分子生物学绪论

Introduction to Molecular Biology

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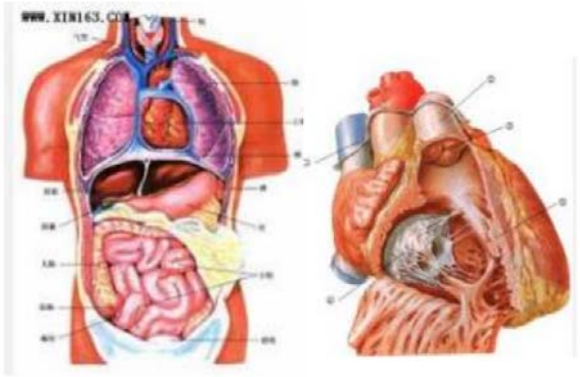
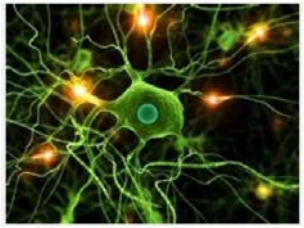
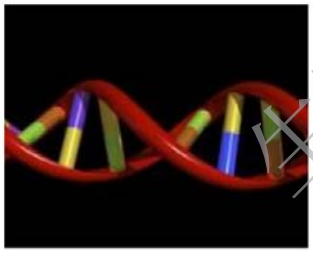
生命的奇迹蕴藏着无穷的奥秘







临床表现

器官、组织

细胞

基因

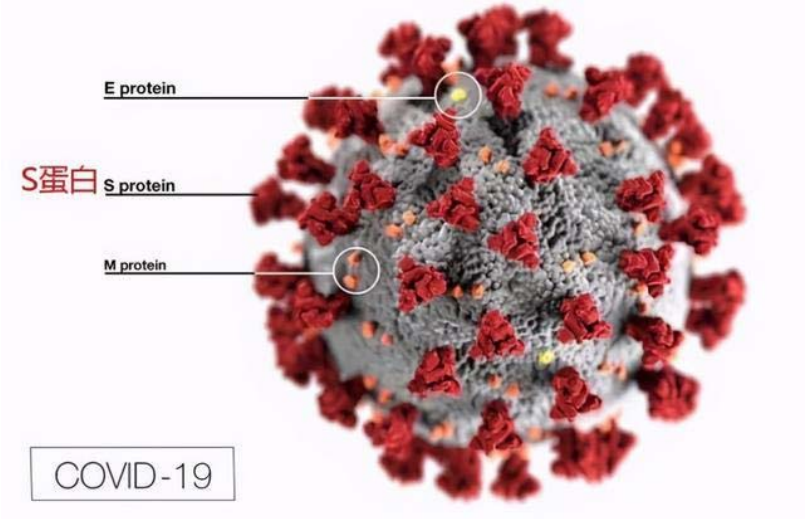
调控（机制）

器官运动 ⟵ 器官 ⟶ 器官相互作用

细胞运动 ⟵ 细胞 ⟶ 细胞相互作用

分子运动 ⟵ 分子 ⟶ 分子相互作用

疫苗是世界恢复秩序的希望



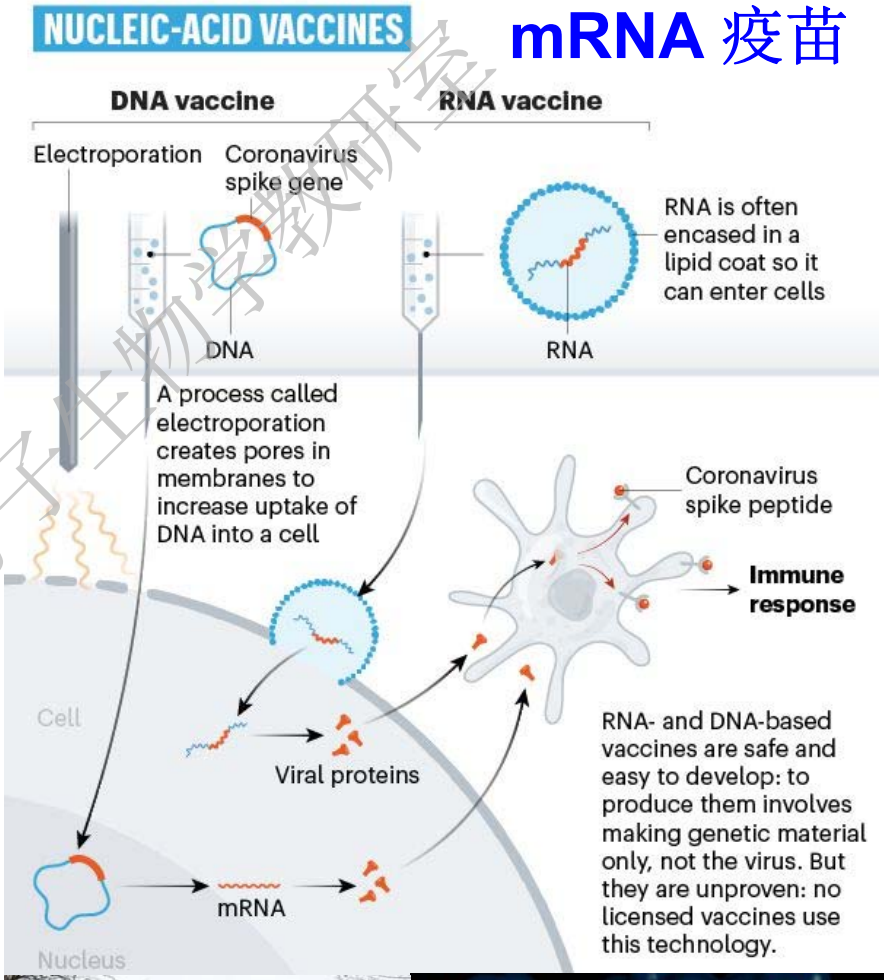
新冠灭活疫苗

中国生物、国药集团、北京科兴

腺病毒载体疫苗

康希诺

mRNA 疫苗



How elephants avoid cancer?

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News & Comment > News > 2019 > May > Article

NATURE | NEWS

How elephants avoid cancer

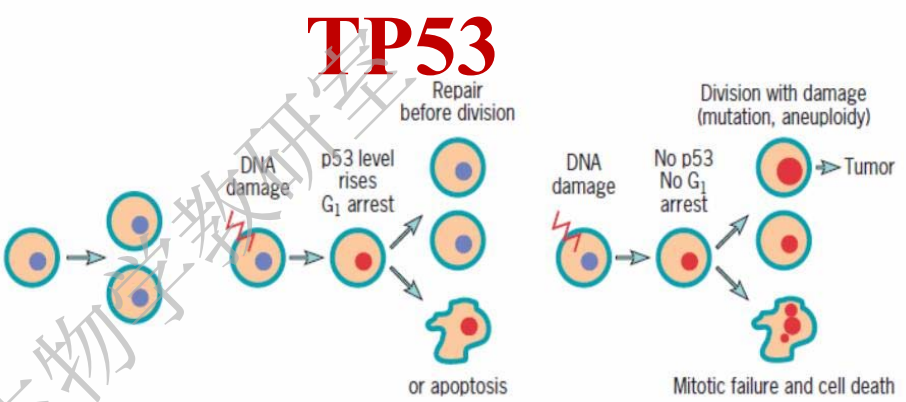
Pachyderms have extra copies of a key tumour-fighting gene.

Ewen Callaway

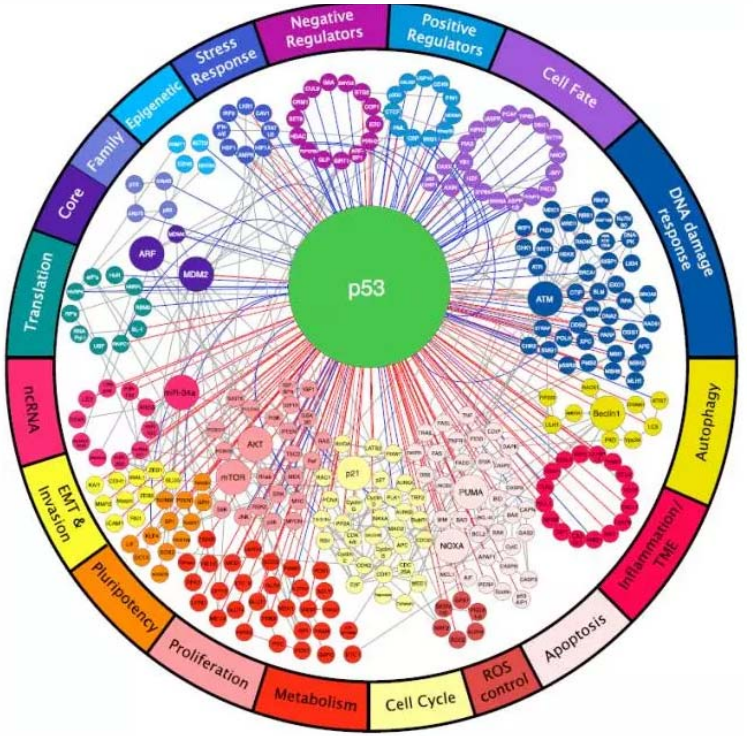
佩托悖论(Peto's Paradox)：癌症发病率与动物的体型或年龄关系并不大

Theo Allofs/Minden Pictures/FLPA

Multiple copies of a tumour-suppressor gene help elephants avoid cancer.



Cell and *Molecular Biology* (© John Wiley & Sons 2010)



p53——基因组卫士

DNA 损伤

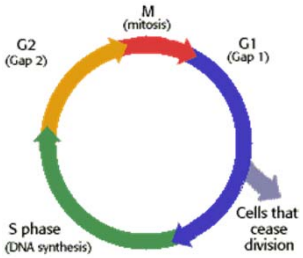
野生型 p53

抑癌基因

点突变

突变型 p53

癌基因



抑制细胞周期

启动DNA修复

修复成功

继续细胞周期

修复失败

诱发细胞凋亡

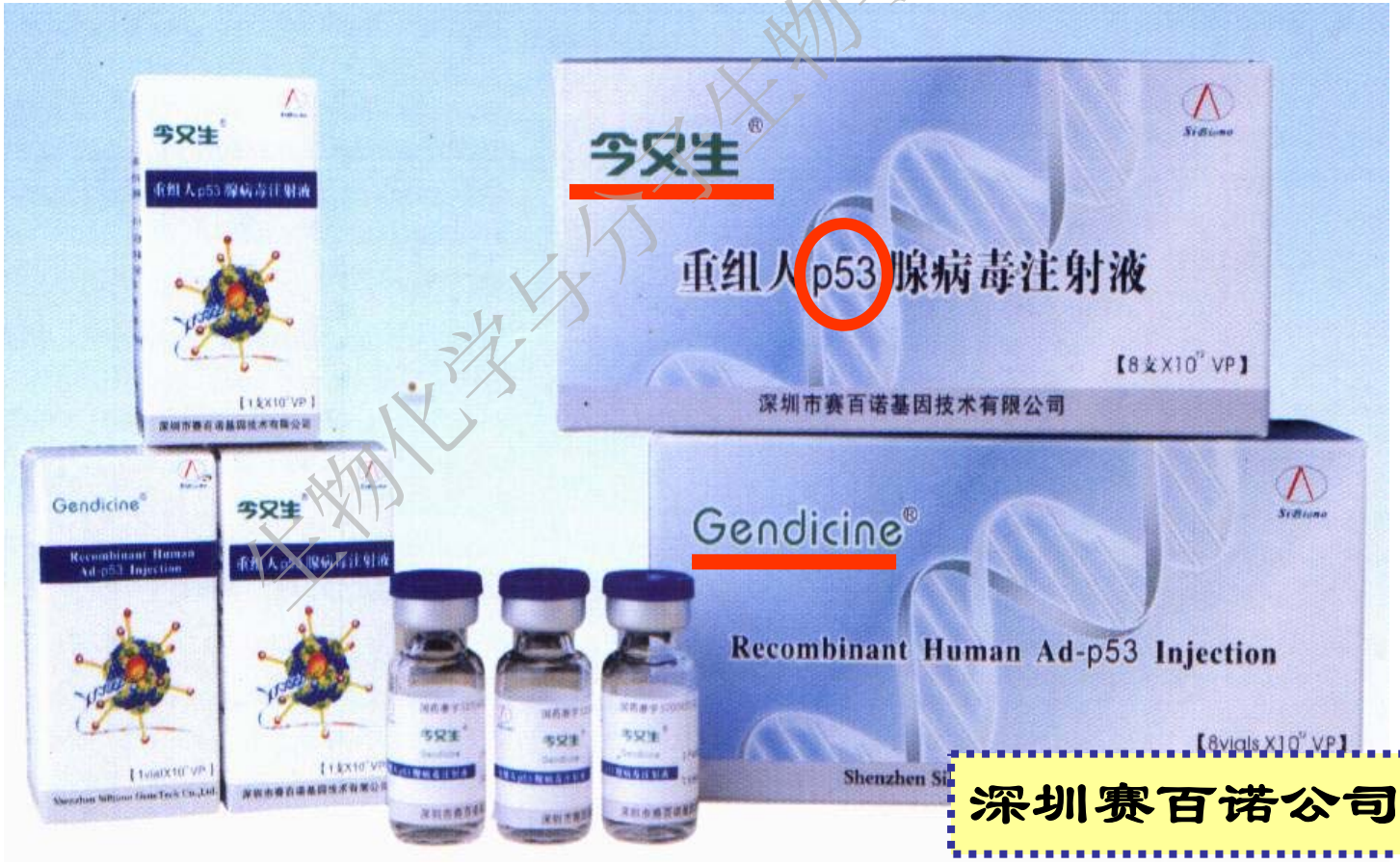
50% 肿瘤相关性

中国视角

http://www.sibiono.com/index.aspx

2004年3月

世界首个上市的基因治疗产品



深圳赛百诺公司

彭朝晖——“今又生”的发明人

赛百诺公司首席执行官

告别奶茶，喝绿茶吧！

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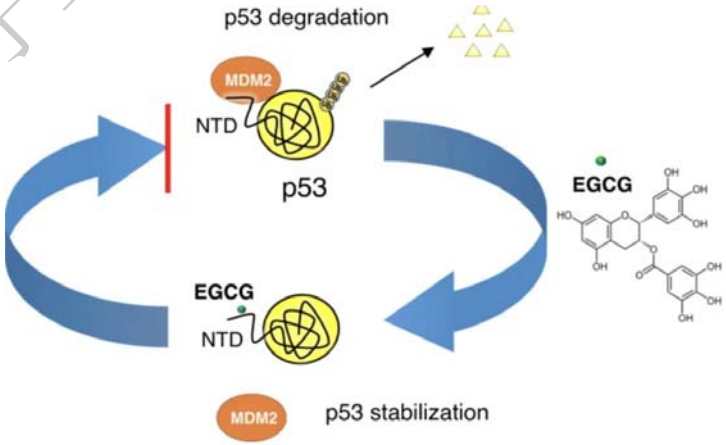
Article | Open Access | Published: 12 February 2021

EGCG binds intrinsically disordered N-terminal domain of p53 and disrupts p53-MDM2 interaction

Jing Zhao, Alan Blayney, [...] Chunyu Wang

Nature Communications **12**, Article number: 986 (2021) | Cite this article

表没食子儿茶素没食子酸酯（**EGCG**）是绿茶中的多酚类物质（儿茶素类），具有抗癌的功效。



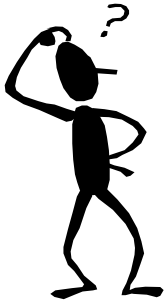
EGCG通过与p53的N末端结合来破坏p53-MDM2的相互作用

主要内容

分子生物学简介

分子生物学的发展历程

课程内容及考核要求



分子生物学

- Molecular Biology

- 研究核酸、蛋白质等生物大分子的结构与功能及其在遗传信息传递中的作用和功能等内容的一门前沿学科。

与生物化学的关系

分子生物学是生物化学的重要组成部分，是生物化学的发展和延续。

20世纪下半叶，生物化学进入其发展的分子生物学时期，研究手段融入了生理学、细胞生物学、遗传学、免疫学、生物信息学等的理论和技术。

为何学分子生物学

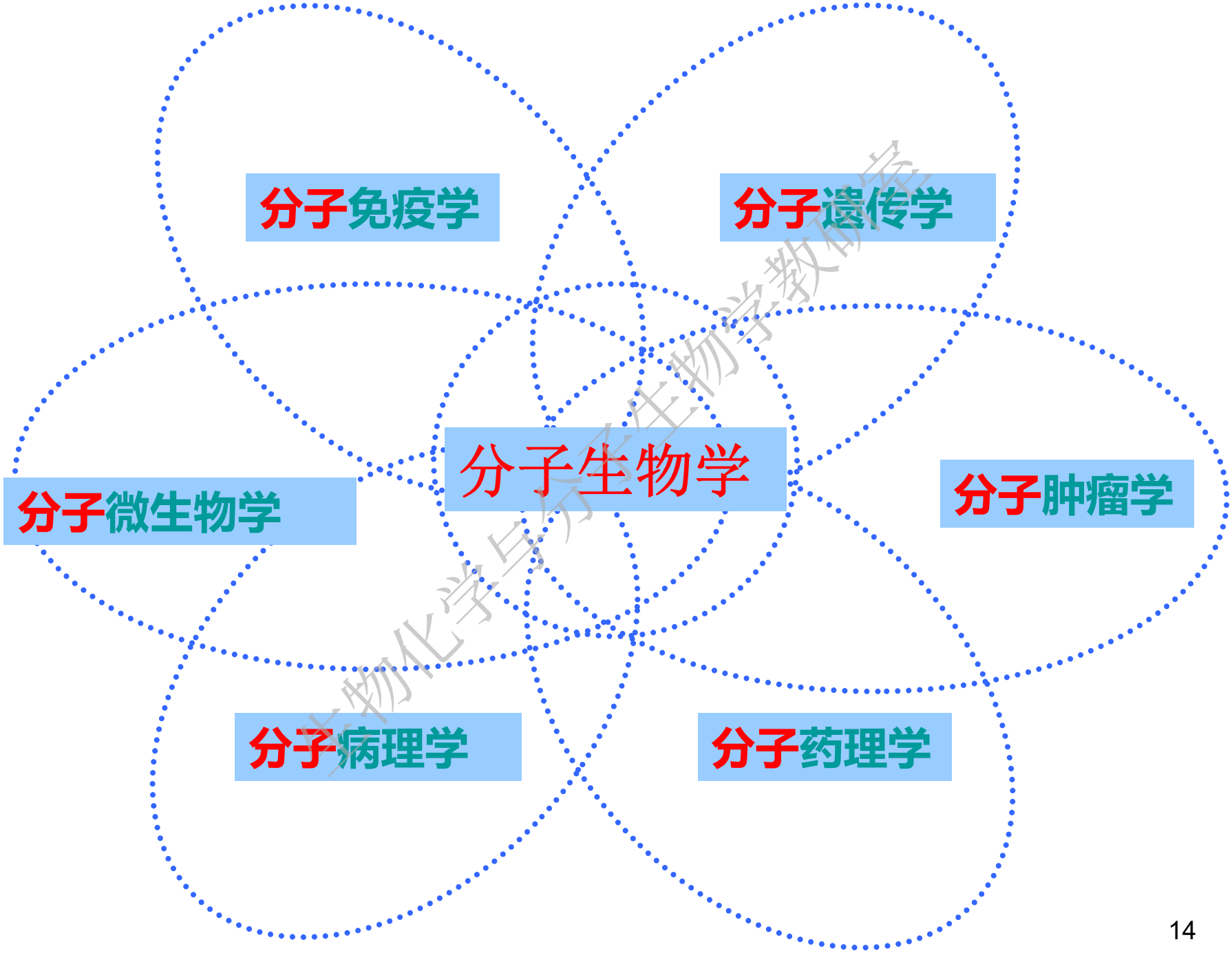
重要的医学专业基础课之一

与临床医学关系密切

渗透到医学学科的各个领域

与临床医学关系密切

- 阐明了某些疾病的致病机理
- 为临床疾病的诊断、治疗和预后提供检测方法、指标
- 协助阐明某些药物的作用机理，并为某些疾病的治疗提供新药研究的方向(利福平、赫赛汀)
- 分子生物学技术的发展为某些疾病的诊断和治疗奠定了基础



分子生物学在解码生命
Decoding life中取得了辉煌成就

1901年—2018年

85项诺贝尔奖颁给了生物化学与分子生物学领域

分子生物学发展历程

标志：1953年，Watson和Crick提出DNA的双螺旋结构模型

1958年：Crick提出遗传中心法则

60年代：遗传密码的破译

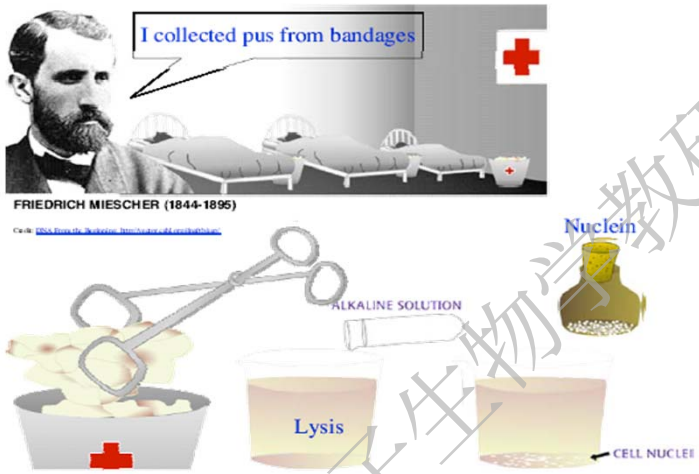
70年代：DNA重组技术、测序技术

80年代：PCR技术

90年代：个体克隆技术

人类基因组计划（HGP）

Milestones of molecular biology



Friedrich Miescher

米歇尔(1844-1895)

Albrecht Kossel

科赛尔(1853-1927)

1868年，瑞士科学家从脓细胞中提取到一种富含磷元素的酸性化合物

核　素(nuclein)

The Nobel Prize in Physiology or Medicine 1910

"in recognition of the contributions to our knowledge of cell chemistry made through his work on proteins, including the nucleic substances"

1885-1901年，Kossel等证实核酸由A、T、C、U四种碱基，核苷酸由碱基-戊糖-磷酸组成。

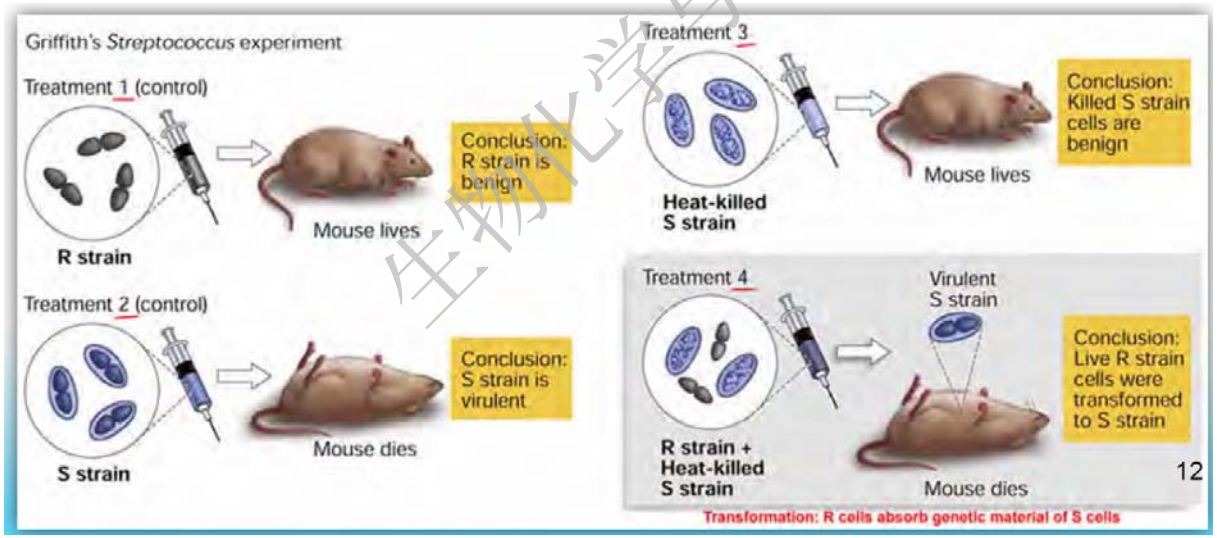
Milestones of molecular biology

DNA is genetic material

转化因子

Frederick Griffith
(1879-1941)

Oswald Theodore Avery
(1877-1955)

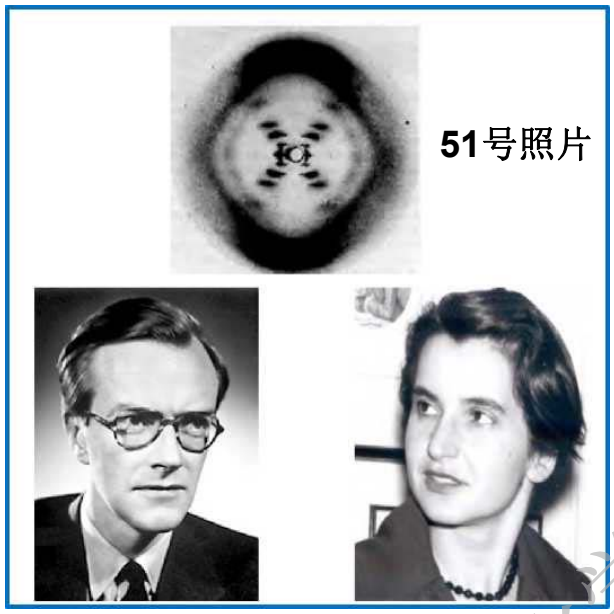


结构?

如何遗传?

Milestones of molecular biology

1962年诺贝尔生理与医学奖



Frederick Wilkins (1916-2004)

Rosalind Franklin (1920-1958)

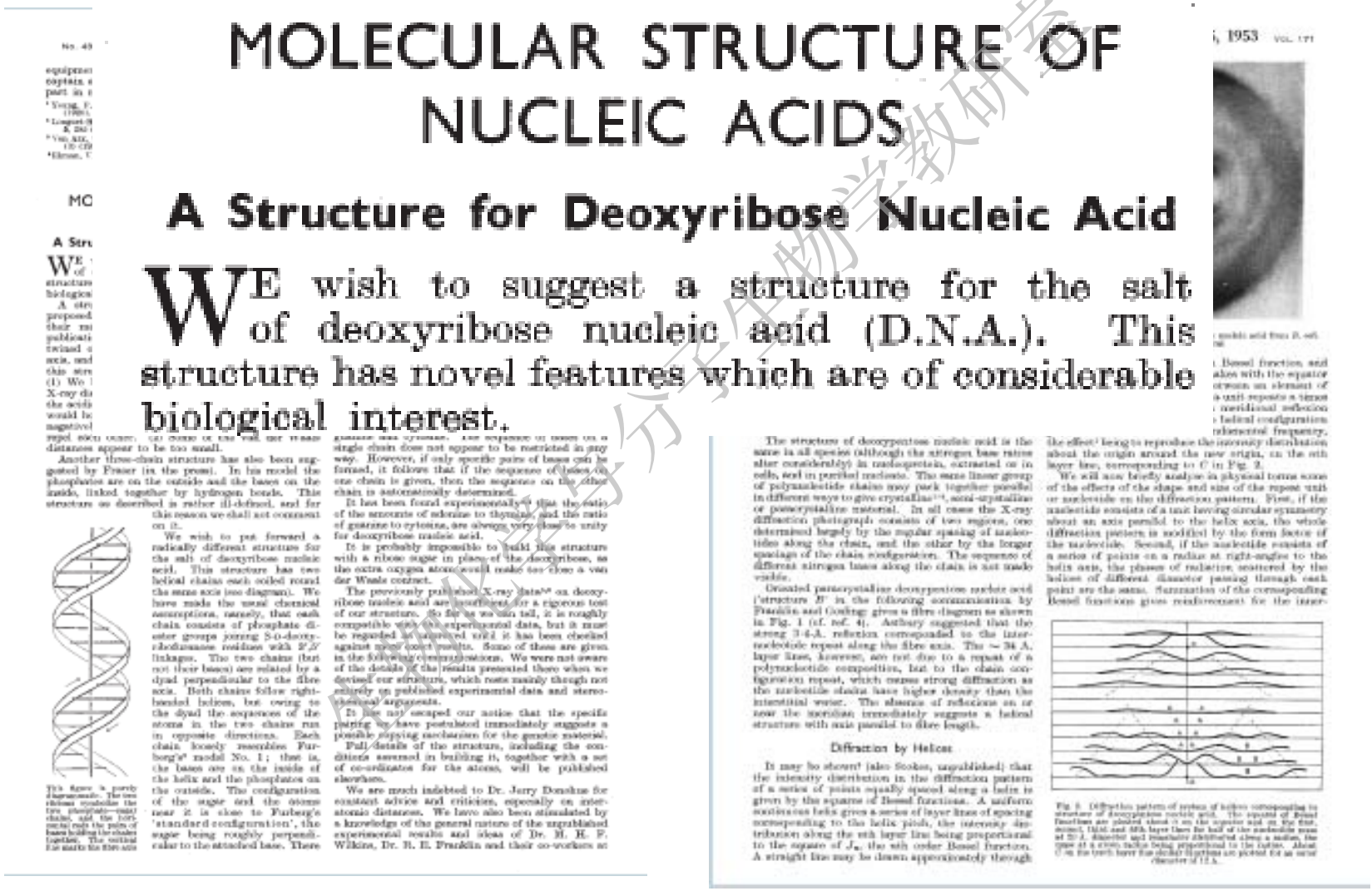
James Dewey Watson (1928-)

Francis Harry Comton Crick (1916-2004)

DNA双螺旋结构（1953）

The foundation of molecular biology

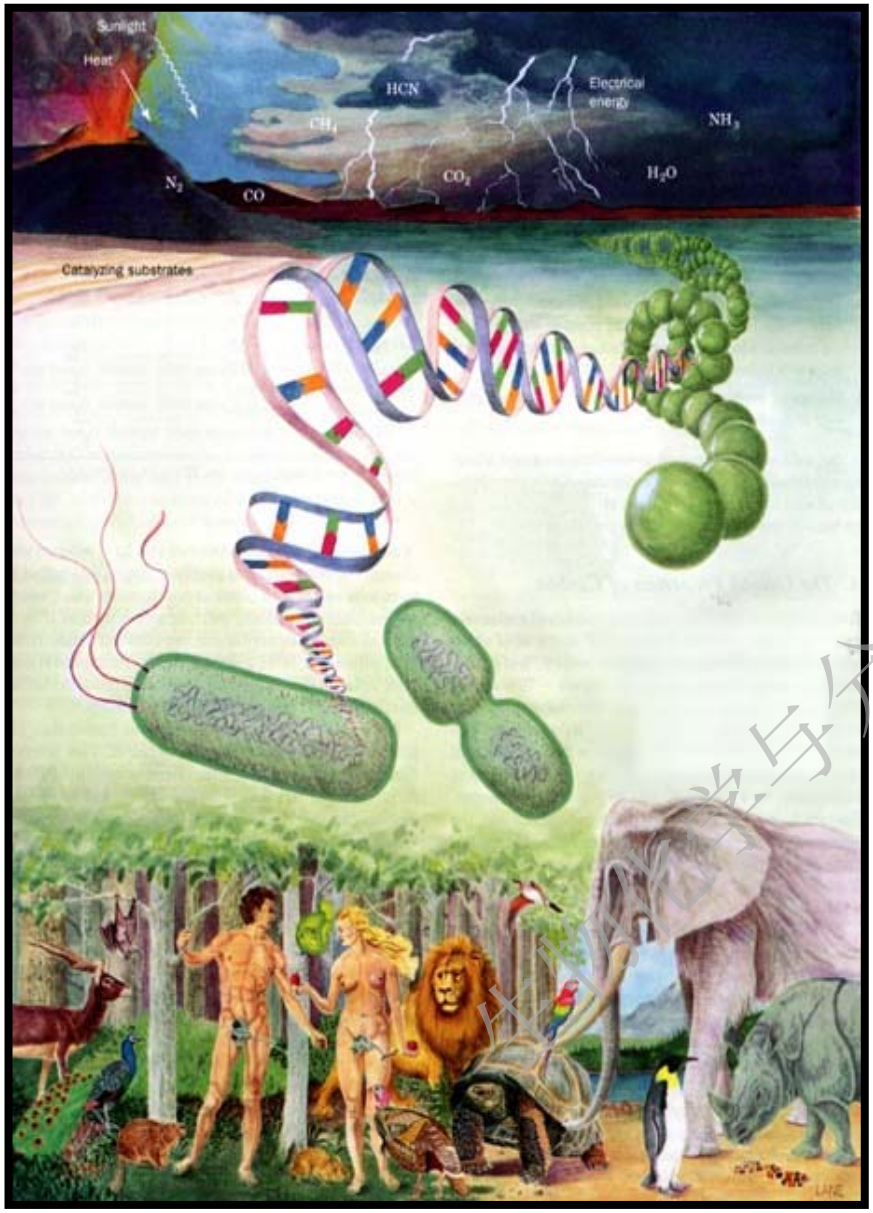
James Dewey Watson, Francis Harry Compton Crick



MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.



解码生命

Decoding life

DNA双螺旋带来的分子生物学重大理论突破

中心法则

DNA半保留复制机制

遗传密码的破译

操纵子学说的提出

蛋白质合成机制

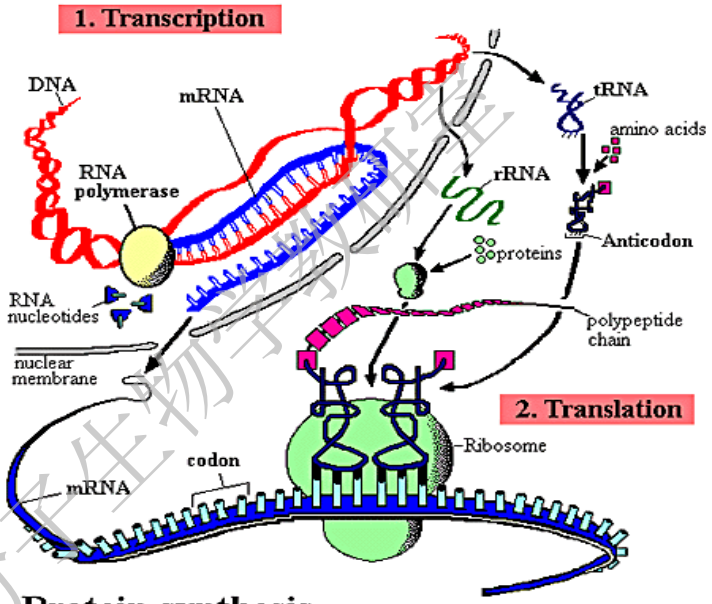
反转录机制

转录因子

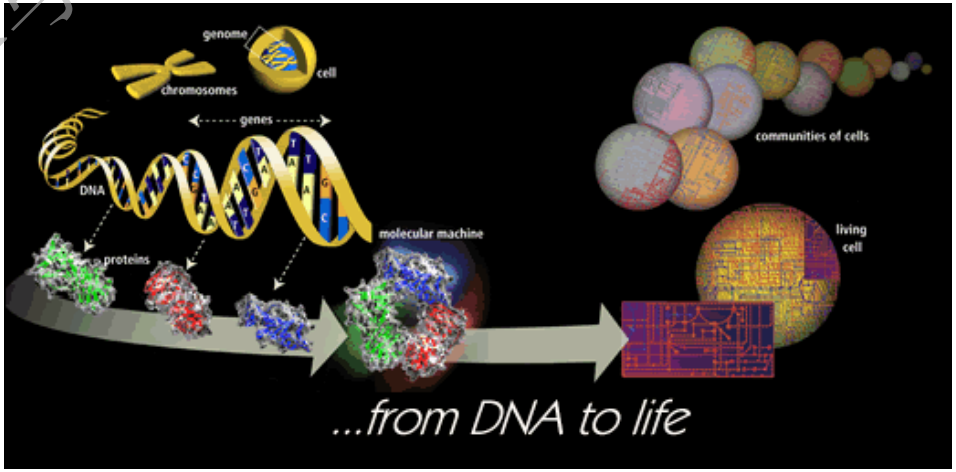
癌基因

蛋白质选择性降解

非编码**RNA**

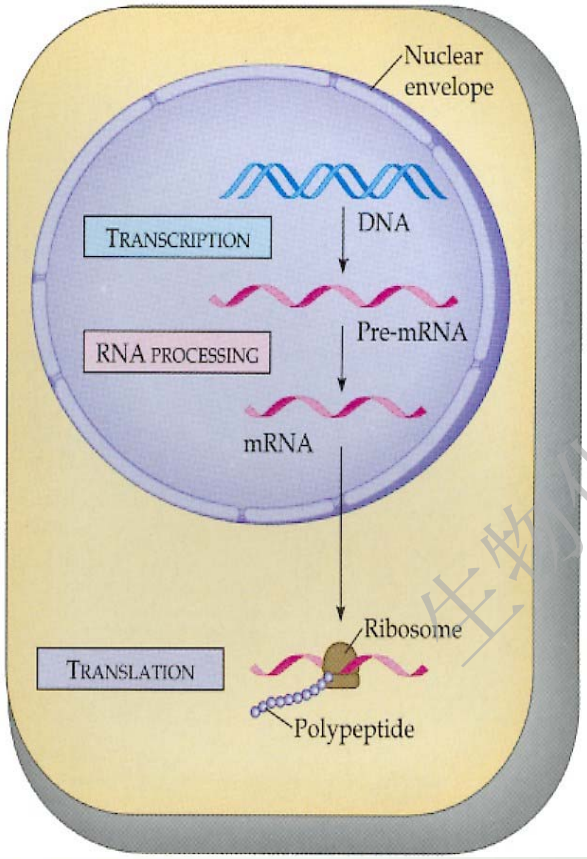


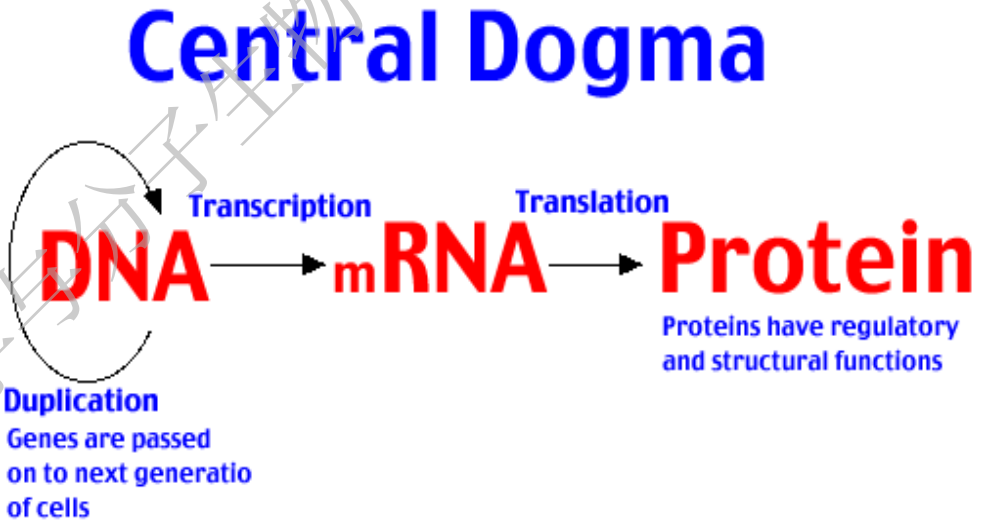
Protein synthesis



1958 - Francis Crick

首次提出了蛋白质合成的“中心法则”，即遗传信息的走向是由**DNA**传递给**RNA**，再由**RNA**传递给蛋白质。





1971年补充加入逆转录（仅见于病毒）

DNA复制机制

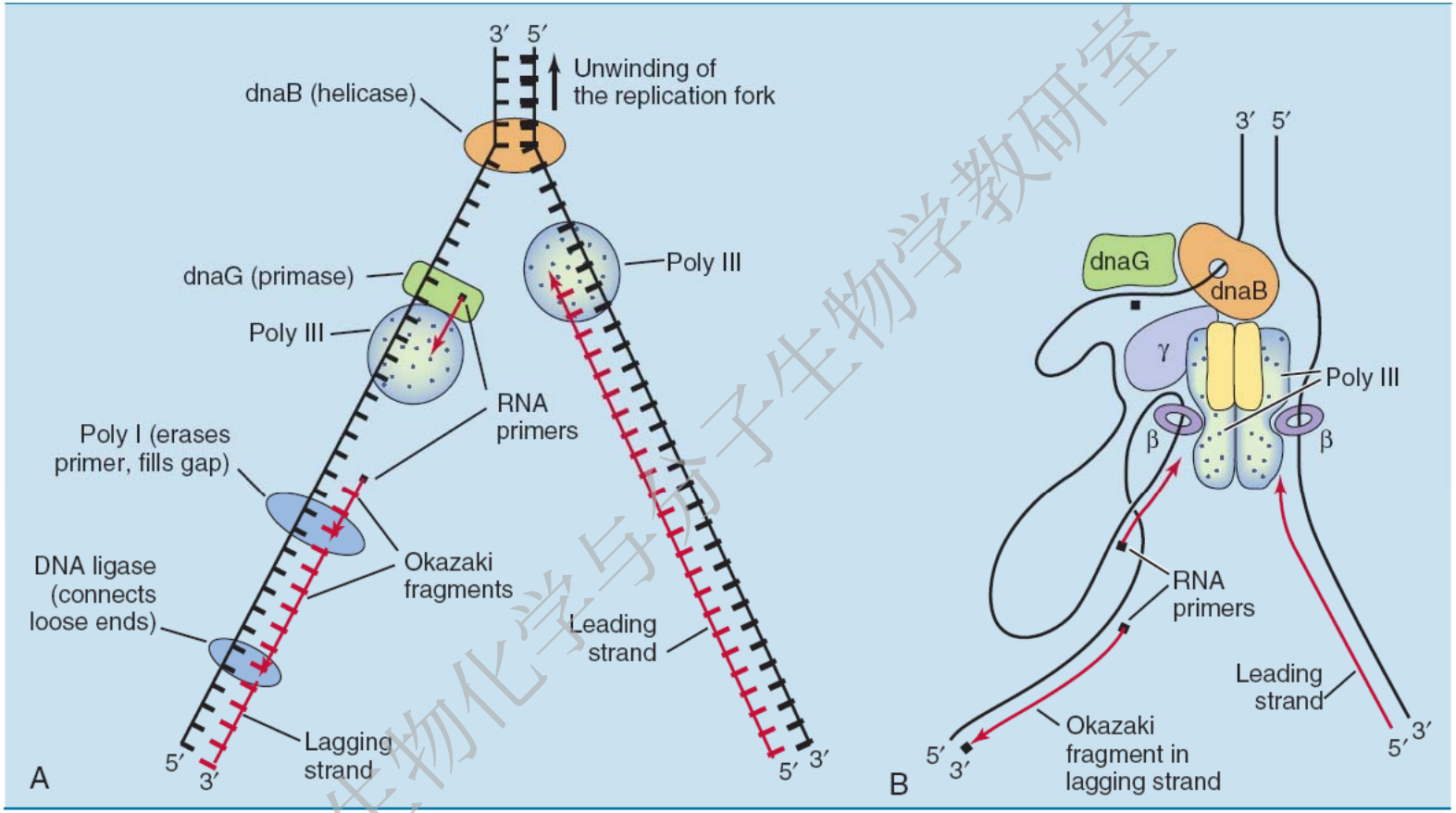


Fig. 6.15 Replication fork of *Escherichia coli*. **A,** Because new DNA can be synthesized only in the 5′→3′ direction, one of the two new strands (the "lagging strand") is synthesized piecemeal. The primer has to be removed from the lagging strand by DNA polymerase I (*Poly I*), and the Okazaki fragments have to be connected by DNA ligase. **B,** Model for the actual assembly of proteins in the bacterial replication fork. Note that the DNA template for the lagging strand has to spool through the β clamp backward to account for the direction of DNA synthesis. *β*, Clamp protein; *γ*, clamp loader; *dnaB*, helicase; *dnaG*, primase; *Poly III*, DNA polymerase III.

1961 - Holley, Khorana & Nirenberg

1865

破译遗传密码，揭示了DNA编码的遗传信息是如何传递给蛋白质的秘密，为基因工程的发展奠定了理论基础。

The Nobel Prize in Physiology and Medicine（1968）

Robert Holley, Gobind Khorana
& Marshall Nirenberg

遗 传 密 码 表

第一位（5'端）	第二位 U	第二位 C	第二位 A	第二位 G	第三位（3'端）
U	UUU phe	UCU ser	UAU tyr	UGU cys	U
	UUC phe	UCC ser	UAC tyr	UGC cys	C
	UUA leu	UCA ser	UAA 终止	UGA 终止	A
	UUG leu	UCG ser	UAG 终止	UGG trp	G
C	CUU leu	CCU pro	CAU his	CGU arg	U
	CUC leu	CCC pro	CAC his	CGC arg	C
	CUA leu	CCA pro	CAA gln	CGA arg	A
	CUG leu	CCG pro	CAG gln	CGG arg	G
A	AUU ile	ACU thr	AAU asn	AGU ser	U
	AUC ile	ACC thr	AAC asn	AGC ser	C
	AUA ile	ACA thr	AAA lys	AGA arg	A
	AUG 起始	ACG thr	AAG lys	AGG arg	G
G	GUU val	GCU ala	GAU asp	GGU gly	U
	GUC val	GCC ala	GAC asp	GGC gly	C
	GUA val	GCA ala	GAA glu	GGA gly	A
	GUG val	GCG ala	GAG glu	GGG gly	G

60年代分子生物学最辉煌的成就

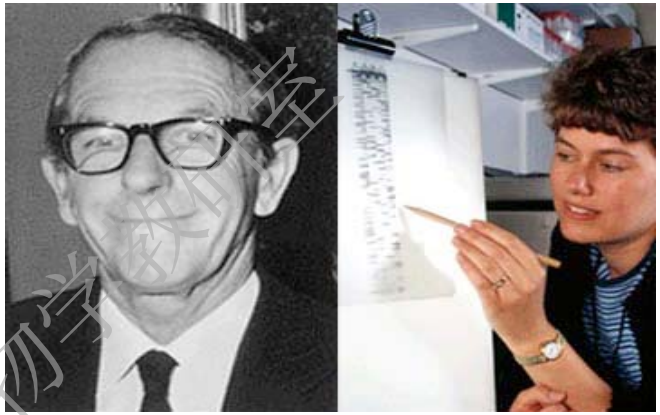
DNA双螺旋带来的分子生物学重大技术突破

Paul Berg

(1926-)

DNA重组技术

1972



Frederick Sanger

(1918-2013)

双脱氧链终止法测序

1978

Kary B. Mullis

(1944-2019)

PCR技术

1986

The Nobel Prize in Chemistry 1980

Paul Berg

Walter Gilbert

Frederick Sanger

The Nobel Prize in Chemistry 1980 was divided, one half awarded to Paul Berg *"for his fundamental studies of the biochemistry of nucleic acids, with particular regard to recombinant-DNA"*, the other half jointly to Walter Gilbert and Frederick Sanger *"for their contributions concerning the determination of base sequences in nucleic acids"*.

Frederick Sanger
Facts （1918-2013）

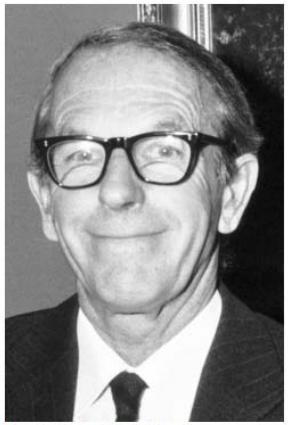


Photo from the Nobel Foundation archive.

Frederick Sanger
The Nobel Prize in Chemistry 1980

Born: 13 August 1918, Rendcombe, United Kingdom

Died: 19 November 2013, Cambridge, United Kingdom

Affiliation at the time of the award: MRC Laboratory of Molecular Biology, Cambridge, United Kingdom

Prize motivation: "for their contributions concerning the determination of base sequences in nucleic acids."

Prize share: 1/4

Also awarded: The Nobel Prize in Chemistry 1958

Work

1955 胰岛素一级结构的测定

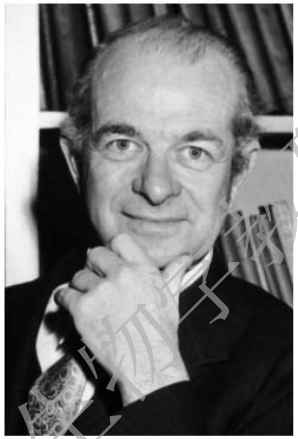
1958 Prize: Proteins, which are molecules made up of chains of amino acids, play a pivotal role in life processes in our cells. One important protein is insulin, a hormone that regulates sugar content in blood. Beginning in the 1940s, Frederick Sanger studied the composition of the insulin molecule. He used acids to break the molecule into smaller parts, which were separated from one another with the help of electrophoresis and chromatography. Further analyses determined the amino acid sequences in the molecule's two chains, and in 1955 Frederick Sanger identified how the chains are linked together.

1978 Sanger 测序法

1980 Prize: An organism's genome is stored in the form of long rows of building blocks, known as nucleotides, which form DNA molecules. An organism's genome can be mapped by establishing the order of the nucleotides within the DNA molecule. In 1977, Frederick Sanger developed a method based on using small amounts of what are known as dideoxynucleotides. These can be inserted into the DNA chain, but at a certain nucleotide they stop growth of the chain so that fragments of different lengths are created. After undergoing what is known as electrophoresis, the nucleotide sequences in a DNA sample can be identified.

1958、1980年诺贝尔化学奖

Linus Pauling
Facts （1901-1994）



Linus Carl Pauling
The Nobel Prize in Chemistry 1954

Born: 28 February 1901, Portland, OR, USA

Died: 19 August 1994, Big Sur, CA, USA

Affiliation at the time of the award: California Institute of Technology (Caltech), Pasadena, CA, USA

Prize motivation: "for his research into the nature of the chemical bond and its application to the elucidation of the structure of complex substances."

Prize share: 1/1

Also awarded: The Nobel Peace Prize 1962

Work

1951 蛋白质的二级结构

1954 Prize: The development of quantum mechanics during the 1920s had a great impact not only on the field of physics, but also on chemistry. During the 1930s Linus Pauling was among the pioneers who used quantum mechanics to understand and describe chemical bonding - that is, the way atoms join together to form molecules. Linus Pauling worked in a broad range of areas within chemistry. For example, he worked on the structures of biologically important chemical compounds. In 1951 he published the structure of the alpha helix, which is an important basic component of many proteins.

1954诺贝尔化学奖

1962 Prize: The atom bombs dropped on Hiroshima and Nagasaki were a turning point in Linus Pauling's life. Together with other scientists he spoke and wrote against the nuclear arms race, and he was a driving force in the Pugwash movement. It sought to reduce the role of nuclear arms in international politics and was awarded the Peace Prize in 1995. In 1959, Linus Pauling drafted the famous "Hiroshima Appeal", the concluding document issued after the Fifth World Conference against Atomic and Hydrogen Bombs. He was one of the prime movers who urged the nuclear powers the USA, the Soviet Union and Great Britain to conclude a nuclear test ban treaty, which entered into force on 10 October 1963. On the same day, the Norwegian Nobel Committee announced that Linus Pauling had been awarded the Peace Prize that had been held over from 1962.

1962年诺贝尔和平奖

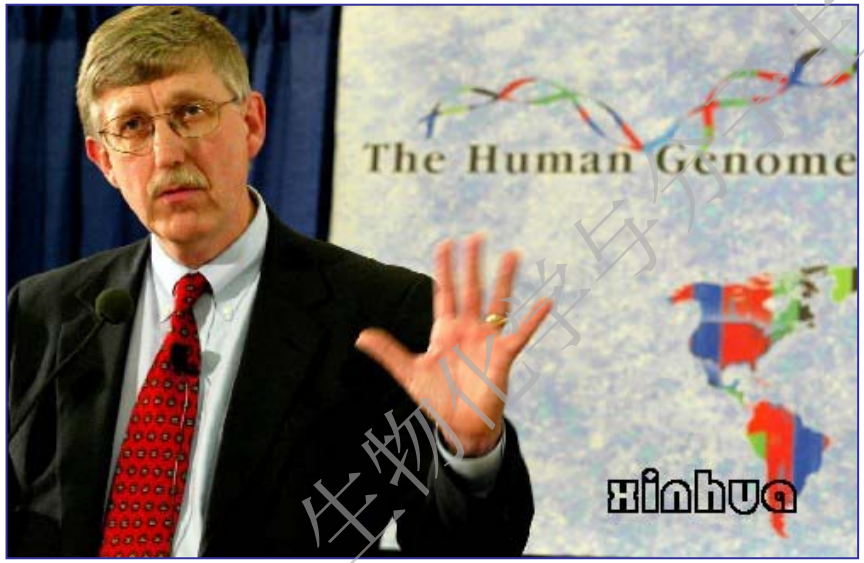
One person, Linus Pauling, has been awarded two undivided Nobel Prizes. In 1954 he was awarded the Nobel Prize in Chemistry. Eight years later he was awarded the Nobel Peace Prize for his opposition to weapons of mass destruction.

人类基因组计划 (Human Genome Program, HGP)

—生命科学的登月计划

基因组（genome）：生物个体全部的遗传信息

- **1990年正式启动（6国合作）**
- **2003年序列图绘制成功**



2003年4月14日，弗朗西斯·柯林斯：

人类基因组计划的所有目标全部实现

首份个人DNA图谱完成(2007)

首份亚洲人基因组图谱

炎黄一号，2007

ATGCCGATCGTACGACACATATCGTCATCGTACTGACTGTCTAGTCTAAACACATCCATCGTACTGACTGCATCGATCCATTTTA
TACTGACTGCATCGTACTGACTGCACATATCGTCATCGTACTGACTGTCTAGTCTAAACACATCCCACATATCGTTTACCCCATG
CATCGTACTGACTGTCTAGTCTAAACACATCCCACATATCGTCATCGTACTGACTGTCTAGTCTAAACACATCCCAGCATCCATC
CATATCGTCATCGTACTGACTGTCTAGTCTAAACACATCCTATGCCGATCGTACGACACATATCGTCATCGTACTGCCCTACGGG
ACTGTCTAGTCTAAACACATCCATCGTACTGACTGCATCGTACTGACTGCATCGTACTGACTGCACATATCGTCATACATAGACT
TCGTACTGACTGTCTAGTCTAAACACATCCCACATATCGTCATCGTACTGACTGTCTAGTCTAAACACATCCCACTTTACCCATG
ATATCGTCATCGTACTGACTGTCTAGTCTAAACACATCCCACATATCGTCATCGTACTGACTGTCTAGTCTAAACACATCCTATA
GCCGATCGTACGACACATATCGTCATCGTACTGCCCTACGGGACTGTCTAGTCTAAACACATCCATCGTACTGACTGCATCGTAC
TGACTGCATCGTACTGACTGCACATATCGTCATACATAGACTTCGTACTGACTGTCTAGTCTAAACACATCCCACATATCGTCAT
CGTACTGACTGTCTAGTCTAAACACATCCCACTTTACCCATGCATCGTACTGACTGTCTAGTCTAAACACATCCCACATATCGTC
ATCGTACTGACTGTCTAGTCTAAACACATCCCAGCATCCATCCATATCGTCATCGTACTGACTGTCTAGTCTAAACACATCCTAT
GCCGATCGTACGACACATATCGTCATCGTACTGCCCTACGGGACTGTCTAGTCTAAACACATCCATCGTACTGACTGCATCGTAC
TGACTGCATCGTACTGACTGCACATATCGTCATACATAGACTTCGTACTGACTGTCTAGTCTAAACACATCCCACATATCGTCAT
CGTACTGACTGTCTAGTCTAAACACATCCCACTTTACCCATGATATCGTCATCGTACTGACTGTCTAGTCTAAACACATCCCACA
TATCGTCATCGTACTGACTGTCTAGTCTAAACACATCCTATACATATCGTCATCGTACTGACTGTCTAGTCTAAACACATCCTAT
GCCGATCGTACGACACATATCGTCATCGTACTGCCCTACGGGACTGTCTAGTCTAAACACATCCATCGTACTGACTGCATCGTAC
TGACTGCATCGTACTGACTGCACATATCGTCATACATAGACTTCGTACTGACTGTCTAGTCTAAACACATCCCACATATCGTCAT
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TATCGTCATCGTACTGACTGTCTAGTCTAAACACATCCTATAGCCGATCGTACGACACATATCGTCATCGTACTGCCCTACGGGA
CTGTCTAGTCTAAACACATCCATCGTACTGACTGCATCGTACGCCGATCGTACGACACATATCGTCATCGTACTGCCCTACGGGA
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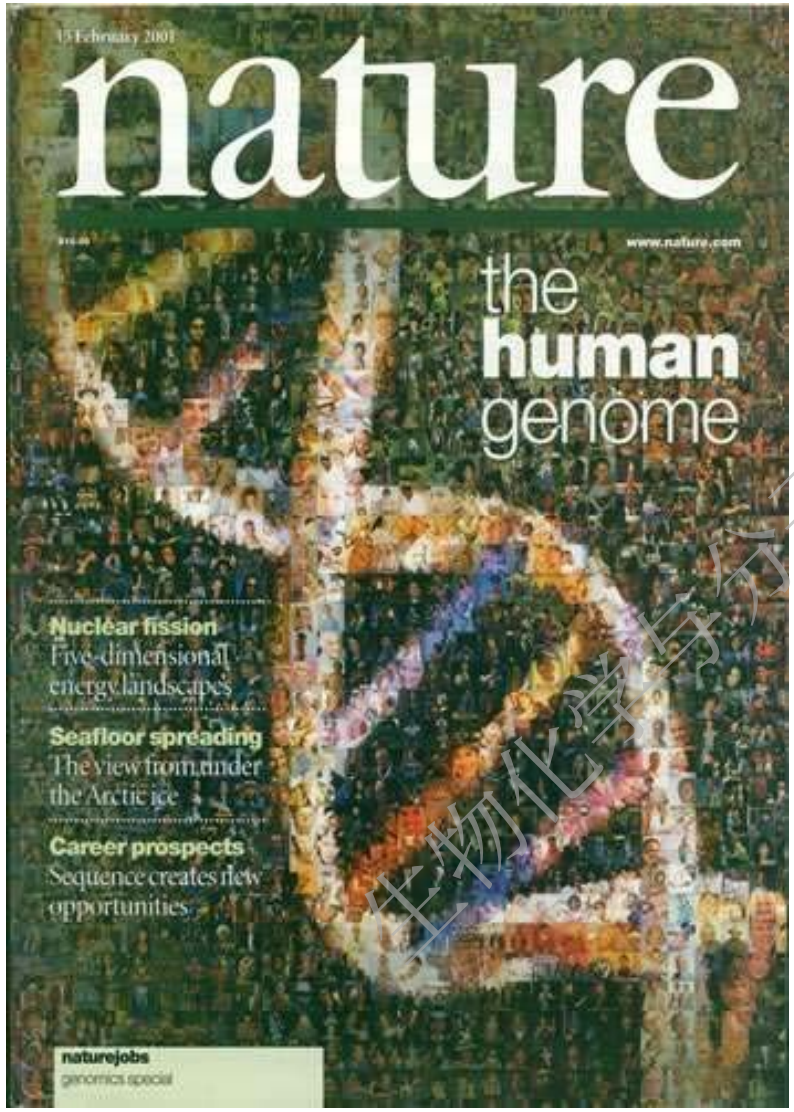
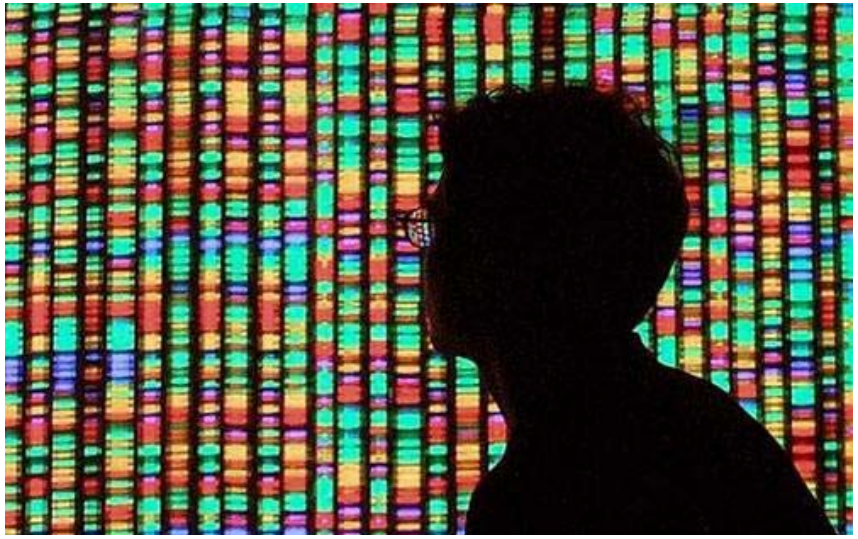
CGTACTGACTGTCTAGTCTAAACACATCCCACATATCGTCATCGTACTGACTGTCTAGTCTAAACACATCCCACTTTACCCATGC
ATCGTACTGACTGTCTAGTCTAAACACATCCCACATATCGTCATCGTACTGACTGTCTAGTCTAAACACATCCCAGCATCCATCC
ATATCGTCATCGTACTGACTGTCTAGTCTAAACACATCCTATGCCGATCGTACGACACATATCGTCATCGTACTGCCCTACGGGA
CTGTCTAGTCTAAACACATCCATCGTACTGACTGCATCGTACGACTGCATCGTACTGACTGCACATATCGTCATACATAGACTTC
GTACTGACTGTCTAGTCTAAACACATCCCACATATCGTCATCGTACTGACTGTCTAGTCTAAACACATCCCACTTTACCCATGAT
ATCGTCATCGTACTGACTGTCTAGTCTAAACACATCCCACACTGTCTAGTCTAAACACATCCATCGTACTGACTGCATCGTACGC
CGATCGTACGACACATATCGTCATCGTACTGCCCTACGGGACTGTCTAGTCTAAACACATCCATCGTACTGACTGCATCGTACTG

A book of life: The beauty of life is hidden here…

后基因组时代





功能基因组学研究

Functional genomics

确认每个基因的功能、各个基因之间的相互调控关系、基因信息如何整合以形成生物的特定功能。

- **基因组学(Genomics)**

  研究基因组的结构及基因之间的相互作用

- **蛋白质组学(Proteomics)**

  研究细胞内所有蛋白质的结构与功能

- **转录组学 (Transcriptomics)**

  研究细胞中所有**mRNA**

- **RNA组学 (RNomics)**

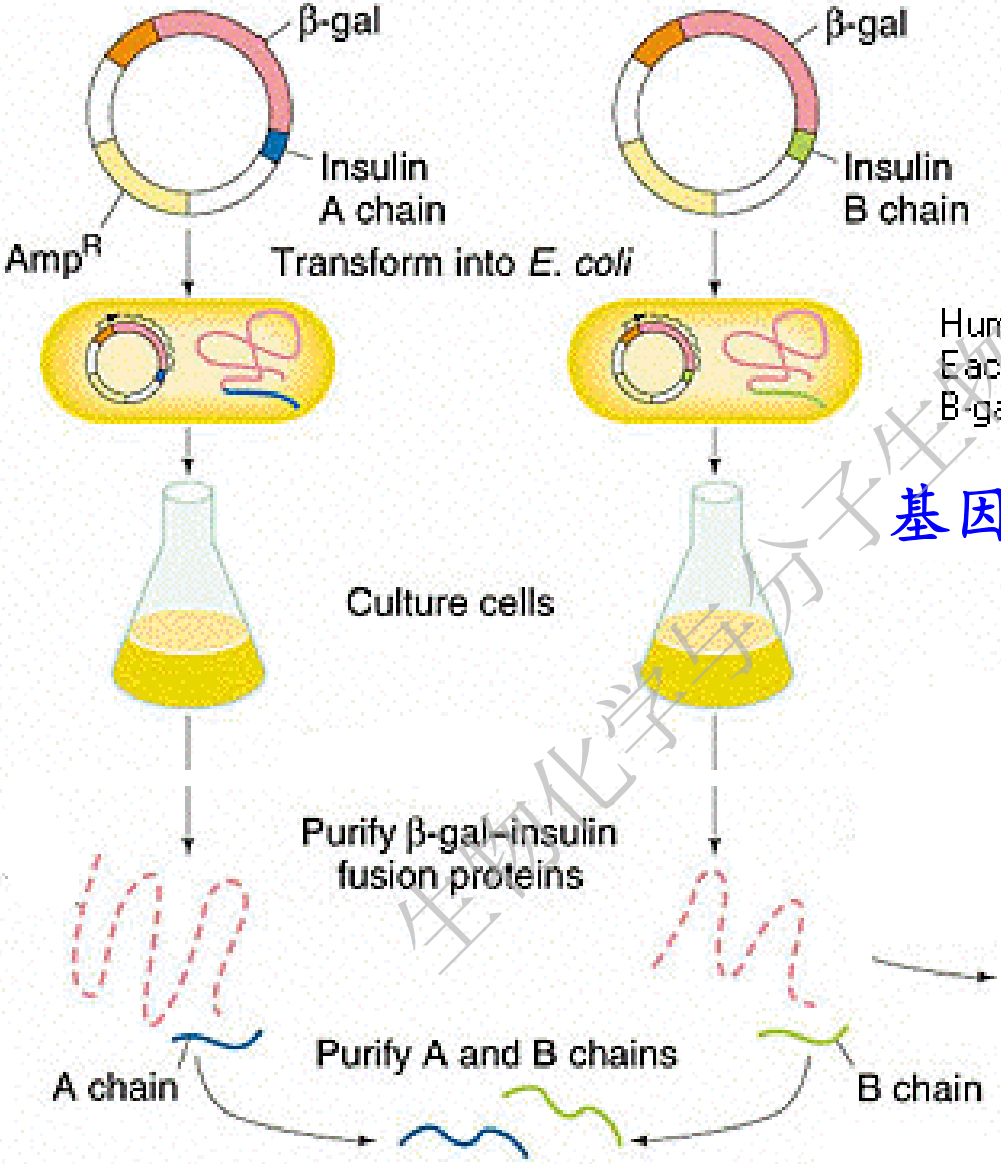
  研究除**mRNA**之外的全部小**RNA**

基因操作-改造生物体、设计生命

To create a new life

- 基因工程 –生物产业
- 转基因、基因打靶技术
- 细胞重编程
- 基因编辑
- 基因诊断与治疗

现代炼丹术—基因工程药物

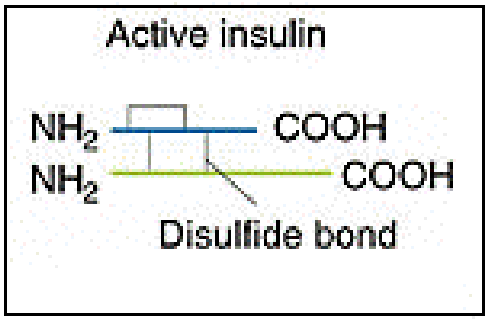


Cloning of human insulin in a bacterial host

(after Griffiths et al. 1996)

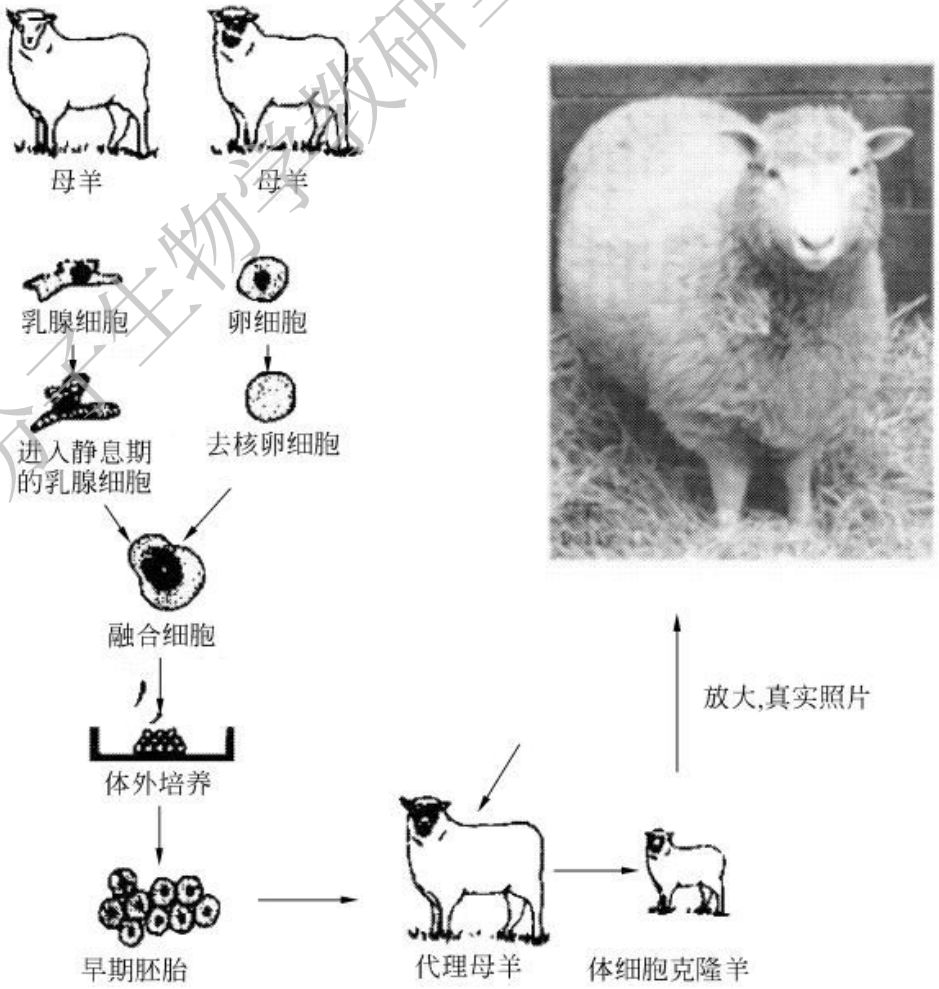
Human A- & B-chains are cloned separately.
Each is attached to the plasmid B-gal.
B-gal (+) colonies carry cloned insulin genes.

基因工程胰岛素的生产原理



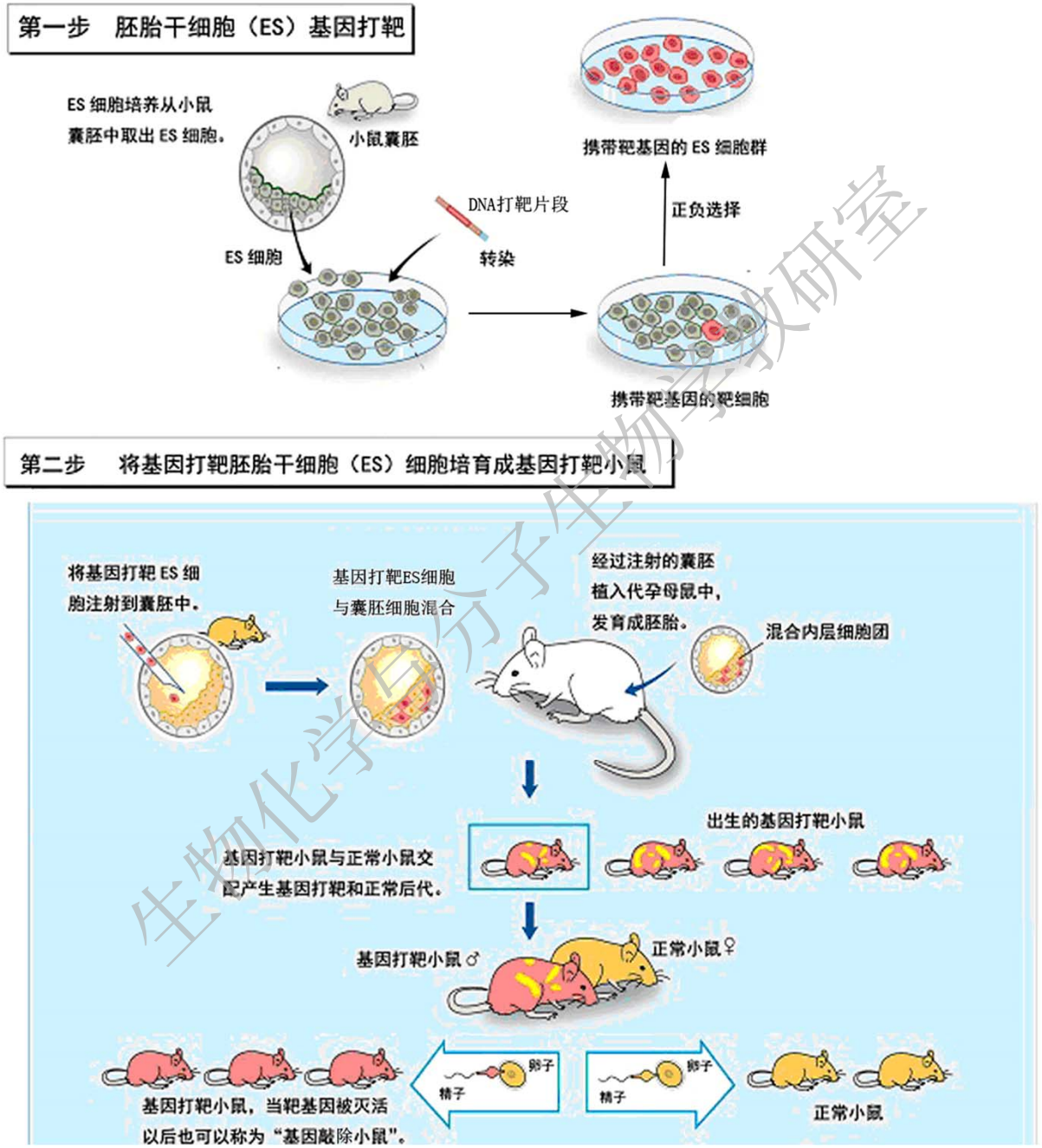
When cysteine residues are oxidized,
A- & B-chains spontaneously re-fold.

克隆羊多莉（1997-2003）



动物育种的革命

基因打靶的原理示意图

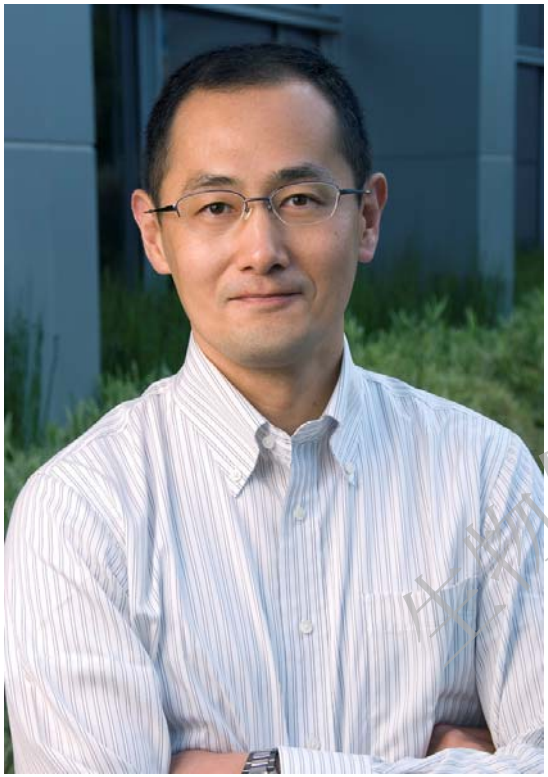


诱导多能干细胞
iPS（induced pluripotent stem cell）

2006 mouse iPS　Cell. 2006 Aug 25;126(4):663-76.

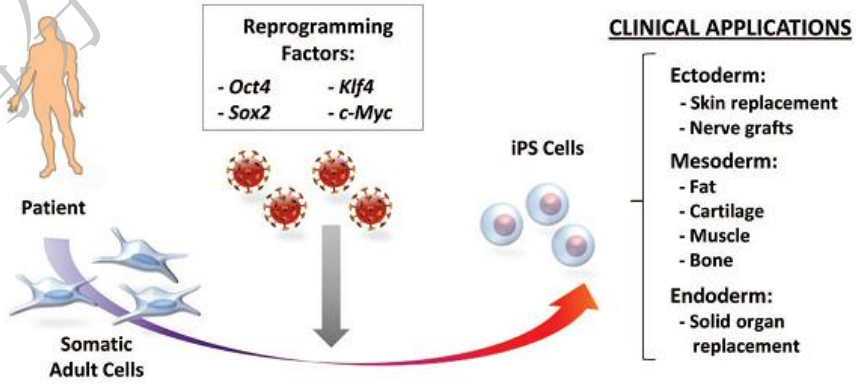
2007 human iPS　Cell. 2007 Nov 30;131(5):861-72

Science. 2007 Dec 21;318(5858):1917-20.



Shinya Yamanaka

成体细胞“返老还童”



Mouse Fibrobalsts

Human Fibrobalsts

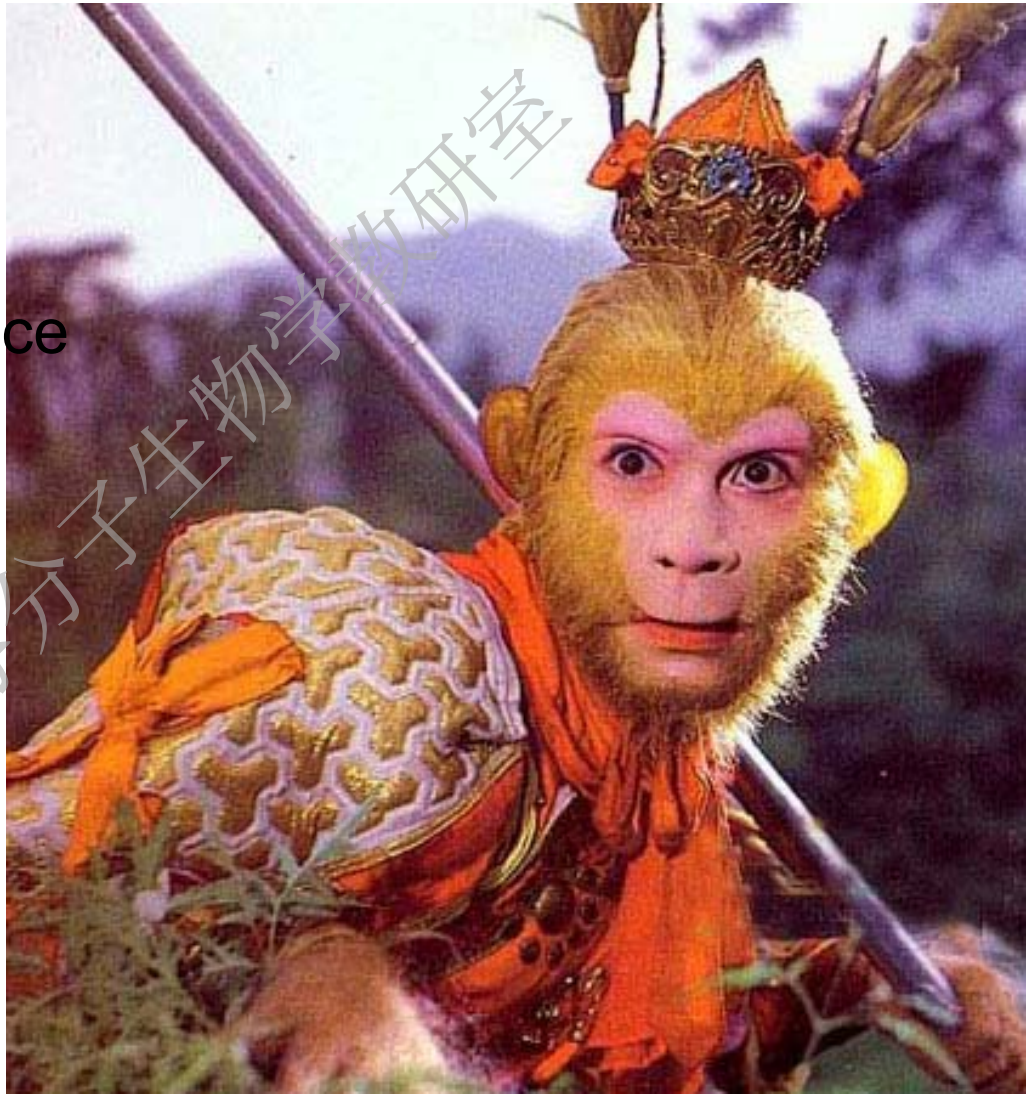
iPS Cells

2006 mouse iPS

2007 human iPS

2008 Diseases iPS

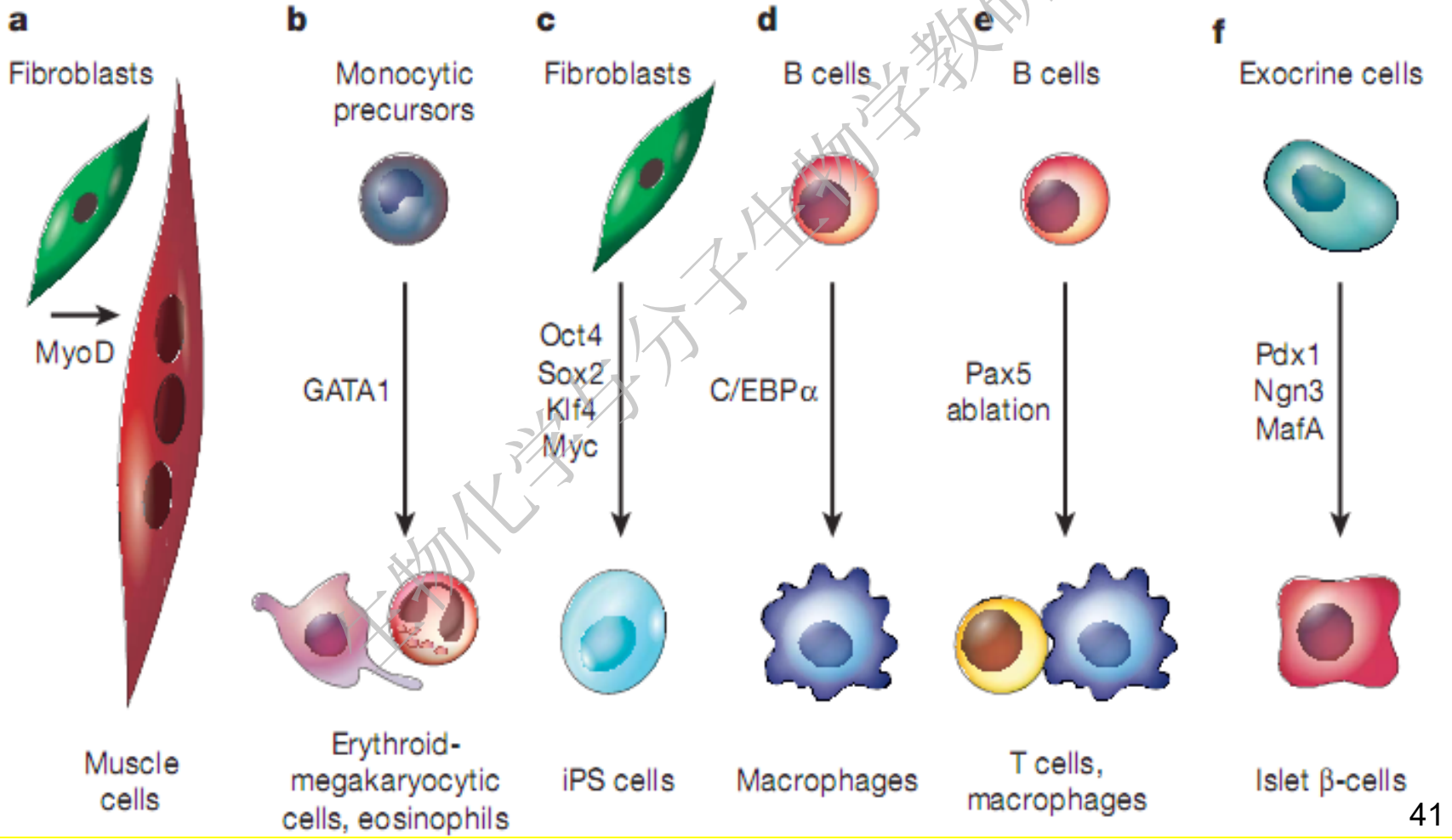
2009 from iPS to viable mice



Nature 2009, 461:86-90.

细胞命运重编程

Examples of transcription factor overexpression or ablation experiments that result in cell fate changes



The Nobel Prize in Physiology or Medicine 2012

Sir John B. Gurdon, Shinya Yamanaka

The Nobel Prize in Physiology or Medicine 2012

Photo: U. Montan

Sir John B. Gurdon

Photo: U. Montan

Shinya Yamanaka

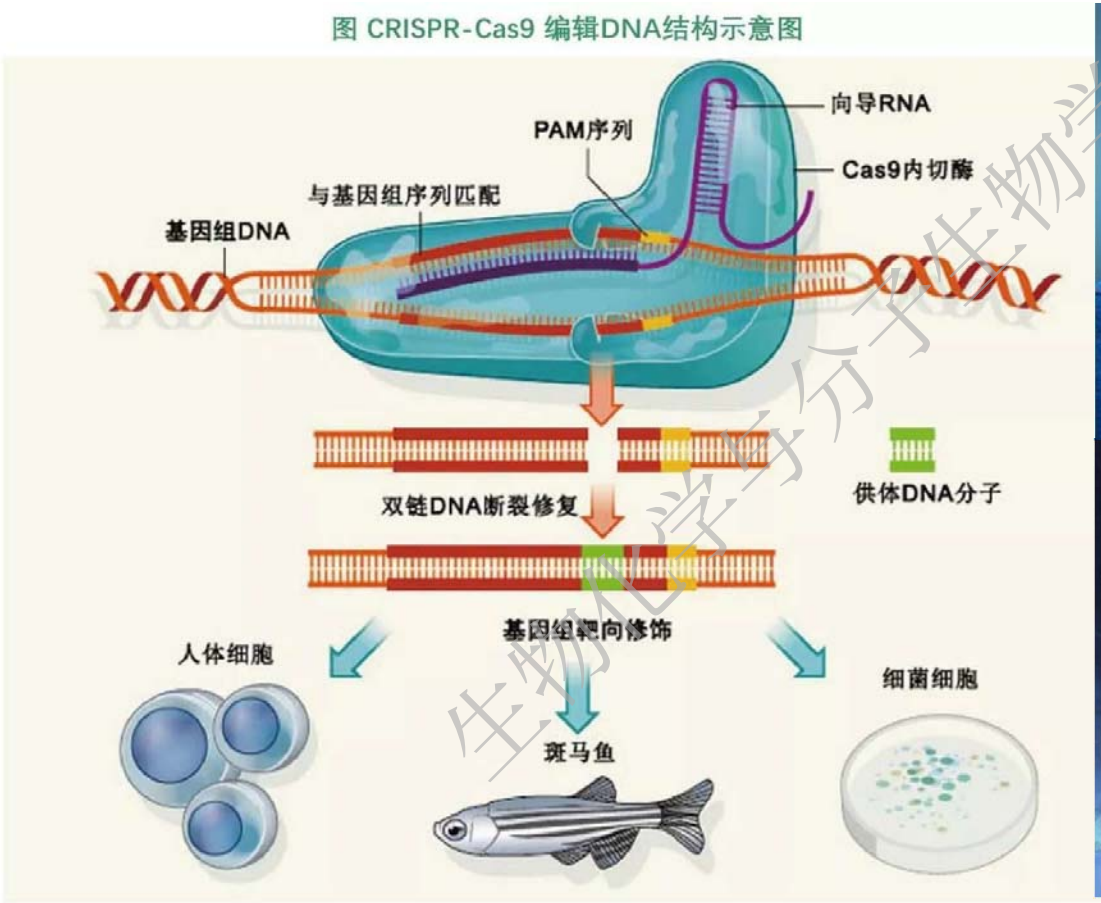
约翰•戈登（John B. Gurdon）
山中伸弥（Shinya Yamanaka）

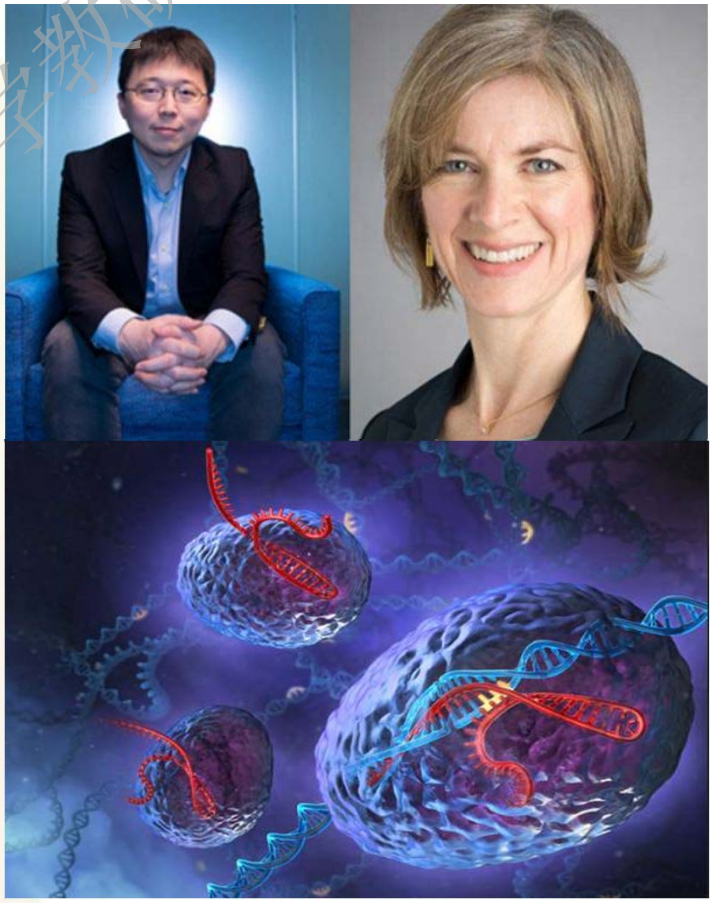
The Nobel Prize in Physiology or Medicine 2012 was awarded jointly to Sir John B. Gurdon and Shinya Yamanaka *"for the discovery that mature cells can be reprogrammed to become pluripotent"*

基因编辑技术

--划时代的基因靶向操作技术

Feng Zhang & Jennifer Doudna





第三代基因编辑技术：**CRISPR-Cas9**（基因魔剪）

The Nobel Prize in Chemistry 2020

© Nobel Prize Outreach. Photo: Bernhard Ludewig

Emmanuelle Charpentier

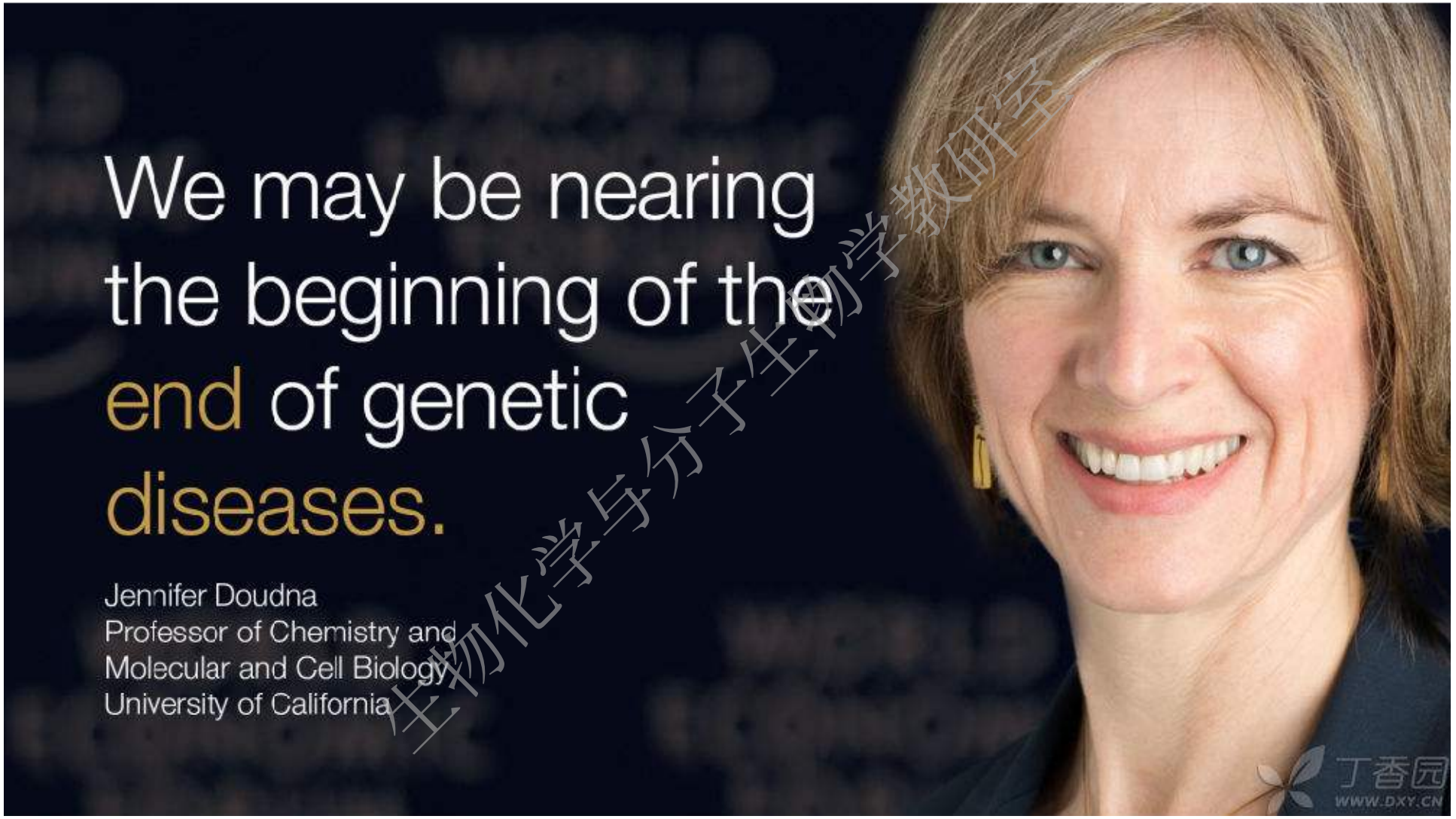
1968-

© Nobel Prize Outreach. Photo: Brittany Hosea-Small

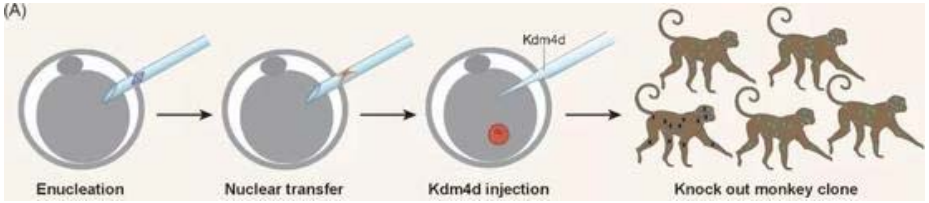
Jennifer A. Doudna

1964-

The Nobel Prize in Chemistry 2020 was awarded jointly to Emmanuelle Charpentier and Jennifer A. Doudna "for the development of a method for genome editing."

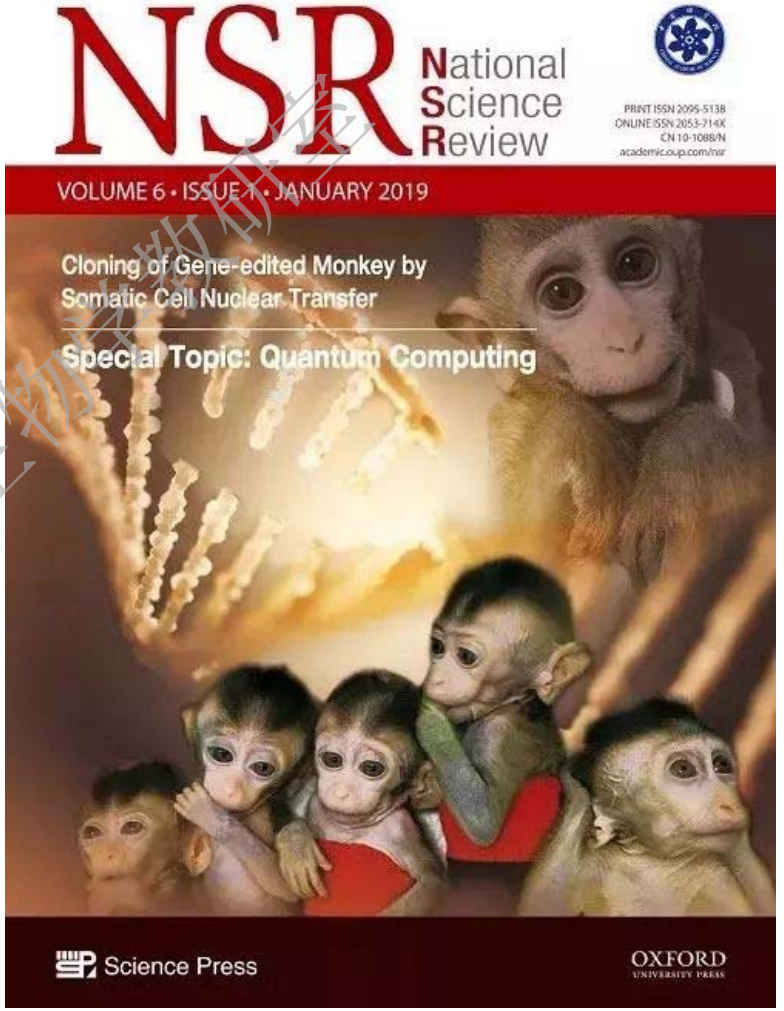


世界生命科学领域的里程碑式突破



克隆猴“中中”、“华华”

2017.11，中国科学家成功突破了现有技术无法克隆灵长类动物的世界难题



2019.1.24，中科院神经所克隆出了五只带有生物节律缺陷的基因编辑猴

21世纪是分子医学时代

分子生物学的发展已经引领现代医学进入了
分子医学时代

古代医学　　经验和哲学思考为主导

现代医学　　实验、解析、认知为主导

从经验主体到技术主体的发展

个性治疗 → 共性治疗 → 个体化医疗

分子医学

- 从分子水平研究疾病的发病机理，以实现对疾病发生的早期预防、诊断和治疗
- 主要研究内容包括：

1）疾病的分子机理

2）疾病的基因诊断

3）疾病的基因治疗

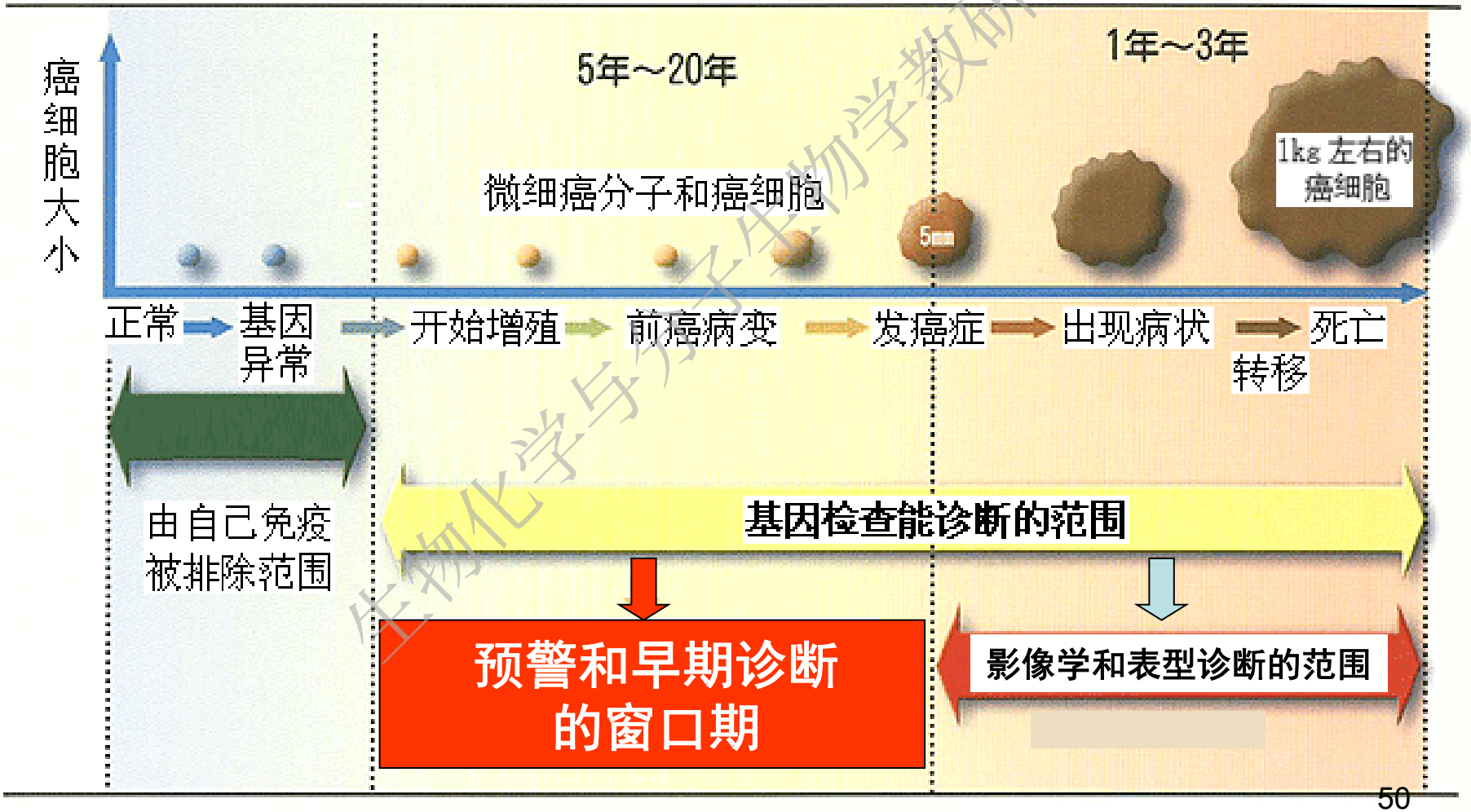
4）疾病的基因预防

基因诊断之父—简悦威

1978年加州大学华裔科学家Kan YW用核酸分子杂交技术首次对α地中海贫血进行诊断，开创了基因诊断技术在临床应用的新时代。

Yuet Wai Kan 1936～

基因诊断——预警和早期诊断



基因治疗

发展历史：准备期——狂热期——理性期

1. 准备期（1980—1989）

Pilot Study　Dr. Martin Cline：University of California

——未经许可

1980年7月　Italy

人β-珠蛋白基因 ⇨骨髓细胞⇨β-地中海贫血的两患者

研究结果：β-珠蛋白基因短暂表达，失败

评价：开创了基因治疗的先河

受到处分 (系主任职务 + 基金)

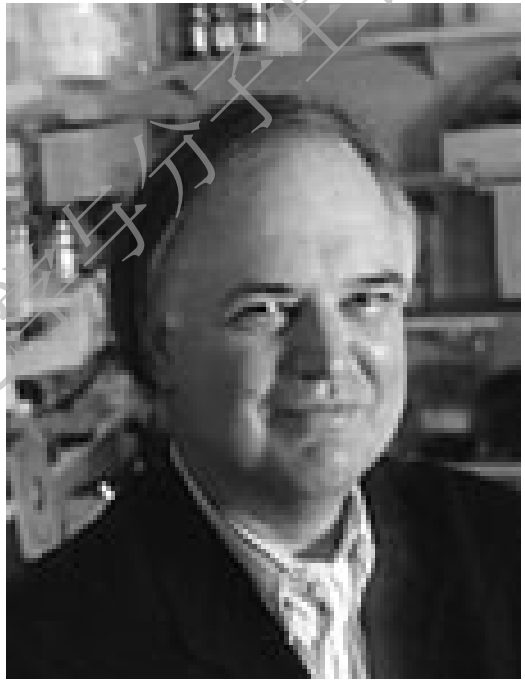
2. 狂热期（1990—1999）

首例报道的基因治疗

1990年9月——SCID患者

美国国家心肺和血液研究所

William French Anderson

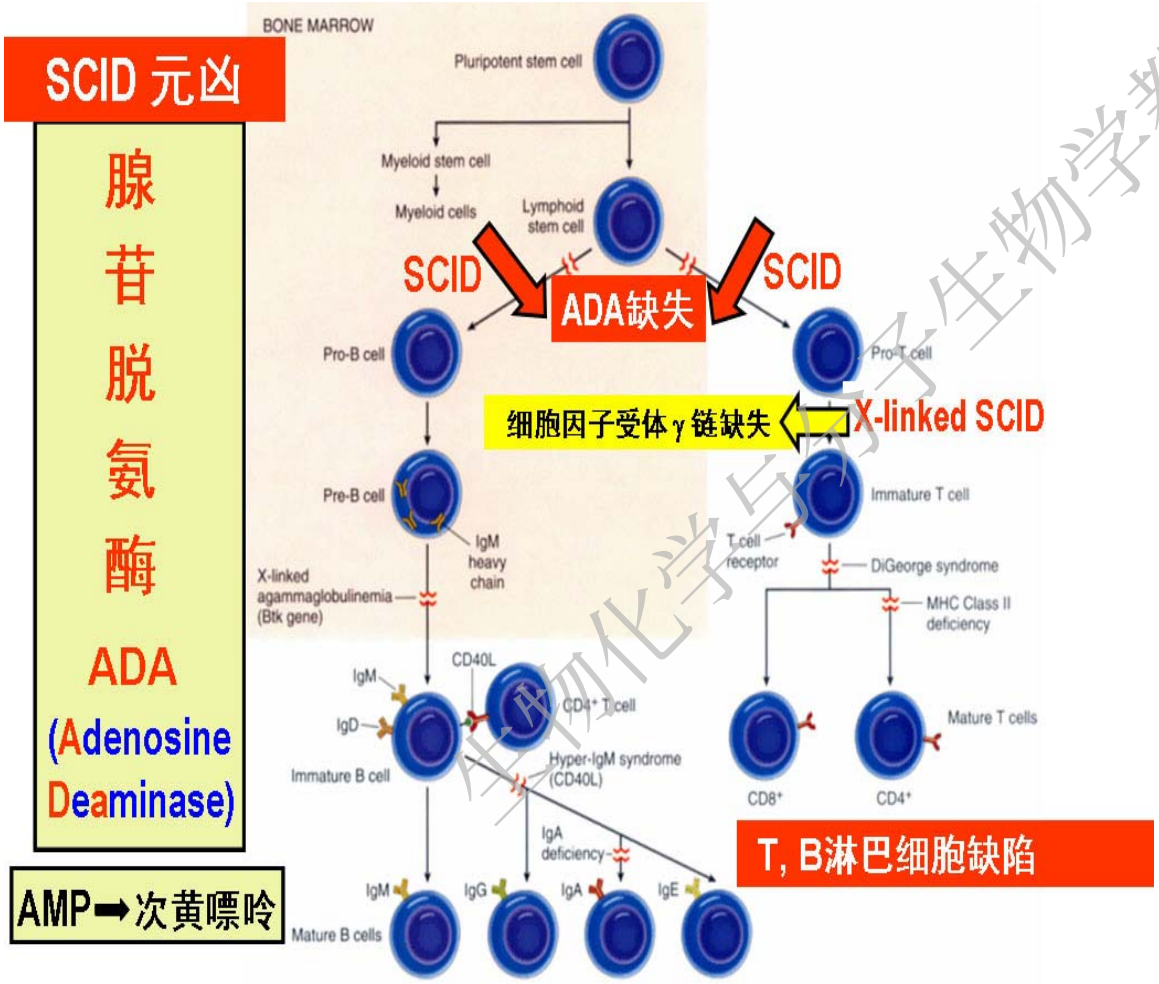


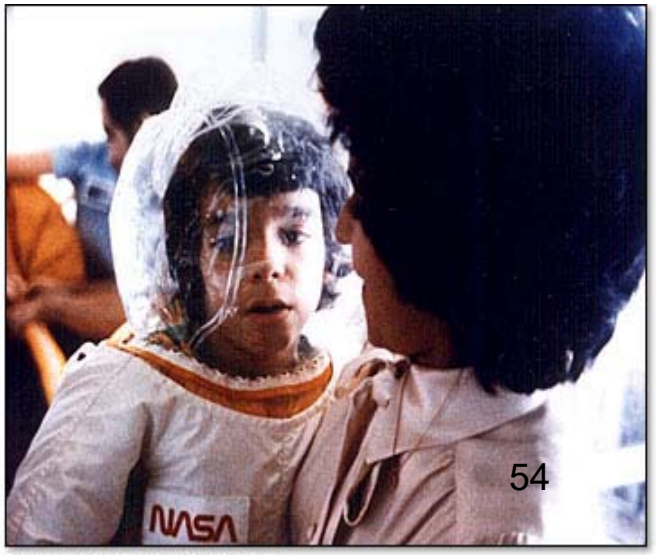
Michael Blaese

Kenneth Culver

严重联合免疫缺陷症

(Severe Combined Immunodeficiency, SCID)





BAYLOR COLLEGE OF MEDICINE ARCHIVES

1990年9月　美国

人 ADA基因 ⟹ T淋巴细胞 ⇨ 患SCID 的4岁女孩

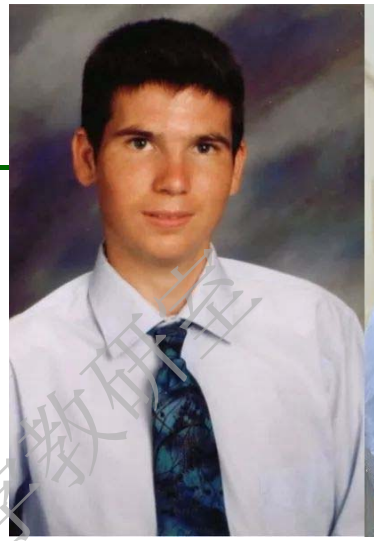
逆转录
病毒载体

研究结果：Bubble girl 离开无菌仓

评价：第一例成功的基因治疗

2021年 Ashanti De Silva
35岁，生存良好

3. 理性期（1999—2009）



Jesse Gelsinger　　Jim Wilson

负面报道-1

1999年9月　美国　　***University of Pennsylvania***

鸟氨酸氨甲酰基转移酶 (OTC) 基因 —动脉注射至肝脏，腺病毒载体→ 患OTC缺陷病的18 岁男孩

研究结果：患者 4 天后死亡

评价：第一例正式报道的基因治疗死人案

死亡原因：腺病毒违规操作，引起强烈免疫反应

负面报道-2

2000年　法国　　*Dr. Fisher A,　Necker儿童医院*

IL-2RG/γc基因 ⟹（逆转录病毒载体）造血干细胞 ⟹ 20位 X-SCID 患者

研究结果： 3 年后

5 例患白血病，1例死亡。

原因： 逆转录病毒插入激活LMO-2基因。

Rhys Evans

美国FDA中止了27项类似临床试验。

评论文章 *Circulation. 2000;101:e9023-e9024*

“Human Gene Therapy ——Science Under Fire”

2000年1月类似的研究被中止

MEDICINE

（2009-至今）
A Comeback for Gene Therapy

基因治疗入选Sicence
2009年度十大突破之一

2009 Eight-year-old Corey Haas, who has a rare inherited eye disease and is almost blind, gains normal vision following gene therapy to replace a retinal pigment protein.

2009 Progression of the degenerative disease adrenoleukodystrophy is halted in two boys using gene therapy.

2010 An adult with blood disorder beta-thalassaemia no longer needs monthly blood transfusions following gene therapy to insert a corrected beta-globin gene into stem cells that make blood.

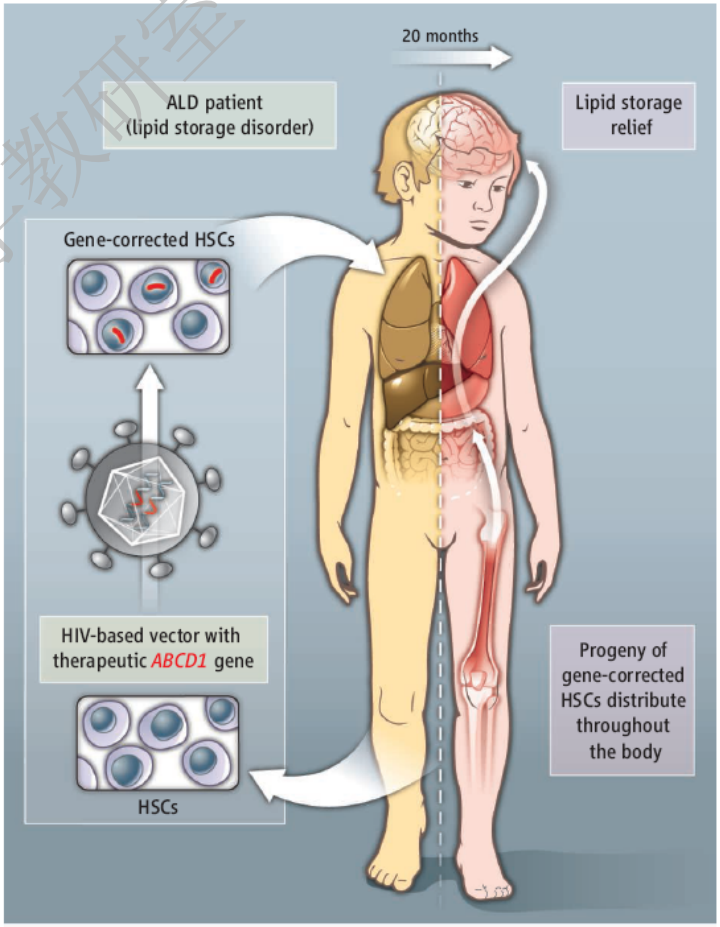
2011 Six people with clotting disorder haemophilia B see a reduction in symptoms after gene therapy on liver cells.

2012 Glybera becomes the first gene therapy drug to be approved in the West, with European approval to treat lipoprotein lipase deficiency.

2013 Two papers describe the treatment of children with a degenerative disorder called metachromatic leukodystrophy and immune disorder Wiskott-Aldrich syndrome using gene therapy (*Science*, doi.org/pnv; doi.org/ppk).

2009年 宾夕法尼亚大学 **AAV2过表达RPE65成功治疗雷伯氏先天性黑蒙症（LCA）。**

2011年 英国伦敦大学 **AAV8过表达凝血因子IX，缓解了B型血友病患者的症状。**



Promising treatment. Progeny of HSCs that were engineered to carry the correct version of a gene (through the integration of a lentiviral vector) distribute throughout the body. Cartier *et al.* show that some cells replaced diseased microglia in the brain and relieved lipid storage in patients suffering from ALD.

X-连锁肾上腺脑白质营养不良

基因治疗2.0时代

欧盟

2014年 UniQure第一例基因治疗药物Glybera 脂蛋白脂肪酶缺陷（LPLD）
开创了基因治疗的新时代 售价100万美元，只用了一次（17退市）

2016年 GSK第二例基因治疗药物Strimvelis 重症联合免疫缺陷（ADA-SCID）
基因治疗走向临床的又一个里程碑 66.5万美元，无效退款

美国

2014.4	Celladon公司旗下的心衰基因疗法MYDICAR“突破性疗法”	
	FDA首次批准的基因疗法	
2014.11	Spark Therapeutics公司SPK-RPE65	先天性利伯氏黑蒙症(2017正式)
2015.2	Bluebird公司的LentiGlobin BB305	地中海贫血病的基因治疗
2016.7	辉瑞和Spark共同研发新药SPK-9001	B型血友病
2016.7	AveXis公司AVXS-101	Ⅰ型脊髓性肌萎缩症
2017.1	uniQure公司AMT-060	B型血友病
2017.2	Tocagen公司Toca 511 & Toca FC	复发性高级别胶质瘤
2019	FDA批准诺华 最贵药物（210万美元）	脊髓性肌萎缩症

课程内容

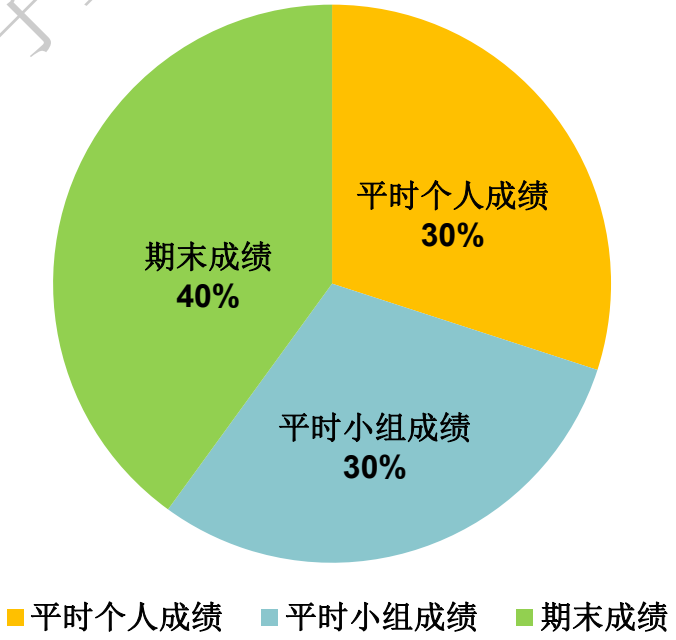
绪论	理论	周珏宇
基因组、基因组学与转录组学	理论	赵蕊
蛋白质组、蛋白质组学	理论	赵蕊
基因信息的传递-复制	自主	赵蕊
文献汇报[4]	讨论	赵蕊
DNA损伤与修复的分子机制	理论	丁大鹏
基因信息的表达-转录、翻译	自主	丁大鹏
基因表达调控[4]	讨论	周珏宇
基因结构与表达分析的基本方法[4]	自主	周珏宇
基因克隆与基因体外表达	自主	张超
基因功能研究的基本策略	理论	张超
科研案例分析讨论[4]	讨论	张超
基因诊断	自主	殷志新
基因治疗	理论	殷志新
疾病的分子基础	理论	殷志新
临床病例分析讨论[4]	讨论	殷志新
肿瘤分子生物学	理论	丁大鹏
科研案例分析讨论	讨论	丁大鹏

讨论课内容

讨论课内容	组织形式
文献汇报[4]（赵蕊）	根据复制相关知识点找文献，并对文献内容进行分组ppt汇报，也可以针对内容提出问题共大家讨论
基因表达调控[4]（周珏宇）	根据本章内容设计若干个课内知识及课外拓展内容，大家分组ppt汇报、问答及点评，评价方式以组间互评、教师评分相结合
科研案例分析讨论[4]（张超）	课前提供相关材料，按分组设计一个完整的科研课题，进行自由展示
临床病例分析讨论[4]（殷志新）	课前提供有关基因诊断和基因治疗的相关文献，按分组进行ppt课堂汇报
科研案例分析讨论（丁大鹏）	下载爱课平台上有关NER途径中参与DNA损伤修复酶及其与肿瘤易感性的关系，按分组进行ppt汇报，具体要求已上传。

考核要求

- **授课老师：** 周珏宇　赵蕊　丁大鹏
  殷志新　张超
- **考试时间：** 6月28日
- **成绩比例：**



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