# 7 基因与基因组

王强

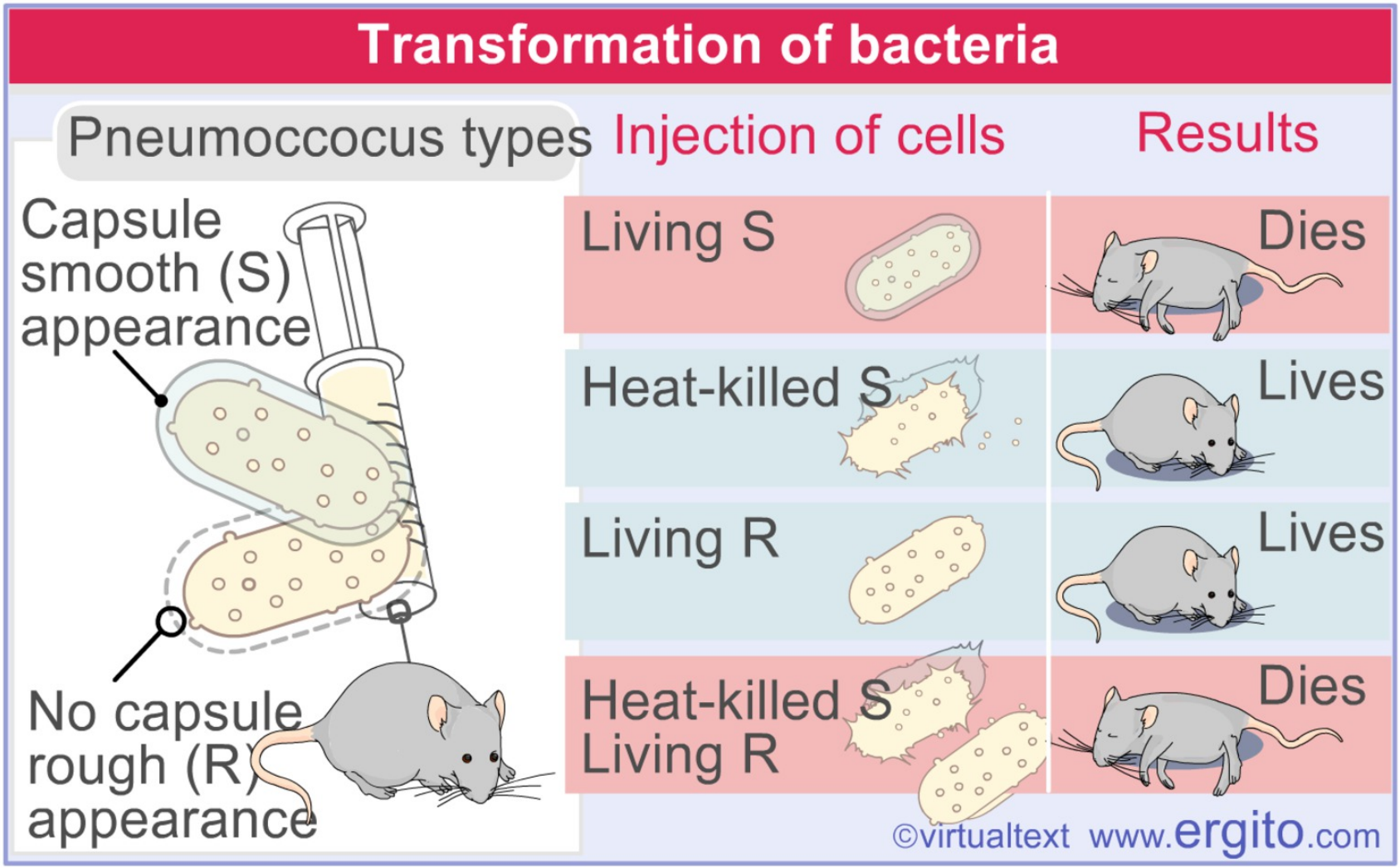
October 30, 2024

南京大学生命科学学院

# Outline

# 7.1 DNA 是遗传物质

# 肺炎链球菌转化实验


Transformation of bacteria
Pneumoccocus types
Injection of cells
Results
Capsule smooth (S) appearance
No capsule rough (R) appearance
Living S
Dies
Heat-killed S
Lives
Living R
Lives
Heat-killed S
Living R
Dies
©virtualtext www.ergito.com

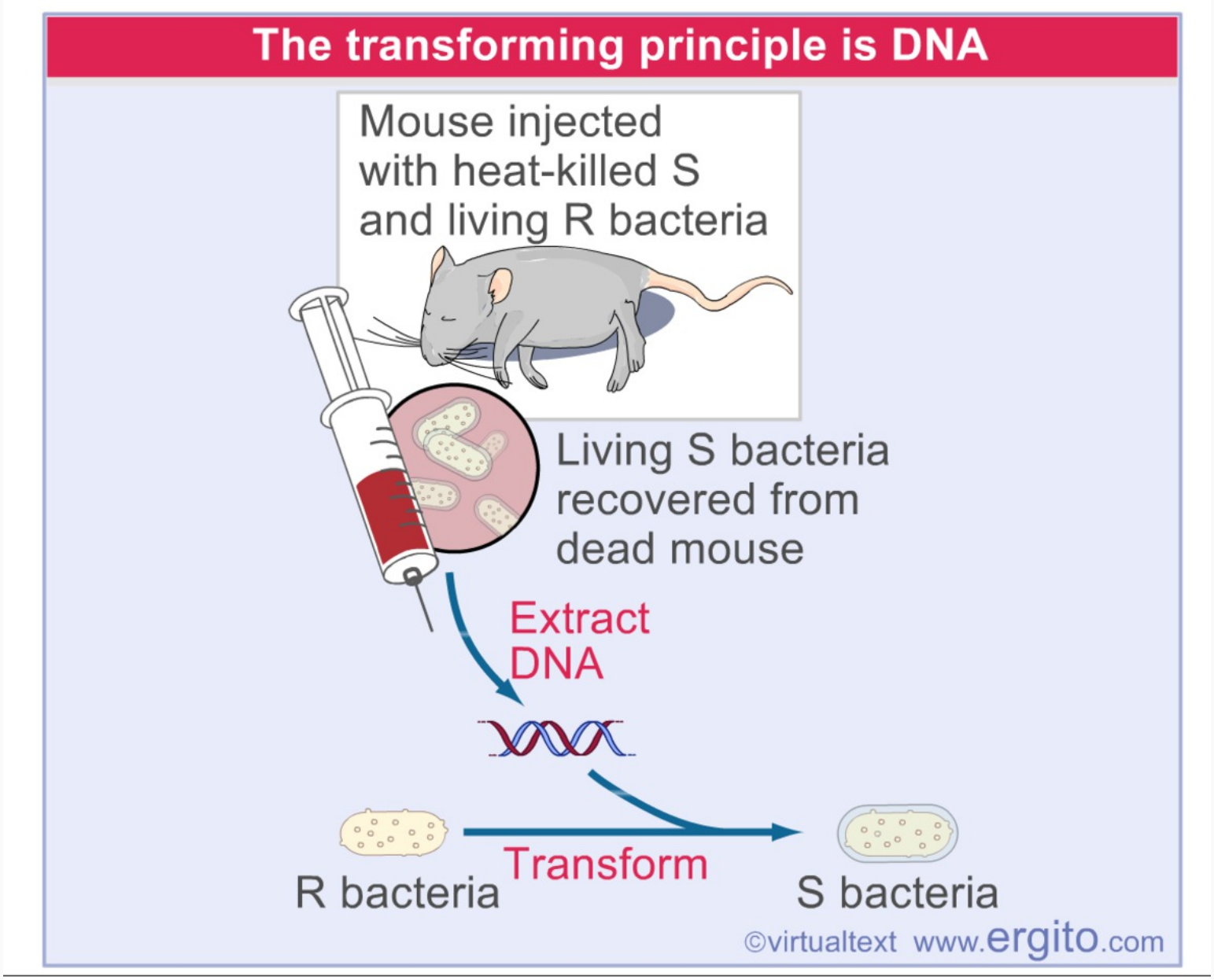



Figure 1. 转化因子是 DNA

# T2 噬菌体感染实验

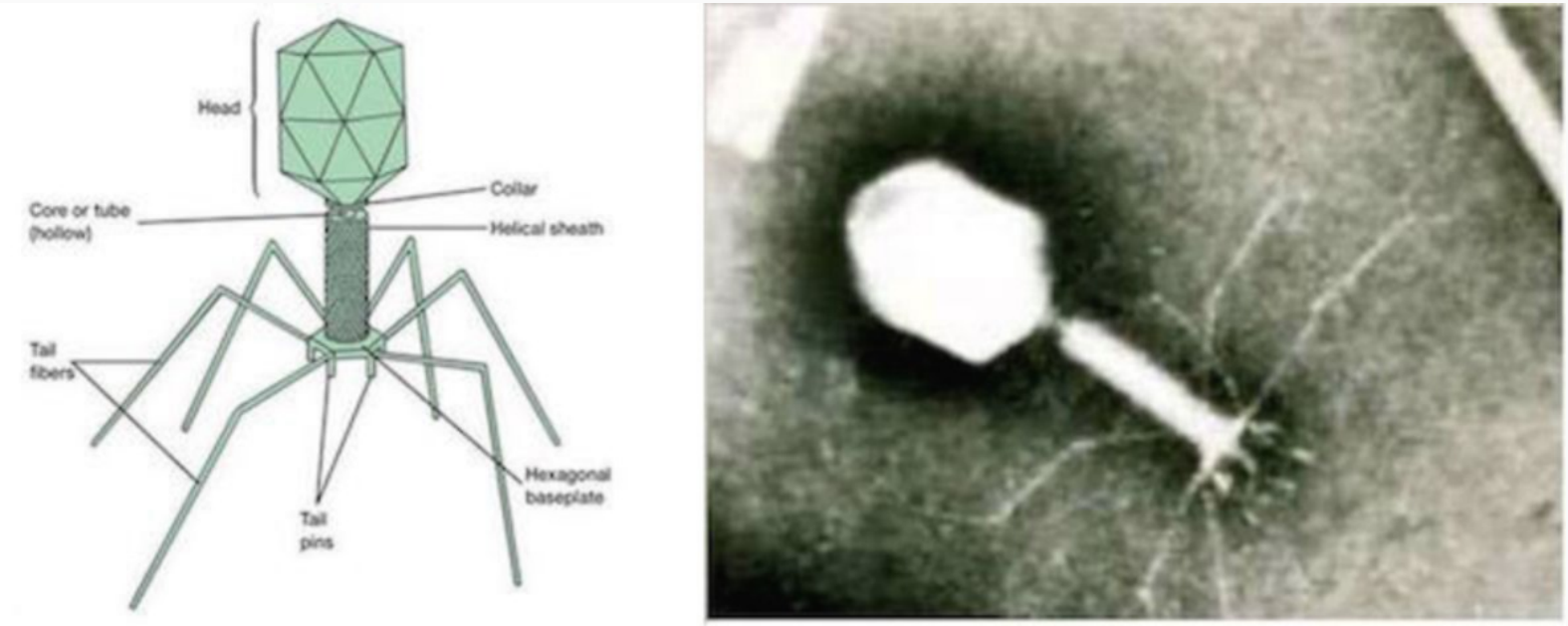



Figure 2. T2 噬菌体. 左: 结构示意图; 右: 透射电镜照片.

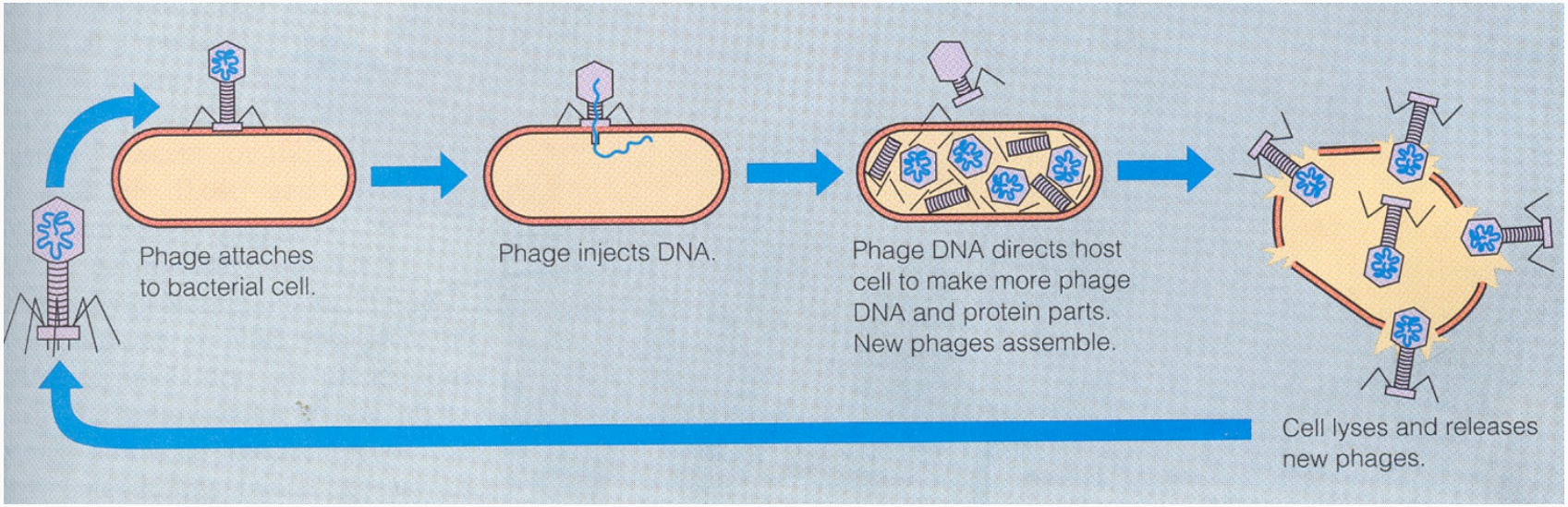



Figure 3. 噬菌体繁殖

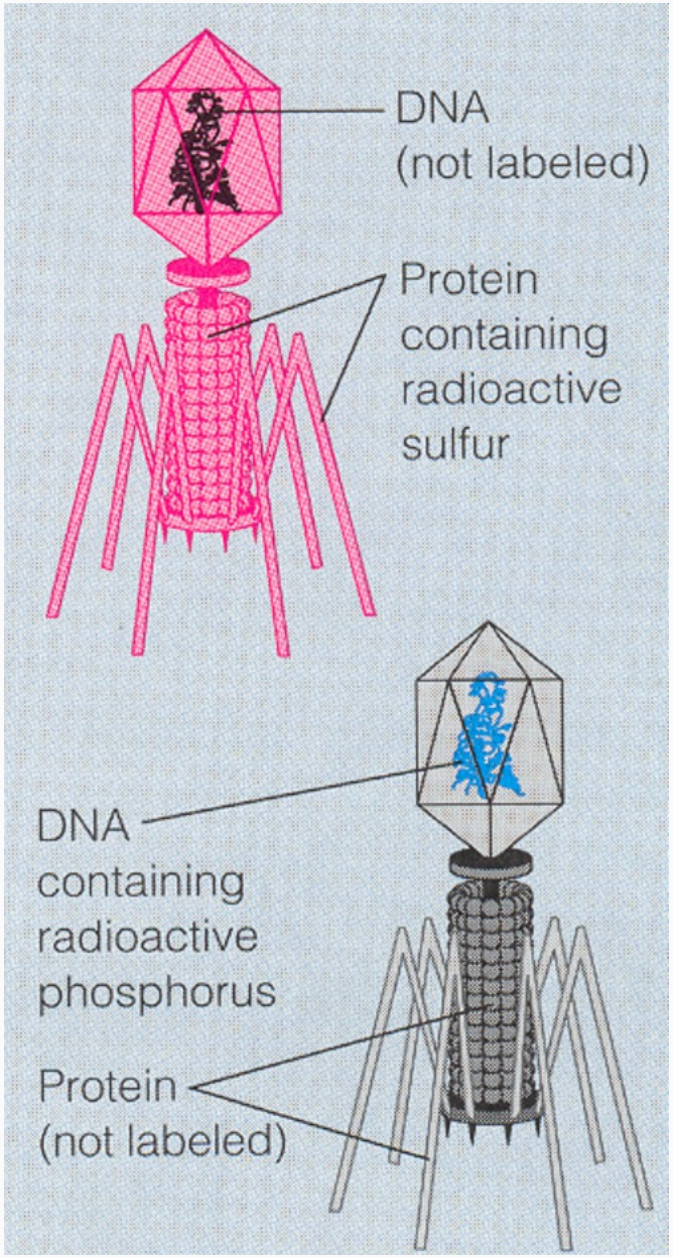



Figure 4. 放射性标记 T2 噬菌体

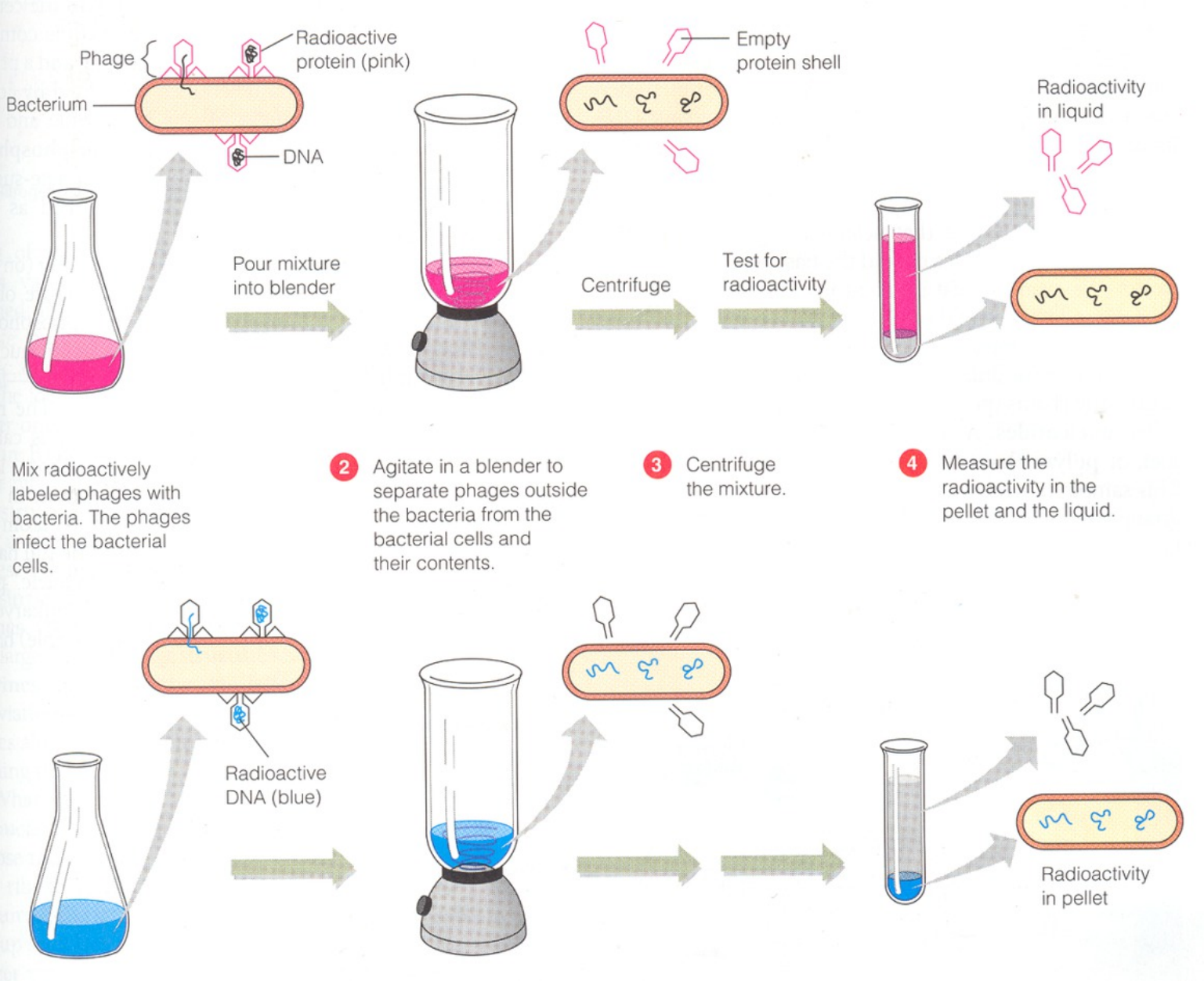



Figure 5. 赫尔希–蔡斯关于 T2 噬菌体的感染实验

# 部分病毒以 RNA 作为遗传物质

- 烟草花叶病毒
- SARS / SARS-CoV-2

# 7.2 DNA 复制

# DNA 与 RNA 是多核苷酸的聚合体

1. Chargaff 法则
   - [A]=[T] [G]=[C]
2. DNA 与 RNA 是多核苷酸的聚合体
   - 核苷
   - 核苷酸
   - DNA 分子的**一级**结构

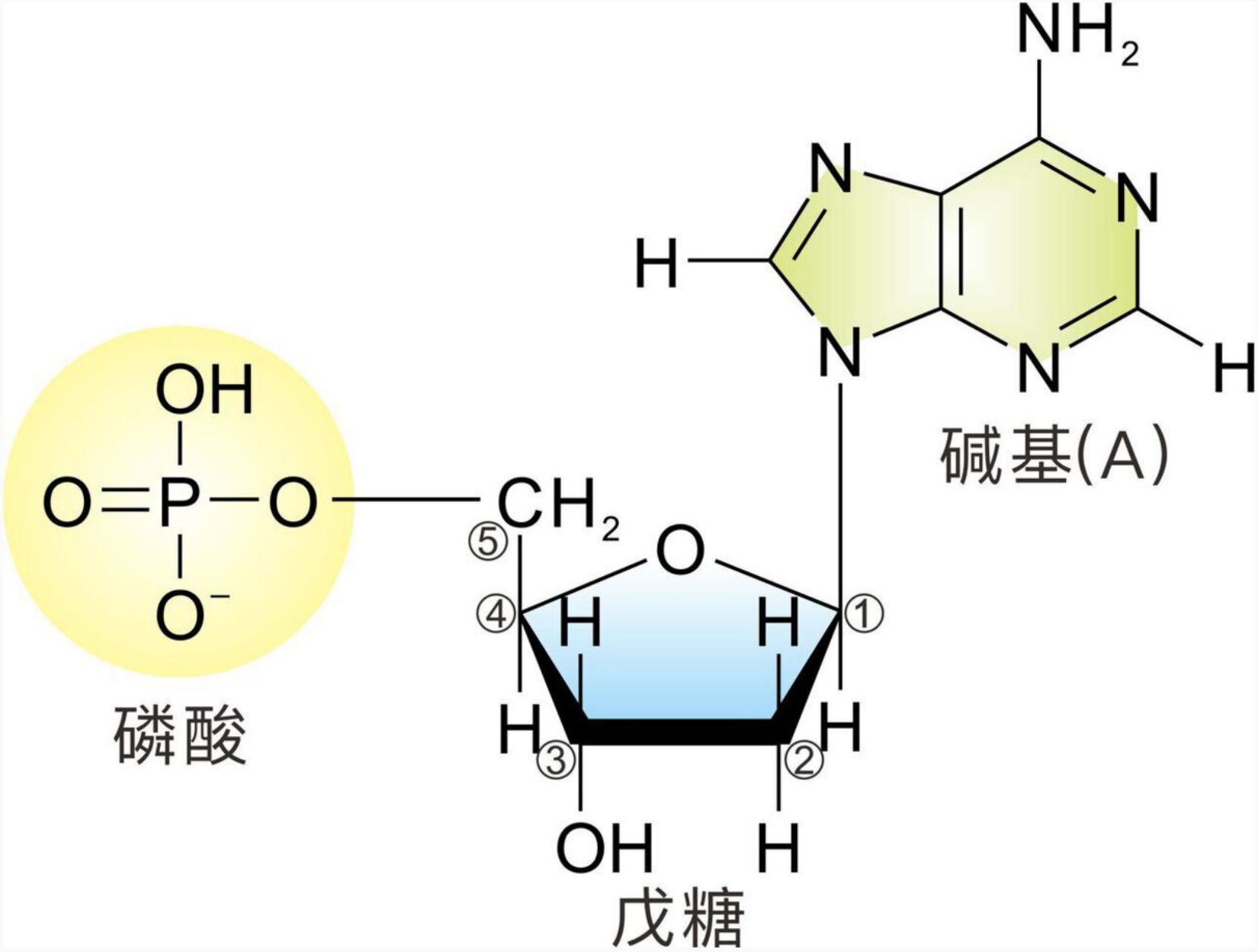



Figure 6. 核苷酸

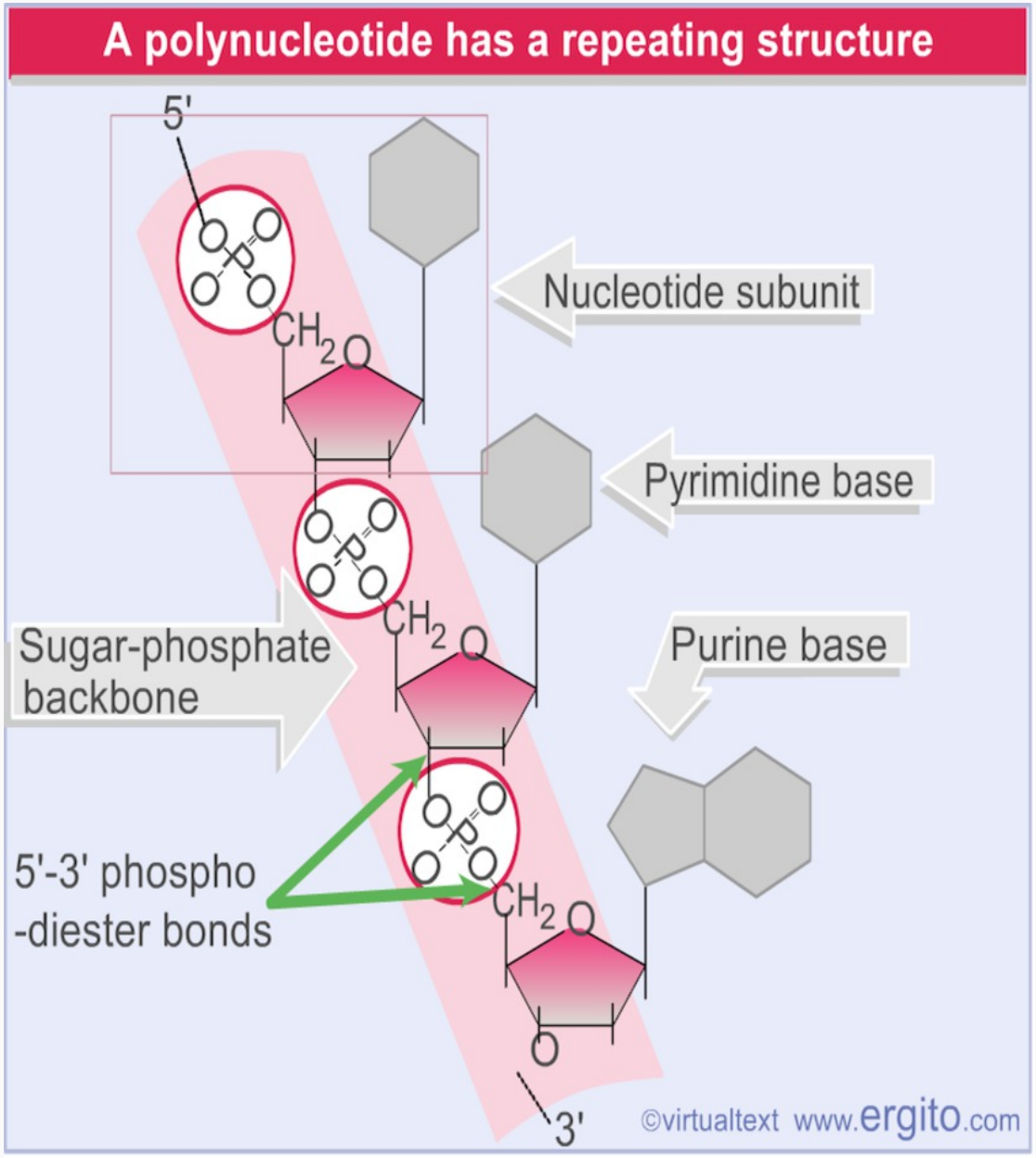



Figure 7. 多核苷酸中的重复结构

# DNA — 不朽的双螺旋

- Watson 和 Crick.
- DNA 分子由两条互补核苷酸单链组成; 两条核苷酸链总是按碱基 A 与 T, G 与 C 互补配对, 成反向平行, 通过氢键形成稳定的双螺旋结构.

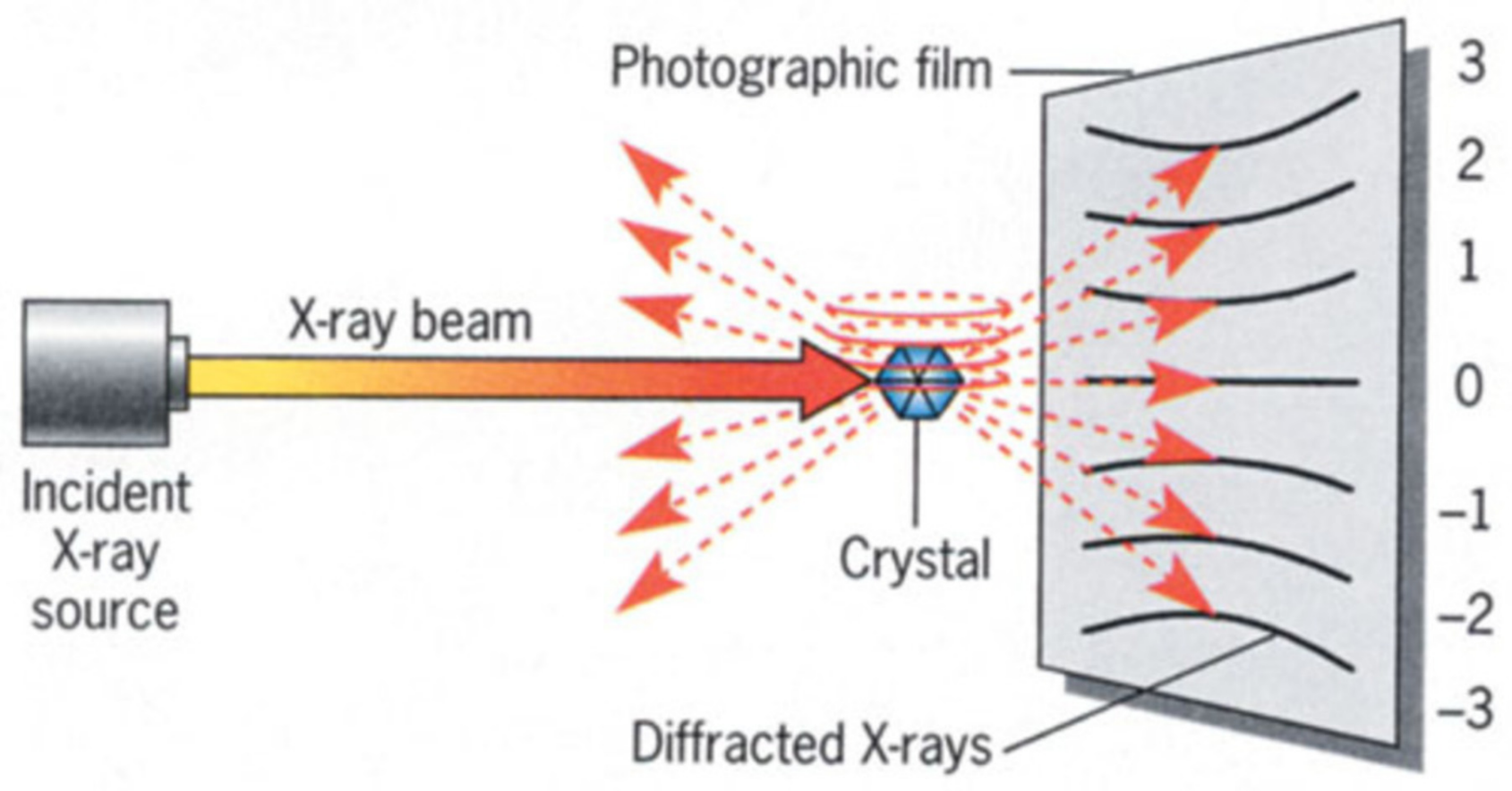



Figure 8. X-射线衍射实验

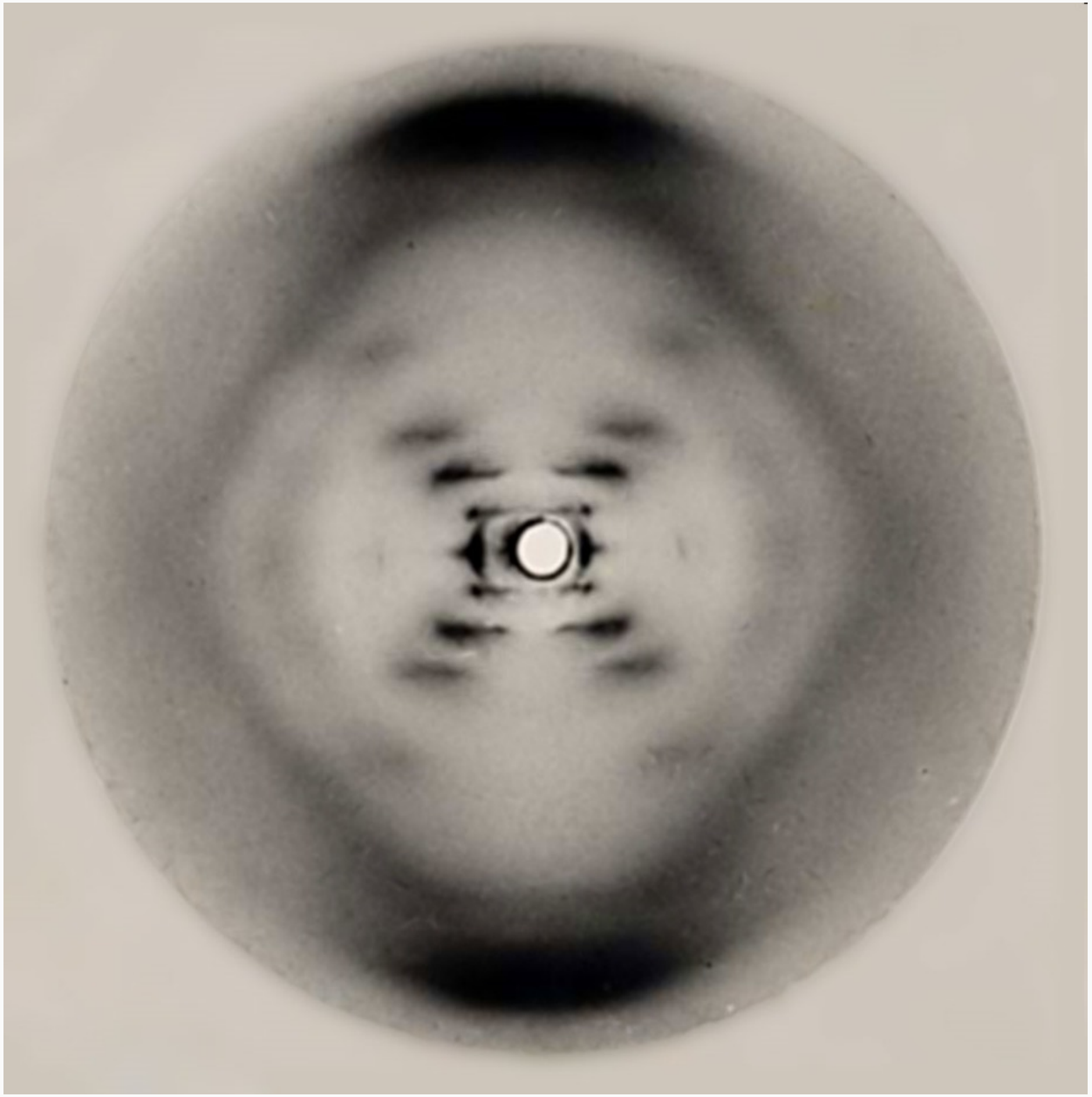


Figure 9. DNA 晶体的 X-射线衍射照片

(a) Rosalind Franklin

(b) Maurice Wilkins

Figure 10. 研究 DNA 晶体的科学家

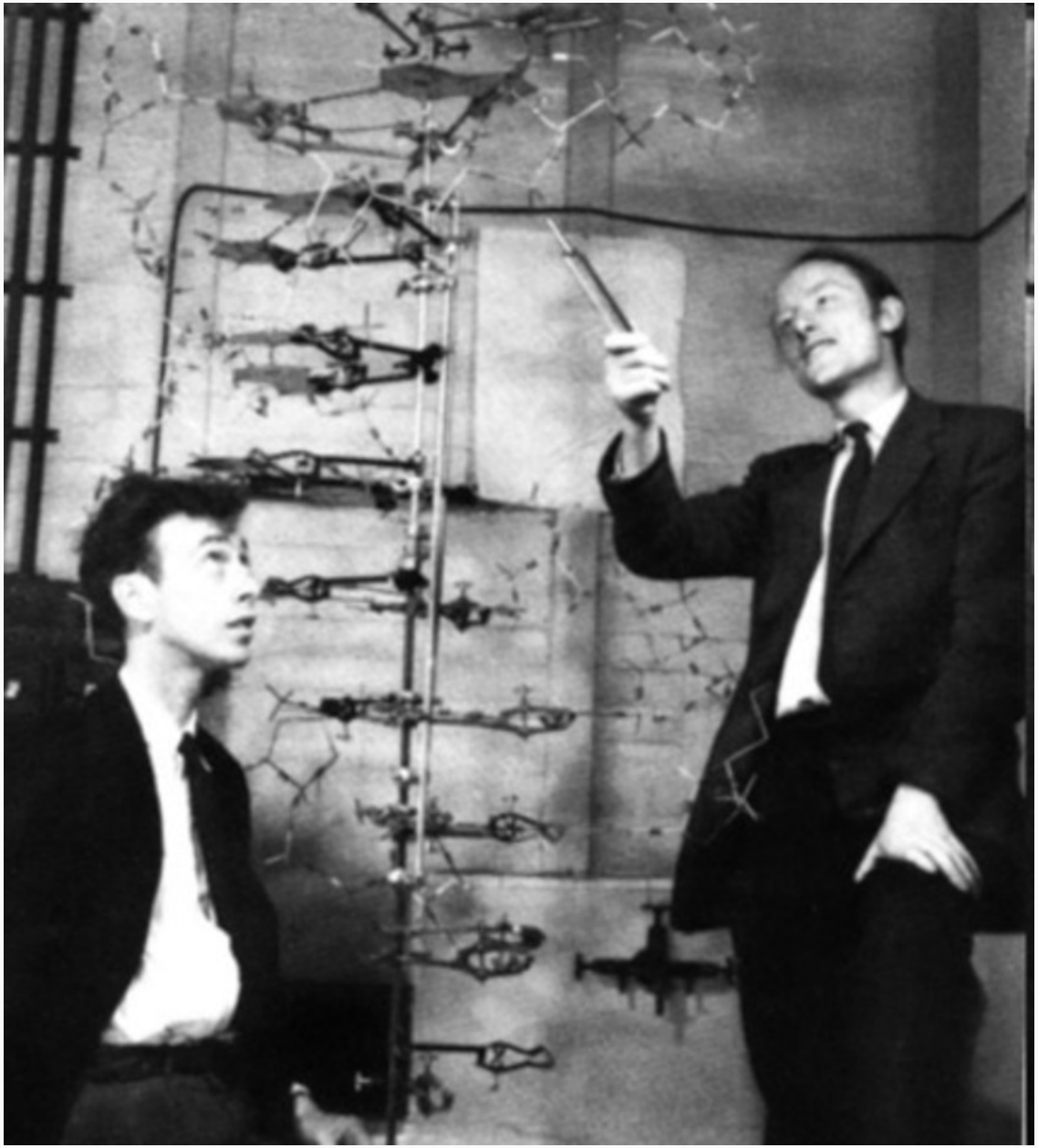


Figure 11. Watson 和 Crick

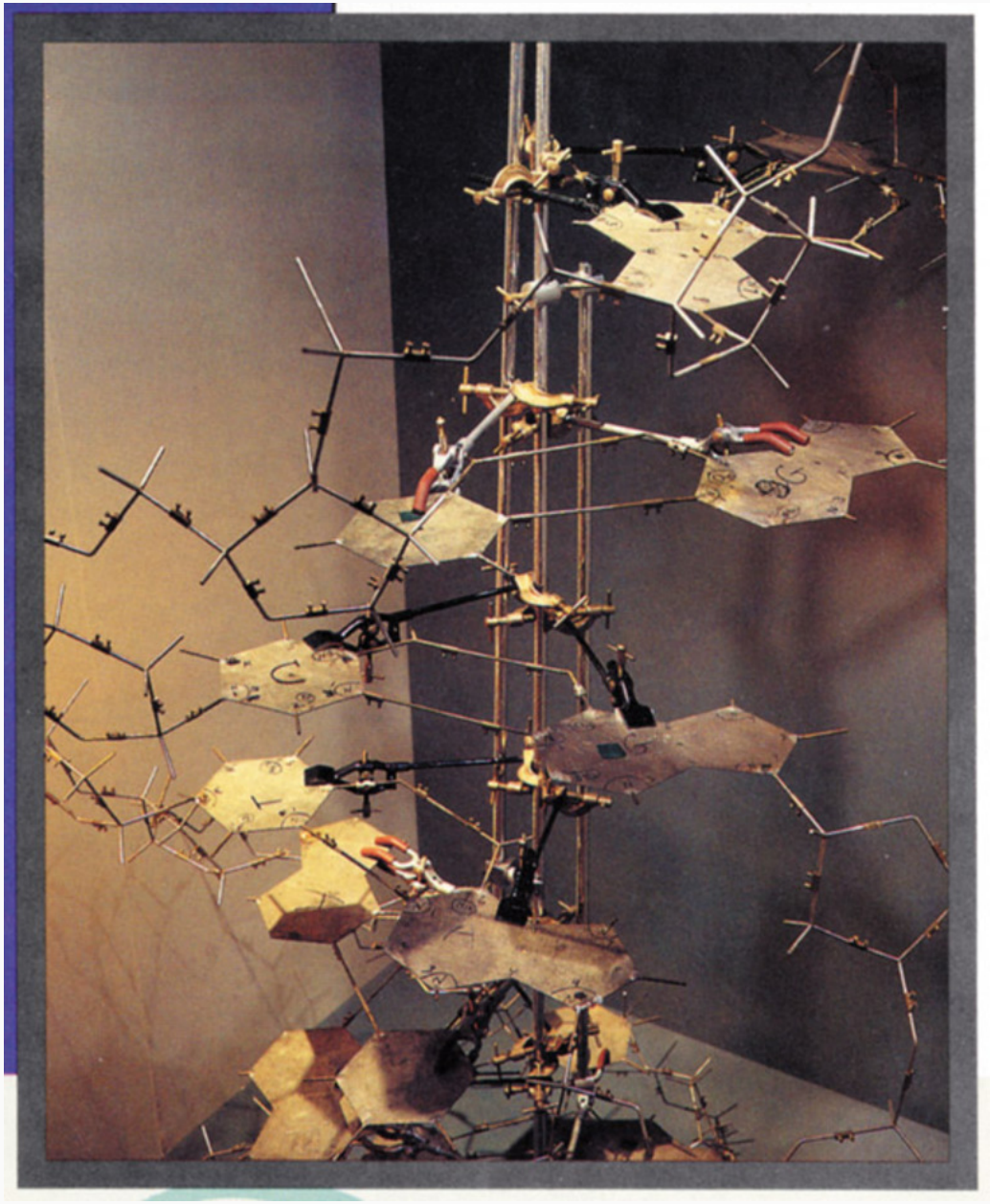


Figure 12. Model of DNA built by James Watson and Francis Crick at Cambridge University

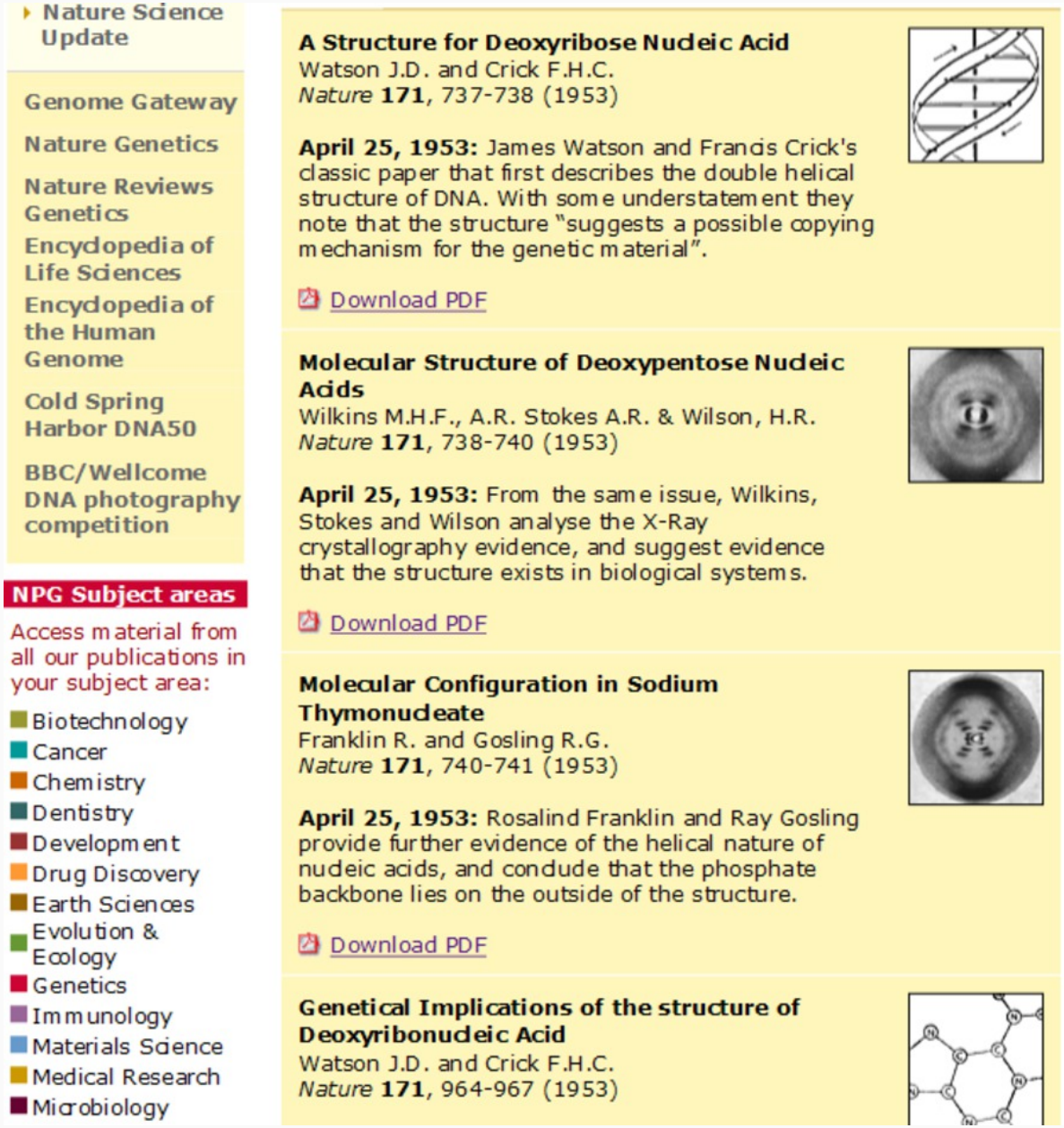



Figure 13. http://www.nature.com/nature/dna50/archive.html

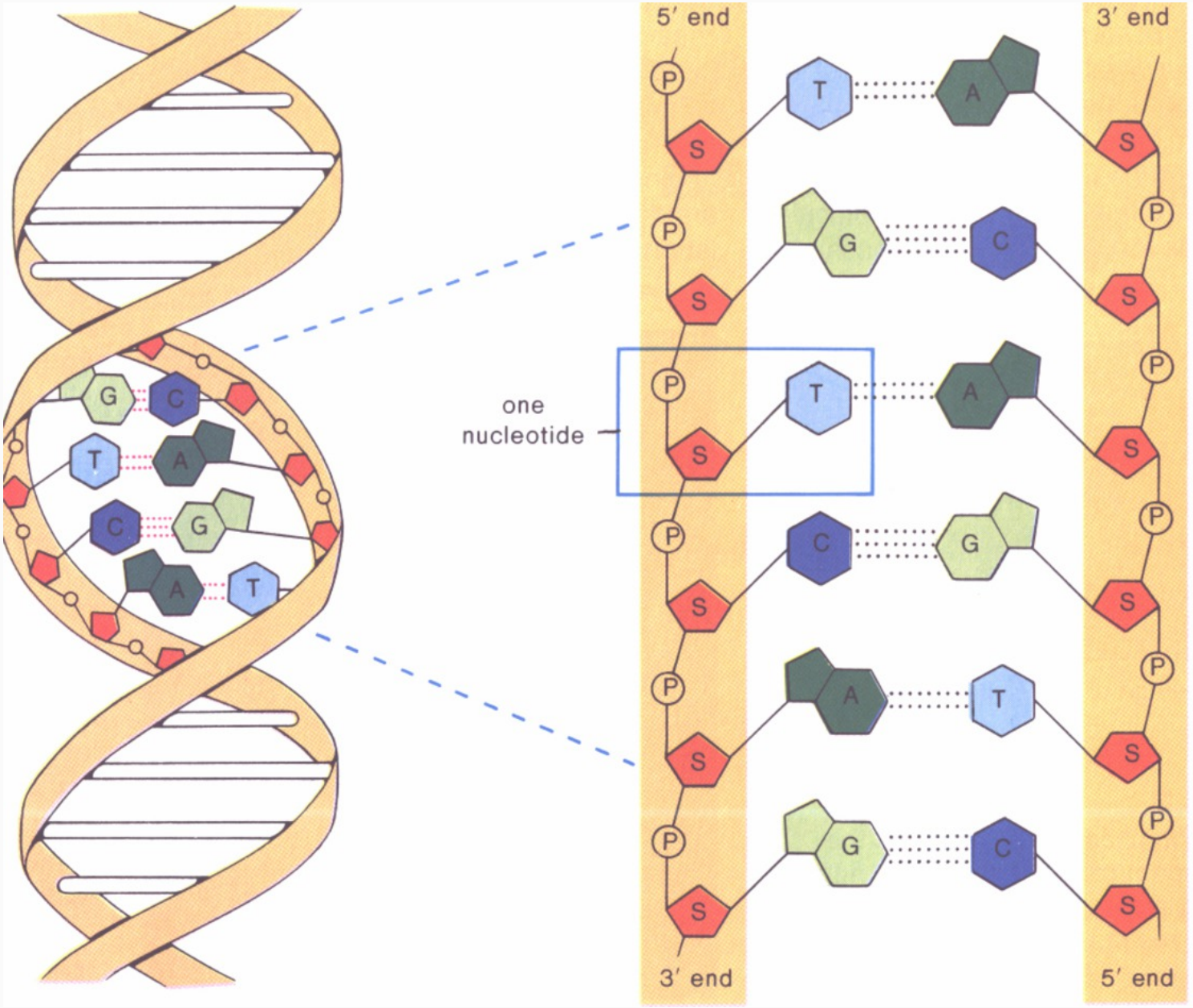



Figure 14. DNA 双螺旋结构

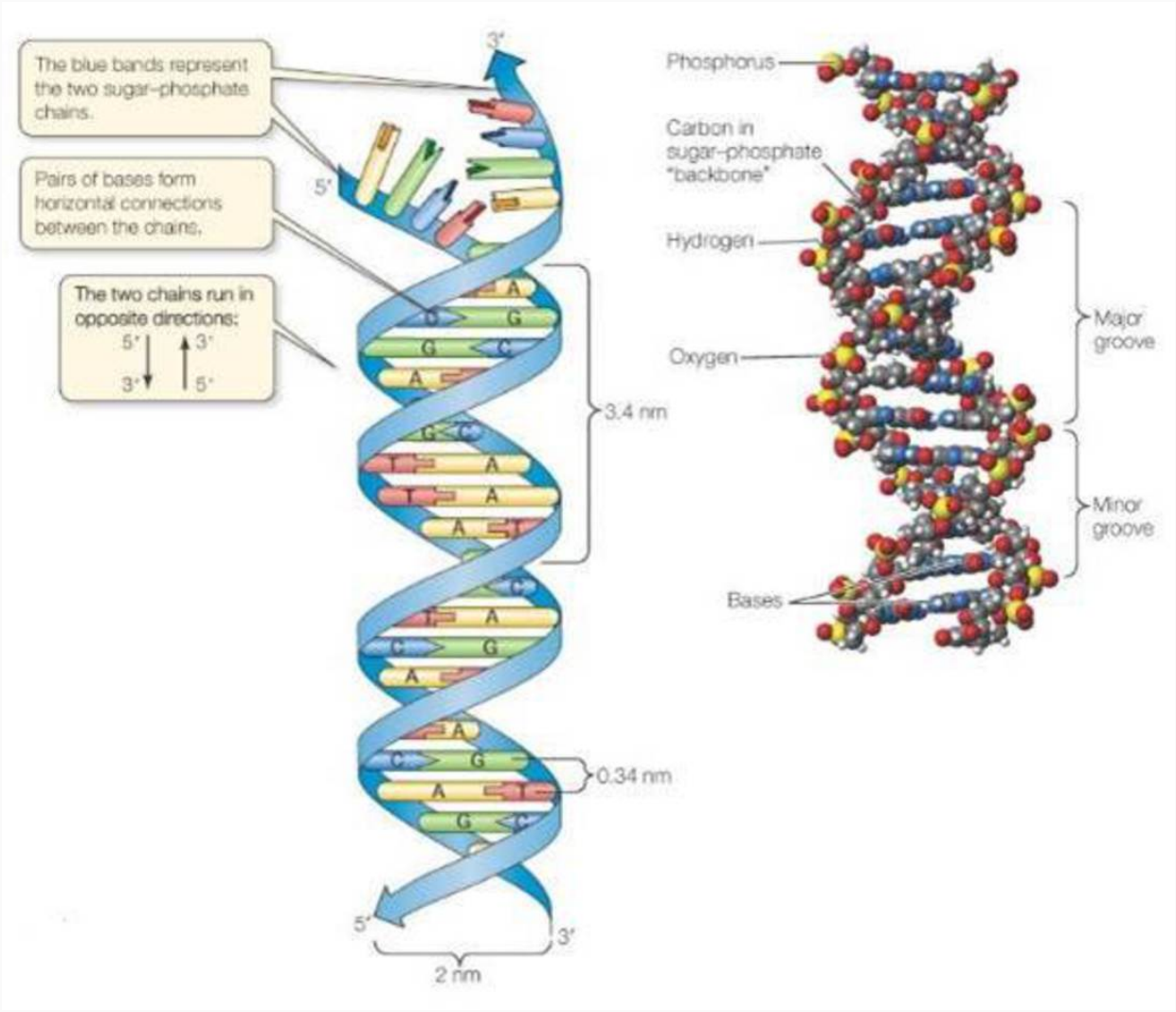



Figure 15. DNA 双螺旋结构

# DNA 复制依赖于碱基配对

A 与 T, G 与 C 配对.

# DNA 复制是半保留式的

DNA 复制形成的两个 DNA 分子, 每个都由一条新链和一条旧链组成.

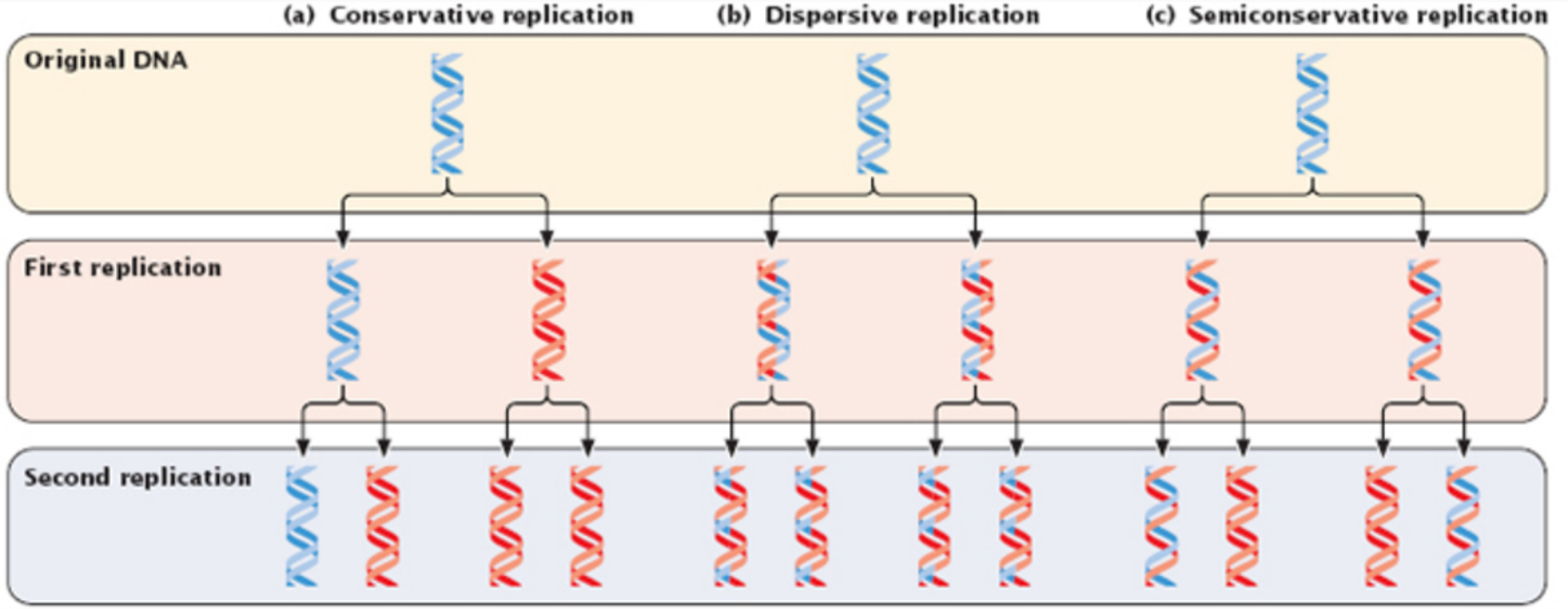



Figure 16. Three alternate schemes of replication

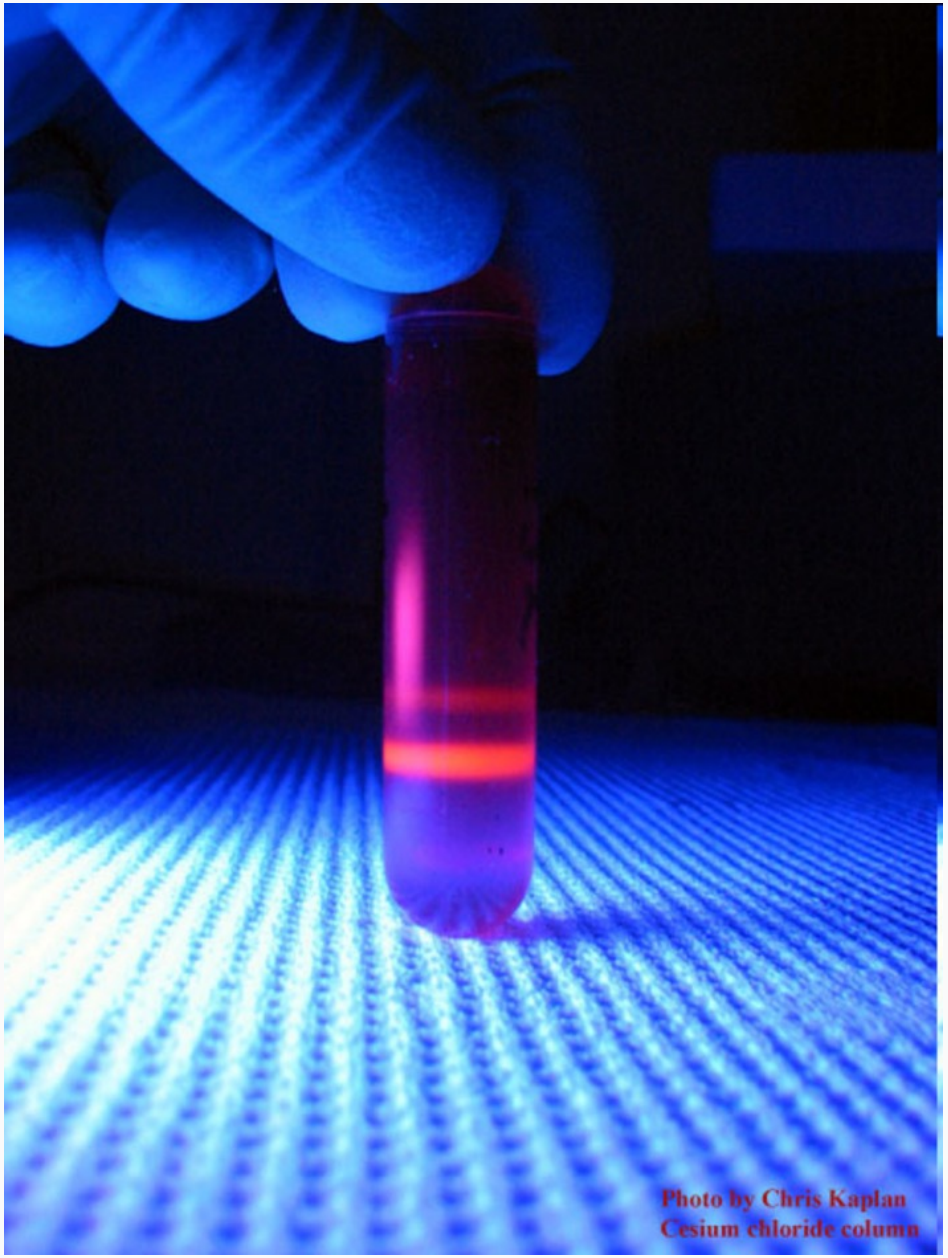



Figure 17. DNA 密度梯度离心 (CsCl, 氯化铯)

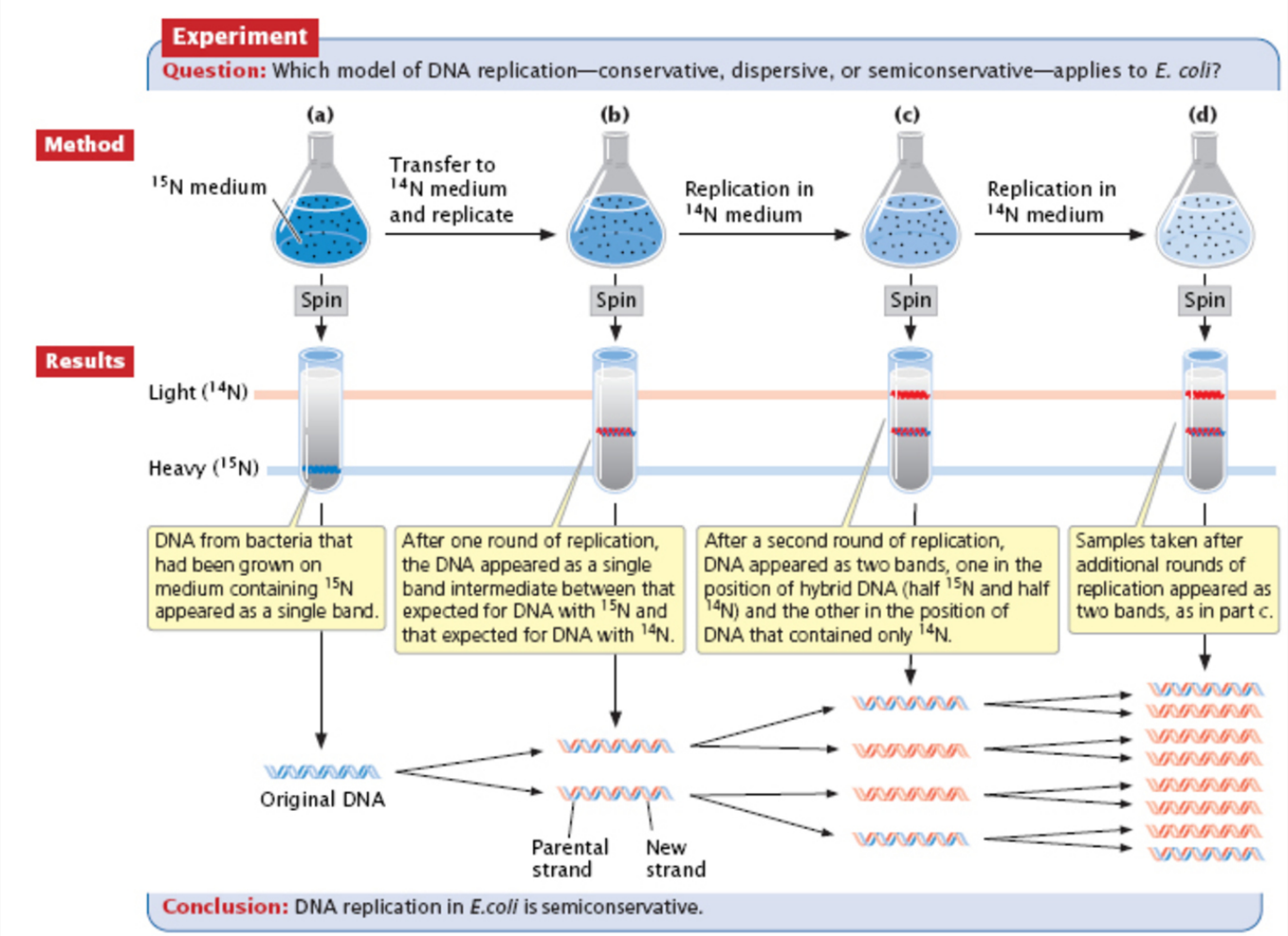



Figure 18. 大肠杆菌中的 DNA 复制[1]

[1] Meselson, M. & Stahl, F. W. **The Replication of DNA in Escherichia Coli.** *Proceedings of the National Academy of Sciences* **44,** 671–682 (1958)

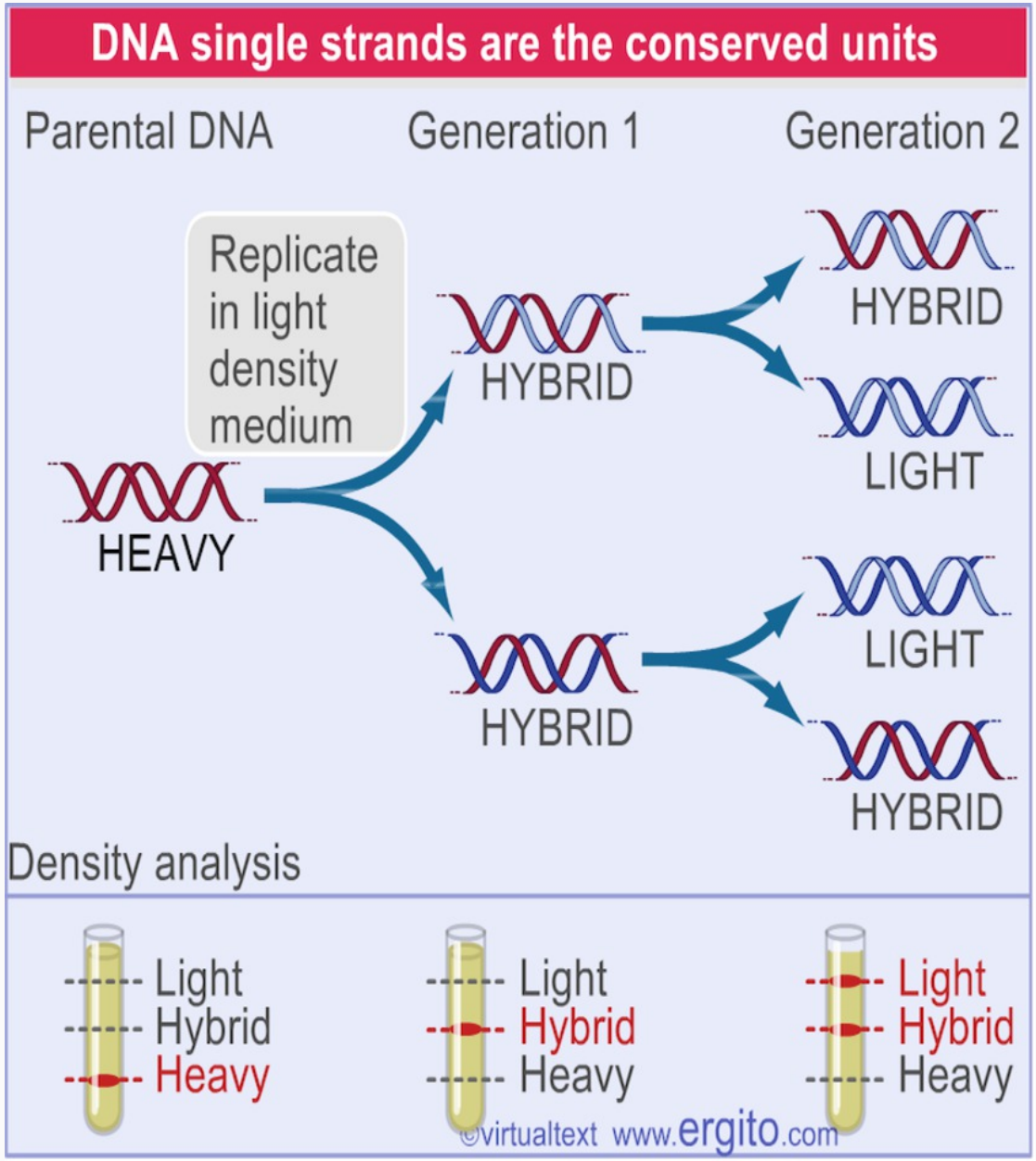



Figure 19. DNA 单链是保留的单元


Figure 20. DNA 半保留复制

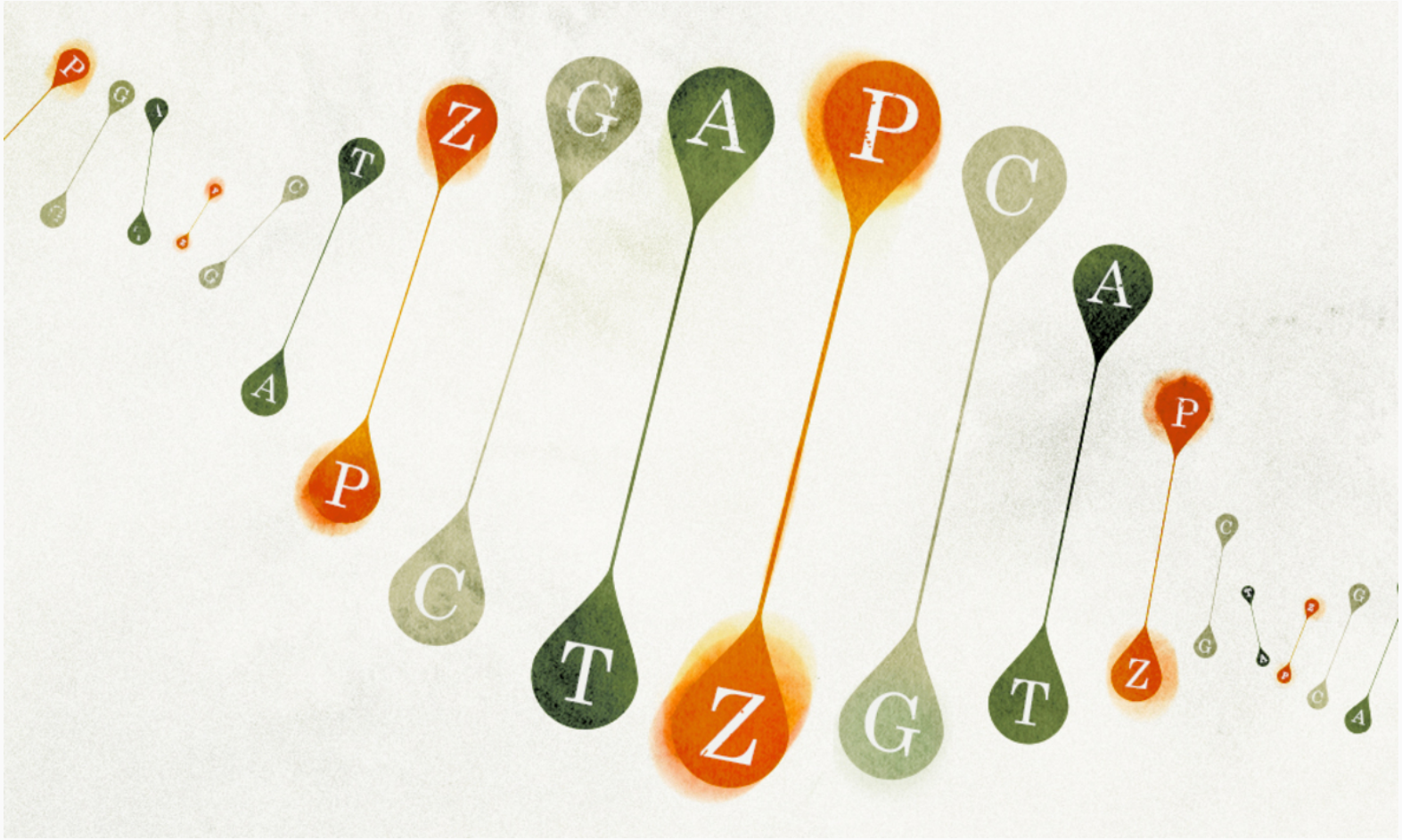



Figure 21. 合成的核苷酸 P 和 Z

# 复制的半不连续性

- DNA 聚合酶**只能**使核苷酸按 $5' \to 3'$ 方向连接成链
- 而 DNA 的两条链的方向相反, 这相反的一条链, DNA 聚合酶是通过冈崎片段来合成它的互补链的.

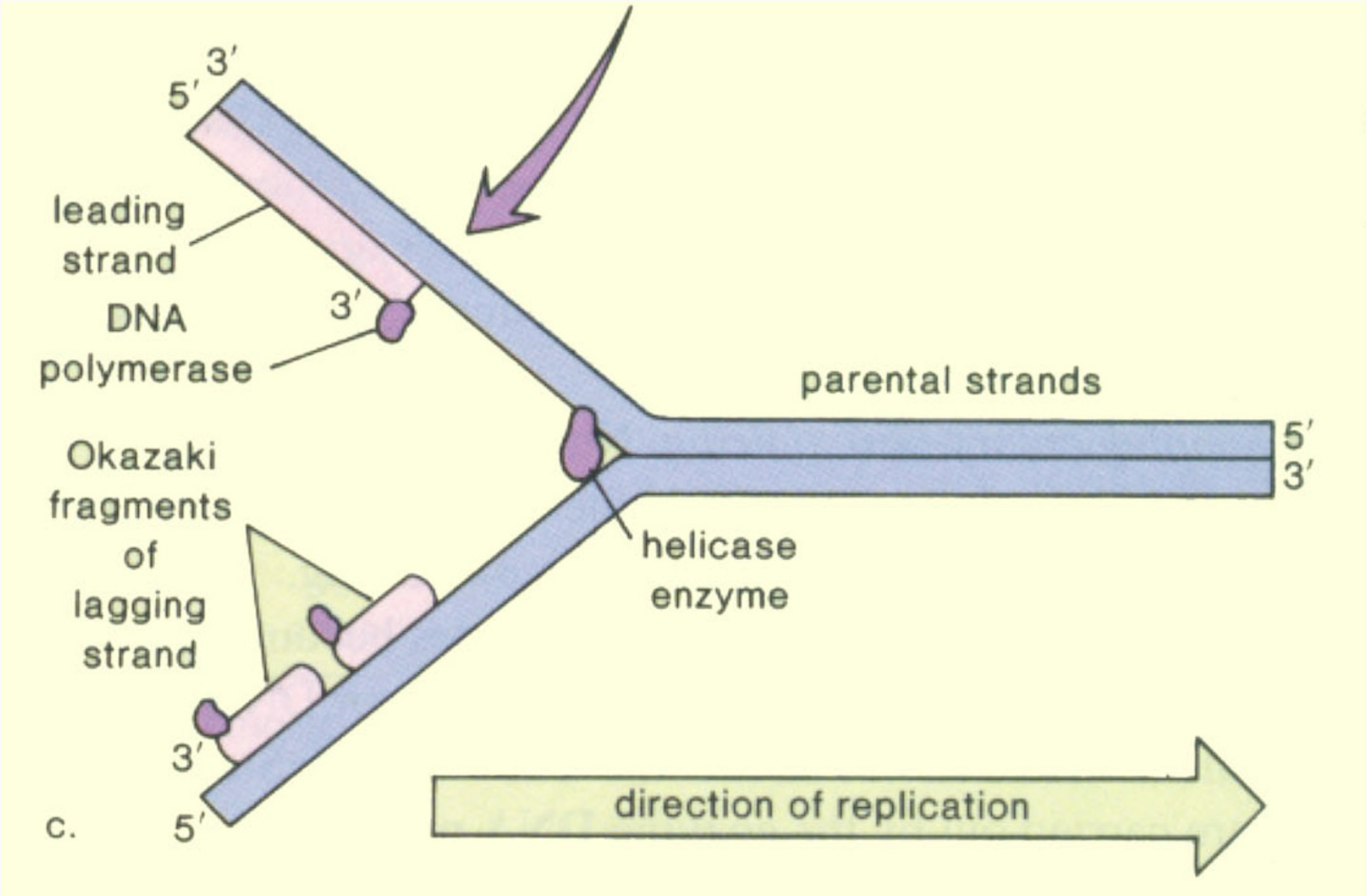



Figure 22. 复制叉

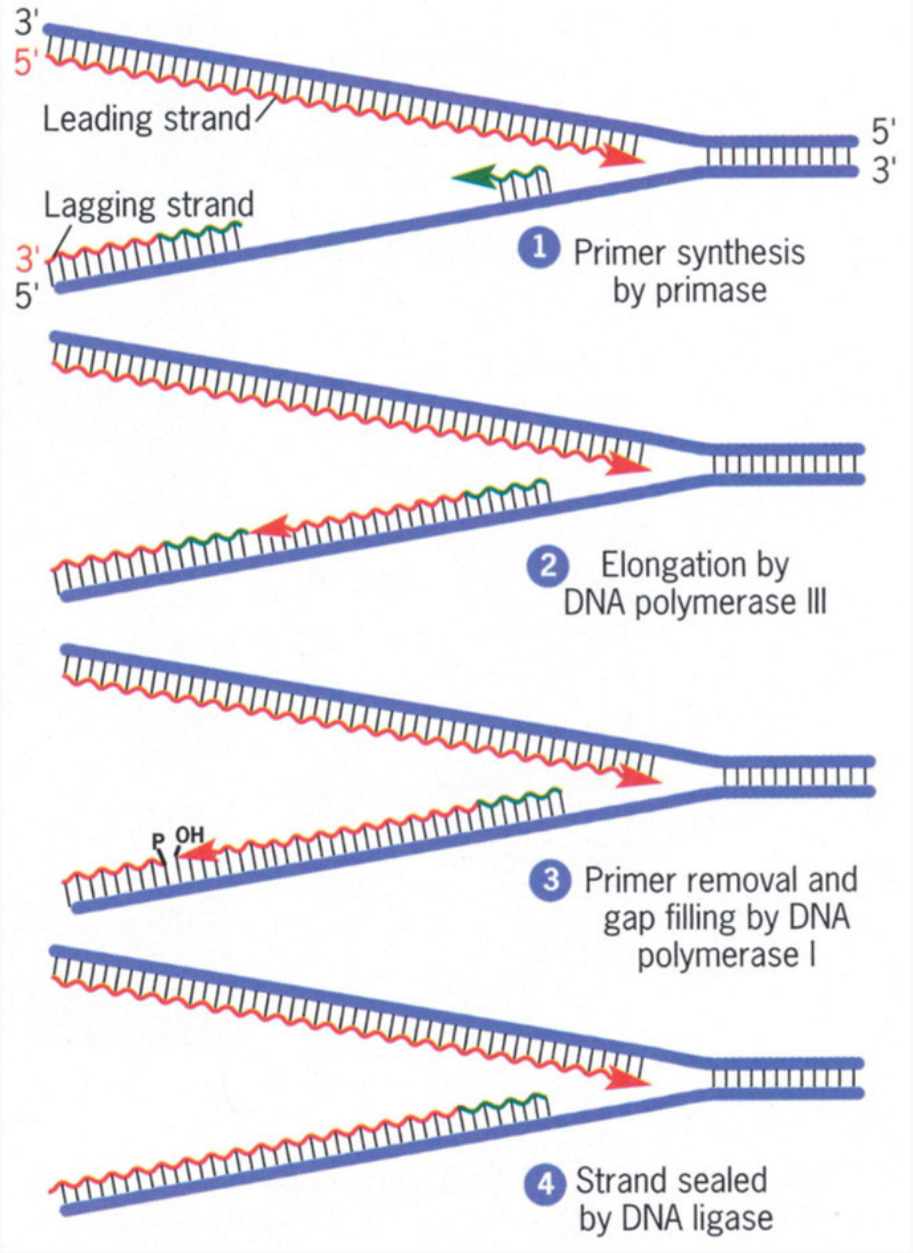



Figure 23. RNA 引物的去除

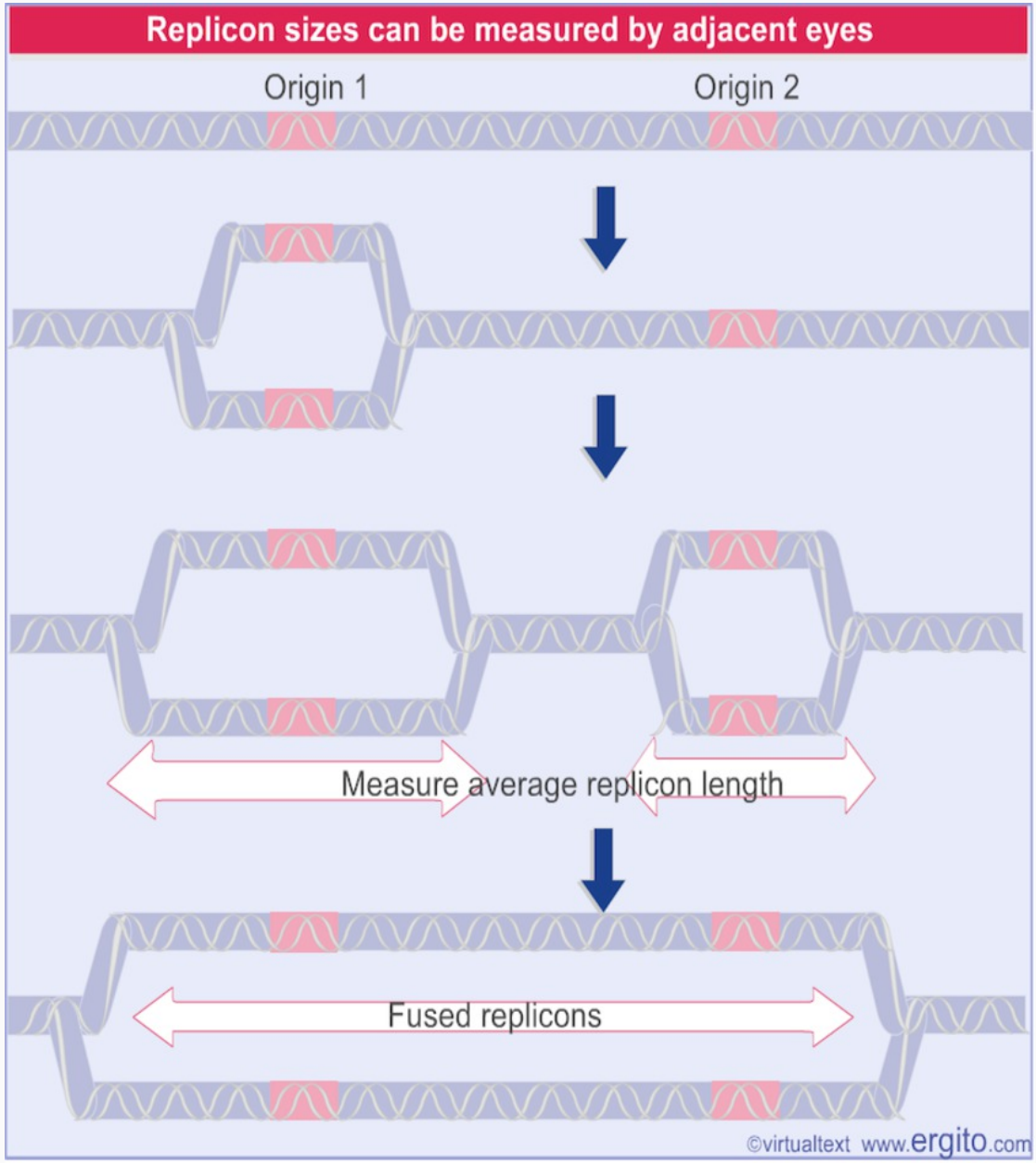



Figure 24. 真核生物的复制起始位点

# 7.3 基因的概念与演变

# 遗传学世纪的大事件 i

- 1865 Genes are particulate factors
- 1903 Chromosomes are hereditary units
- 1910 Genes lie on chromosomes
- 1913 Chromosomes are linear arrays of genes
- 1931 Recombination occurs by crossing over
- 1944 DNA is the genetic material
- 1945 A gene codes for protein
- 1951 First protein sequence
- 1953 DNA is a double helix
- 1958 DNA replicates semiconservatively

# 遗传学世纪的大事件 ii

- 1961 Genetic code is triplet
- 1977 Eukaryotic genes are interrupted
- 1977 DNA can be sequenced
- 1995 Bacterial genomes sequenced
- 2001 Human genome sequenced
- 蛋白质是表型特征的分子基础
- DNA 与蛋白质的合成
- 遗传信息在细胞质中被翻译
- 中心法则

# 7.4 基因组

# 基因组及基因组学

**基因组** 一个生物个体中, DNA 分子所携带的遗传信息总和.

- genome
- 核基因组
- 叶绿体基因组
- 线粒体基因组
- 病毒基因组
- 人的基因组 (22+X+Y)

**基因组学** 研究生物体的基因和基因组的结构, 组成和功能.

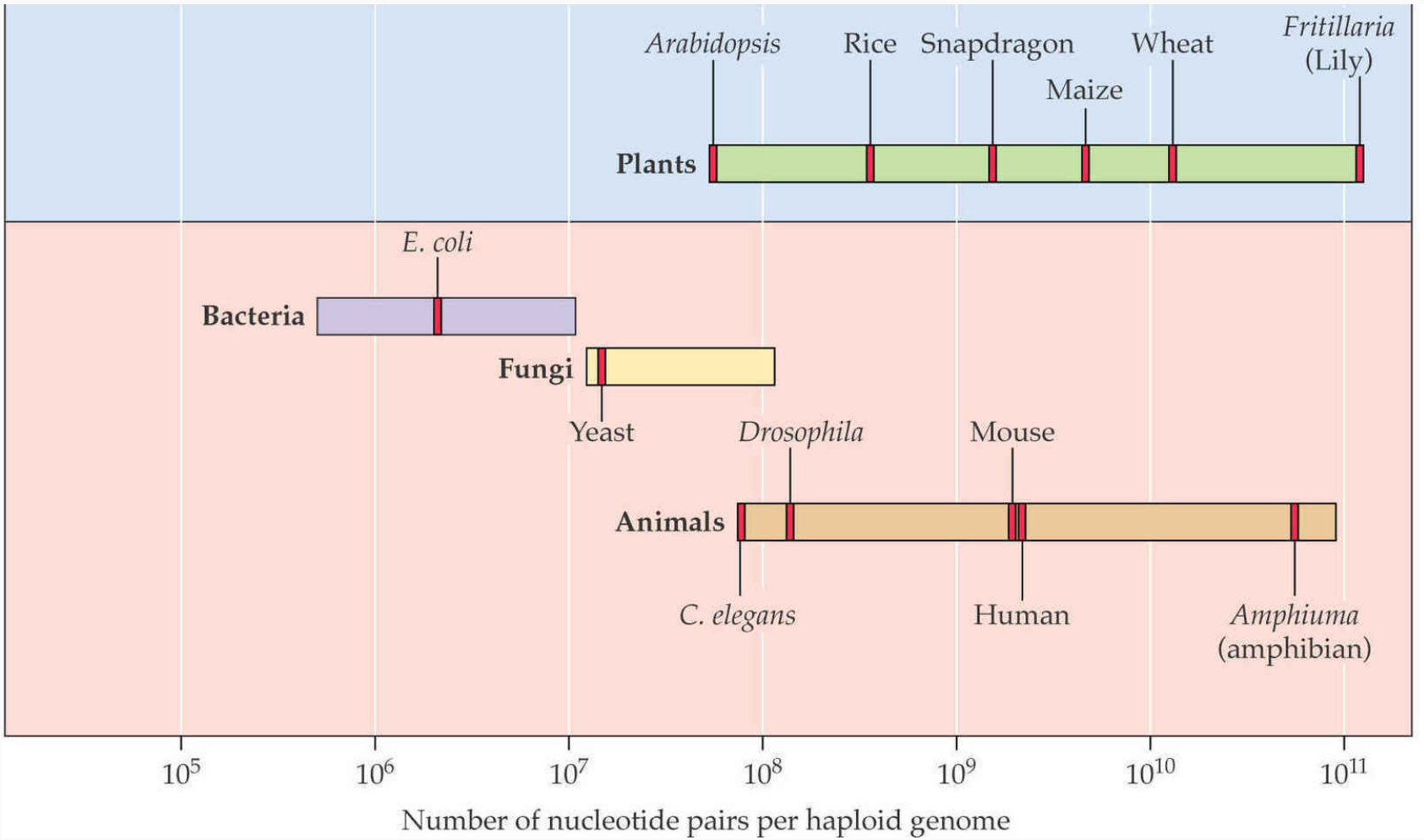



Figure 25. 不同生物基因组碱基对数目比较

## 人类基因组计划

- 1985 年, 美国能源部正式提出人类基因组测序.
- 1990 年, 正式启动人类基因组测序.

1. 绘制人类基因组连锁图
2. 绘制物理图
3. 人类基因组测序
4. 其他物种基因组分析


Figure 26. “绘制”

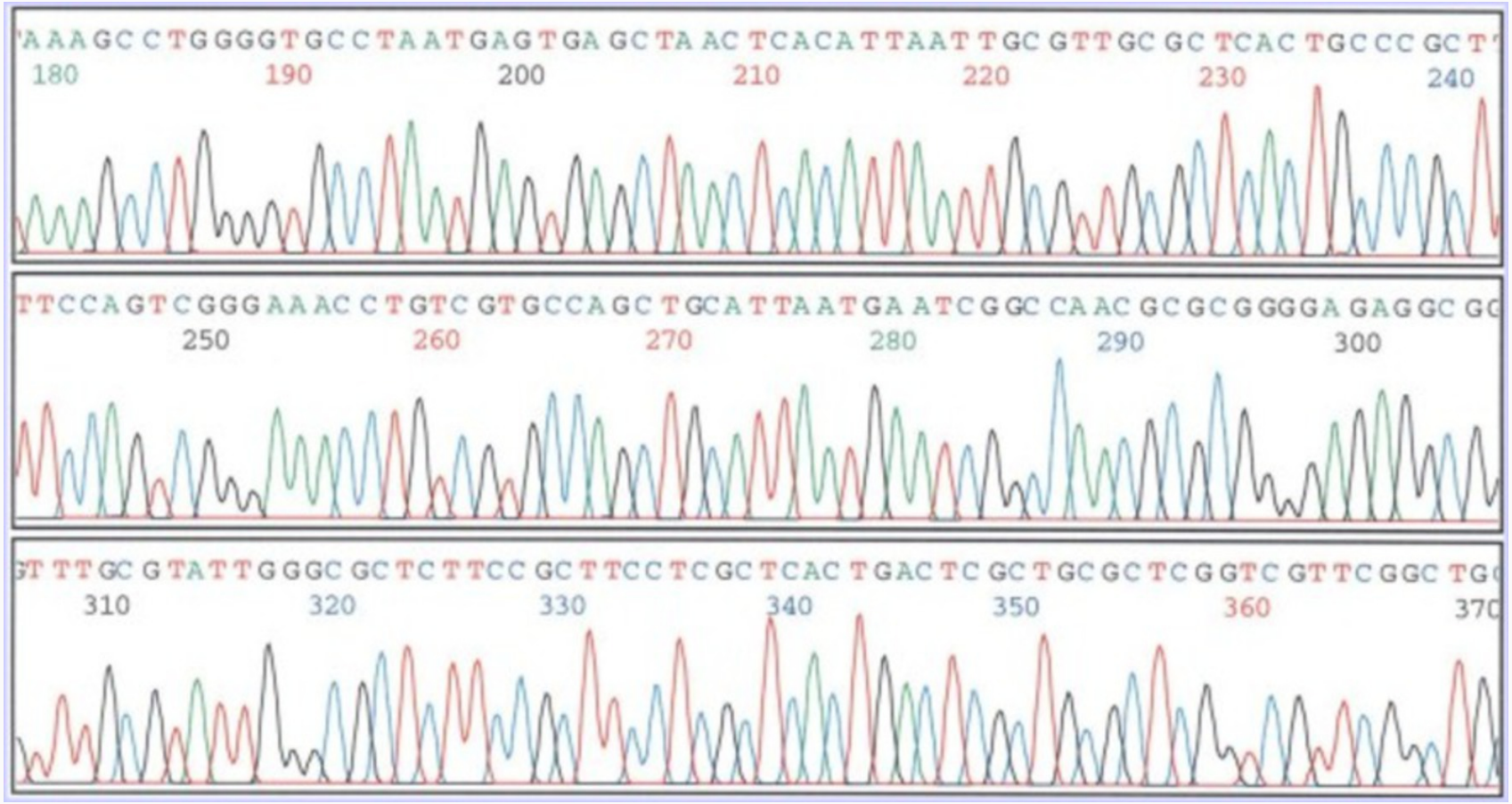



Figure 27. Electropherogram

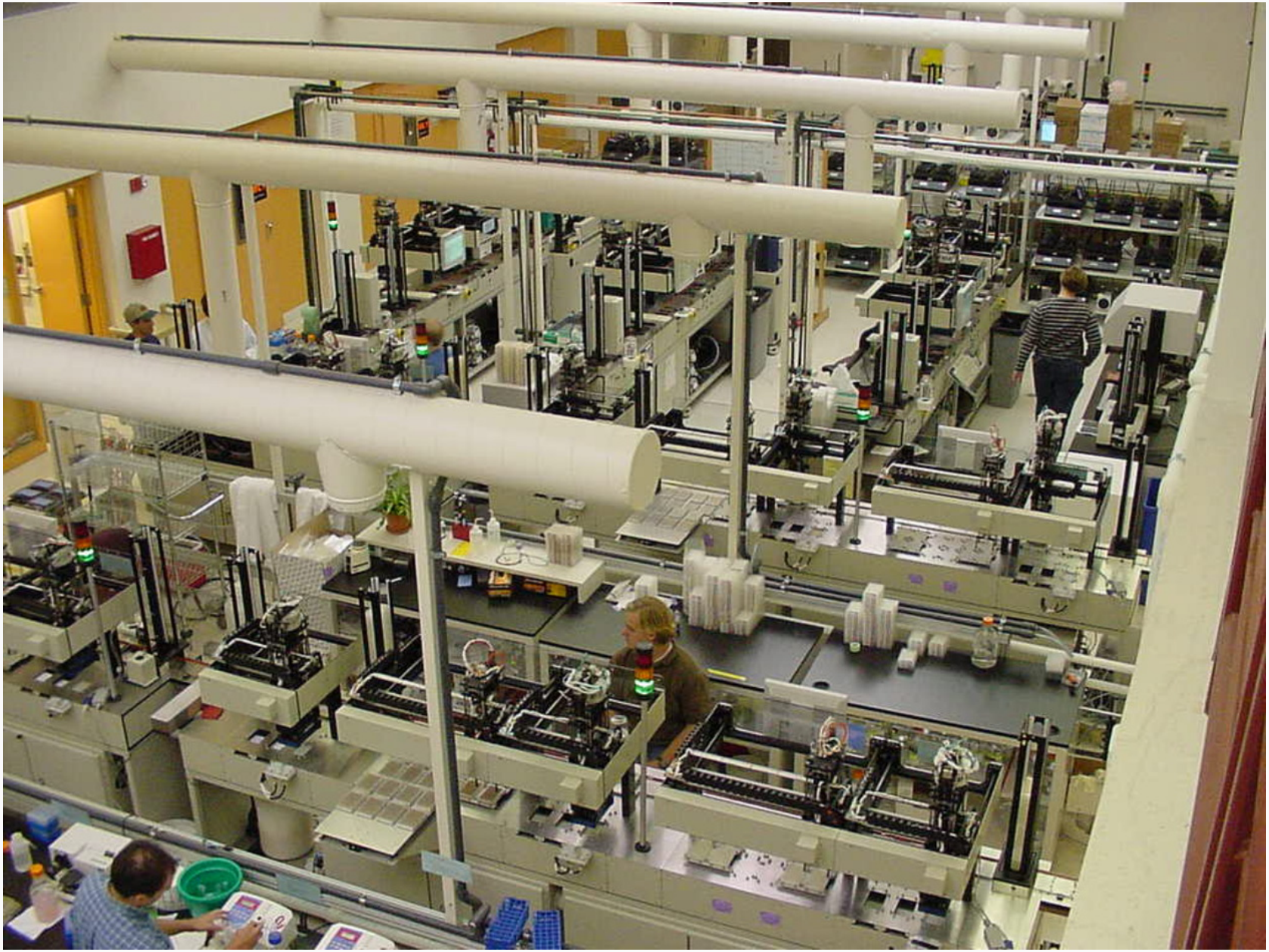


Figure 28. 模板与测序室

Figure 29. Clusters, Storages

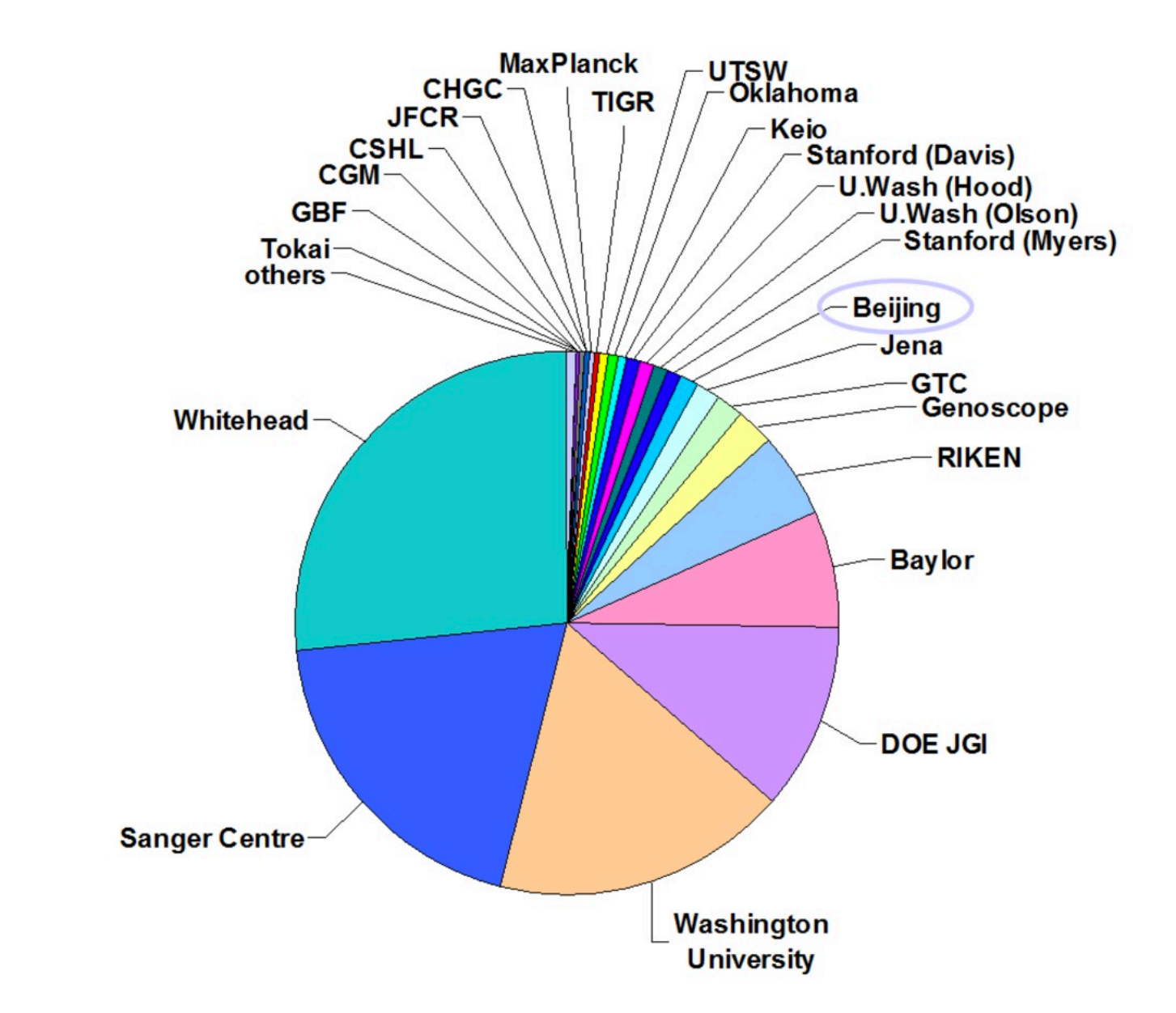

MaxPlanck
UTSW
CHGC
Oklahoma
TIGR
JFCR
Keio
CSHL
Stanford (Davis)
CGM
U.Wash (Hood)
GBF
U.Wash (Olson)
Tokai
Stanford (Myers)
others
Beijing
Jena
GTC
Whitehead
Genoscope
RIKEN
Baylor
DOE JGI
Sanger Centre
Washington
University

Figure 30. 贡献

# 基因专利

- Myriad genetics 公司拥有 *BRCA1* 和 *BRCA2* 基因的国际专利, 乳腺癌与卵巢癌的相关基因.
- Myriad 的测试费为 $869.
- 现在有更便宜的方法, 只要 $100, 但都侵犯了 Myriad 的专利.

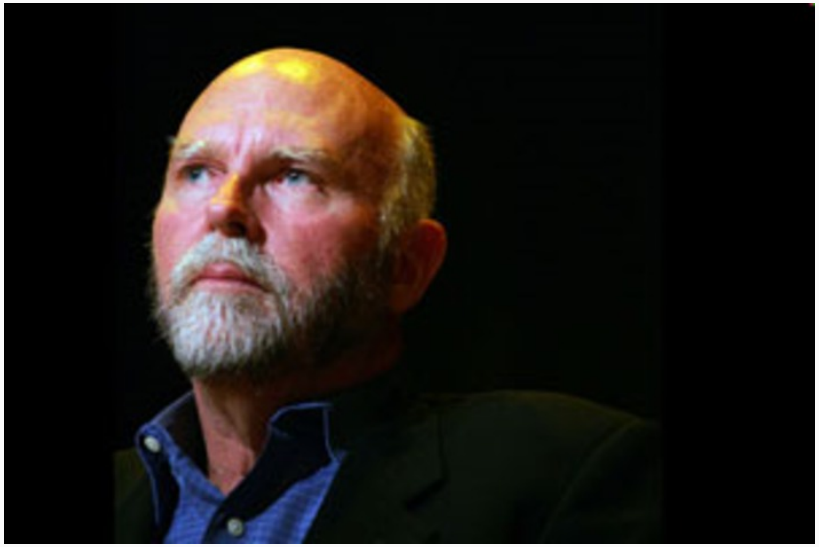


Figure 31. 文特尔, J. Craig Venter

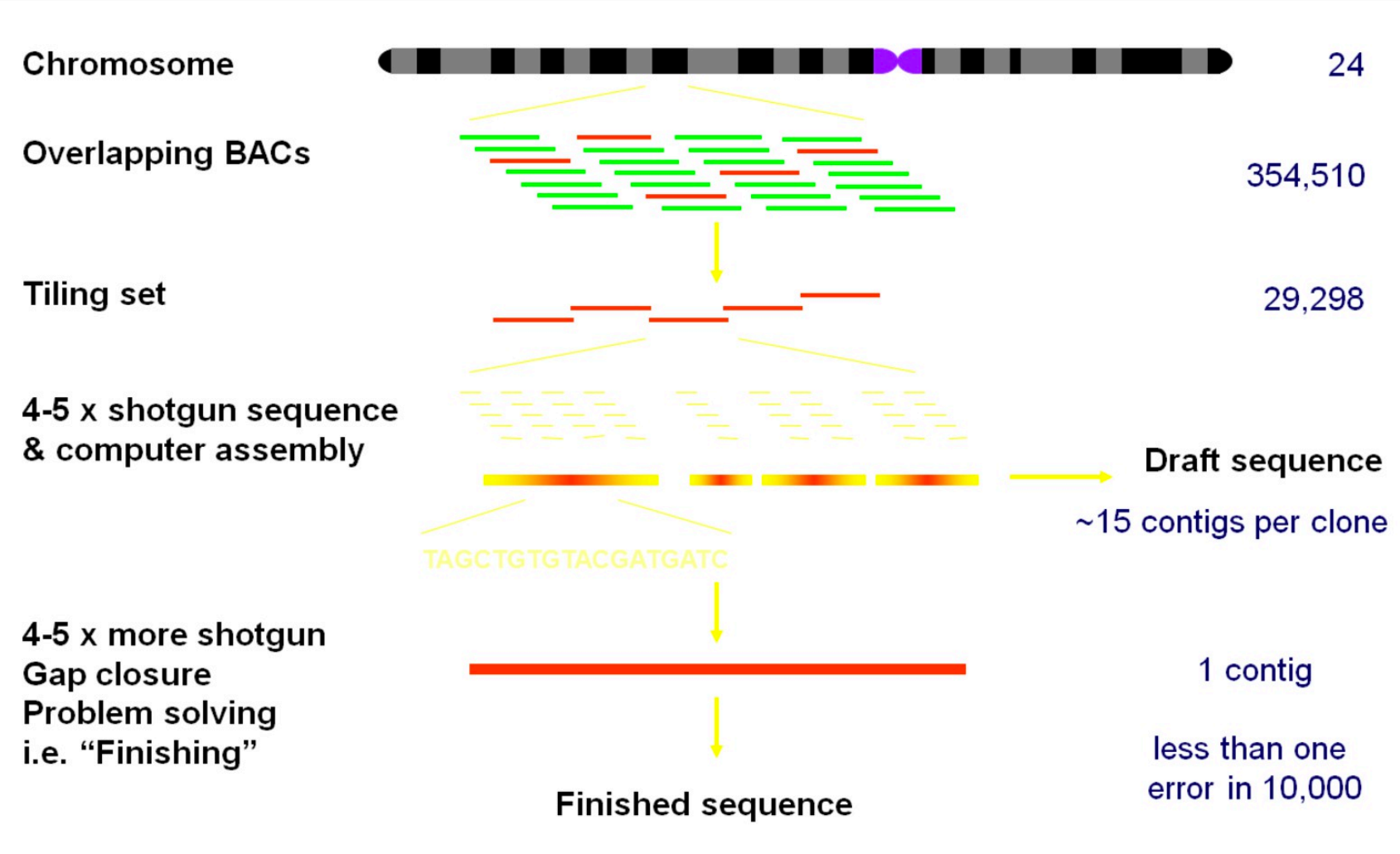



Figure 32. HGP sequencing strategy

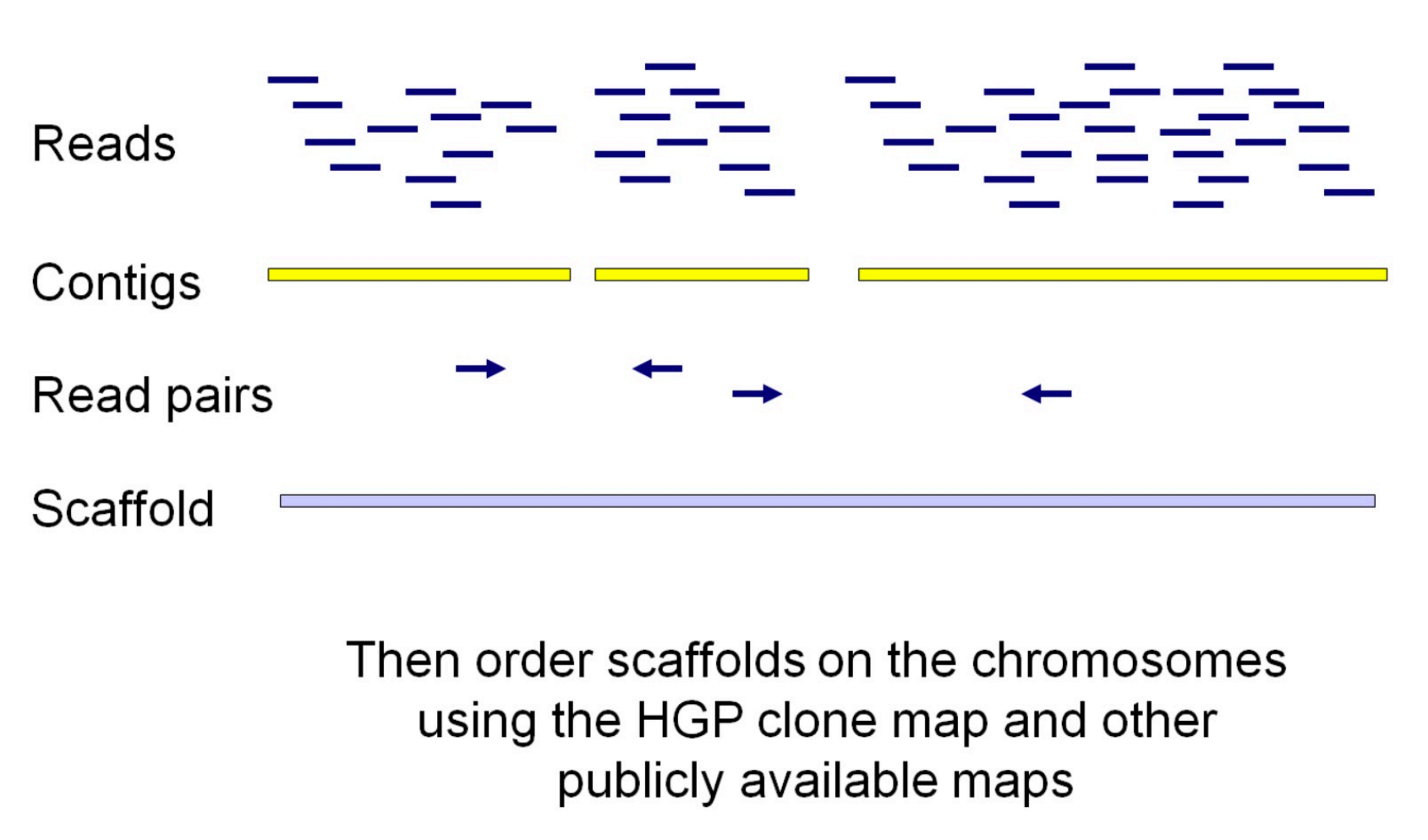


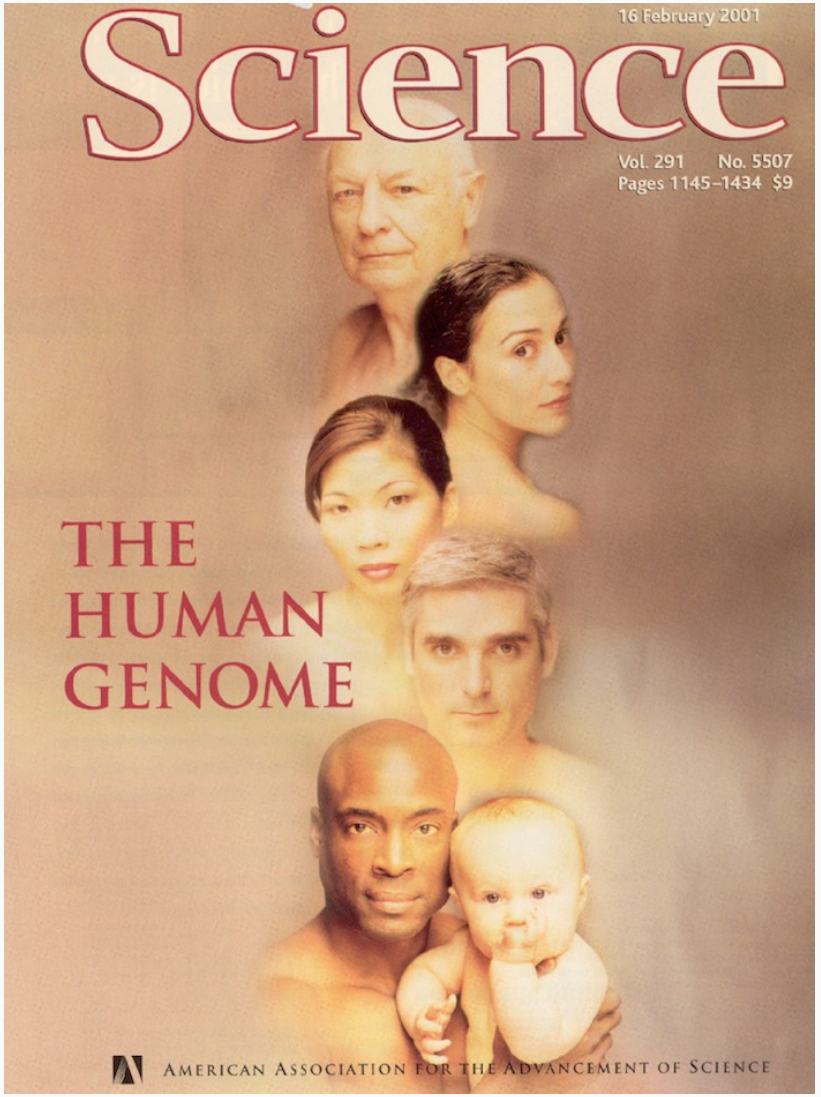

Figure 33. Celera assembly strategy


Figure 34. Celera stock

# 基因组草图, 2001

- International Human Genome Sequencing Consortium
  - **公共项目**
  - Lander, E. S. *et al.* **Initial Sequencing and Analysis of the Human Genome.** *Nature* **409,** 860–921 (2001)
- Celera Genomics, Venter JC *et al.*
  - **私有项目**
  - Venter, J. C. *et al.* **The Sequence of the Human Genome.** *Science* **291,** 1304–1351 (2001)


(a) Nature




(b) Science

Figure 35. 基因组草图, 2001

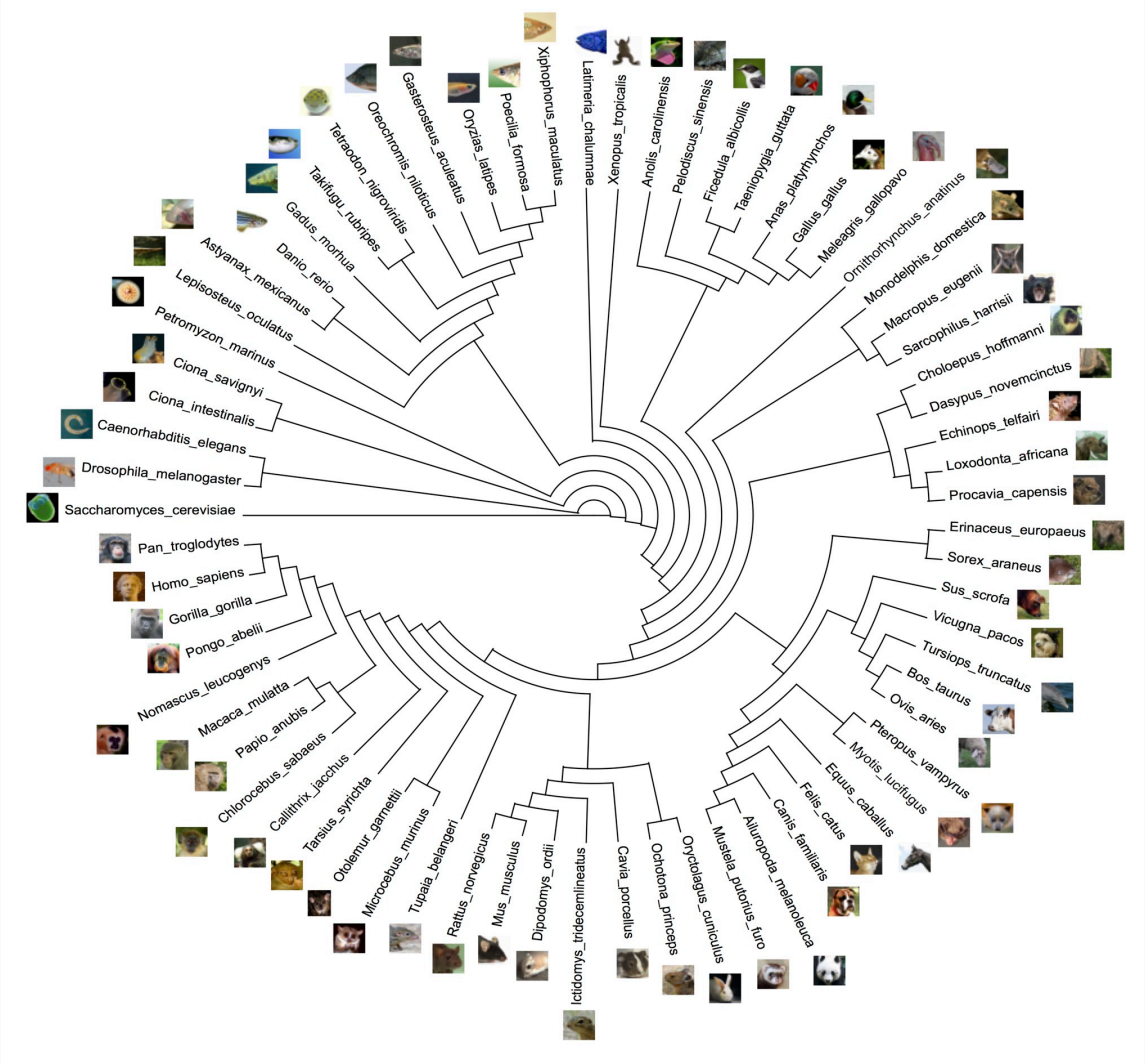



Figure 36. 全基因组测序的生物

# 基因组研究成果

- $3.2 \times 10^9$ bp
- 约 2 万个基因

测序已完成; 进一步的工作是确定各个基因的功能及他们之间的相互关系.

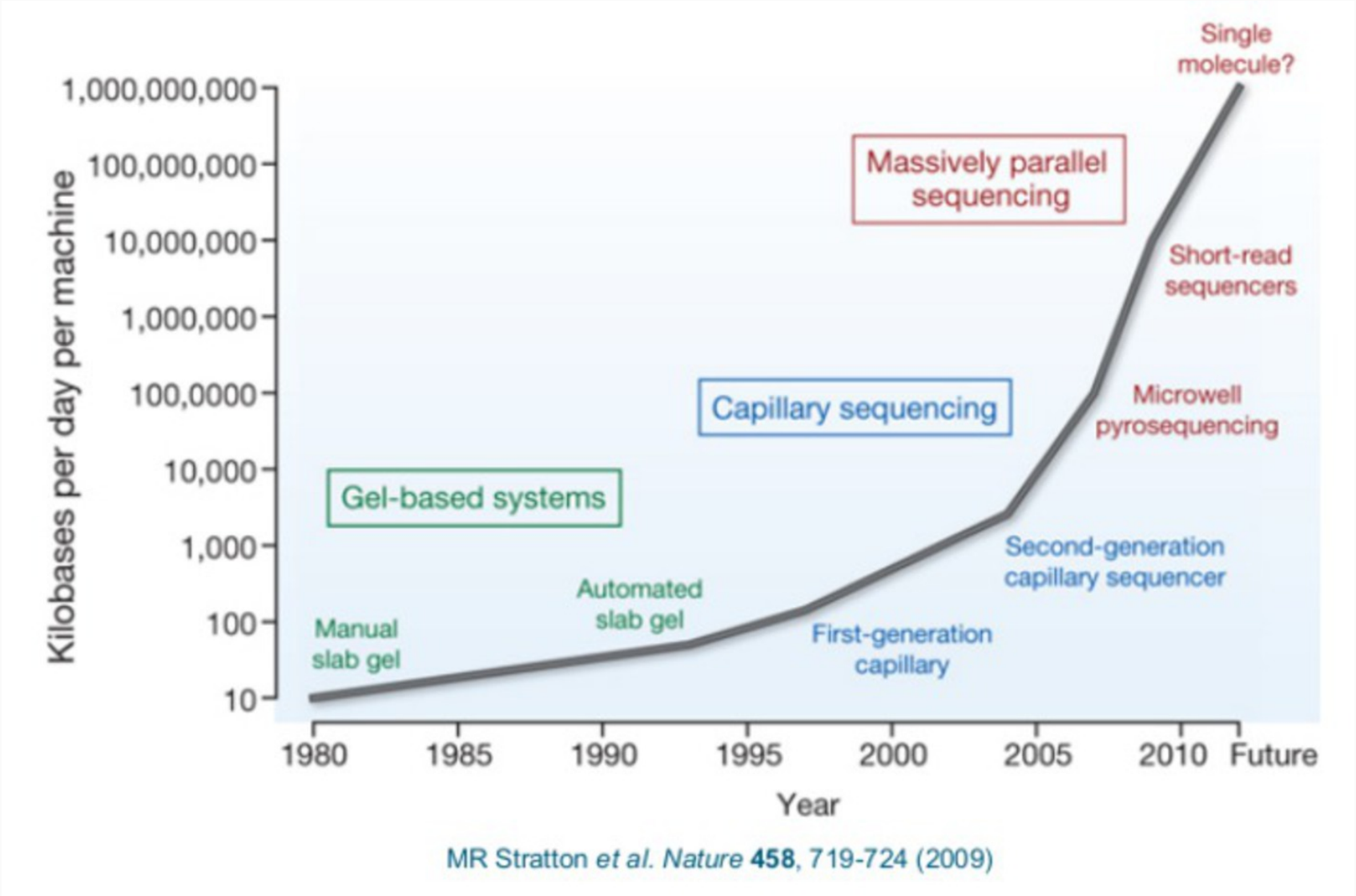



Figure 37. 测序能力的增长

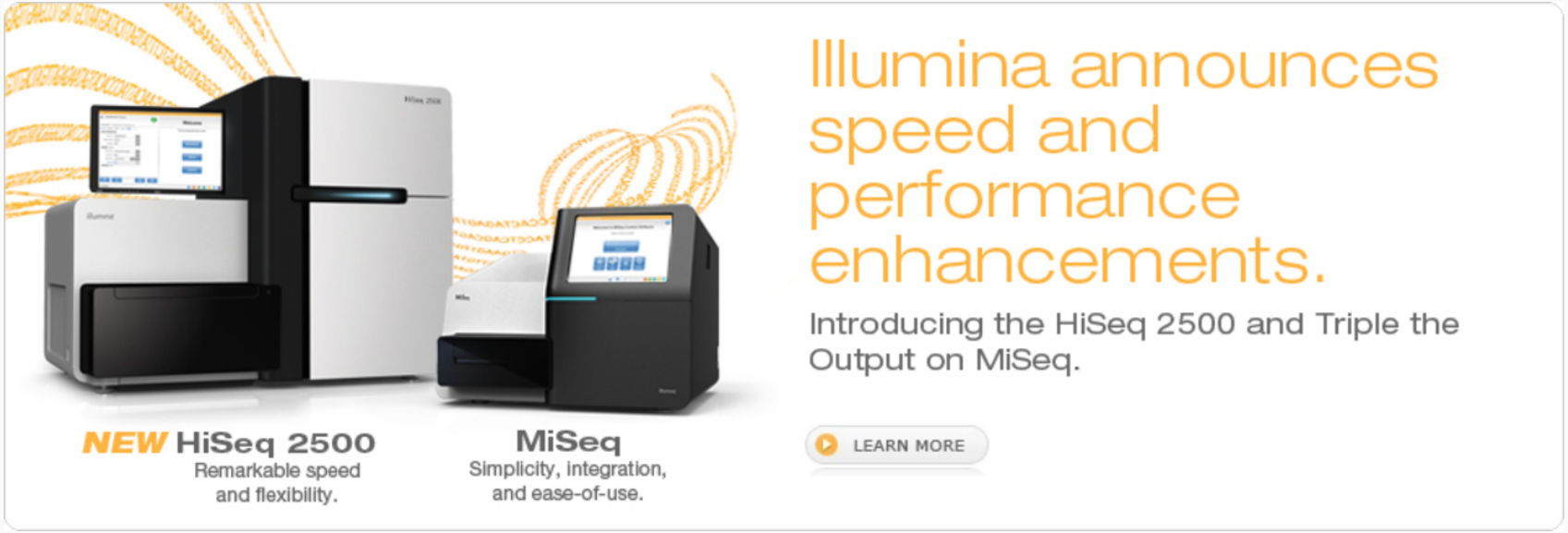



Figure 38. Illumina

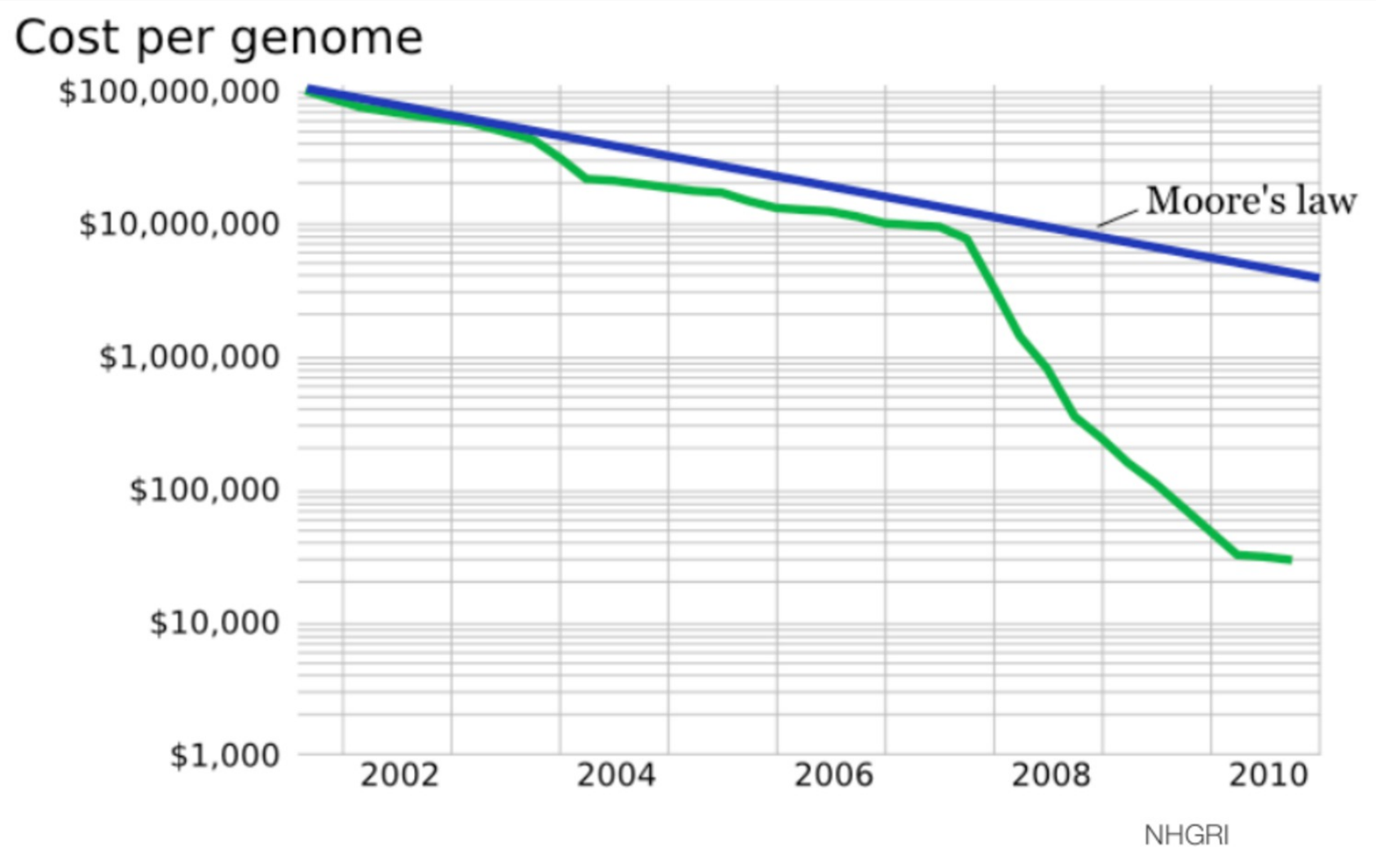



Figure 39. 比摩尔定律更快

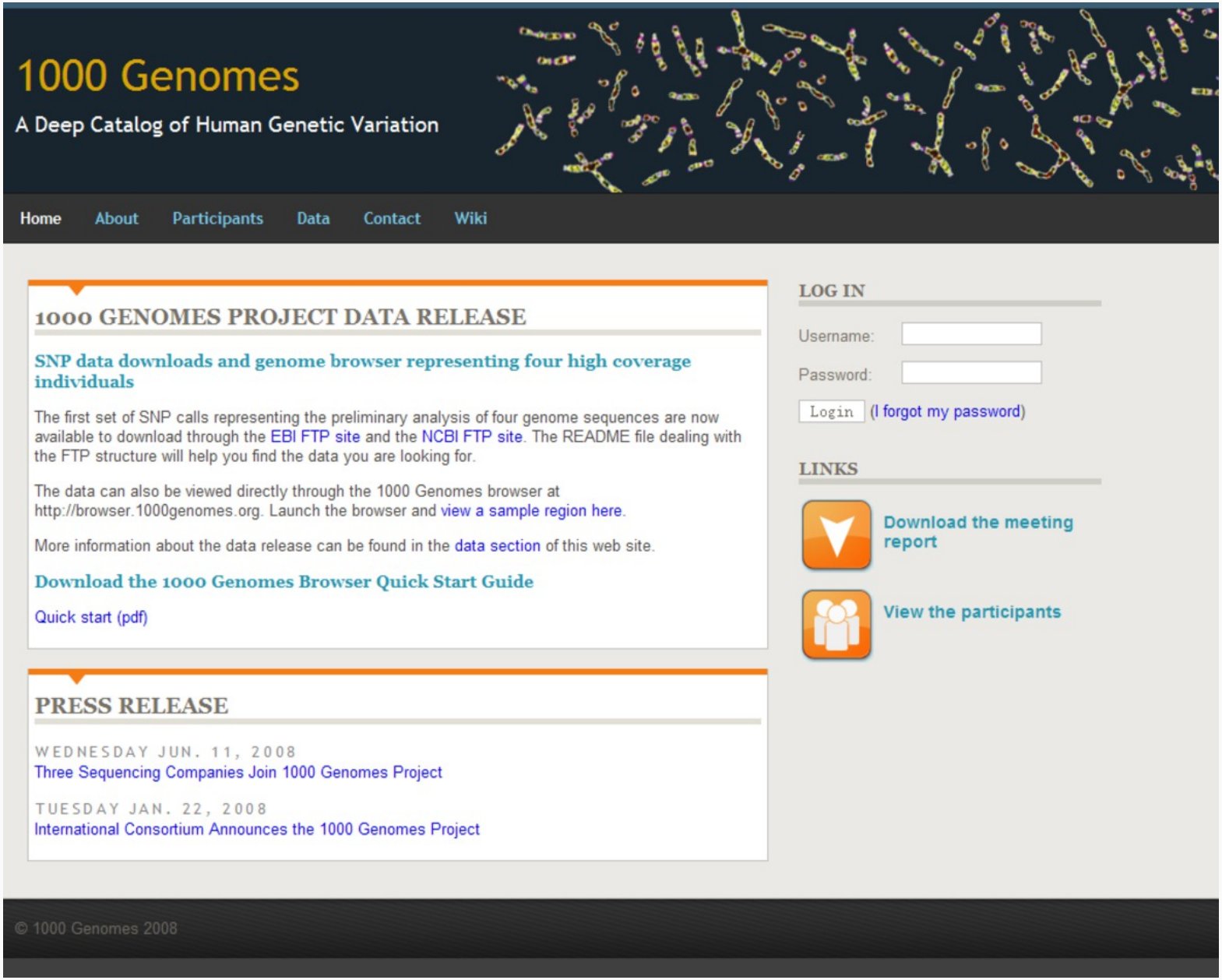


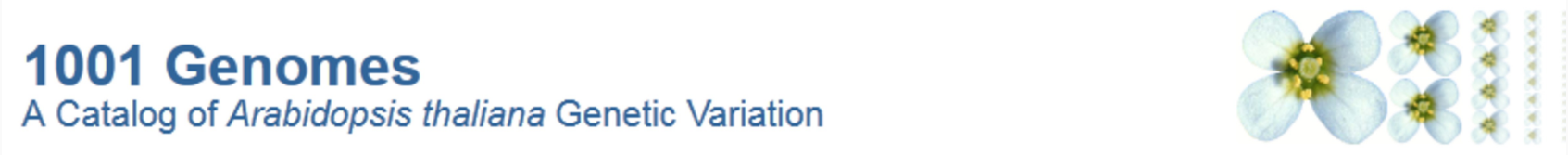

Figure 40. 千个基因组计划

# Personal Genomes

- Craig Venter
- James Watson
- Stephen Quake
- George Church
- Marjolein Kriek
- Hermann Hauser
- Han Chinese
- Seong-Jin Kim
- Korean AK1
- Yoruban African NA18507
- 14 others sequenced by Complete Genomics
- Unknown number sequenced by Knome
- 6 genomes sequenced at high depth by the 1000 Genomes Project
- 180 genomes sequenced at low coverage by the 1000 Genomes Project
- Two acute myeloid leukemia patients


(a) 脊椎动物


(b) 英国人健康计划




(c) 拟南芥

Figure 41. 其它计划

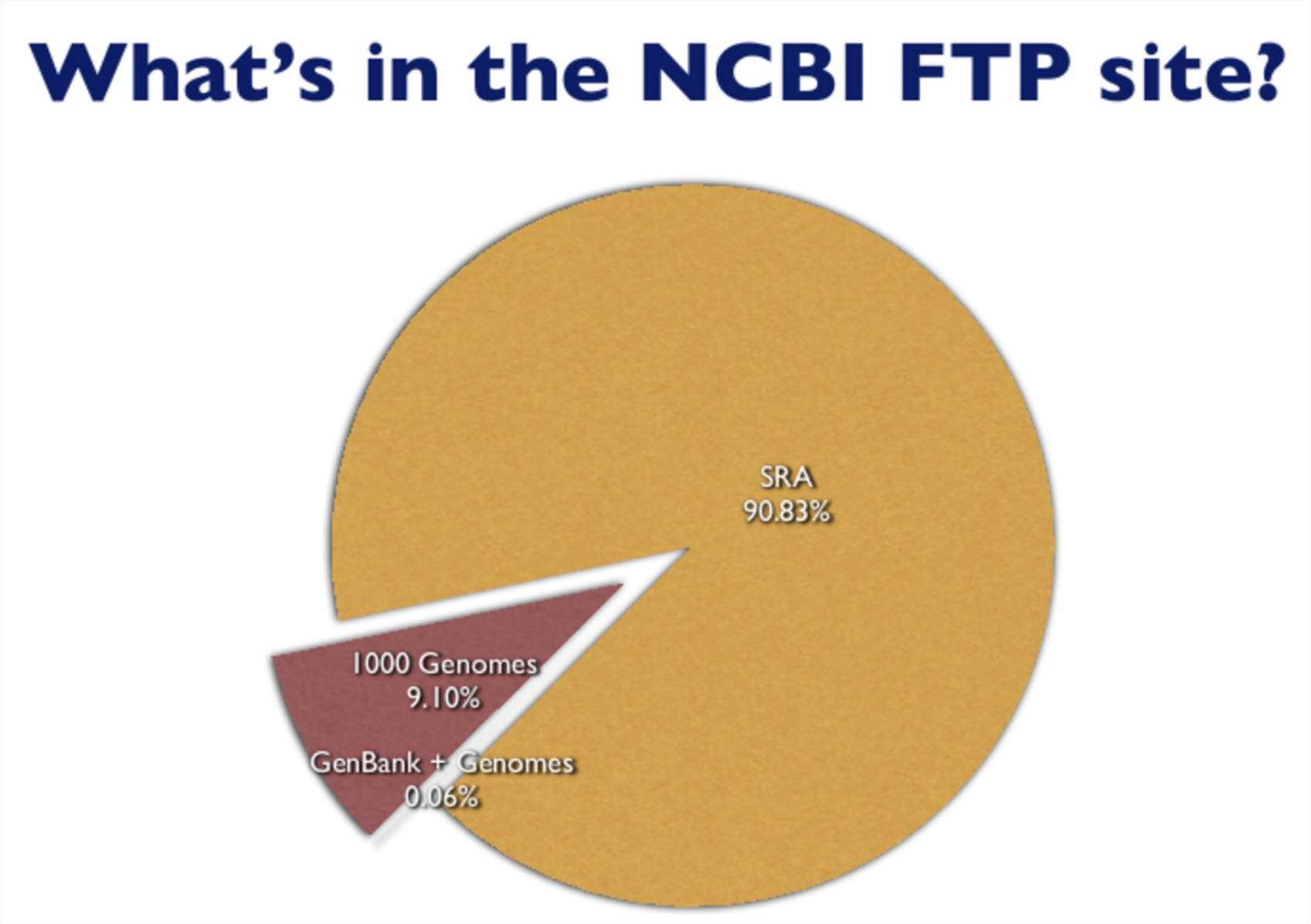



Figure 42. 爆发性增长的数据量

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Whole-Genome Sequencing in a Patient with Charcot–Marie–Tooth Neuropathy

James R. Lupski, M.D., Ph.D., Jeffrey G. Reid, Ph.D., Claudia Gonzaga-Jauregui, B.S., David Rio Deiros, B.S., David C.Y. Chen, M.Sc., Lynne Nazareth, Ph.D., Matthew Bainbridge, M.Sc., Huyen Dinh, B.S., Chyn Jing, M.Sc., David A. Wheeler, Ph.D., Amy L. McGuire, J.D., Ph.D., Feng Zhang, Ph.D., Pawel Stankiewicz, M.D., Ph.D., John J. Halperin, M.D., Chengyong Yang, Ph.D., Curtis Gehman, Ph.D., Danwei Guo, M.Sc., Rola K. Irikat, B.S., Warren Tom, B.S., Nick J. Fantin, B.S., Donna M. Muzny, M.Sc., and Richard A. Gibbs, Ph.D.

Figure 43. 追踪罕见遗传疾病的致病基因[2]

[2] Lupski, J. R. *et al.* **Whole-Genome Sequencing in a Patient with Charcot–Marie–Tooth Neuropathy.** *N Engl J Med* **362,** 1181–1191 (2010)

# 人类基因组各组成成分的基本特征

1. 基因
   - 断裂基因
2. 基因外 DNA
   - 单拷贝序列和低拷贝数序列占 70–80%
   - 中度和高度重复序列占 20–30%
3. 分散重复序列
4. 簇状重复序列

# 7.5 非孟德尔式遗传

# 高等植物的细胞质遗传

- 细胞质中的遗传物质控制的遗传, 质体和线粒体.
- 非孟德尔式.
- 母本贡献遗传物质, 而且是随机分配给子细胞.
- F1 通常只表现母本的性状, 后代一般不出现一定比例的分离.

Table 1. 紫茉莉绿白斑植株的细胞质遗传

| 母本枝条的类型 | 父本枝条的类型 | 子代的类型 |
|---|---|---|
| 白 | 白 | 白 |
| 绿 | 白 | 绿 |
| 绿白斑 | 白 | 绿, 白或绿白斑 |
| 白 | 绿 | 白 |
| 绿 | 绿 | 绿 |
| 绿白斑 | 绿 | 绿, 白或绿白斑 |
| 白 | 绿白斑 | 白 |
| 绿 | 绿白斑 | 绿 |
| 绿白斑 | 绿白斑 | 绿, 白或绿白斑 |