

红霉素的合成生物学研究

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Biotechnology Evolution:

Fleming (1928), Florey, Chain, Heatley (1940s)



Penicillium notatum

Alexander Fleming discovered penicillin by accident in 1928.

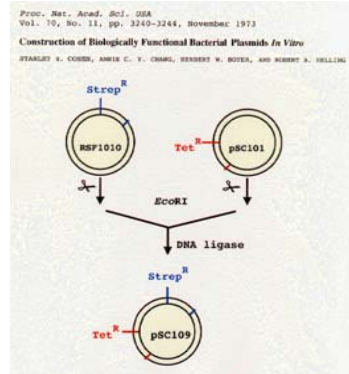


It was largely due to the technical ingenuity of one man that enough penicillin was produced for the first hospital tests. That man was Norman Heatley

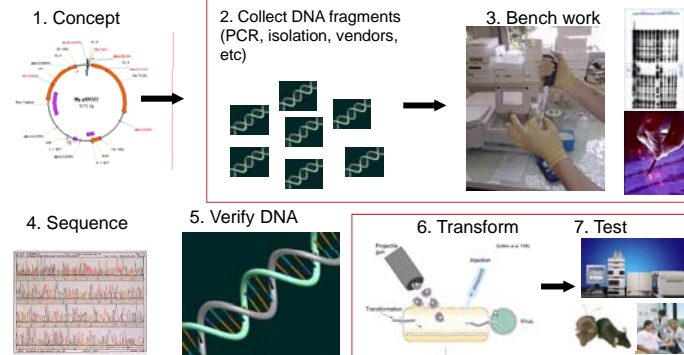
Cohen and Boyer, 1973

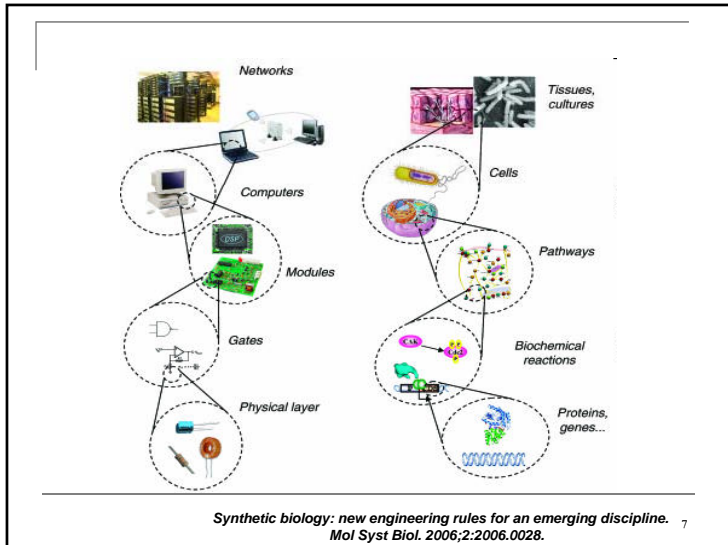
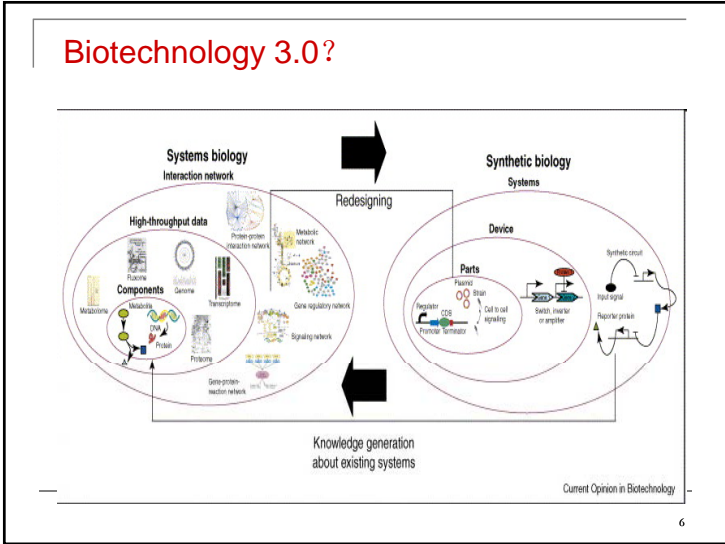
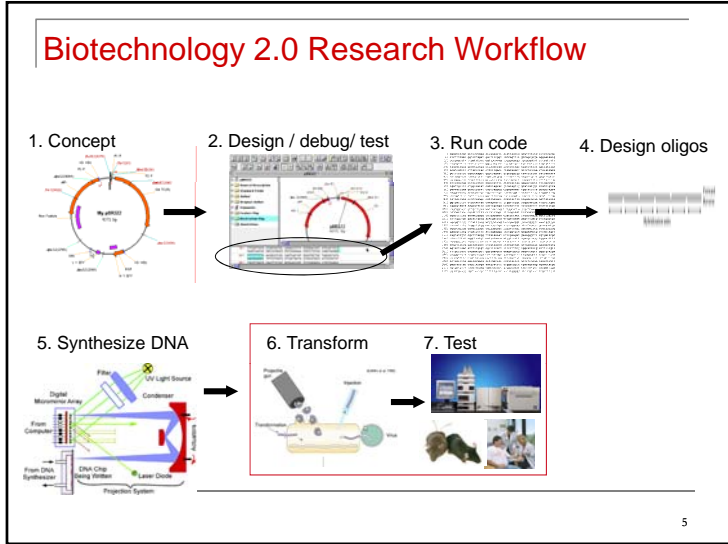
Recombinant human insulin, 1982

- First recombinant DNA experiments
- Human insulin produced in *E.coli*



Biotechnology 1.0 Research Workflow





生物医药产业:

抗生素、维生素、氨基酸、有机酸

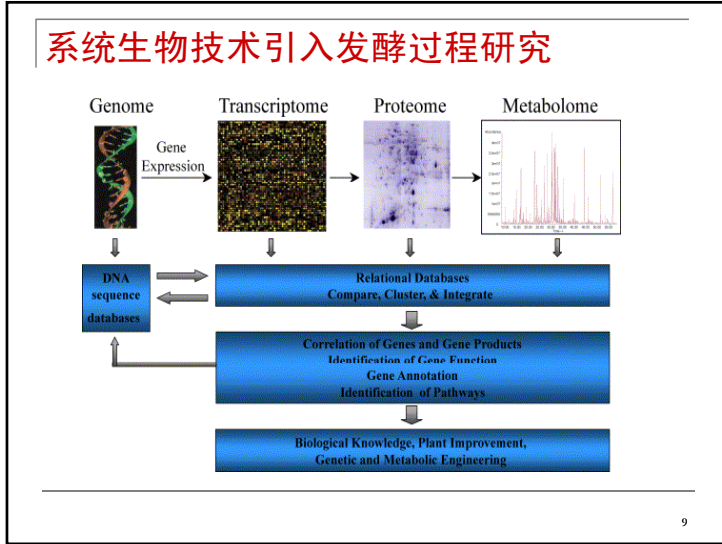
传统生物技术

抗体、重组蛋白、疫苗

现代生物技术

微生物，动物细胞、植物细胞大规模培养

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“The discovery of drugs does not always translate to the people who need them, the most because drug production processes can be difficult and costly.”

—Ahmad S. Khalil & Jams J. Collins
Nature reviews Genetics 11,367-379 (May,2010)

- 已知的聚酮类化合物超过7000种，但进入药物开发的不足100种
- ✓ 生长特性差（难培养或不可培养，珍稀植物来源）
- ✓ 培养特性差（难以大规模培养）
- ✓ 遗传改造难
- ✓ 沉默基因
- ✓ 共生宿主

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合成生物学： 对系统不同层次的重新设计和装配组合

Systems

Devices

Parts

- 一是设计和构建新的生物零件、组件和系统；
- 二是对现有的、天然存在的生物系统进行重新设计和改造。
- 合成生物学就是通过设计和构建自然界中不存在的人工生物系统，来解决能源、材料、健康和环保等问题。

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天然产物的合成生物学研究

- 过去二十年中上市的新药中有61%来自于天然产物
- 人类已知的天然产物超过100万种，其中具有生物活性的约25万种

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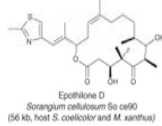
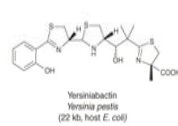
graph TD
    NP[Natural Products (secondary metabolites)] --> TS[Terpenoids, Steroids]
    NP --> AL[Alkaloids]
    NP --> FAP[Fatty acids, Polyketides]
    NP --> NRP[Nonribosomal polypeptides]
    NP --> EC[Enzyme cofactors]
    
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Candidate hosts for heterologous production

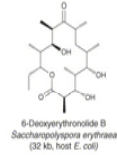
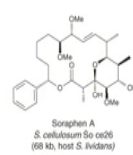
Streptomyces

- S. lividans*
- S. coelicolor*
- S. fradiae*



Bacteria

- E. coli*
- B. subtilis*
- Pseudomonas putida*
- Myxococcus xanthus*



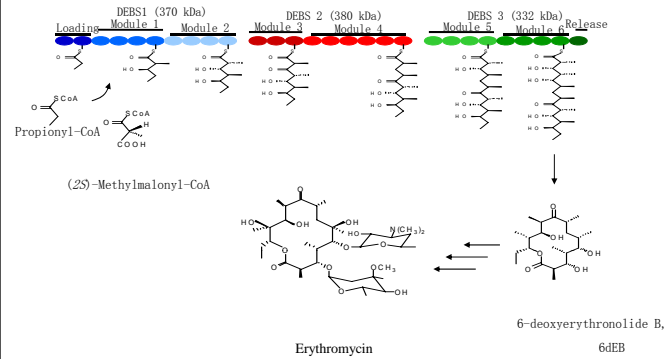
Fungi

- S. cerevisiae*

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Introduction: Modular Polyketide Synthase (PKS)

-Deoxyerythronolide B Synthase (DEBS)



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Summary

- Strain phenotype improvement coupled with the bioprocess optimization has become the trend in the context of systems biotechnology;
- Synthetic biology, with multivariate design, has been becoming an important approach for the complex metabolites production.



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