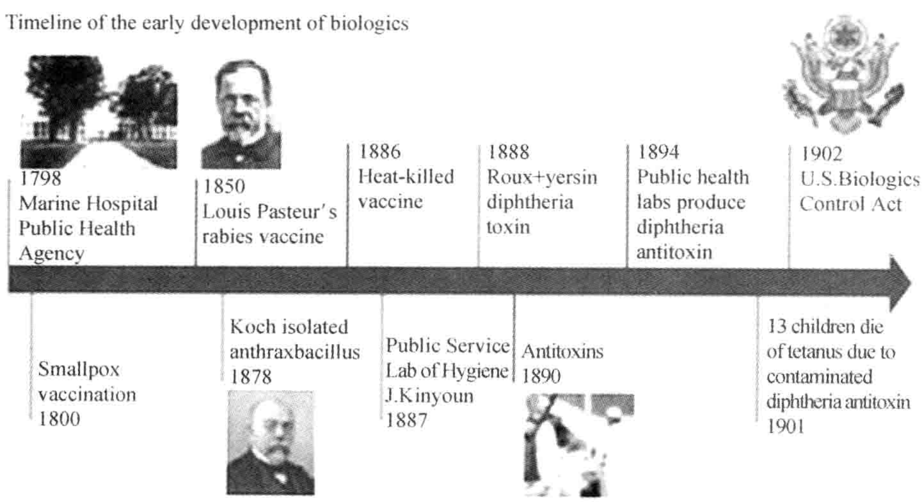

Figure 1-1. The significant events in the progression of biologics.
(Adapted from the CBER Web site)

Trends in Biologics

While biologics have been used to treat disease for more than 100 years, the advent of modern day molecular biologic techniques has accelerated their use in modern day medicine tremendously in the last decade.

Today, newer biologics are created by splicing (拼接) genetic material into living cell cultures. The resultant new proteins have led to breakthrough therapies, from bevacizumab (贝伐单抗) (trade name Avastin, 阿瓦斯汀), which chokes off (阻塞) the blood supply to cancerous (癌的) tumors, to imiglucerase (伊米苷酶, 葡糖脑苷脂酶) (trade name Cerezyme), which treats a rare genetic disorder known as Gaucher's disease (戈谢病). According to IMS Health (艾美仕市场研究公司), a consulting and data services company that supplies the pharmaceutical industry with sales data and consulting services, the total cost of biologics reached MYM 52.7 billion in 2005 and represented 13 percent of U. S. drug spending. IMS Health estimates that this figure will rise to $90 billion by 2009.

Research and development are top priorities for drug manufacturers. IMS Health reports, "At the end of 2006, some 2075 molecules were in development, up 7 percent from 2005 levels, and up 35 percent from the end of 2003. In addition, a promising range of drugs are now in Phase Ⅲ clinical trials or pre-approval stage, including 95 oncology (肿瘤,肿瘤学) products, 40 for viral infections and HIV, and 27 for arthritis/pain. Of the total pipeline (准备中), 27 percent of these products are biologic in nature."

In short, it appears that biologics will likely continue to provide patients with new, lifesaving treatment options well beyond the scope of traditional chemical medicines.

Chapter 2

Cytokine Medications

细胞因子是人类或动物的各类细胞分泌的具有多样生物活性的因子。它们是一组不均一的蛋白质分子或糖蛋白类物质。其功能是担任细胞间的分子信使，调节体内的正常细胞过程，如细胞的生长与分化，或机体对疾病和感染的反应。细胞因子通过与靶细胞表面的细胞因子受体特异结合而触发或刺激靶细胞产生特异性应答，发挥生物学效应，包括促进靶细胞的增殖、分化，增强抗感染和杀肿瘤细胞效应，促进或抑制其他细胞因子的合成，促进炎症反应，影响细胞代谢等。细胞因子作为人体的一种“免疫激素”，对人体免疫调节和各种疾病的防治，都有着极其重要和无可替代的作用。细胞因子可用于治疗肿瘤、感染性疾病、造血功能障碍等疾病，或作为佐剂与疫苗共用，预防感染性疾病。

What Are Cytokines?

Cytokines are small signaling molecules produced by cells and serve as molecular messengers for cellular communication. They can be classified as proteins, peptides, and glycoproteins. Cytokines can also trigger the immune system for body to respond to diseases and mediate normal cellular processes in the body.

Types of Cytokines

Functionally, cytokines are diverse and can be divided into different types of:

- Colony stimulating factors (stimulate production of blood cells).
- Growth and differentiation factors (function primarily in development).
- Immunoregulatory and proinflammatory (促炎的) cytokines (interferon, interleukins, and TNF-alpha that function in the immune system).

How Cytokines Work

The immune system is complex-different types of immune cells and proteins do different jobs. Cytokines are released by cells into the circulation or directly into tissue. The cytokines locate target immune cells and interact with receptors on the target immune cells by binding to them. The interaction triggers or stimulates specific responses by the target cells.

Cytokine analogues and cytokine mimics

Biopharmaceuticals of natural growth factors and cytokines comprise a huge and growing market. Blockbusters (重磅炸弹,了不起的人或事) such as EPO ($12B, 2006 worldwide sales), Insulins ($9B), Interferons ($7B), GCSF ($4. 5B), and hGH ($2. 5B) are the most commercially successful members of the cytokine family and there are dozens more currently-marketed and potentially-useful protein agents for a growing number of important indications (指征, 适应证). Because they address important and otherwise unmet medical needs, these agents have attained great commercial success despite significant shortcomings, including serious side effects, immunogenicity, short half-lives, poor chemical stability, and high cost. Therefore, an opportunity exists to develop new medicines that mimic the desired activities, but overcome the deficiencies of the natural cytokine (激动剂).

New and superior "designer" cytokine drugs (novel cytokine and growth factor drugs) have being investigated, with new tissue and signaling pathway specificities to enhance the positive actions and reduce the negative effects of the natural pleiotropic (多效的,多效性的,多向性的) proteins.

Another potential drug sources to be discovered and developed are small compounds that activate cytokine receptors in the same fashion as the natural factors, but differ completely in their chemical composition from the natural protein ligands. These novel compounds have equivalent or greater agonist bioactivities, improved medicinal properties (PK, safety, etc.), and manufacturing economics superior to the marketed protein products.

Role of STATs in Normal Signal Transduction

Signal transducer and activator of transcription (STAT,信号转导子和转录活化子) proteins are important intracellular mediators of cytokine-induced signal transduction (信号转导) pathway. The following sequence of events illustrates the prevailing model of the role of STATs in normal signaling (Fig. 2 – 1). This signal cascade initiates when cytokines (such as IFNs and members of the interleukin [IL] family) or growth factors (epidermal growth factor and platelet-derived growth factor, for example) bind to their cognate (相应的) cell surface receptors. Growth factor receptors possess intrinsic tyrosine kinase (激酶) activity and phosphorylate (使磷酸化) STATs directly, thereby activating STAT signaling. In contrast, cytokine receptors lack intrinsic kinase activity and must recruit members of the Janus kinase (JAK, 蛋白酪氨酸

激酶) family of cytoplasmic tyrosine kinases to activate STATs. Depending on which STAT family members are activated, STATs may associate as homodimers or heterodimers and then translocate to the nucleus. The activated STAT dimers then bind to specific DNA-response elements in promoters and induce expression of target genes.

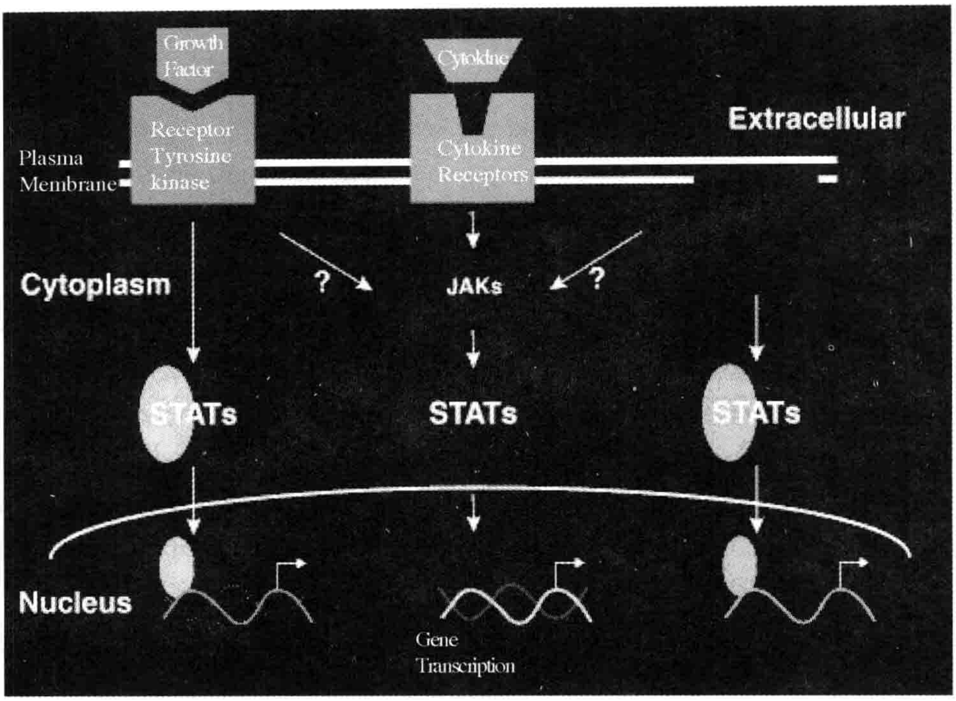

Figure 2-1. Signal transduction pathways leading to STAT activation.

Stimulation with growth factors or cytokines at the cell surface results in receptor activation and subsequent tyrosine phosphorylation of STATs. Phosphorylation of STATs induces dimerization and translocation to the nucleus, where STAT dimers bind to specific STAT response elements and directly regulate gene expression. In contrast to normal signaling, oncogenic PTKs (蛋白酪氨酸激酶) constitutively activate STATs, leading to deregulated (失控) expression of STAT-dependent genes. In some cases, but not all, JAK family tyrosine kinases are known to have a role in STAT activation.

In order for cells to respond to their microenvironments, extracellular stimuli must be received and transmitted to the nucleus such that specific genetic programs are activated, resulting in cell-type-specific biological responses. Regulation of specific cellular responses to extracellular stimuli is primarily determined by integration of the various components involved in the signal transduction pathway. There are several mechanisms by which cells modulate (调整，调节) STAT signaling. For example, JAK family members associate selectively with specific cytokine receptor superfamily members. Thus, depending on ligand and cell type, multiple STAT family members may become activated. Since STAT proteins homodimerize or heterodimerize, the level of signaling diversity increases. In addition, the temporal duration of the STAT activation is another potential mechanism for modulation of the response. In normal signaling, activation of STATs occurs rapidly, but the induction is transient. Finally, activation of parallel signaling pathways, such as mitogen-activated protein (MAP) kinases, also contributes to the complexity of signal transduction.

Interferons(干扰素)

Interferons (**IFNs**) are proteins made and released by host cells in response to invasion of pathogens such as viruses, bacteria, parasites or tumor cells. They allow for communication between cells to trigger the protective defenses of the immune system that eradicate pathogens or tumors.

IFNs belong to a large class of glycoproteins (糖蛋白), which is a superfamily of cytokines. Interferons are named after their ability to "interfere" with viral replication within host cells. IFNs have other functions: they activate immune cells, such as natural killer cells and macrophages; they increase recognition of infection or tumor cells by up-regulating antigen presentation to T lymphocytes; and they increase the ability of uninfected host cells to resist new infection by virus. Certain host symptoms, such as aching muscles and fever, are related to the production of IFNs.

About ten distinct (不同的) IFNs have been identified in mammals, seven of them are found in humans. They are typically categorized into three IFN classes: Type I IFN, Type Ⅱ IFN, and Type Ⅲ IFN. All IFN classes are very important for fighting viral infections.

Types of interferon

On basis of signalling types of receptors, human interferons have been classified into three major types.

- Interferon type Ⅰ: All type I IFNs bind to a specific cell surface receptor complex known as the IFN-α receptor (IFNAR) that consists of IFNAR1 and IFNAR2 chains. The type I interferons present in humans are IFN-α, IFN-β and IFN-ω.
- Interferon type Ⅱ: Binds to IFNGR that consists of IFNGR1 and IFNGR2 chains. In humans this is IFN-γ.
- Interferon type Ⅲ: Signal through a receptor complex consisting of IL10R2 (also called CRF2-4) and IFNLR1 (also called CRF2-12). Acceptance of this classification is less universal than that of type I and type Ⅱ, and unlike the other two, it is not currently included in Medical Subject Headings (医学主题词表,医学主题词分类).