SCIE5508
Synthetic Biology – Solving global challenges

Lecture 2 – Foundational concepts of Synthetic Biology

Dr. Georg Fritz
Senior Lecturer
School of Molecular Sciences

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We are learning on Noongar land

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SEEK WISDOM

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Foundational concepts of Synthetic Biology

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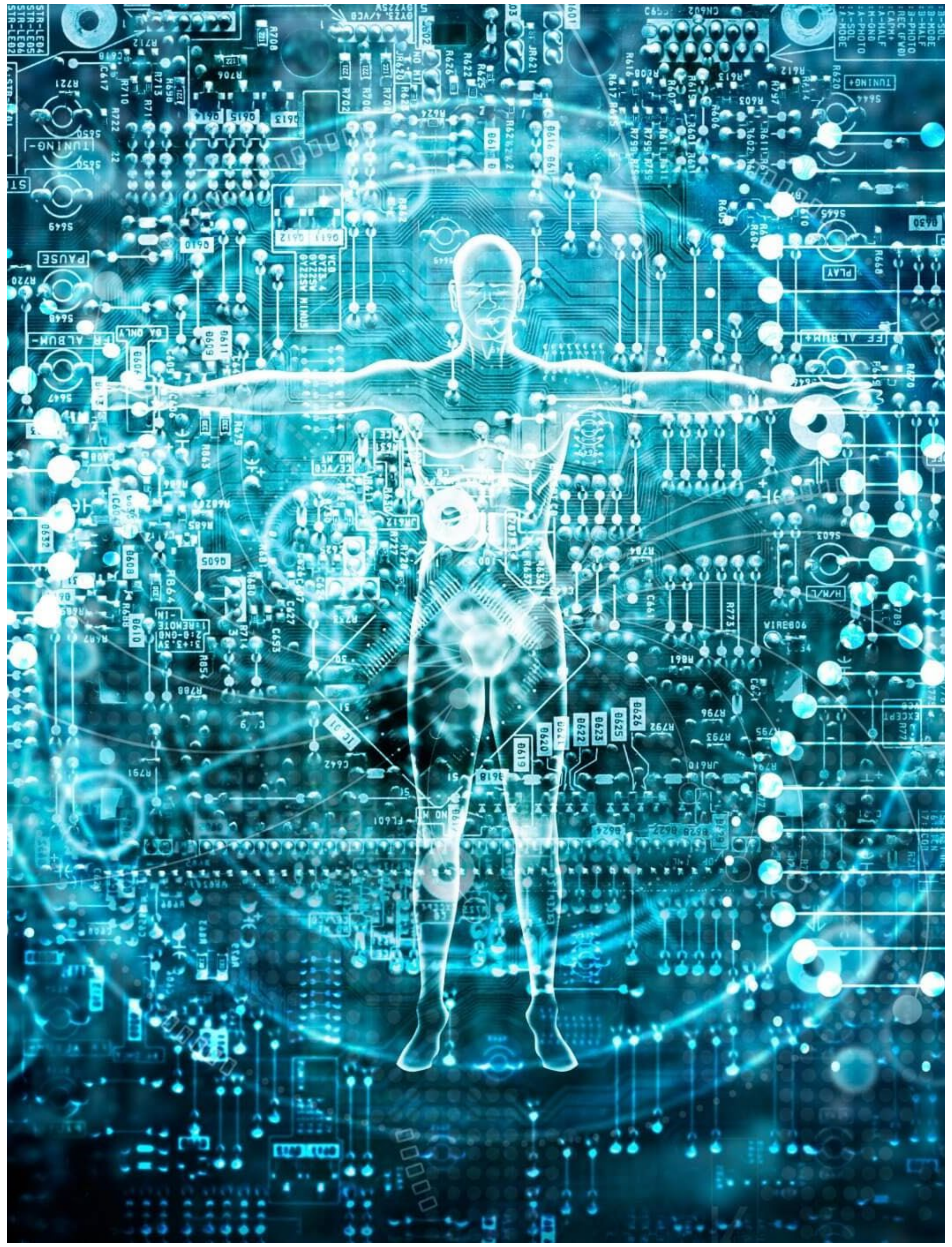
Learning outcomes

After this lecture, students should understand and be able to describe:

- The two key motivations behind Synthetic Biology
- The historic rise of Synthetic Biology and its connection to other fields
- The fundamental engineering principles underlying Synthetic Biology
- The concept of the Design-Build-Test-Learn cycle
- Some of the global challenges that Synthetic Biology seeks to address



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What is Synthetic Biology?

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synthesis noun

syn·the·sis | \ ˈsin(t)-thə-səs \
plural **syntheses** \ ˈsin(t)-thə-ˌsēz \

Definition of *synthesis*

1 a : the composition or combination of parts or elements so as to form a whole

+

biology noun

bi·ol·o·gy | \ bī-ˈä-lə-jē \

Definition of *biology*

1 : a branch of knowledge that deals with living organisms and vital processes

= building life!

Why?

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Historic traces of the field

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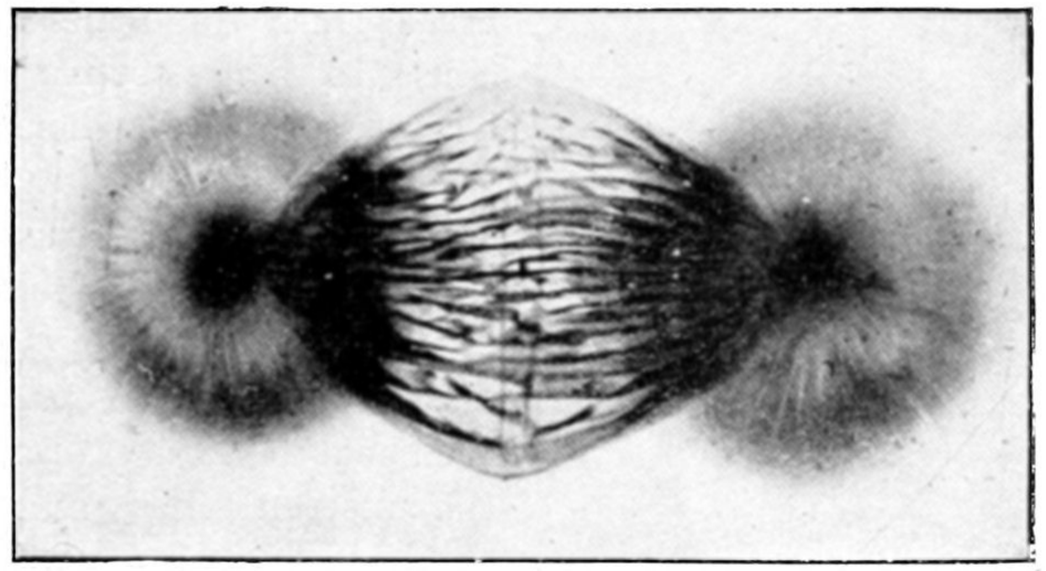
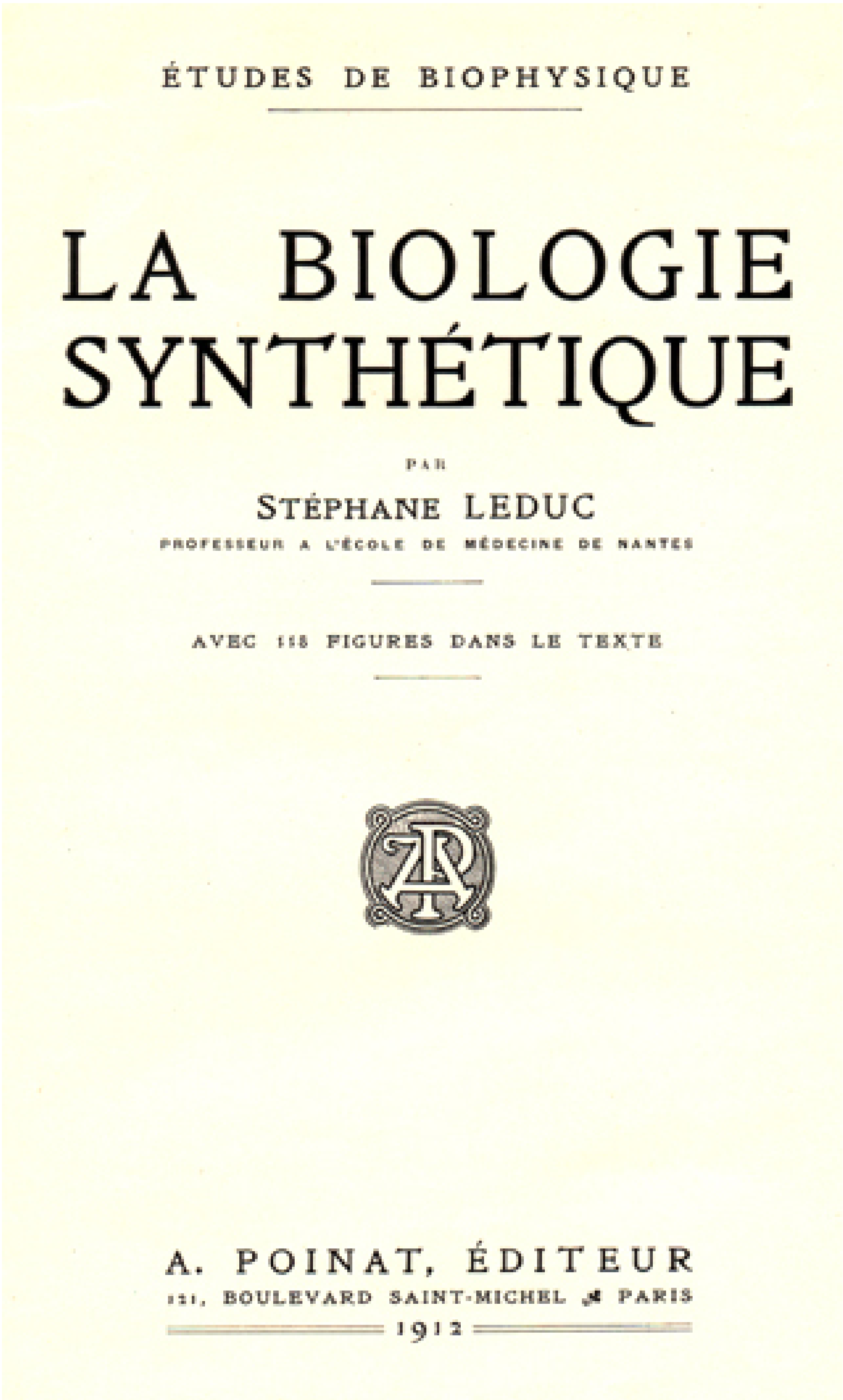
- The philosophical and experimental foundations of synthetic biology were first laid in 1911 by French biophysicist Stéphane Leduc
- He worked on diffusion and osmosis to produce complex (life-like) patterns in physical and chemical systems
- Example: Diffusion pattern of chemicals representing karyokinesis (division of a cell nucleus during mitosis)



S. Leduc, *Mechanisms of life* (1911)

No boundary separates life from ordinary, physical phenomena

Stéphane Leduc (1853-1939)



ÉTUDES DE BIOPHYSIQUE

LA BIOLOGIE SYNTHÉTIQUE

PAR

STÉPHANE LEDUC

PROFESSEUR A L'ÉCOLE DE MÉDECINE DE NANTES

AVEC 118 FIGURES DANS LE TEXTE

A. POINAT, ÉDITEUR

121, BOULEVARD SAINT-MICHEL PARIS

1912

Note: Analogy is not a prove! Biological system relies on more complex mechanisms…

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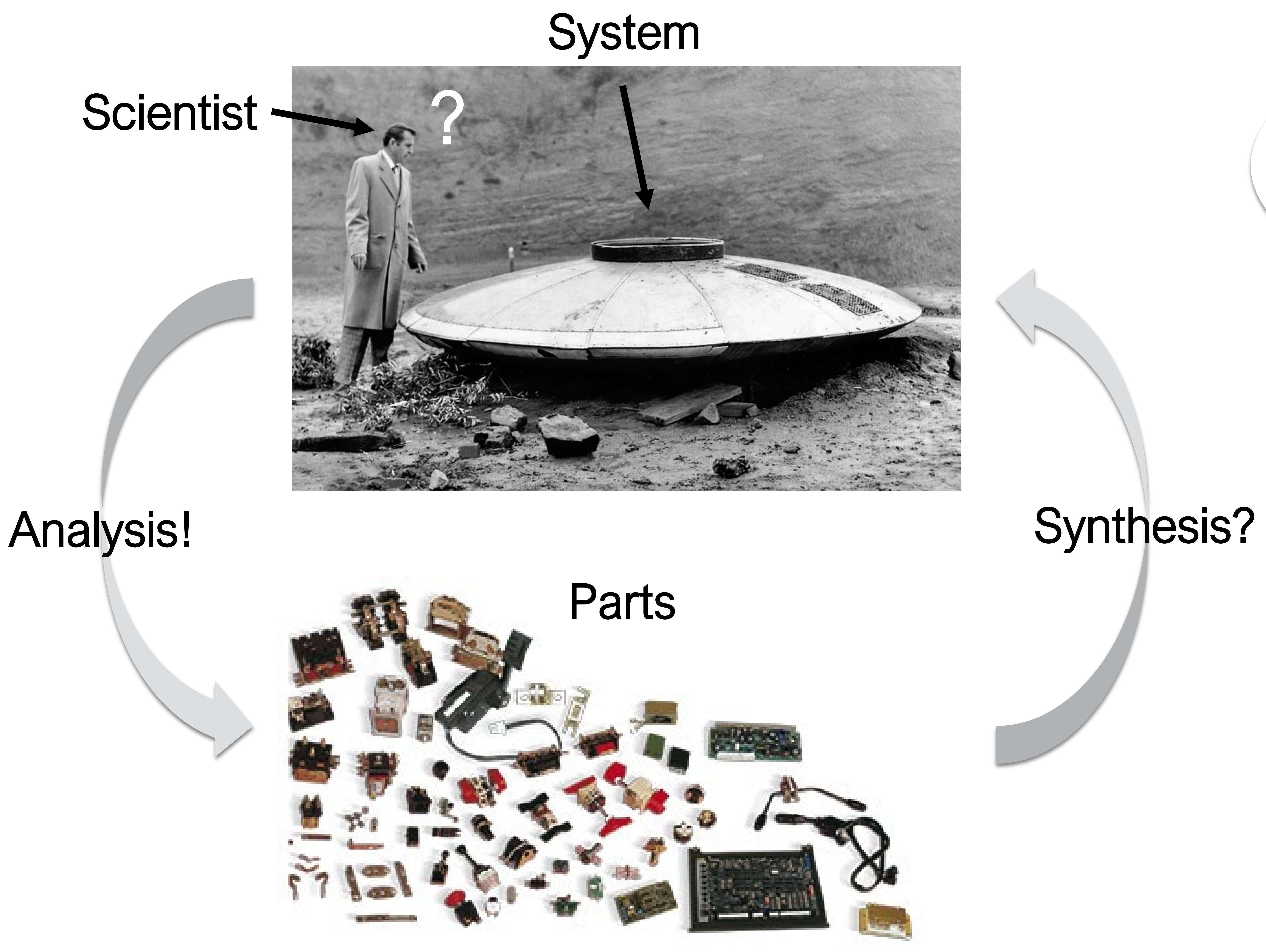
Motivation I: Build to understand!



Synthesis is the counterpart of analysis: Both are required for a genuine understanding of natural phenomena

Richard Feynman (1918 -1988)
Nobel Prize in Physics1965

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Foundational discoveries:
From molecular biology to systems biology

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1953
Structure of DNA
(Watson, Crick, Wilkins & Franklin)

1961
Transcription regulation by enzymes
(Jacob & Monod)

1970
Restriction enzymes
(Smith & Wilcox)

1977
DNA sequencing
(Sanger)

1981
Phosphoramidite DNA synthesis
(Caruthers)

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Polymerase chain reaction
(Mullis)

1995
First whole genome sequence (*H. influenzae*)
(Fraser)

2001
First human genome
(Lander, Venter)

Molecular biology → Molecular cloning → 'Omics' + Systems Biology

Adapted from: Lachance et al., eLife, 8:e36842 (2019)

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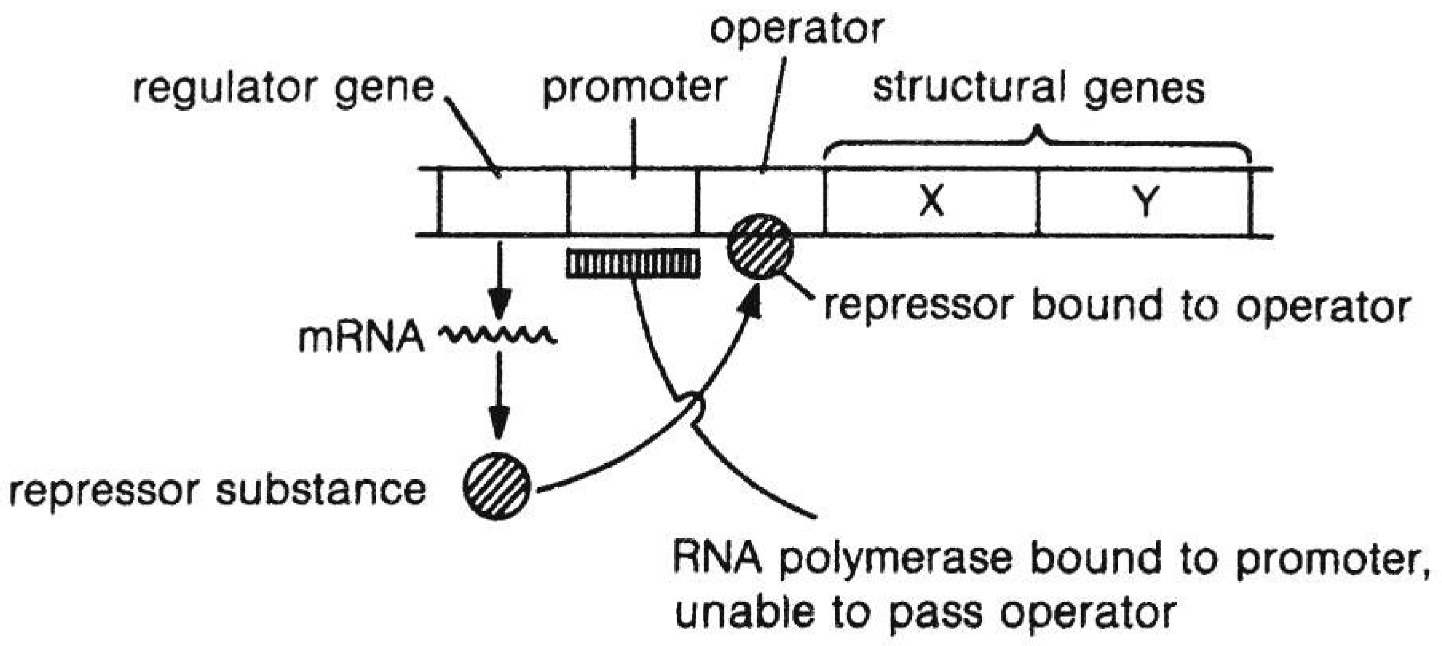
Jacques Monod (1910-1976)

François Jacob (1920-2013)

Nobel Prize in Physiology & Medicine 1965

Lactose absent: OFF state



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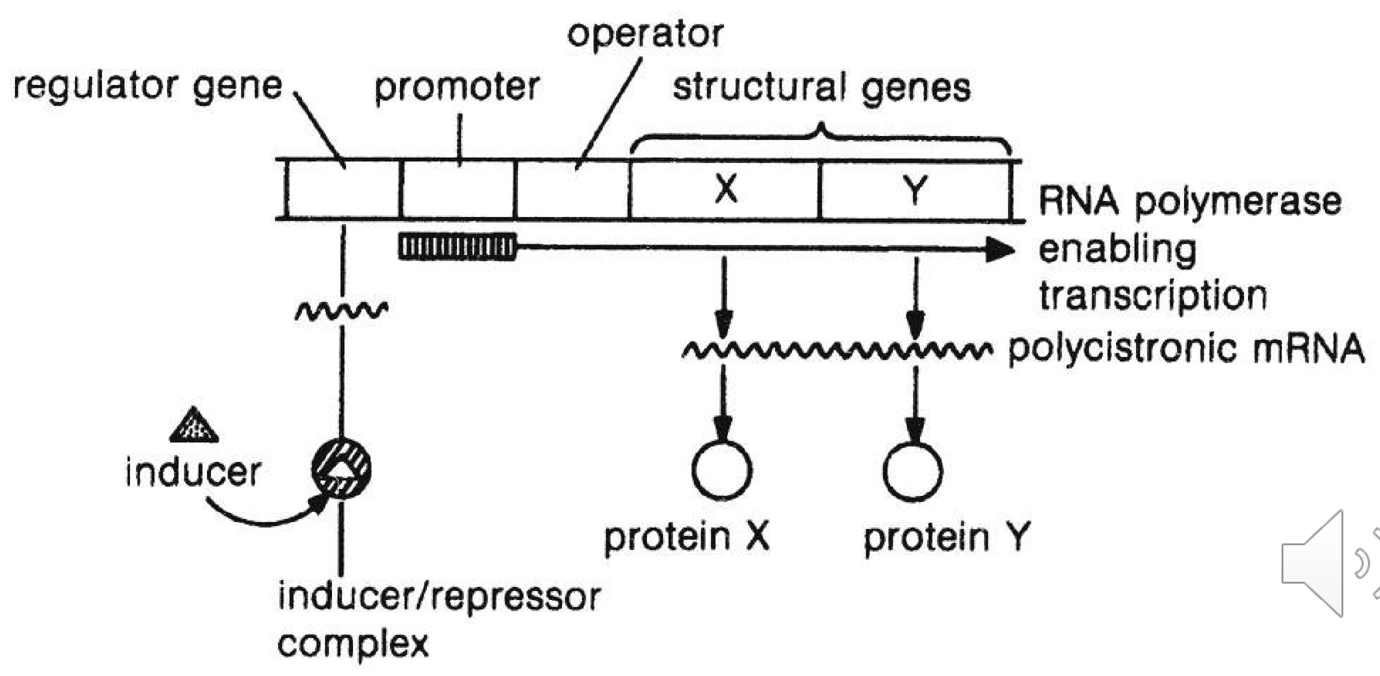

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François Jacob (1920-2013)

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Idea: *Assemble new regulatory systems from molecular components!*

Jacob & Monod, On the regulation of gene activity. Cold Spring Harb. Symp. Quant. Biol. 26, 193–211 (1961)

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Wacław Sybalski (1974)

"Up to now we are working on the descriptive phase of molecular biology... But the real challenge will start when we enter the synthetic phase ... We will then devise new control elements and add these new modules to the existing genomes or build up wholly new genomes."

in Kohn, A. and Shatkay, A. (eds) in Experimental Medicine and Biology vol. 44

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1980's: Genetic manipulation widespread in biology

But: Genetic engineering was mostly restricted to cloning and recombinant gene expression, missing necessary knowledge/tools to create genuinely novel biological systems

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1990’s: Automated sequencing & high-throughput omics techniques for measuring RNA, protein, lipids and metabolites allowed creating a vast catalogue of cellular components & interactions

Biologists, physicists and engineers teamed up to revere-engineer cellular networks

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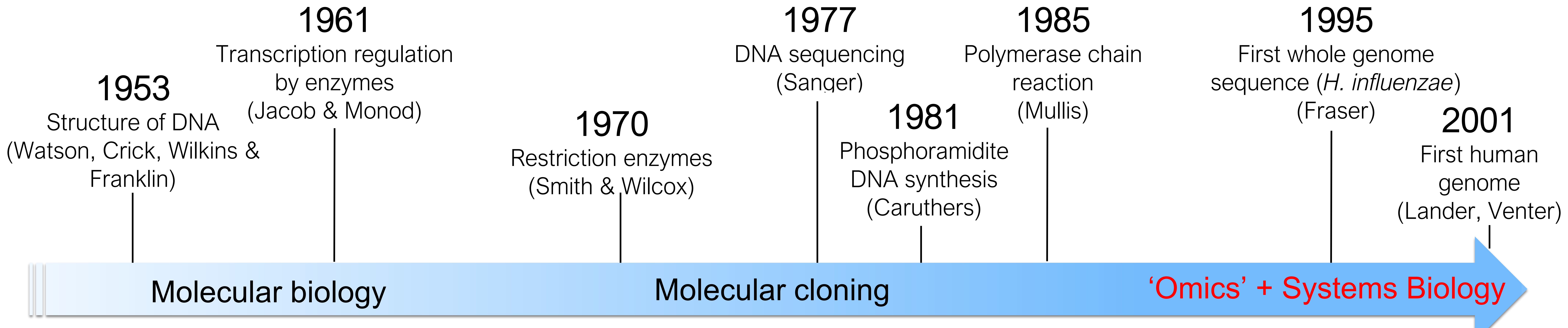

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NATURE | VOL 402 | SUPP | 2 DECEMBER 1999 | www.nature.com

From molecular
to modular cell biology

Leland H. Hartwell, John J. Hopfield, Stanislas Leibler and Andrew W. Murray

Insight: Cellular networks, although vast and intricate, are organized as a hierarchy of clearly discernible functional modules, similar to engineered systems

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Motivation II: Build to improve & innovate!

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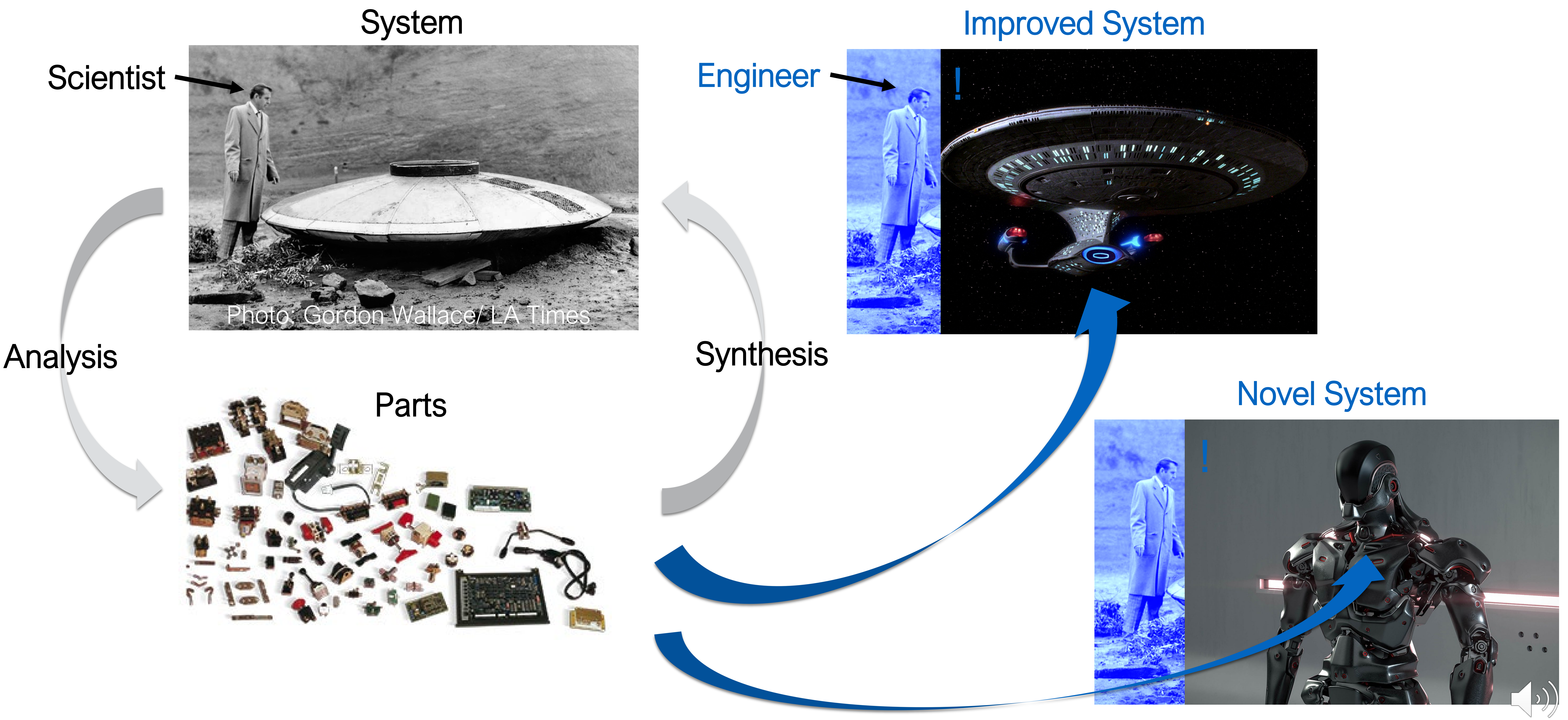

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Advent of the Synthetic Biology era: Building synthetic circuits

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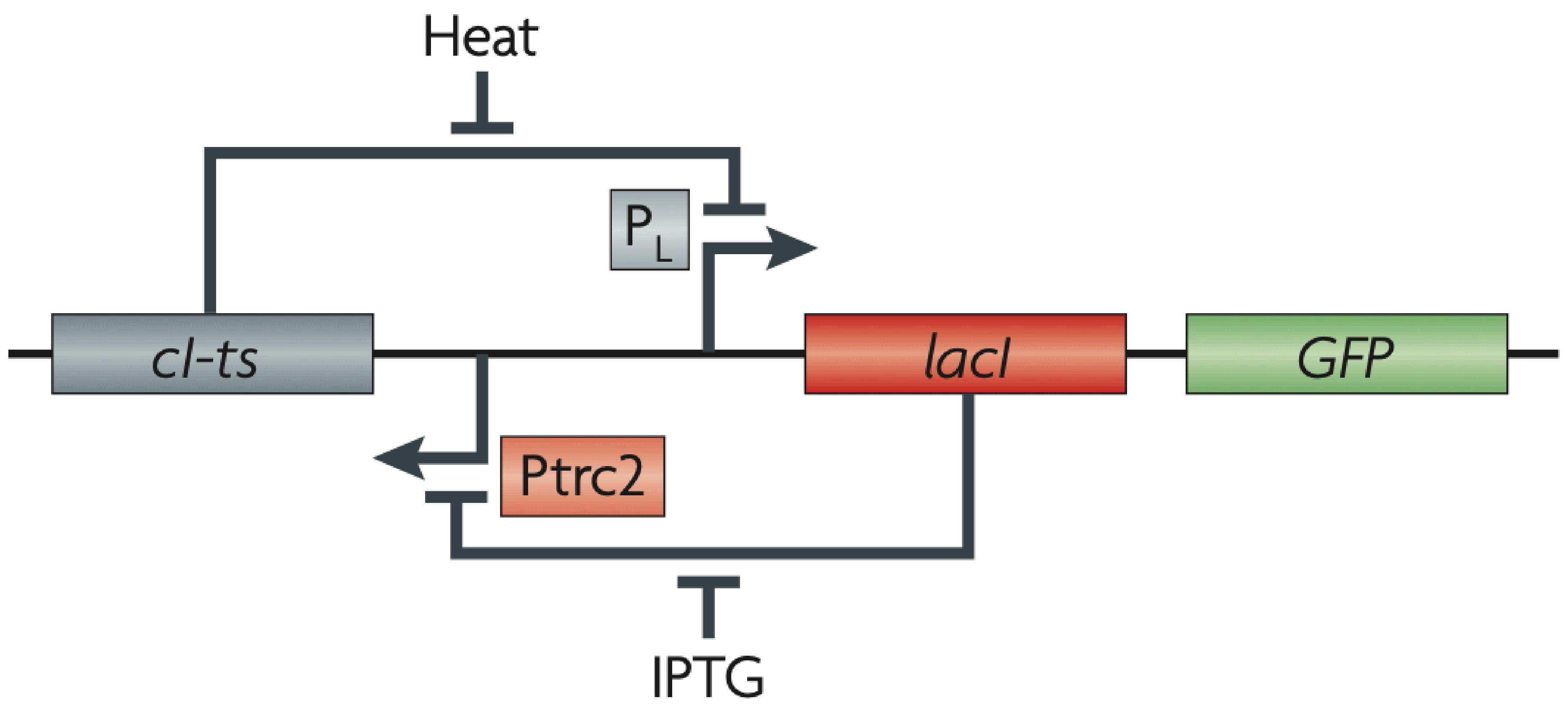
NATURE | VOL 403 | 20 JANUARY 2000 | www.nature.com

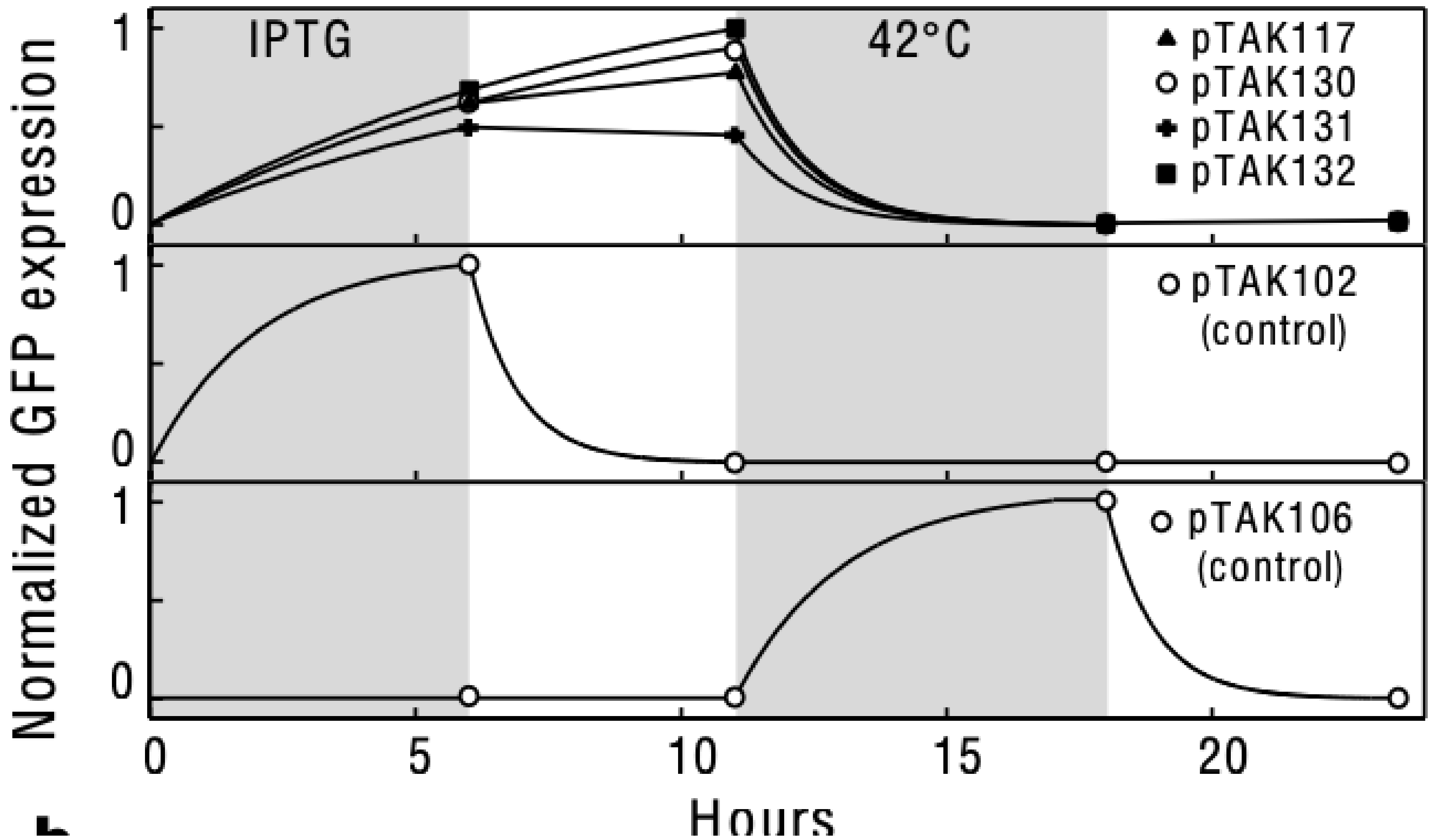
Construction of a genetic toggle switch in *Escherichia coli*

Timothy S. Gardner*†, Charles R. Cantor* & James J. Collins*†

* *Department of Biomedical Engineering, † Center for BioDynamics and ‡ Center for Advanced Biotechnology, Boston University, 44 Cummington Street, Boston, Massachusetts 02215, USA*



- Two transcription factors mutually repress their promoters
- Leads to two stable gene expression states (bistability)
  - ✓ **GFP OFF state**: CI-ts HIGH/LacI LOW
  - ✓ **GFP ON state**: CI-ts LOW/LacI HIGH
- Serves as model system to study epigenetic (non DNA-encoded) memory in single cells



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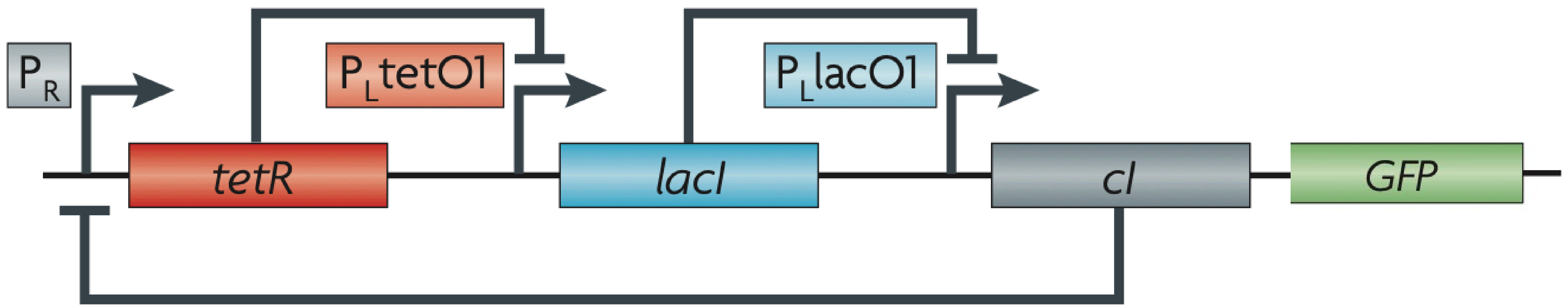
NATURE | VOL 403 | 20 JANUARY 2000 | www.nature.com

A synthetic oscillatory network of transcriptional regulators

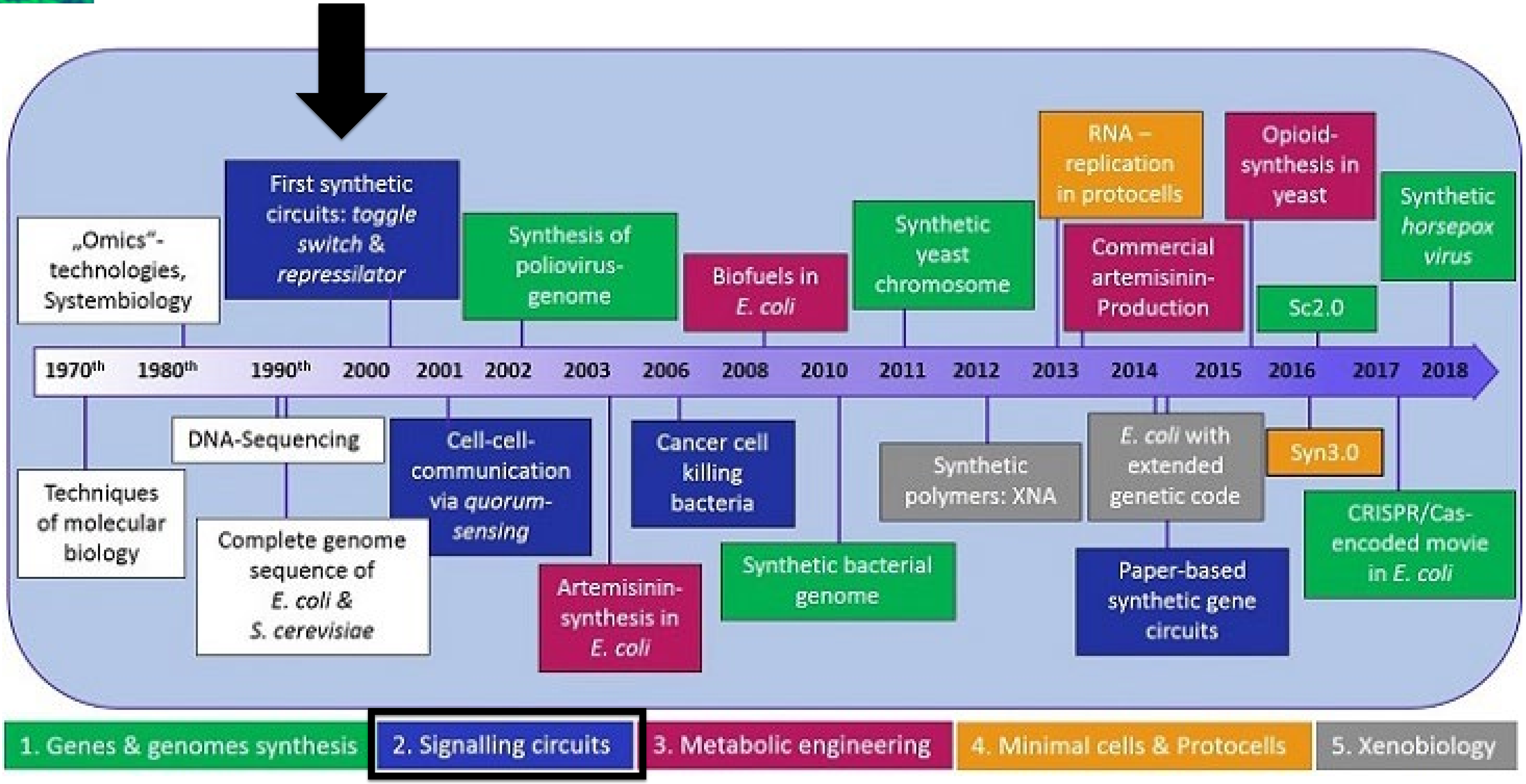
Michael B. Elowitz & Stanislas Leibler

Departments of Molecular Biology and Physics, Princeton University, Princeton, New Jersey 08544, USA



- Three transcription factors sequentially repress their promoters (“Repressilator”)
- Time-delayed negative feedback generates oscillations
- Serves as model system for circadian rhythms in single cells

Key developments in Synthetic Biology



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Key developments in Synthetic Biology

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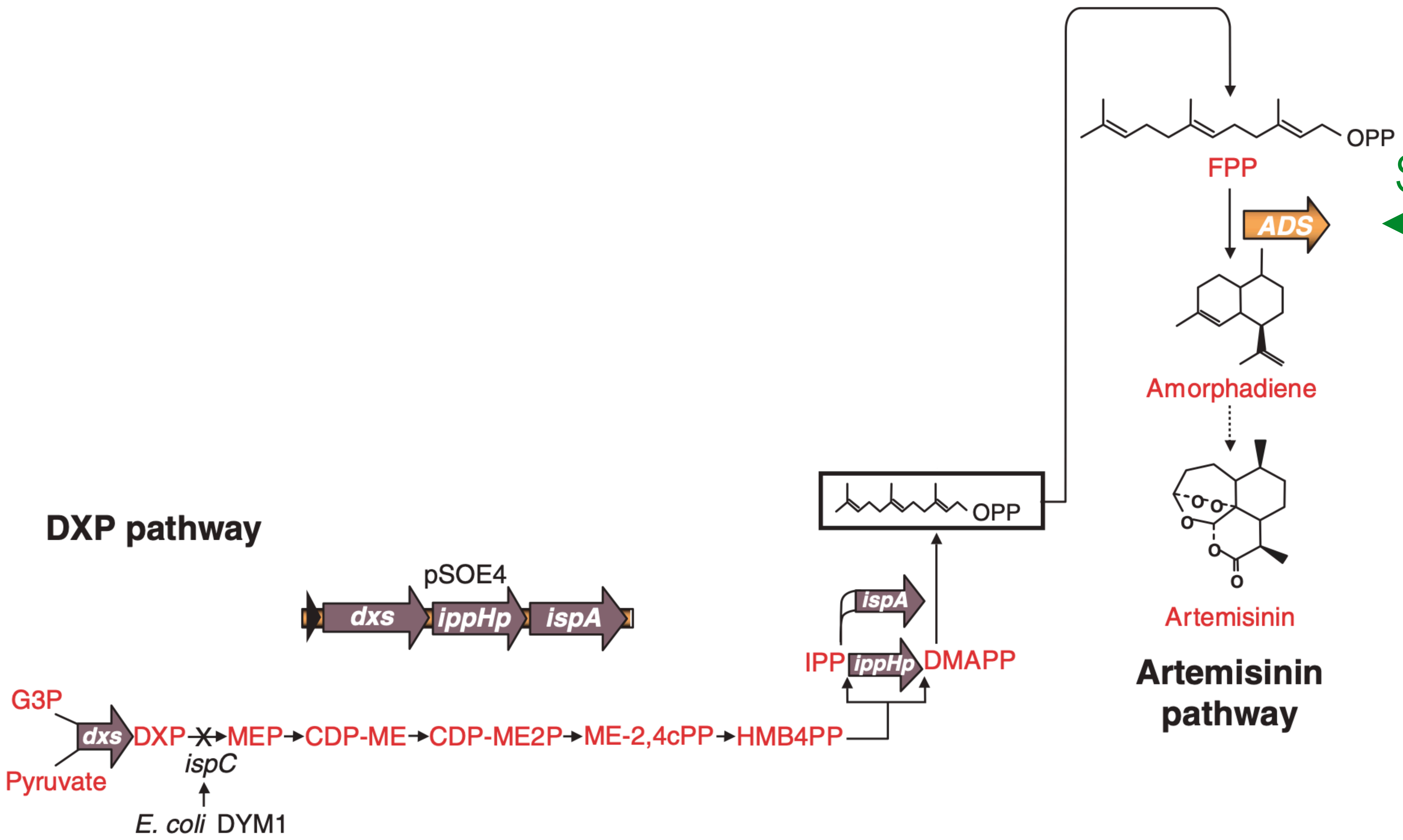
NATURE BIOTECHNOLOGY VOLUME 21 NUMBER 7 JULY 2003

Engineering a mevalonate pathway in *Escherichia coli* for production of terpenoids

Vincent JJ Martin[1,2,3], Douglas J Pitera[1,3], Sydnor T Withers[1], Jack D Newman[1] & Jay D Keasling[1]



Synthetic gene from *Artemisia annua* (plant)

Key developments in Synthetic Biology

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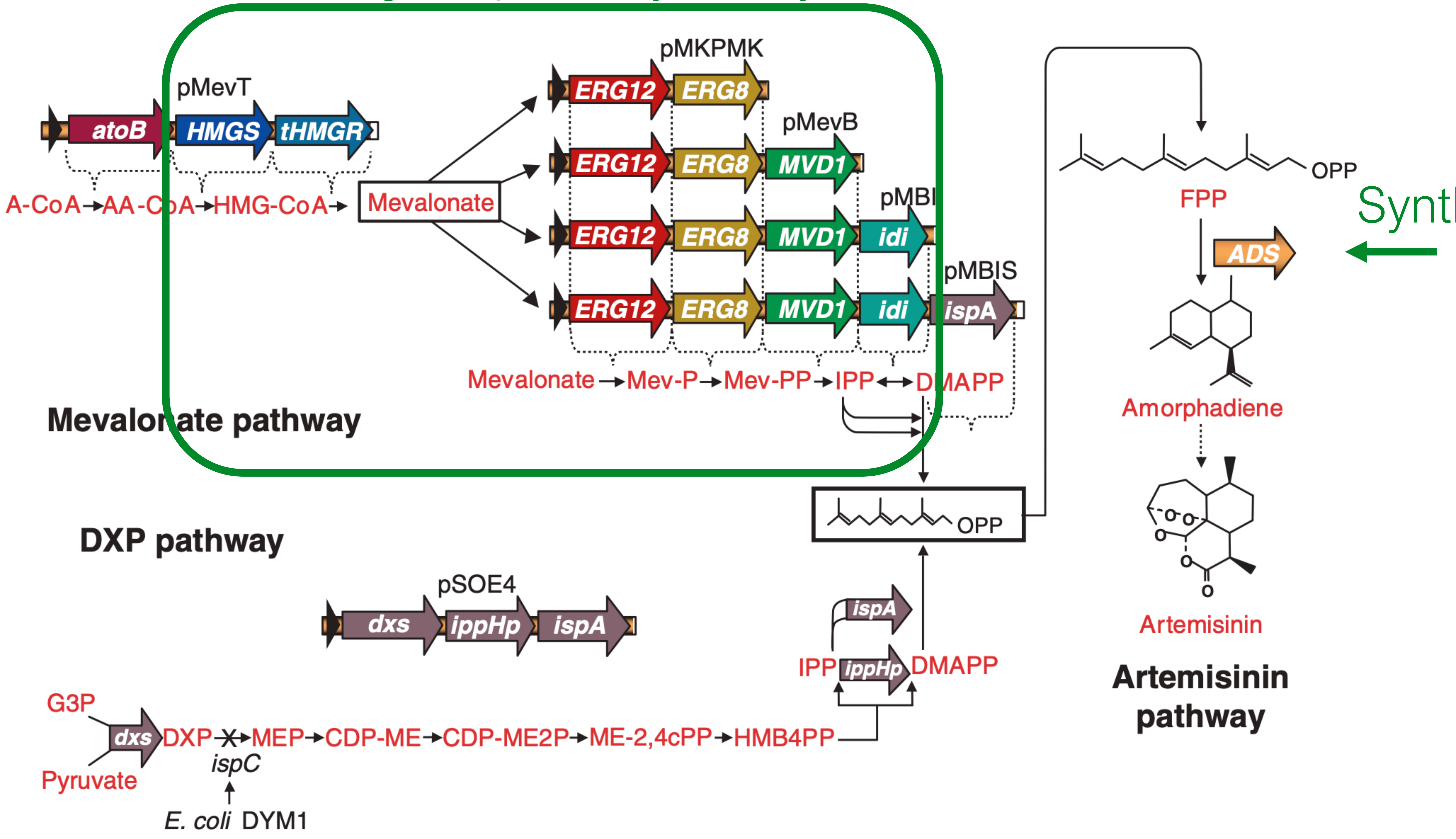
Heterologous pathway from yeast



Synthetic gene from *Artemisia annua* (plant)

Achieved 20- to 300-fold improvement in terpene synthesis!

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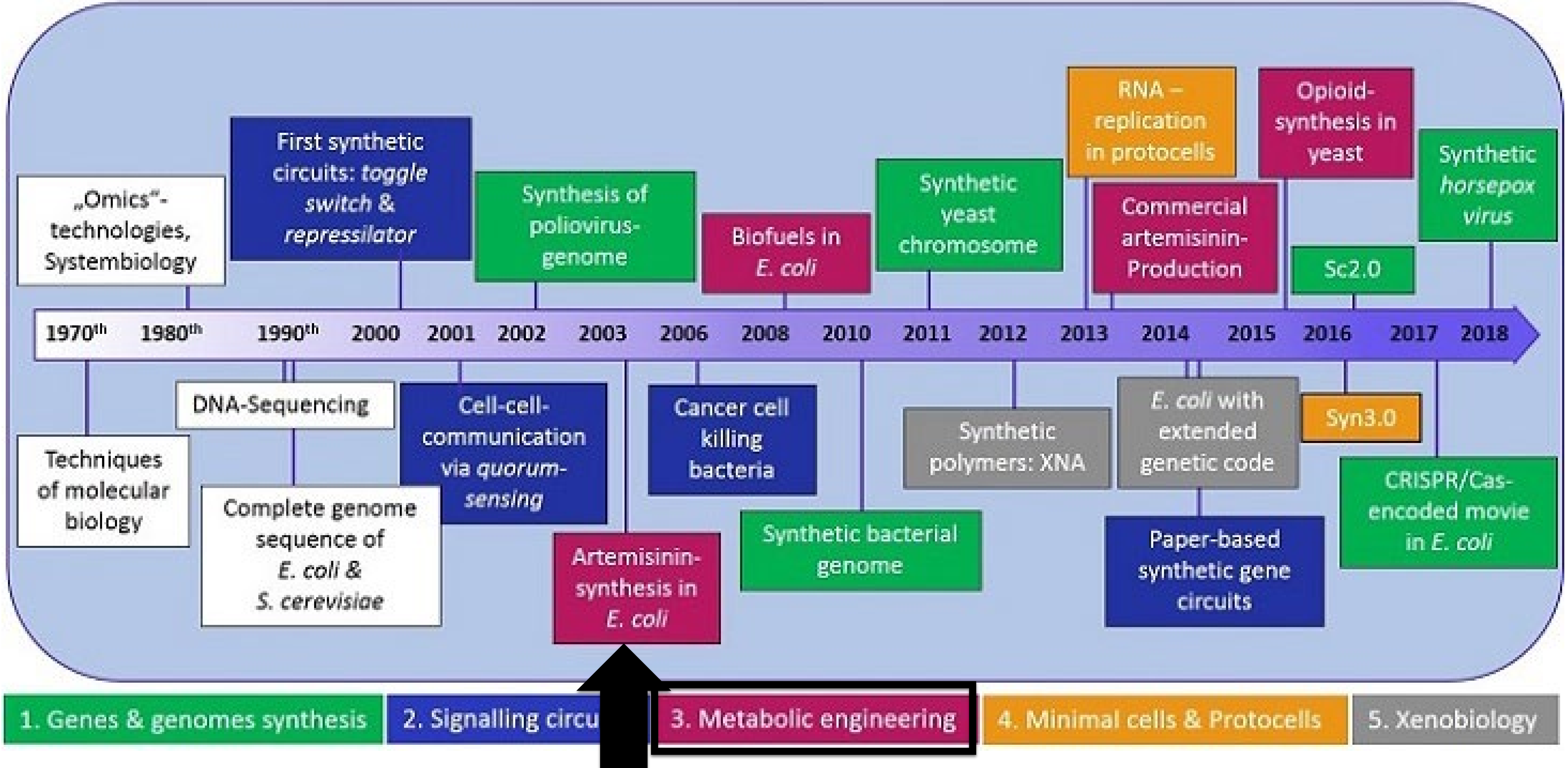
Key developments in Synthetic Biology



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Key developments in Synthetic Biology

9 AUGUST 2002 VOL 297 SCIENCE www.sciencemag.org

Chemical Synthesis of Poliovirus cDNA: Generation of Infectious Virus in the Absence of Natural Template

Jeronimo Cello, Aniko V. Paul, Eckard Wimmer*

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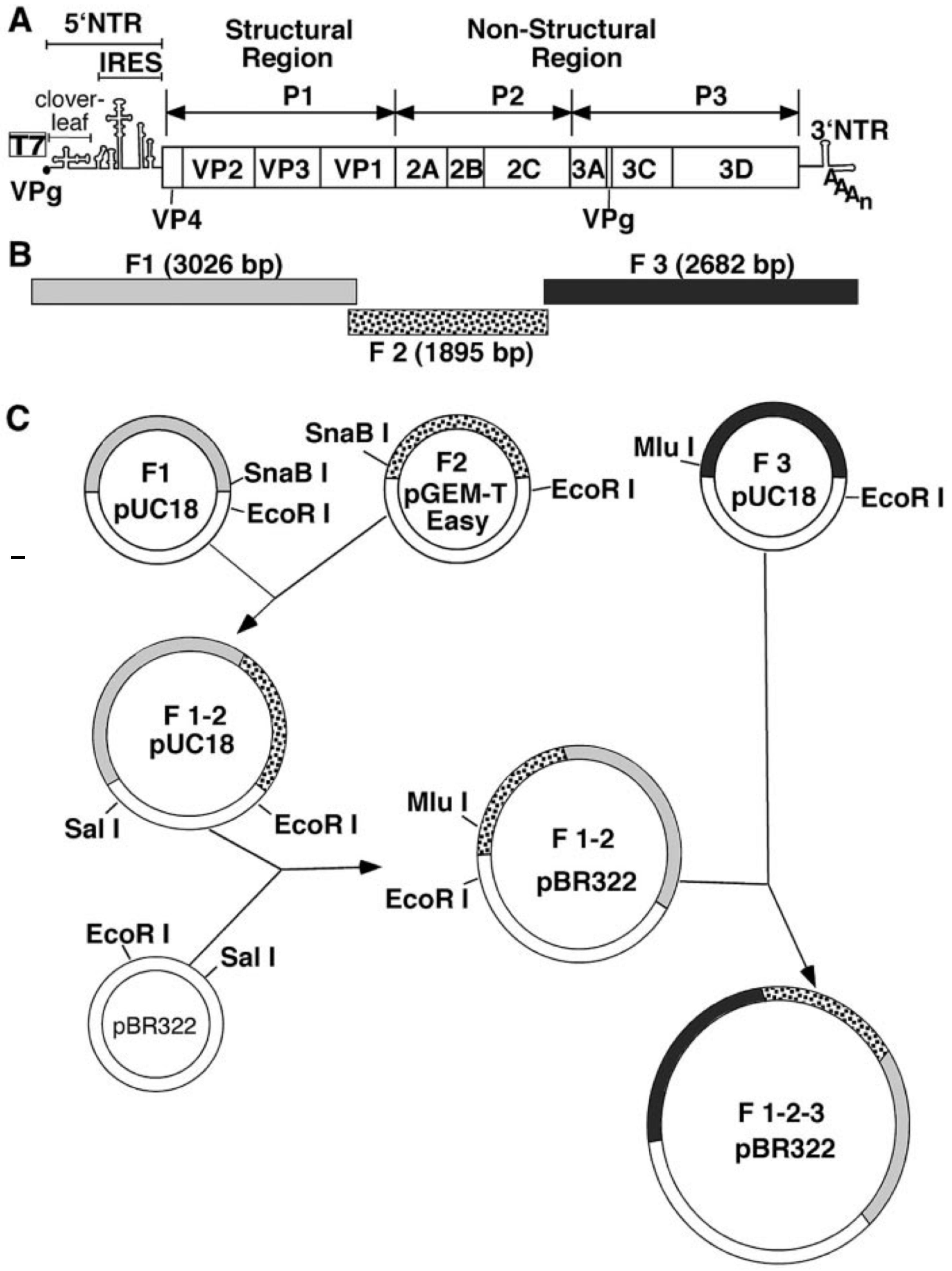
- 3-step assembly of poliovirus cDNA using restriction enzyme-based cloning



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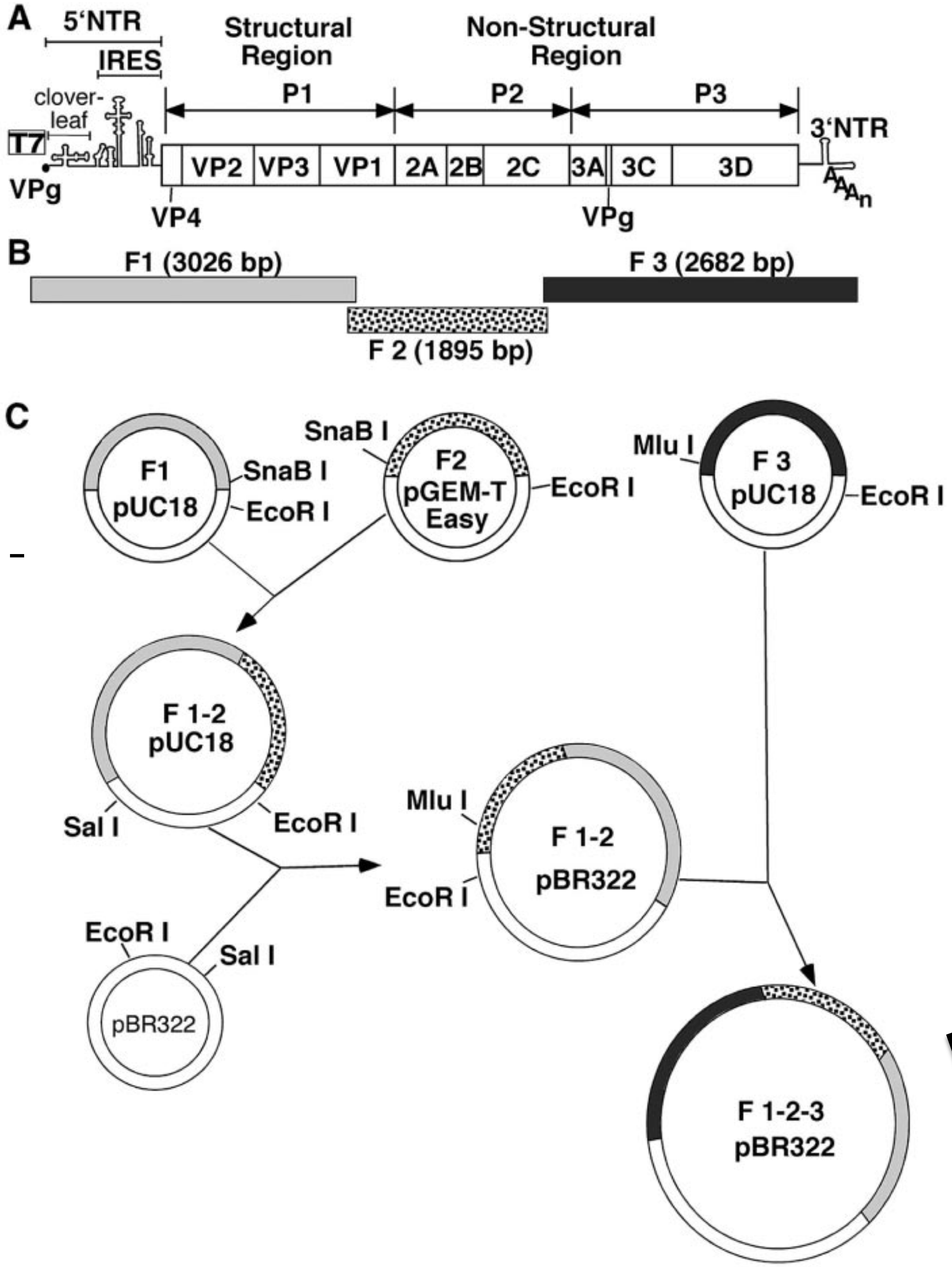
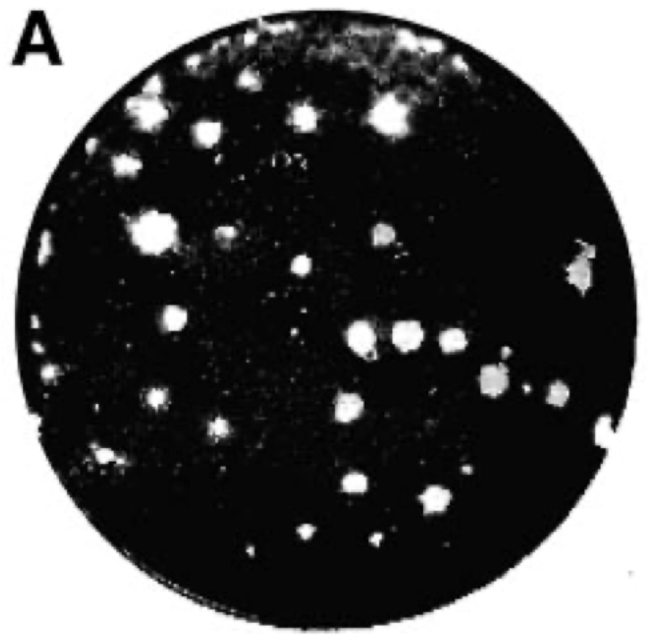
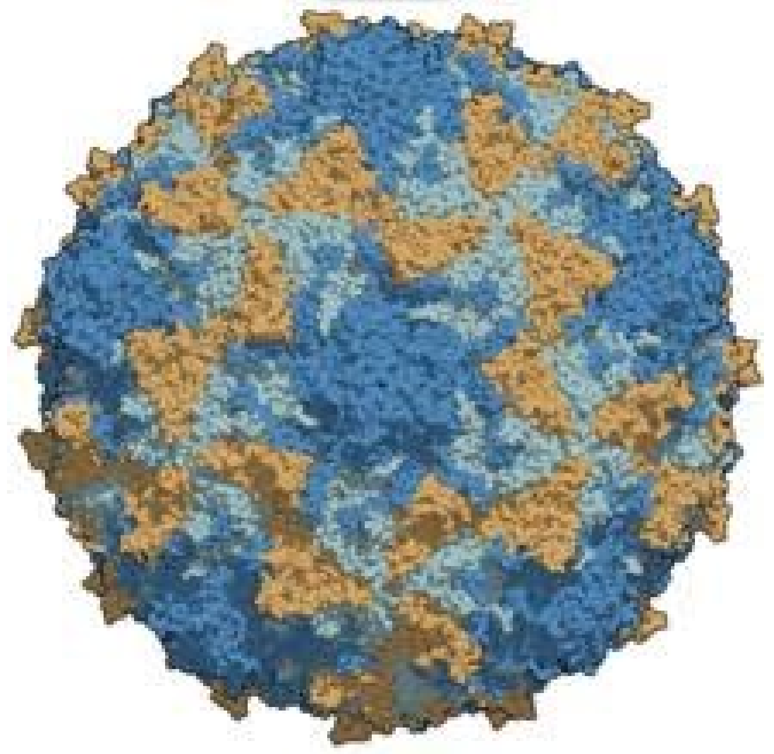
- 3-step assembly of poliovirus cDNA using restriction enzyme-based cloning
- Expression of viral RNA from T7 promoter
- “Our results show that it is possible to synthesize an infectious agent by in vitro chemical-biochemical means solely by following instructions from a written sequence.”



Expression of viral RNA using T7 promoter

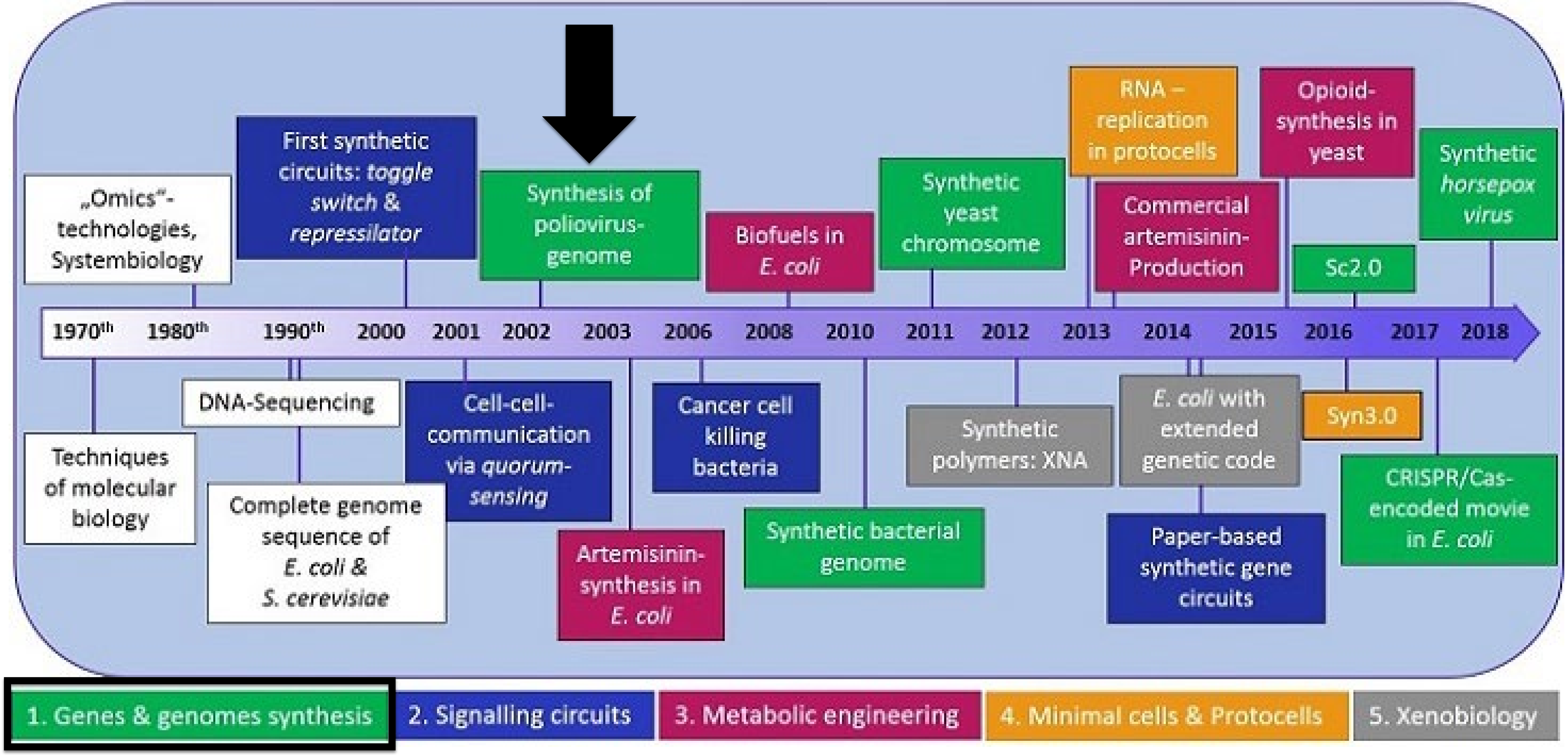


Infection plaques on HeLa cell-free extract



Poliovirus (RNA virus)
Source: Wikipedia

Key developments in Synthetic Biology



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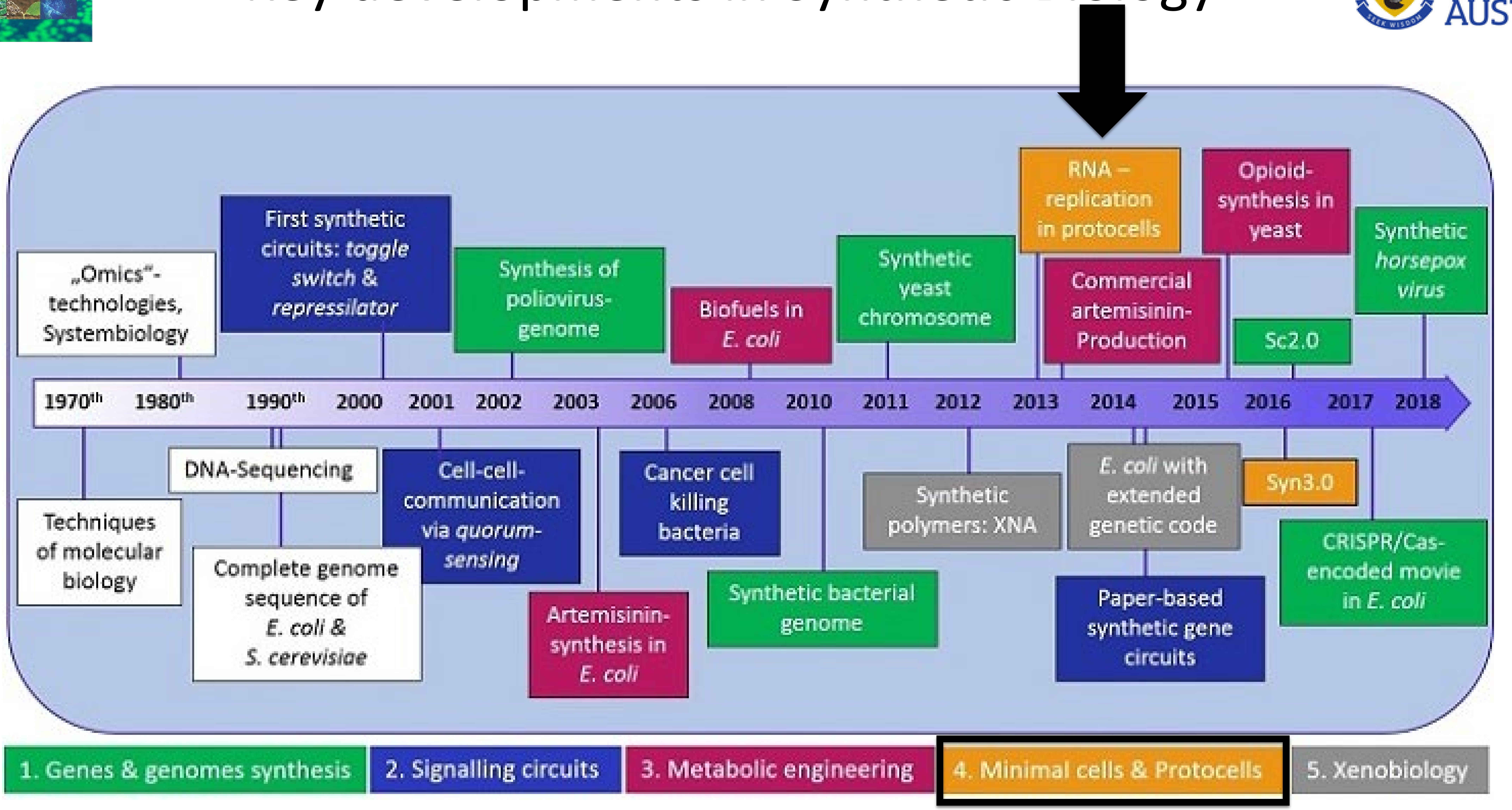
Key developments in Synthetic Biology



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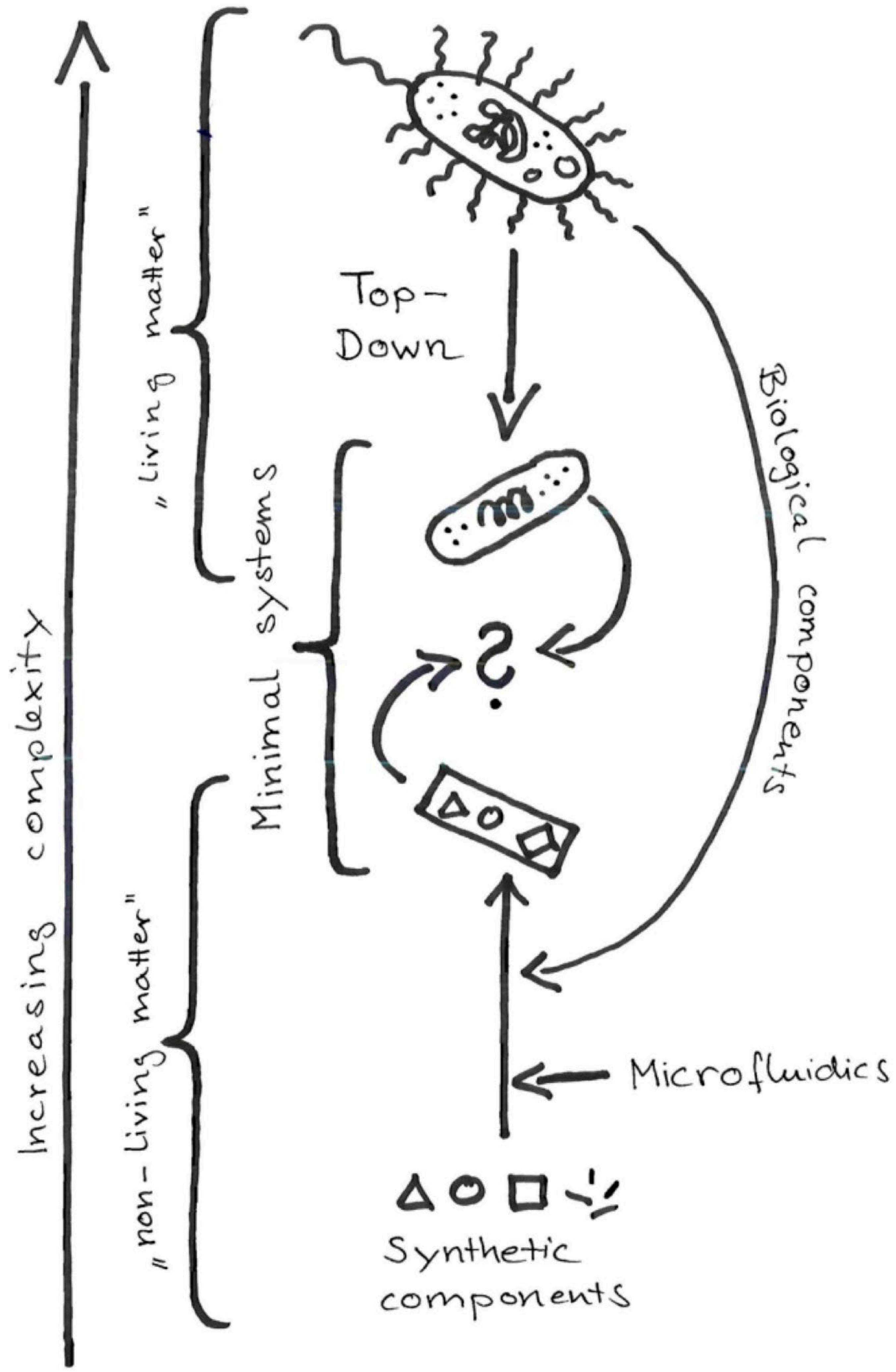
Key developments in Synthetic Biology

Building minimal cells –Towards a definition of life!



Petra Schwille, MPI of Biochemistry

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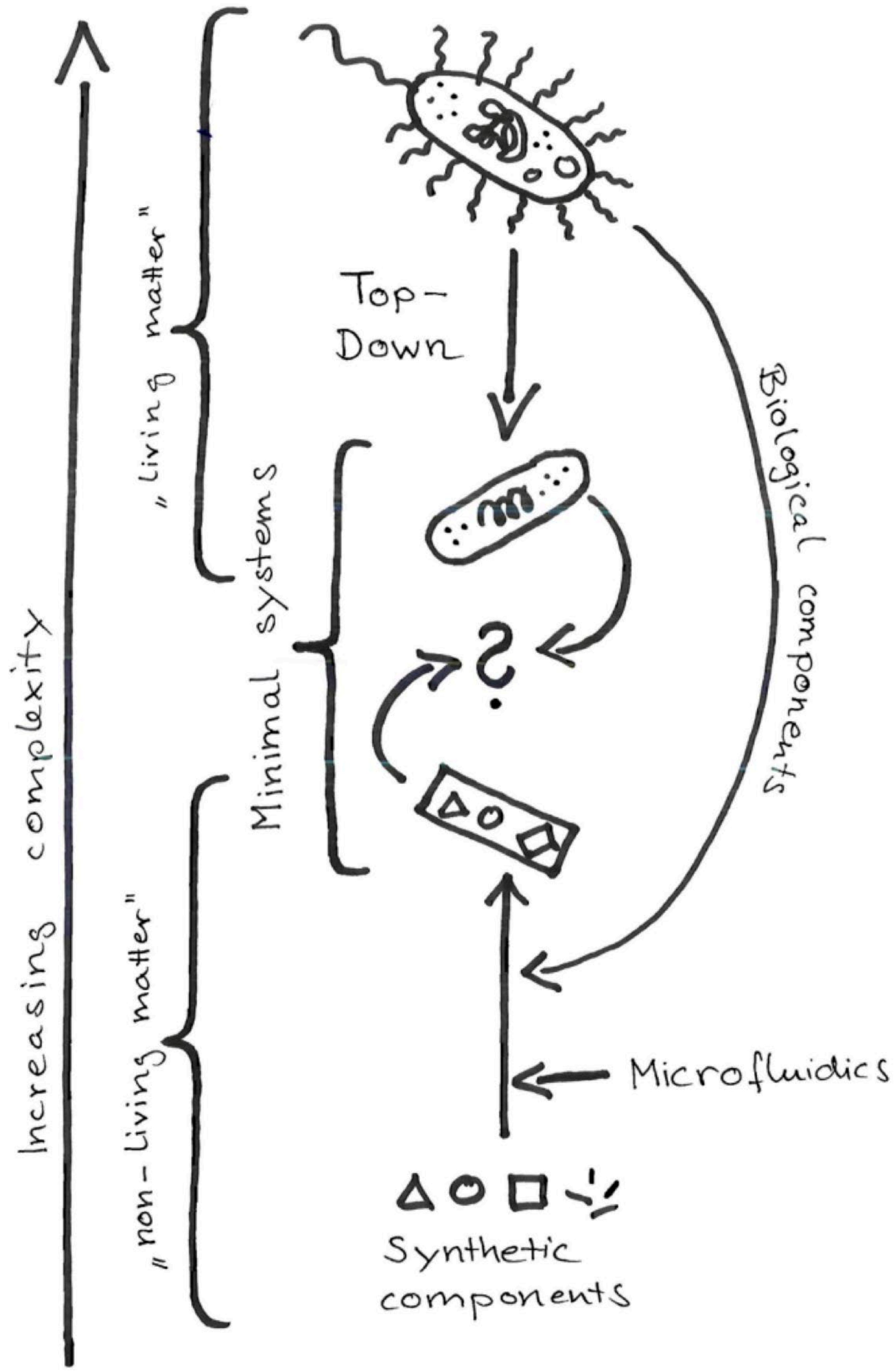

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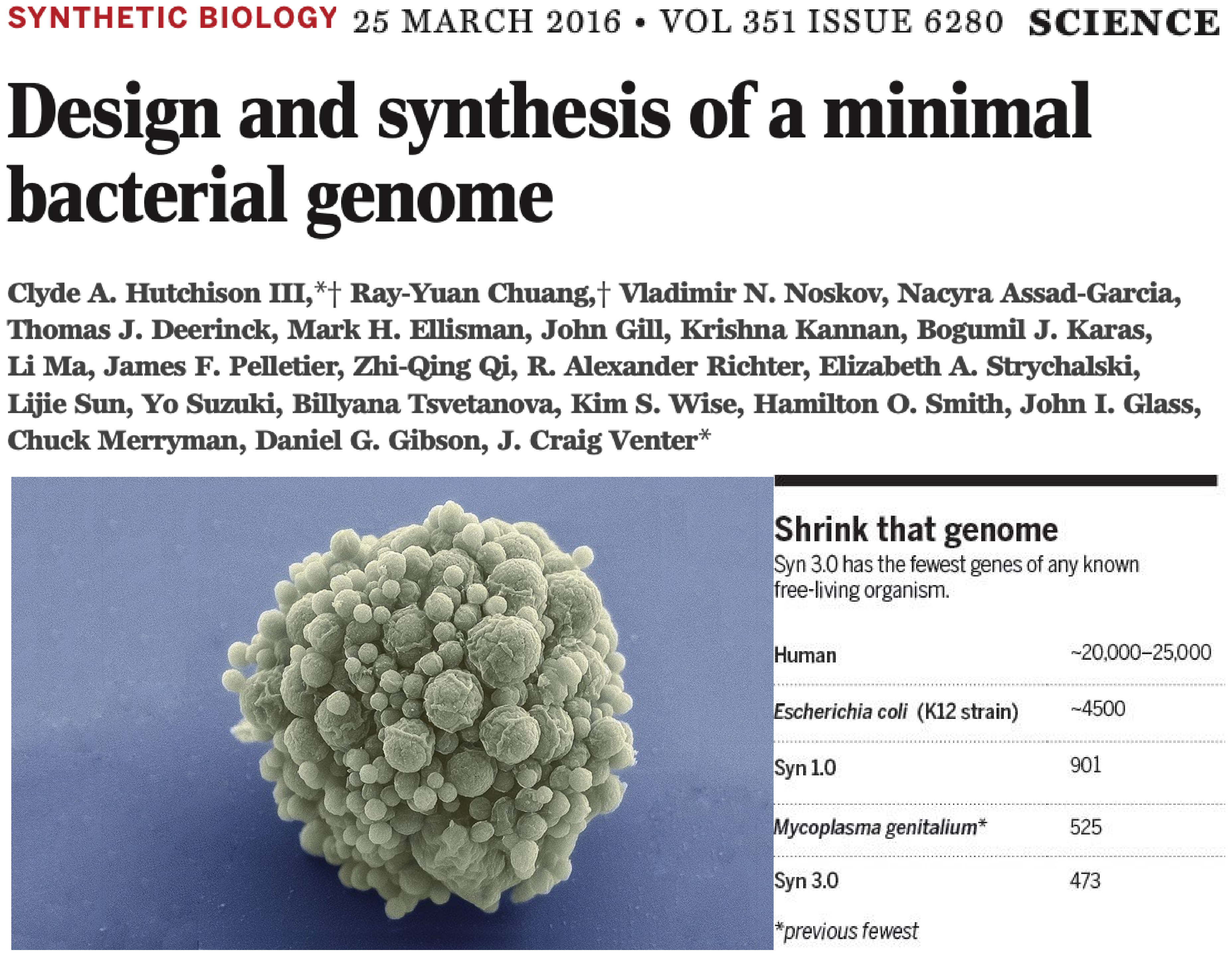
SYNTHETIC BIOLOGY 25 MARCH 2016 • VOL 351 ISSUE 6280 SCIENCE

Design and synthesis of a minimal bacterial genome

Clyde A. Hutchison III,*† Ray-Yuan Chuang,† Vladimir N. Noskov, Nacyra Assad-Garcia, Thomas J. Deerinck, Mark H. Ellisman, John Gill, Krishna Kannan, Bogumil J. Karas, Li Ma, James F. Pelletier, Zhi-Qing Qi, R. Alexander Richter, Elizabeth A. Strychalski, Lijie Sun, Yo Suzuki, Billyana Tsvetanova, Kim S. Wise, Hamilton O. Smith, John I. Glass, Chuck Merryman, Daniel G. Gibson, J. Craig Venter*

Shrink that genome

Syn 3.0 has the fewest genes of any known free-living organism.

Human	~20,000–25,000
Escherichia coli (K12 strain)	~4500
Syn 1.0	901
*Mycoplasma genitalium**	525
Syn 3.0	473

*previous fewest

- Minimization of 1.08 mbp *Mycoplasma mycoides* genome to 531 kbp
- Genome transplantation in *M. capricolum* cells
- Lead to viable cells with all physiological properties of *Mycoplasma mycoides*

Key developments in Synthetic Biology

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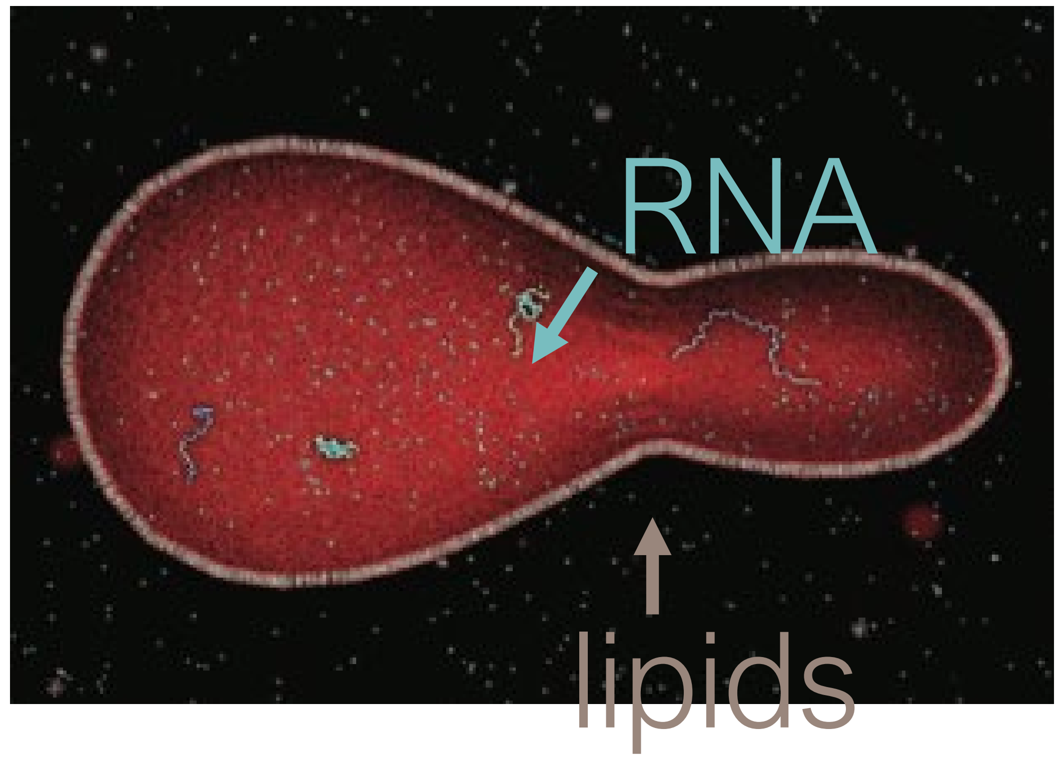
Building minimal cells –Towards a definition of life!

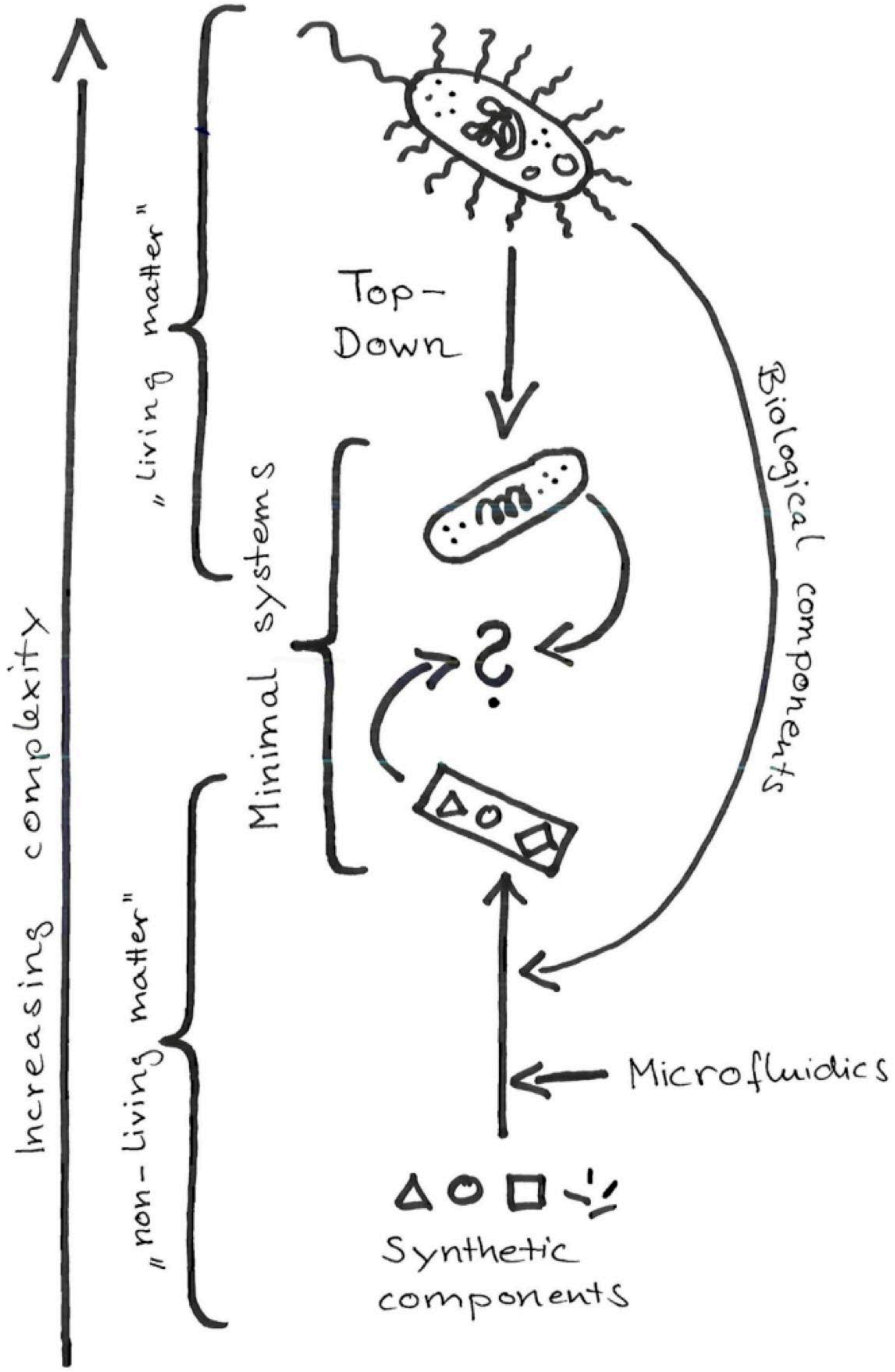
29 NOVEMBER 2013 VOL 342 SCIENCE

Nonenzymatic Template-Directed RNA Synthesis Inside Model Protocells

Katarzyna Adamala[1,2] and Jack W. Szostak[1]*



- Ribozyme-catalyzed and nonenzymatic RNA copying reactions require high Mg2+
- Destabilizing effect of Mg2+ on fatty acid membranes mitigated via citrate
- First demonstration of chemical copying of RNA templates inside fatty acid vesicles



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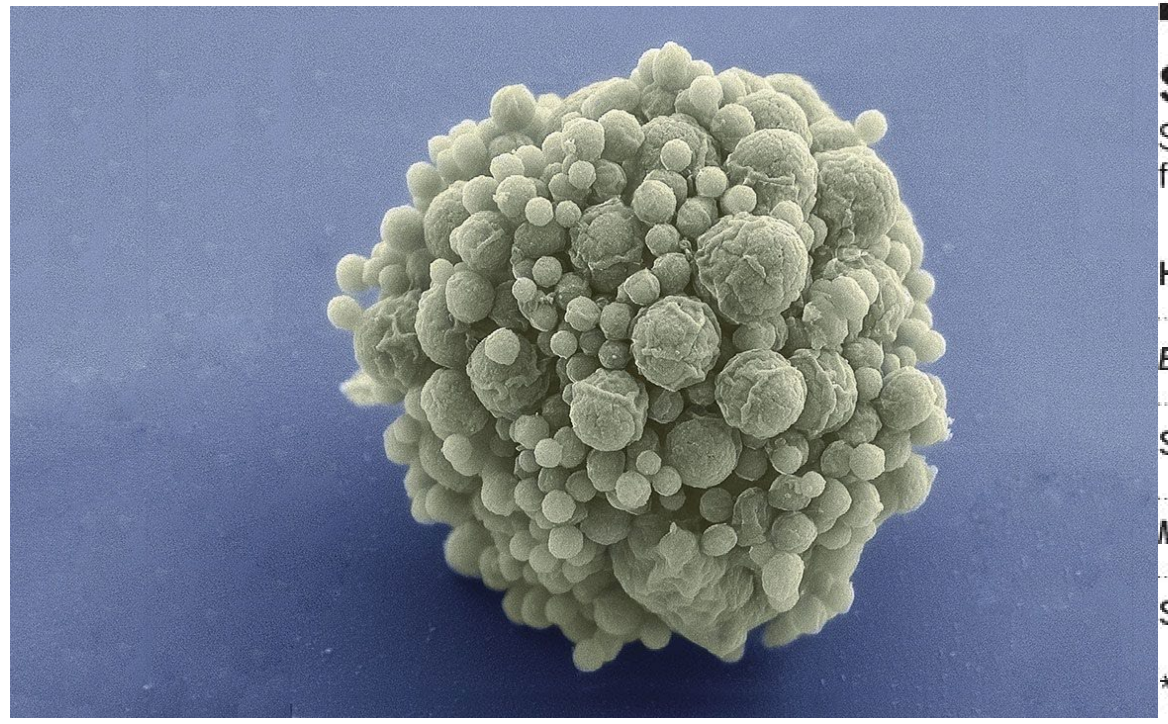

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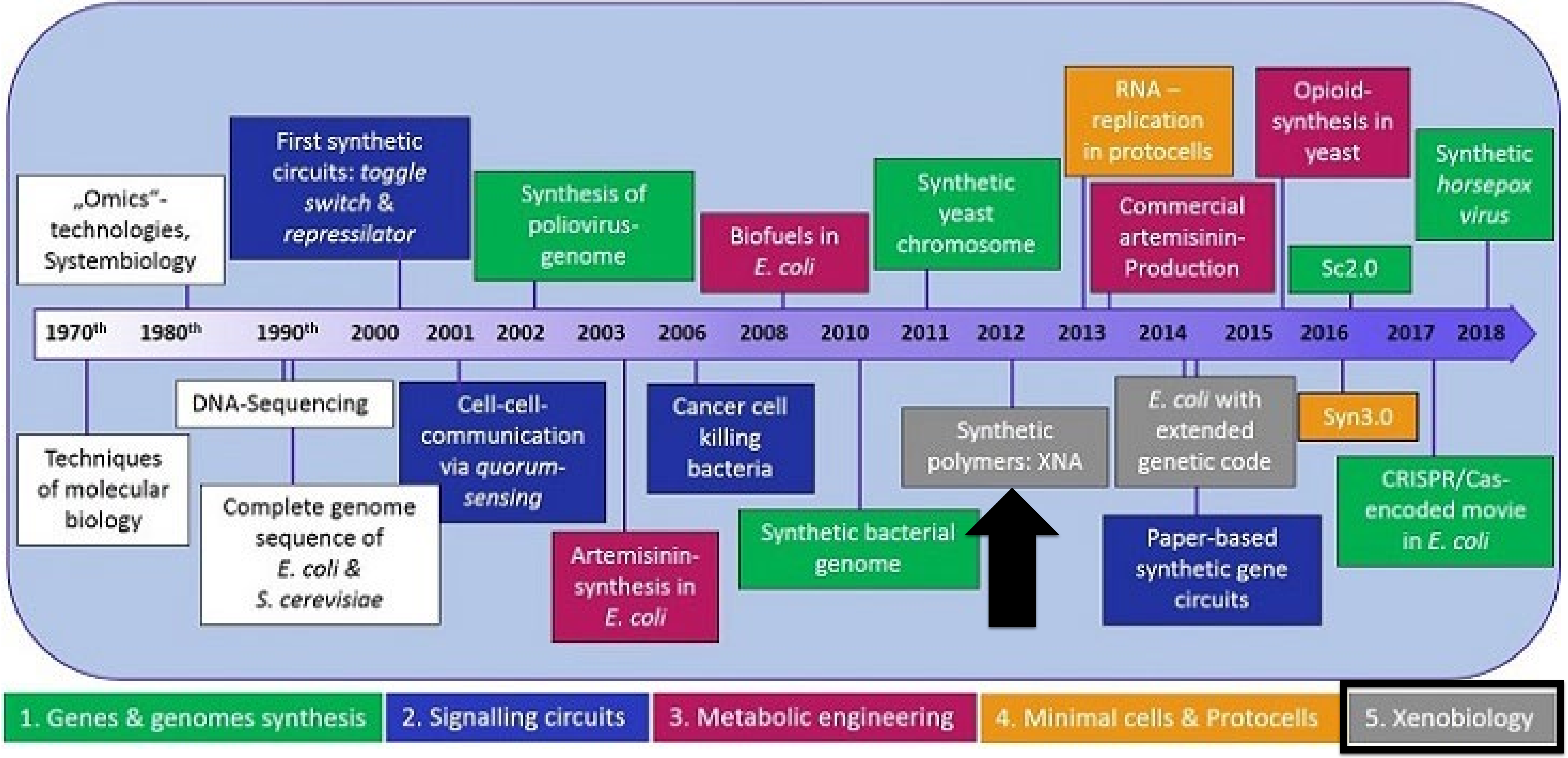

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Key developments in Synthetic Biology

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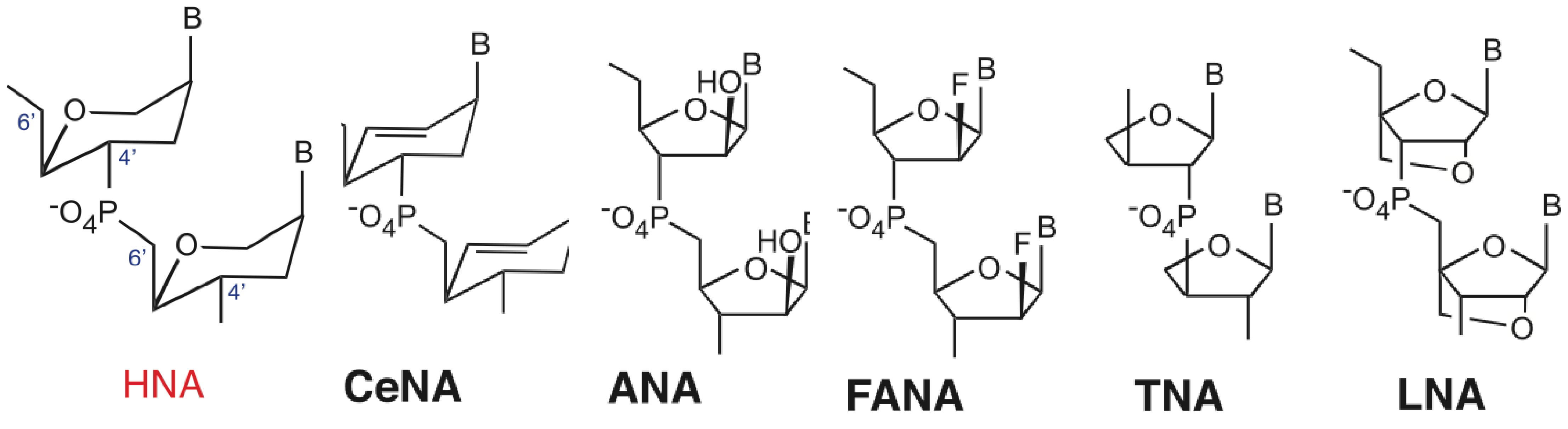
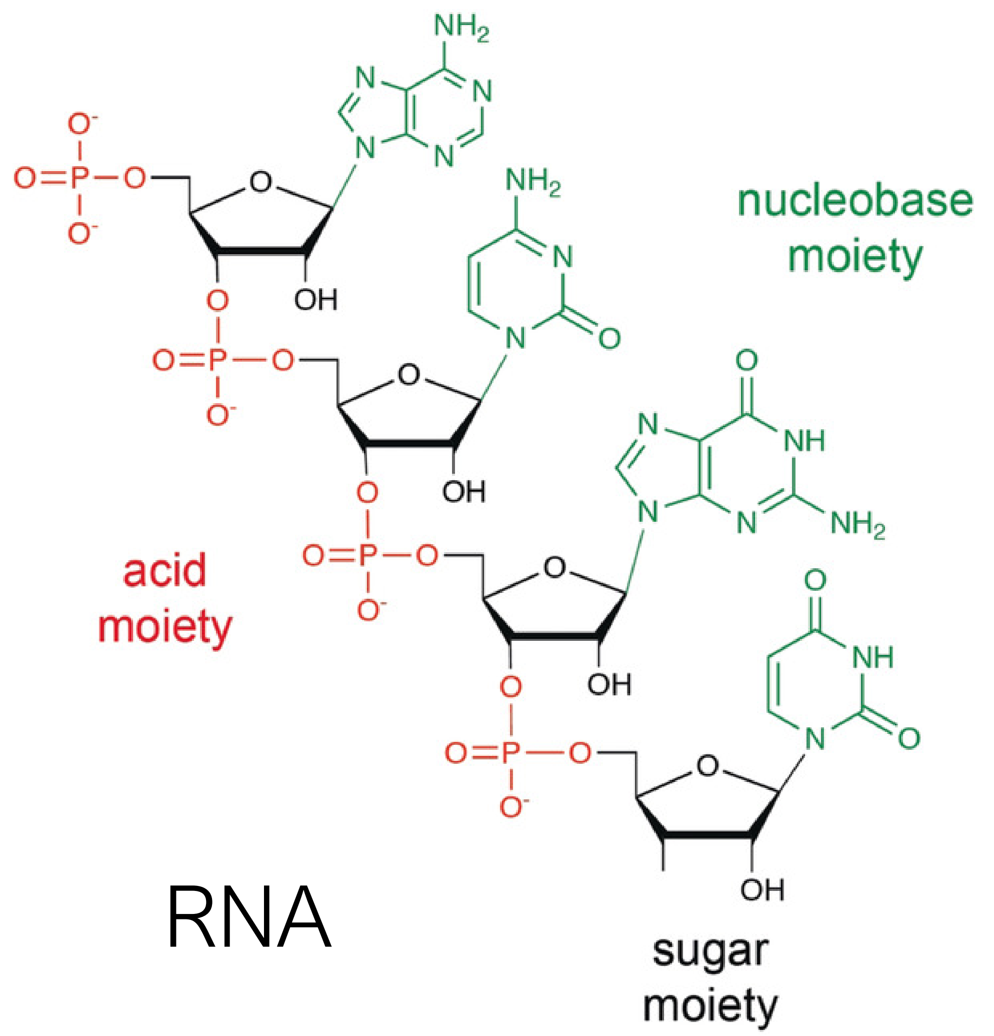
SCIENCE VOL 336 20 APRIL 2012

Synthetic Genetic Polymers Capable of Heredity and Evolution

Vitor B. Pinheiro,[1] Alexander I. Taylor,[1] Christopher Cozens,[1] Mikhail Abramov,[2] Marleen Renders,[2]* Su Zhang,[3] John C. Chaput,[3] Jesper Wengel,[4] Sew-Yeu Peak-Chew,[1] Stephen H. McLaughlin,[1] Piet Herdewijn,[2] Philipp Holliger[1]†

- Ribofuranose ring of DNA and RNA is replaced by five- or six-membered congeners
- Development 6 xenonucleic acids (XNA) capable of specific base pairing with DNA and RNA





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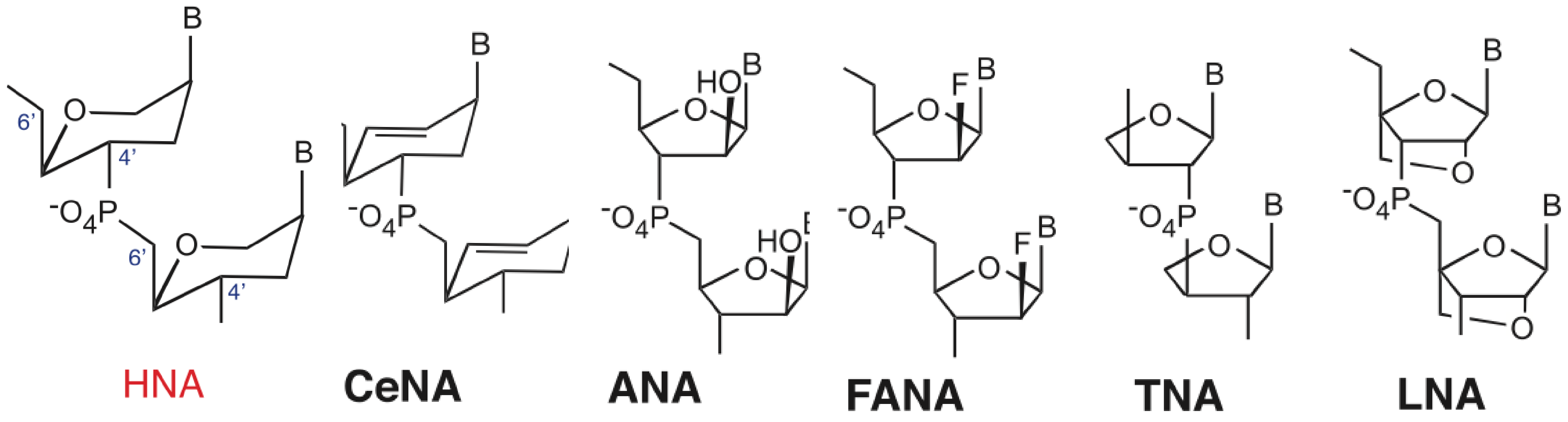
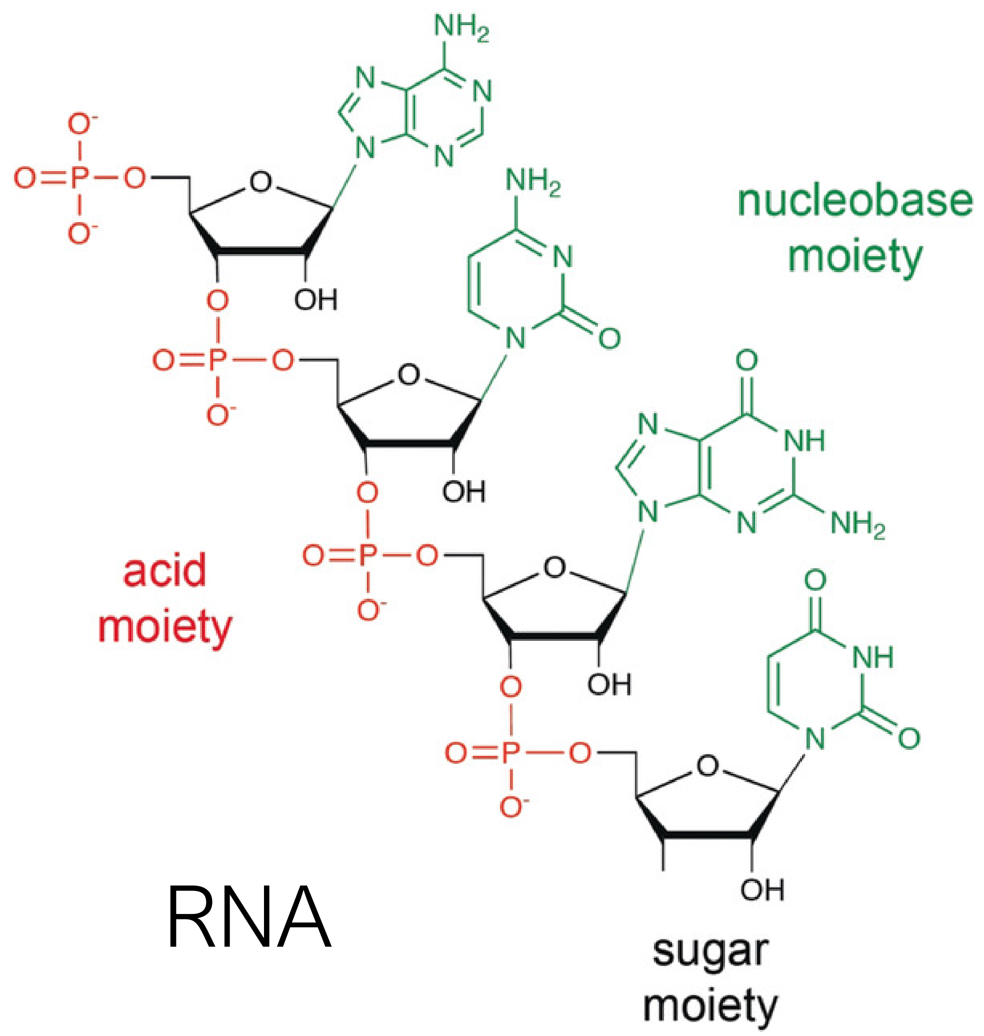
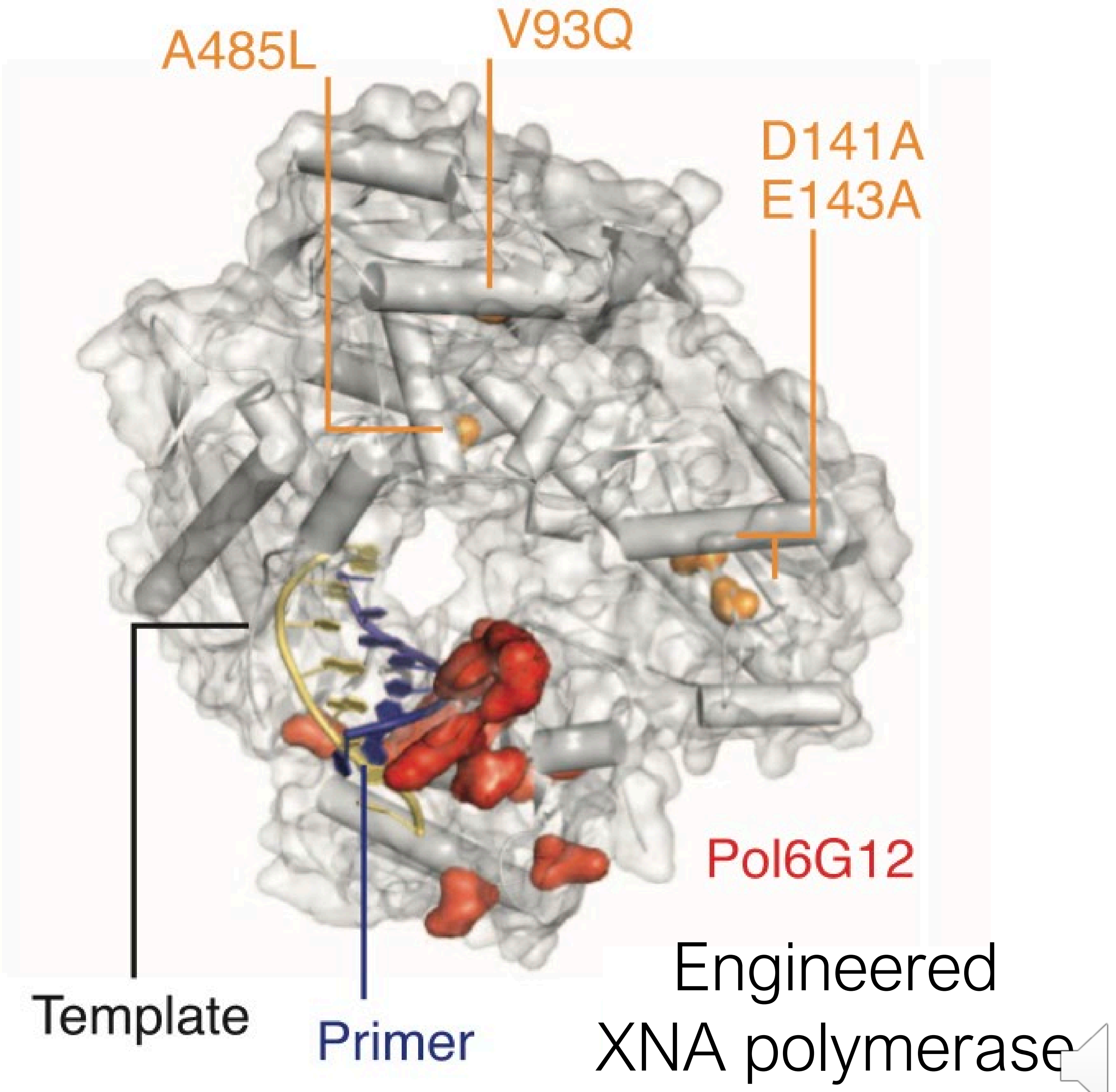
Synthetic Genetic Polymers Capable of Heredity and Evolution

Vitor B. Pinheiro,[1] Alexander I. Taylor,[1] Christopher Cozens,[1] Mikhail Abramov,[2] Marleen Renders,[2]* Su Zhang,[3] John C. Chaput,[3] Jesper Wengel,[4] Sew-Yeu Peak-Chew,[1] Stephen H. McLaughlin,[1] Piet Herdewijn,[2] Philipp Holliger[1]†

- Ribofuranose ring of DNA and RNA is replaced by five- or six-membered congeners
- Development 6 xenonucleic acids (XNA) capable of specific base pairing with DNA and RNA
- Engineering of polymerases that can synthesize XNA from a DNA template
- Engineering of polymerases that can reverse transcribe XNA back into DNA



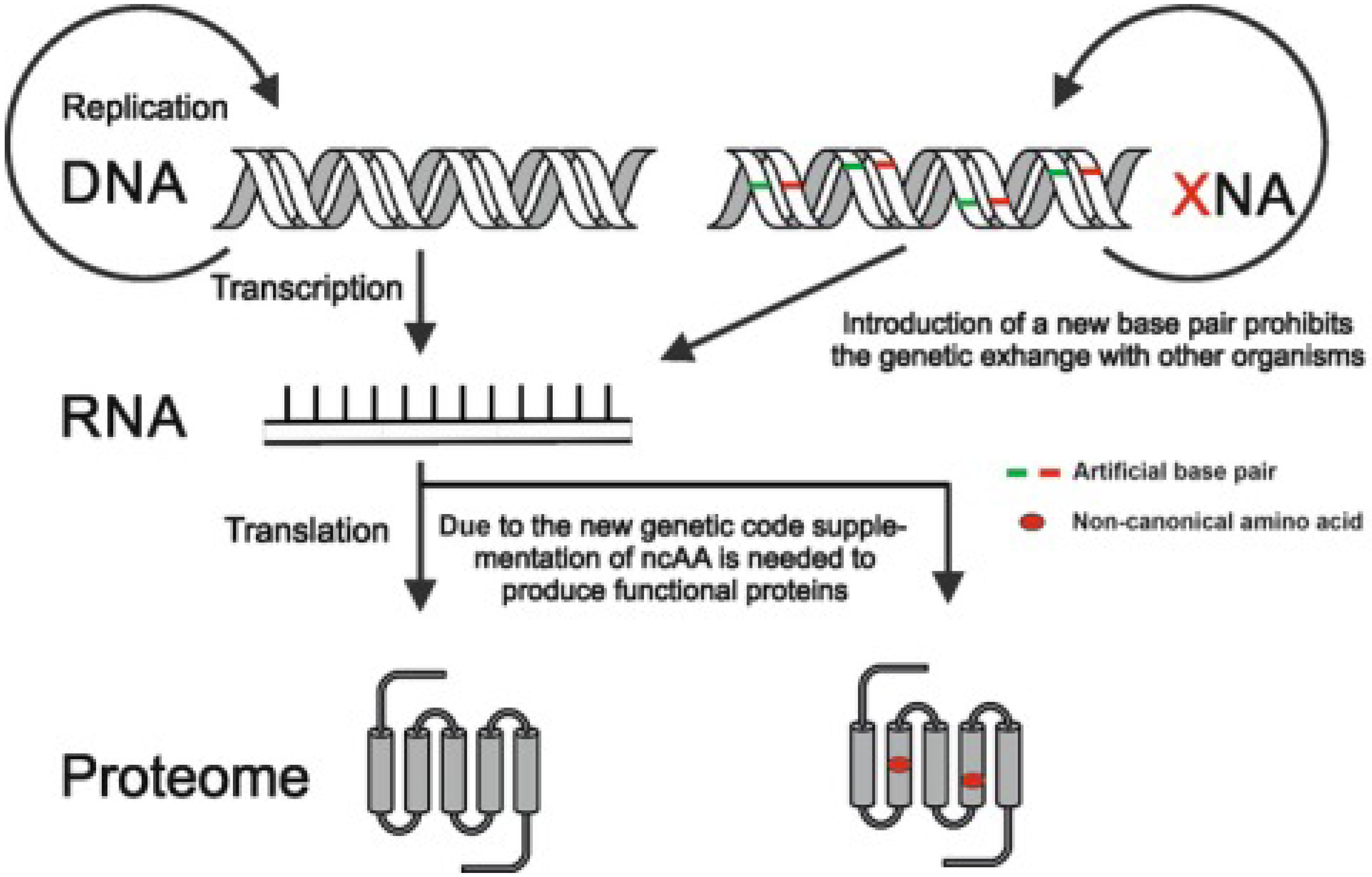




Key developments in Synthetic Biology

Vision: Create xenobiotic organisms that rely on supplementation of synthetic components

- Prevent genetic exchange with other organisms by introducing artificial XNA base-pairing
- Prevent cell replication outside the laboratory by introducing non-canonical amino acids
- Improve biosafety of genetically modified organisms!



Acevedo-Rocha & Budisa, *Microb Biotechnol* (2016)

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How is Synthetic Biology different from previous disciplines?

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Syn•thet•ic Bi•ol•o•gy
noun
The application of engineering principles in biology to (re-)design and fabricate biological components and systems that do not already exist in the natural world.

+knowledge & technology
Synthetic biology
2000's

+knowledge & technology
Systems biology

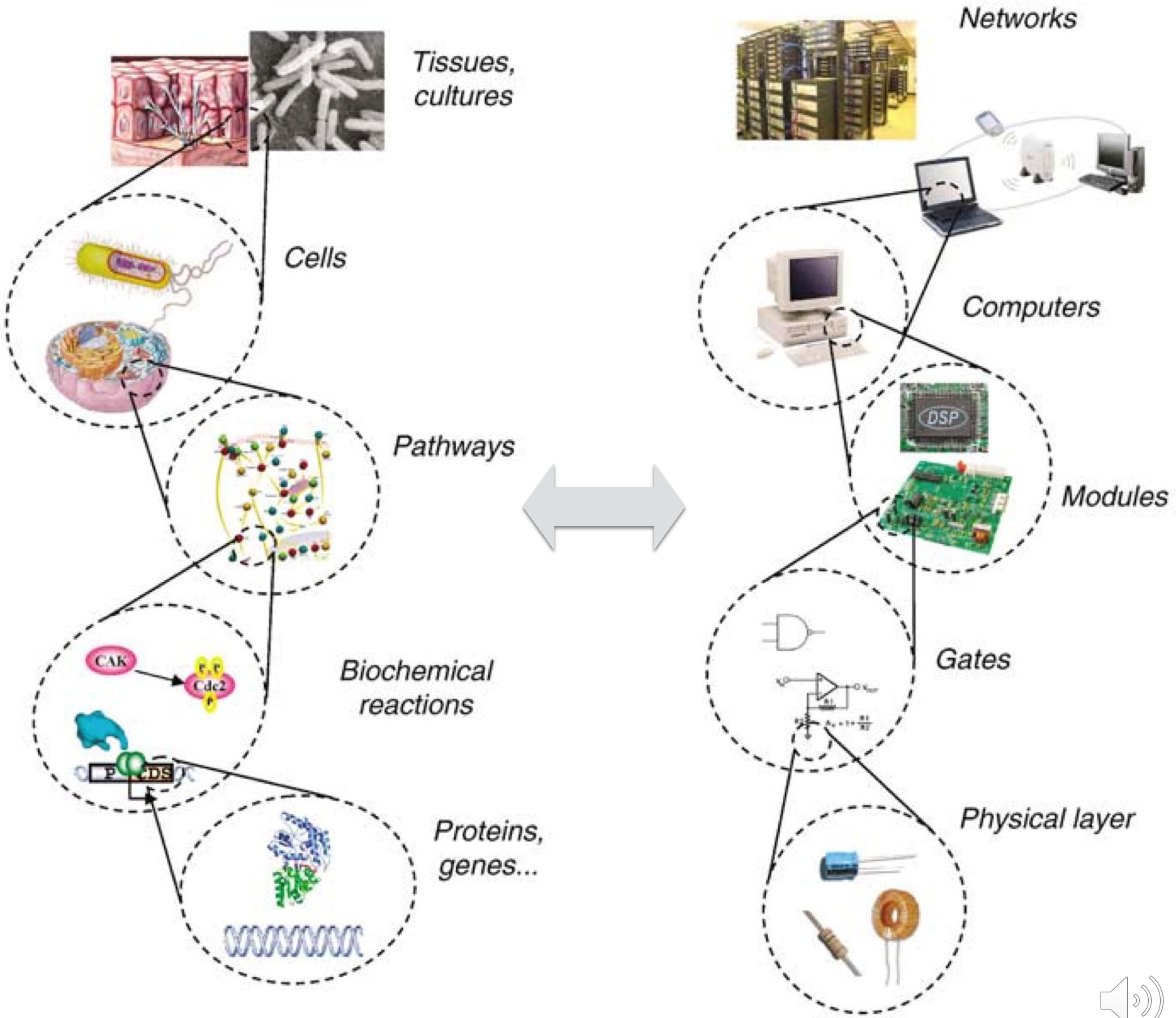
+knowledge & technology
Metabolic engineering
1990's

+knowledge & technology
Genetic engineering
1970's

Molecular biology
1930's

Applying engineering principles to biology

- Abstraction
  - ✓ Facilitate complex biological processes through analogy to electrical engineering
  - ✓ Think binary: genes in ON/OFF state
  - ✓ Ignore unnecessary details
- Modularity
  - ✓ Define modules as closed (insulated) sub-systems with specific input-output characteristics
  - ✓ Ignore minor interactions (cross-talk) with other modules
- Standardisation
  - ✓ Establish commonly used annotations, cloning standards, laboratory procedures, measurement protocols, etc.
  - ✓ Enable re-usability of well-characterized genetic material (=parts!) in different applications
- Modelling & design
  - ✓ Use mathematical models to describe biological function of parts, modules, etc.
  - ✓ Design novel functions based on model predictions



Andrianantoandro et al., Mol Syst Biol, 2006

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The Design-Build-Test-Learn biological engineering cycle

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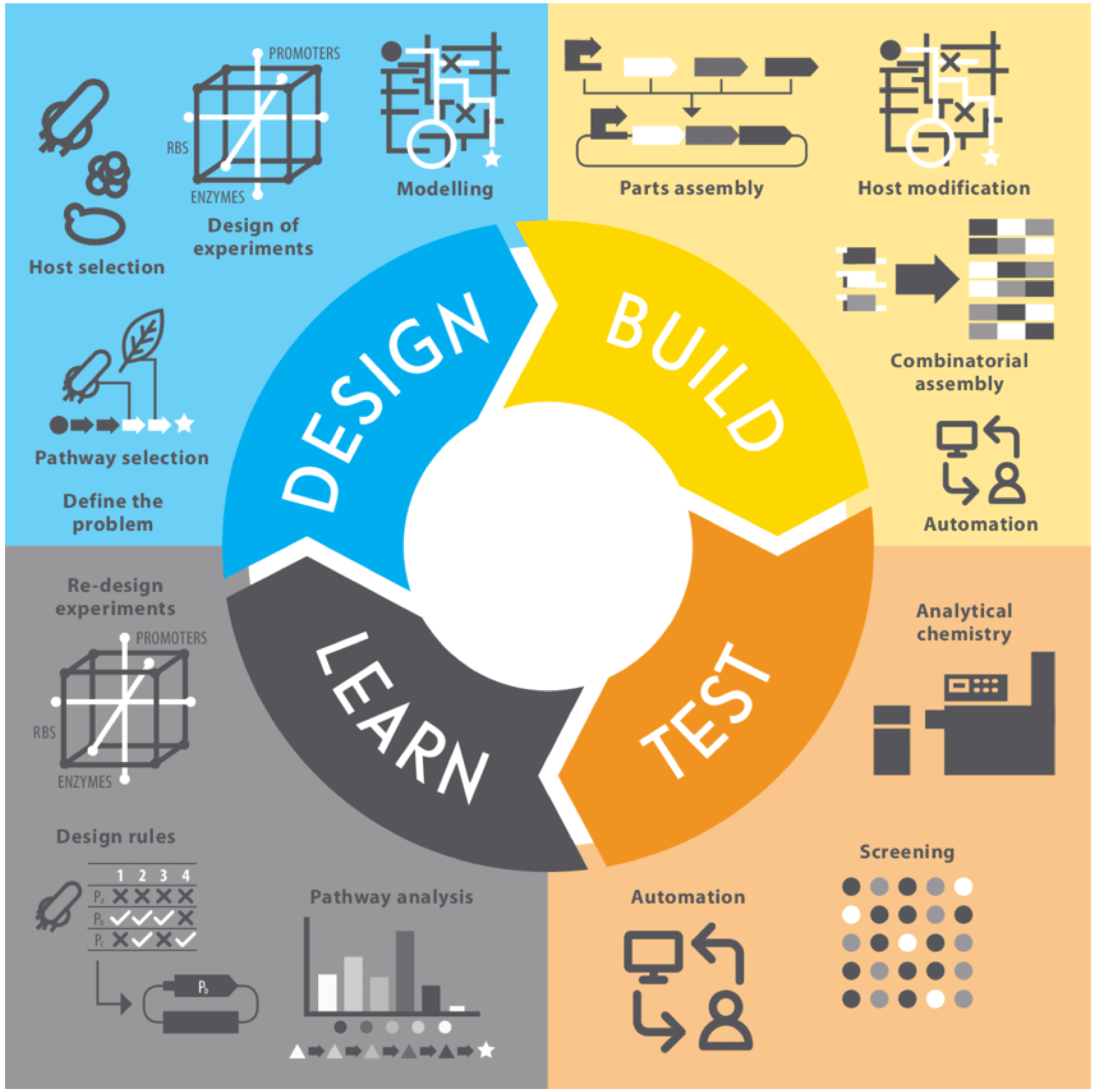
- **Design.** Software-enabled approaches and includes design at all levels, including sequences, engineering approaches, workflows, componentry, organisms etc. Modelling at all levels informs design approaches.



Synthetic Biology in Australia: an outlook to 2030. Australian Council of Learned Academies Expert Working Group Horizon Scanning Project.

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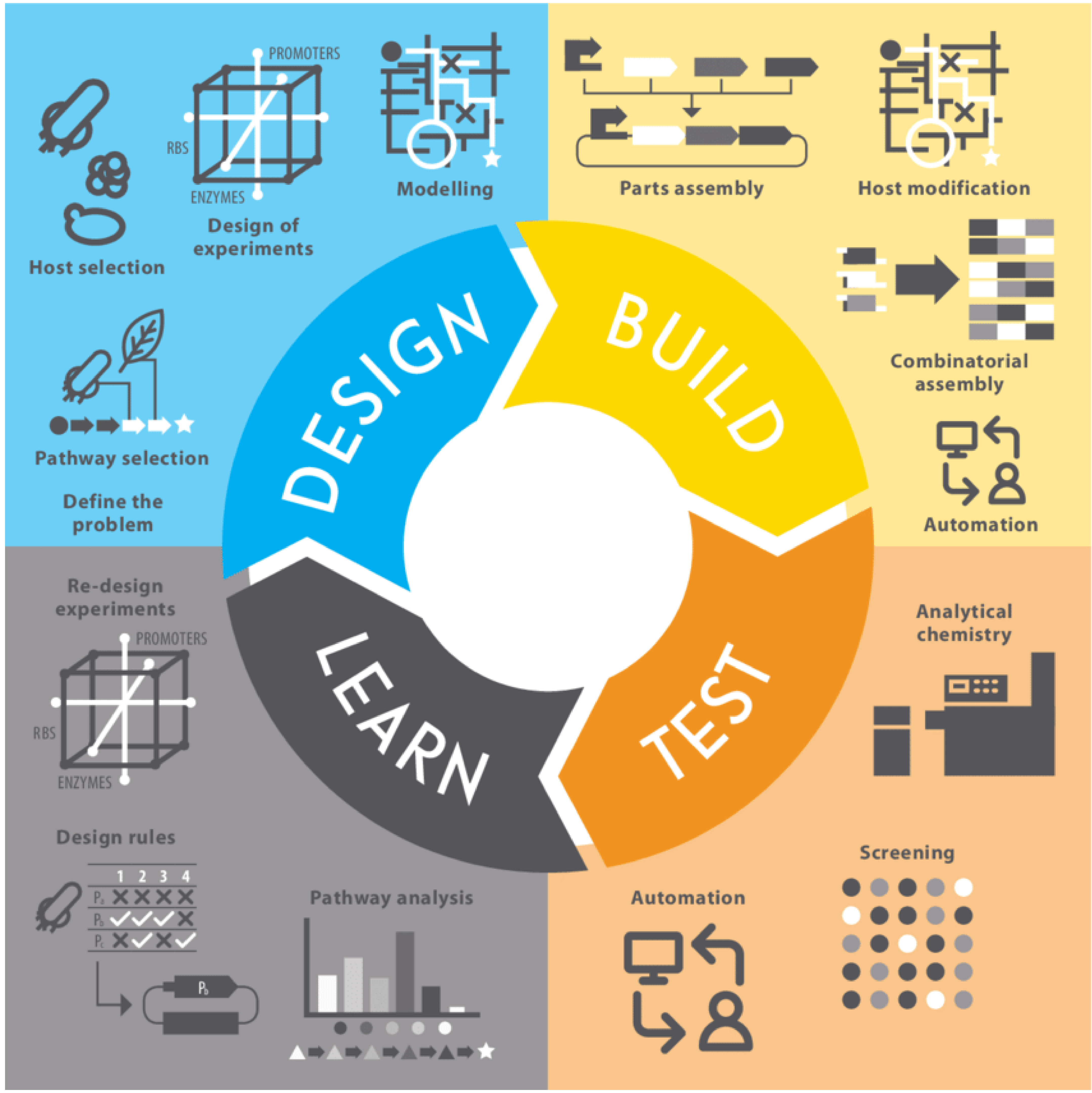

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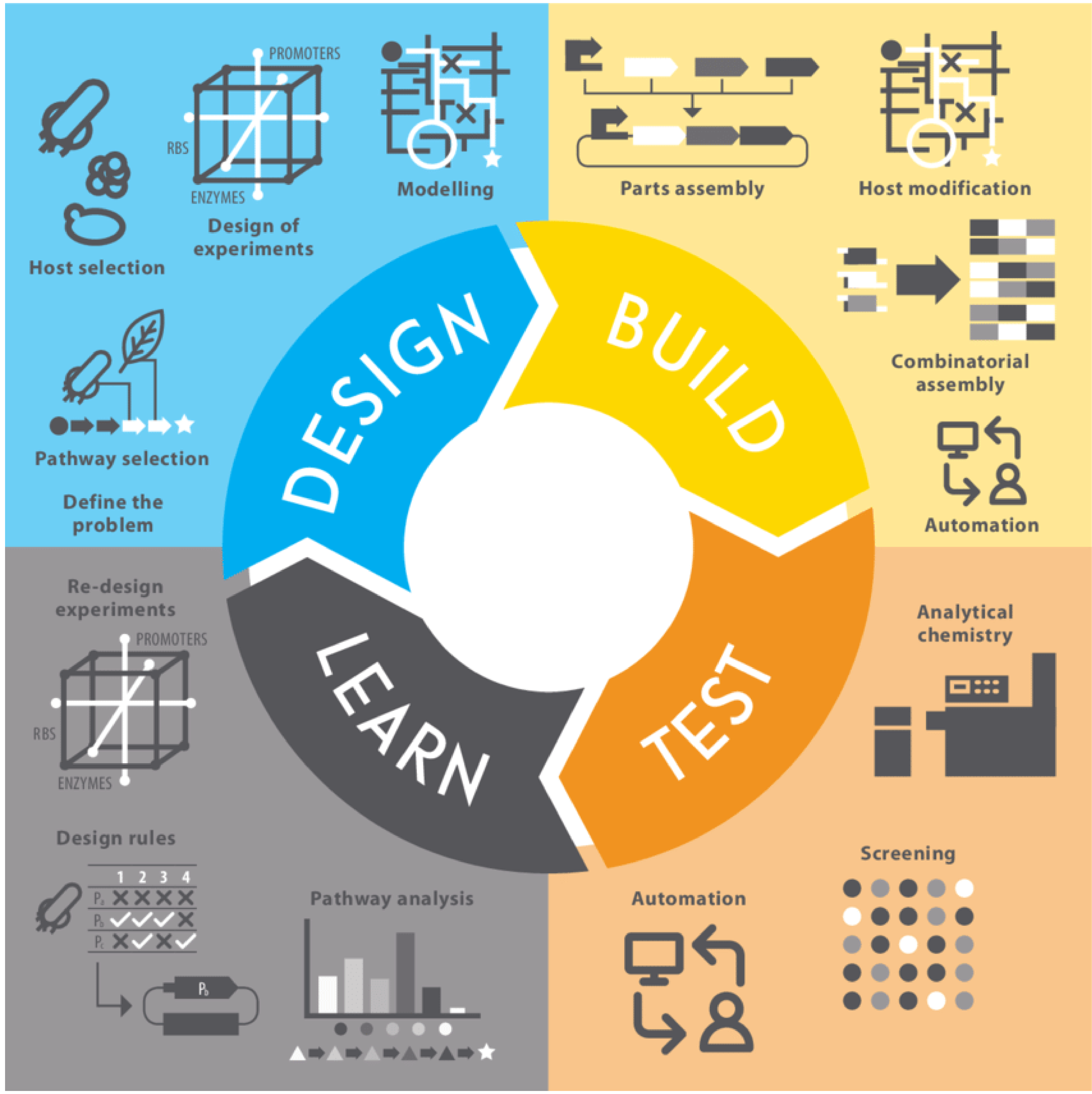
- **Test.** Typically **high throughput methods** as first pass testing (e.g. colony picking robots, FACS, microtitre plates, and high-throughput analytical chemistry to select for markers/reporters/ phenotypes). Once initial selection is performed, **deeper testing** (potentially including bioreactor/scale-up assessments) of a smaller number of strains is then performed. The Test phase generates significant amounts of data.



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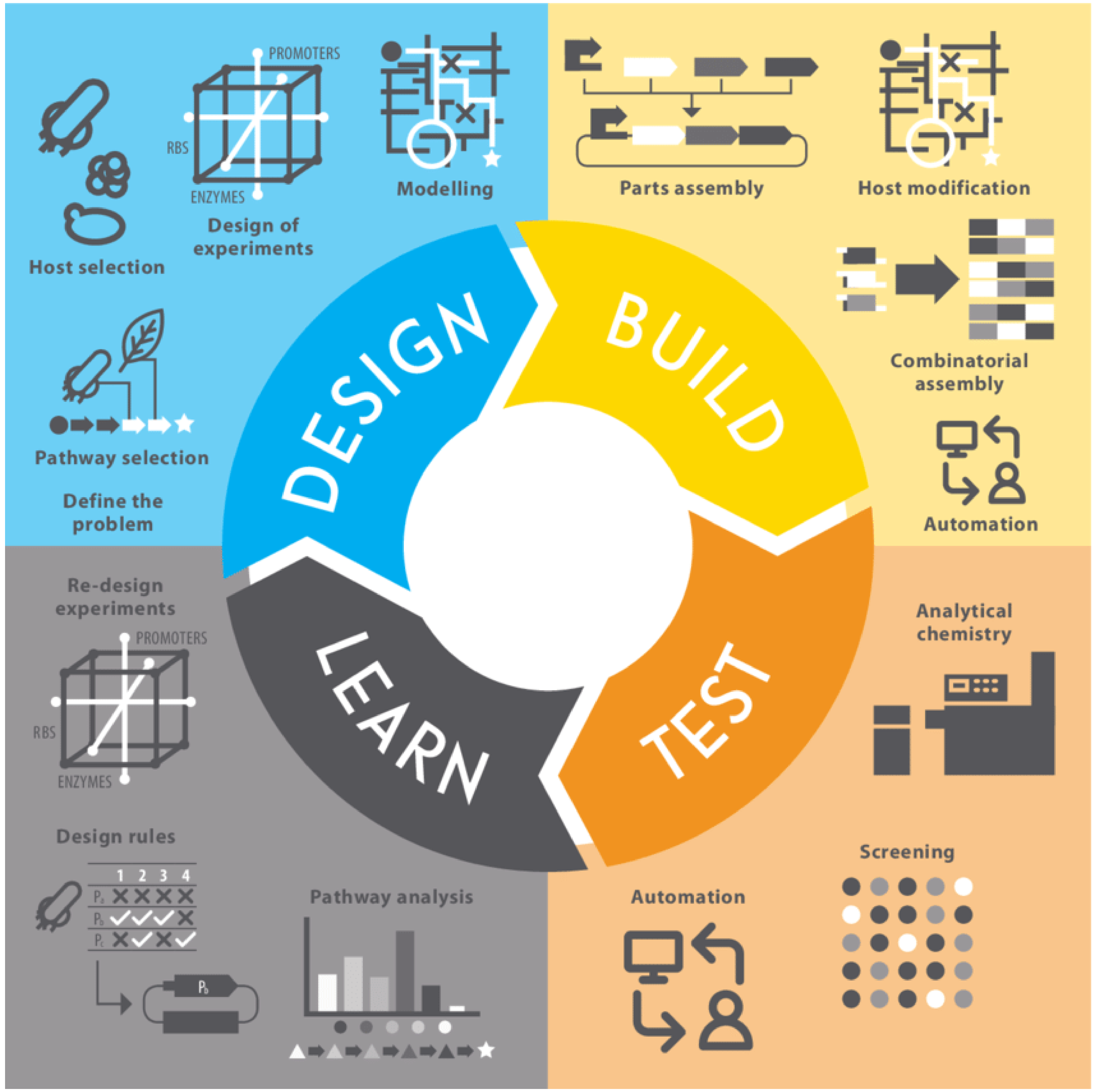
- **Learn.** Data and experience from the DBT phases are collated and examined for learnings. Mechanistic modeling as well as artificial intelligence approaches such as machine learning may be used to extract value from data sets. Learnings are use to generate novel testable hypotheses and incorporated into the next DBT cycle.



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Current & future applications of Synthetic Biology

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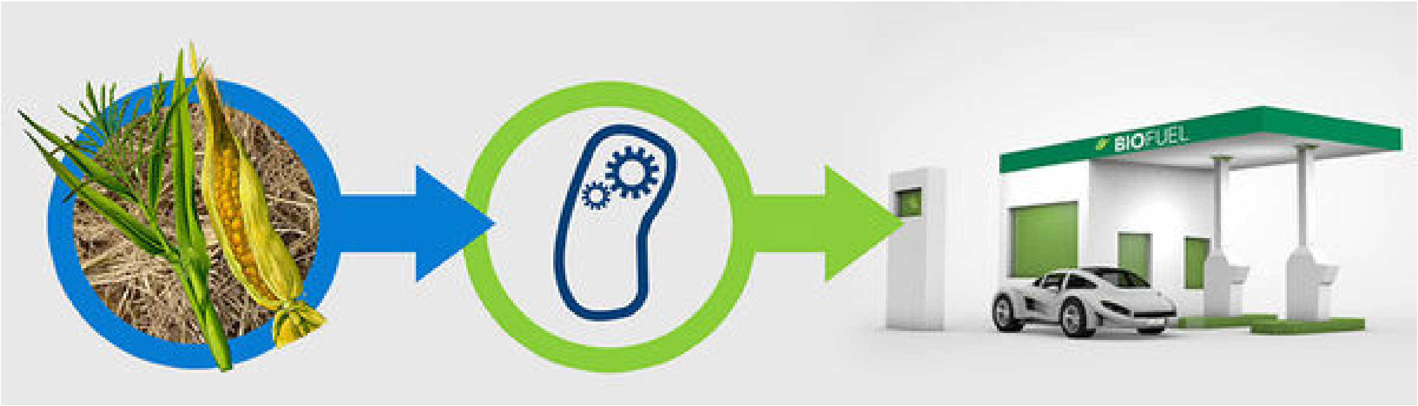
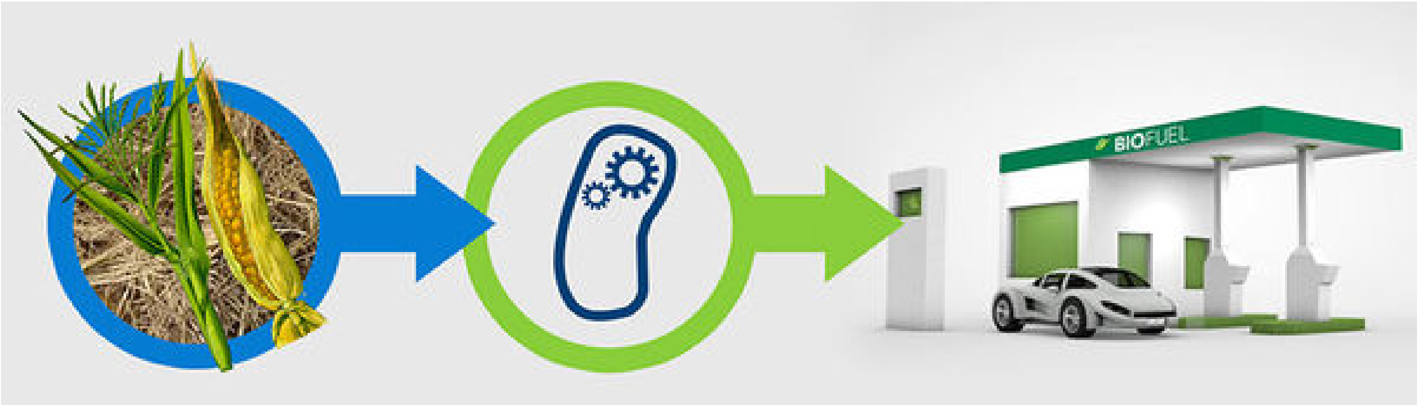


Biofuels and bioenergy

Bio-based chemicals

Biomaterials

Current & future applications of Synthetic Biology



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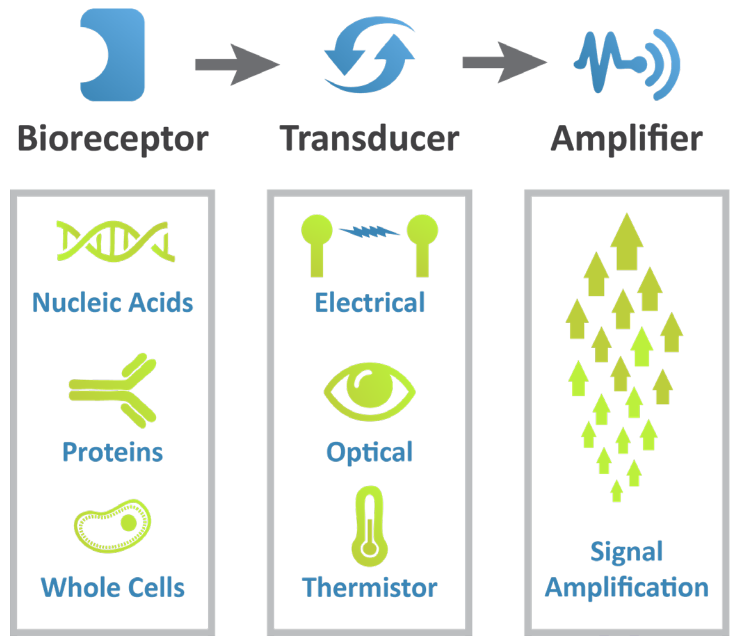
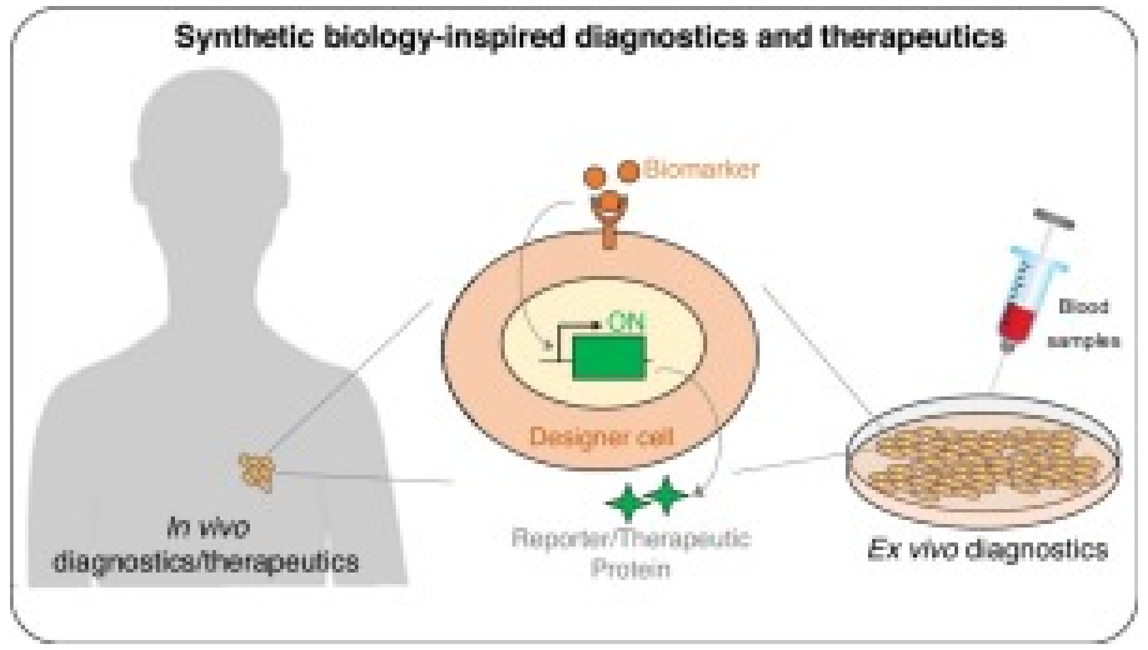
Bioremedation

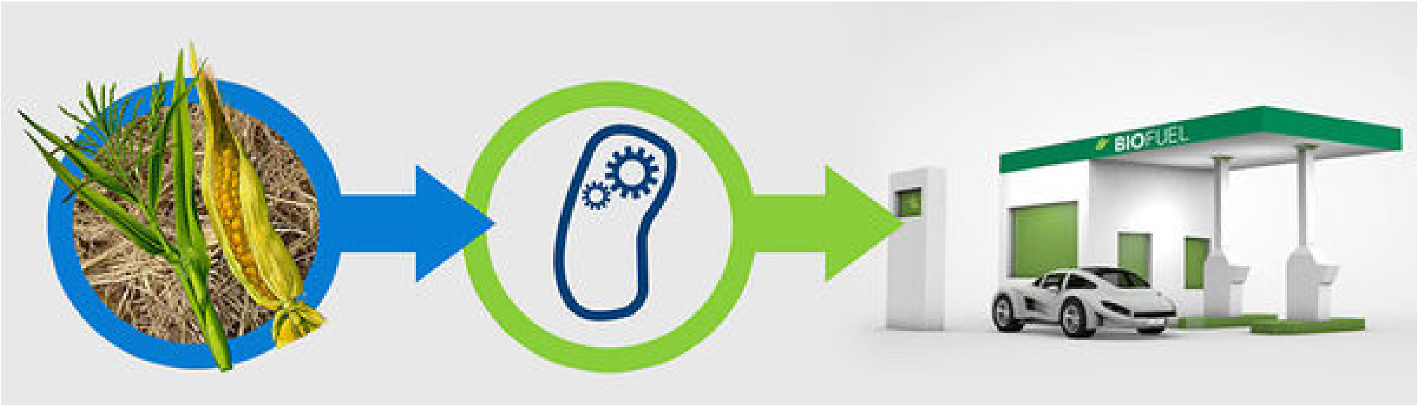


Biosensors



Biomedicine - Diagnostics

Current & future applications of Synthetic Biology



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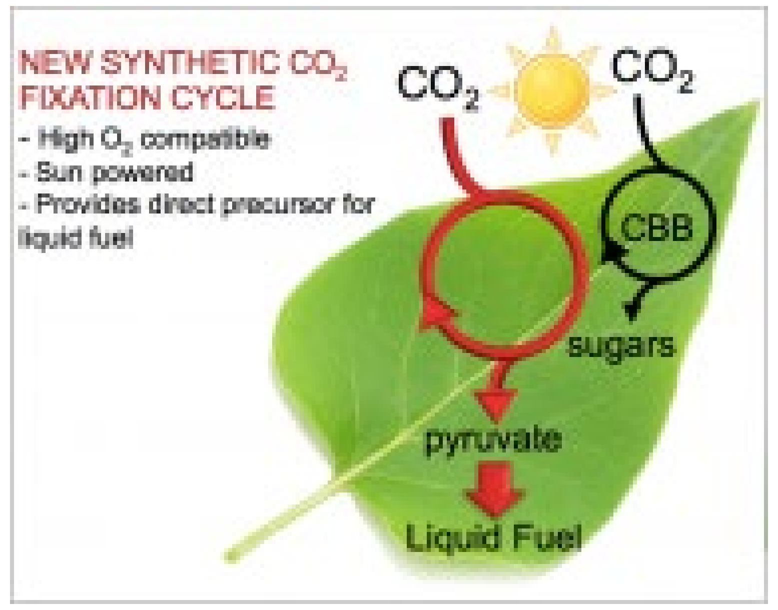
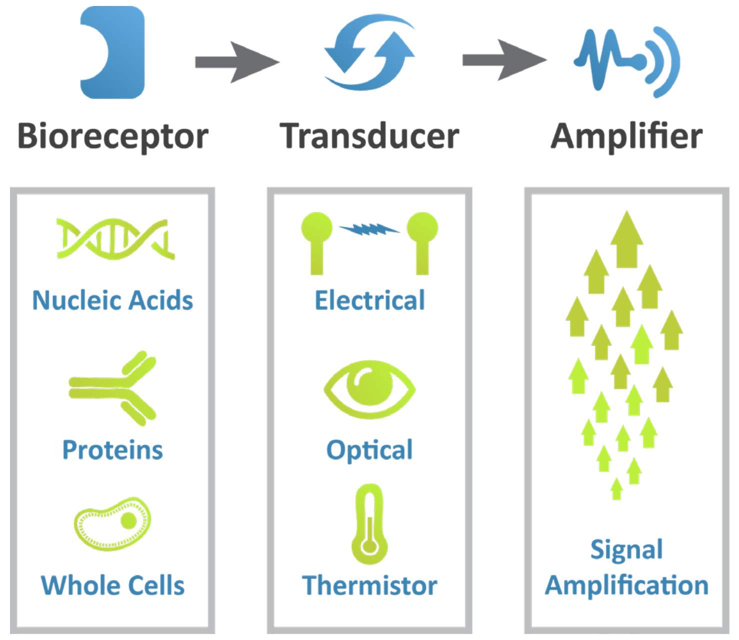


Synthetic CO2 fixation

Food production

Biomaterials

Bioremedation



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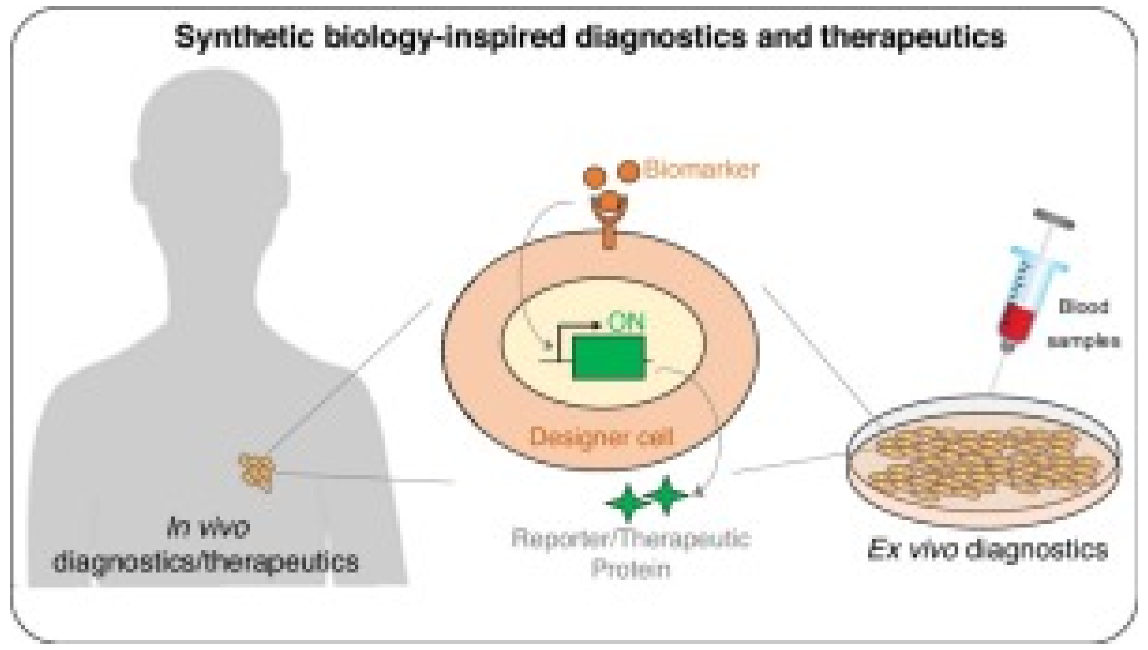

Biomedicine - Diagnostics

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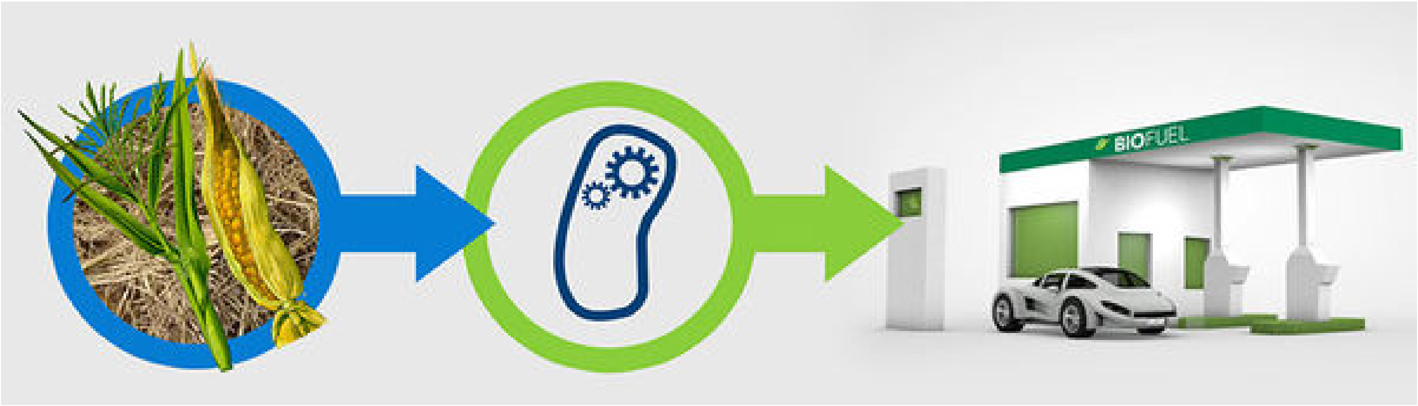

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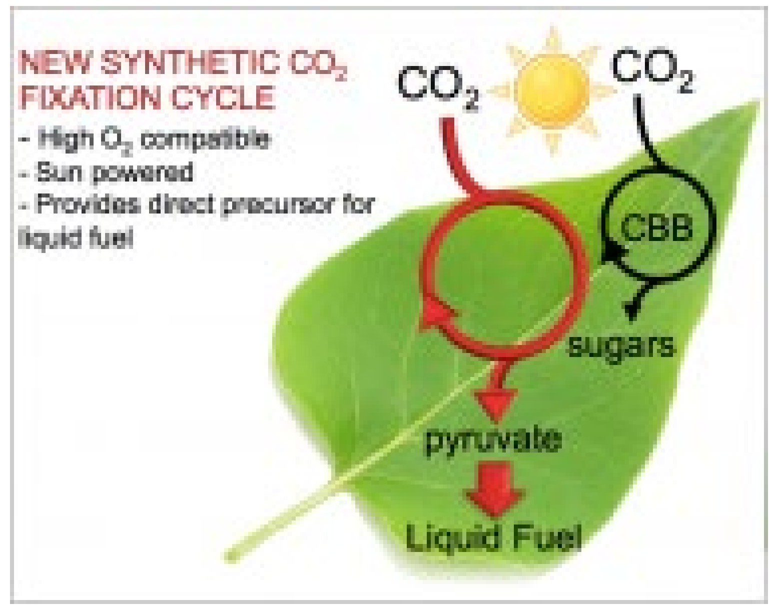

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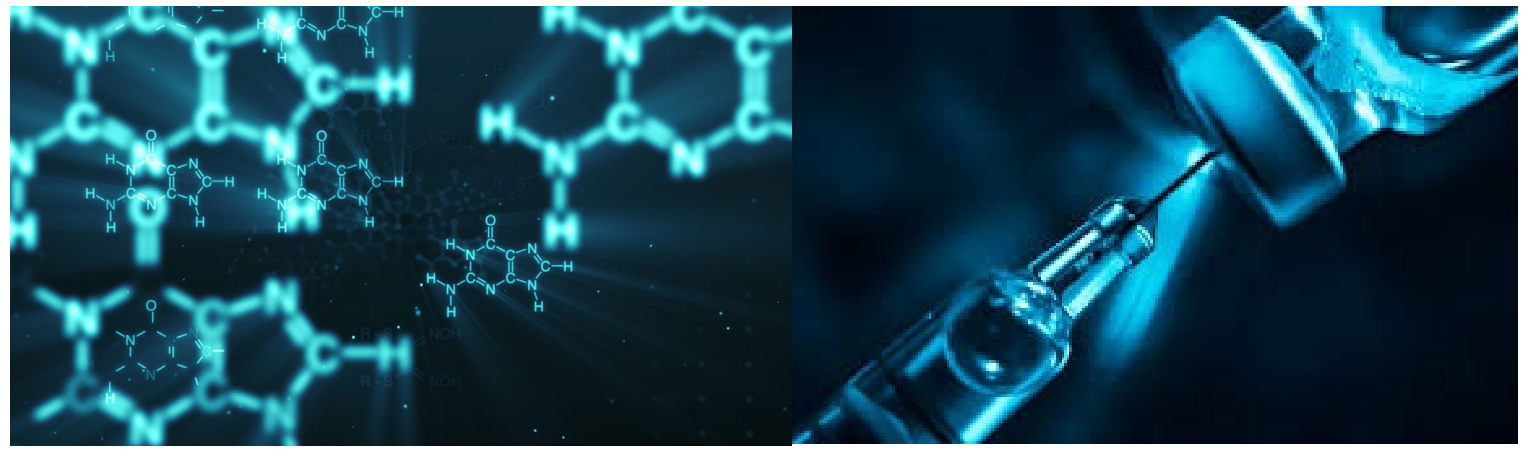
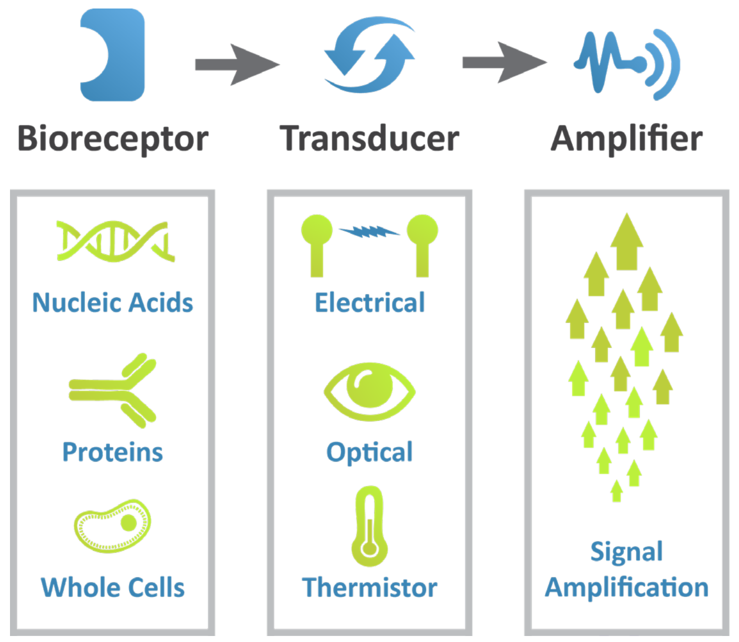


Drugs & Vaccines



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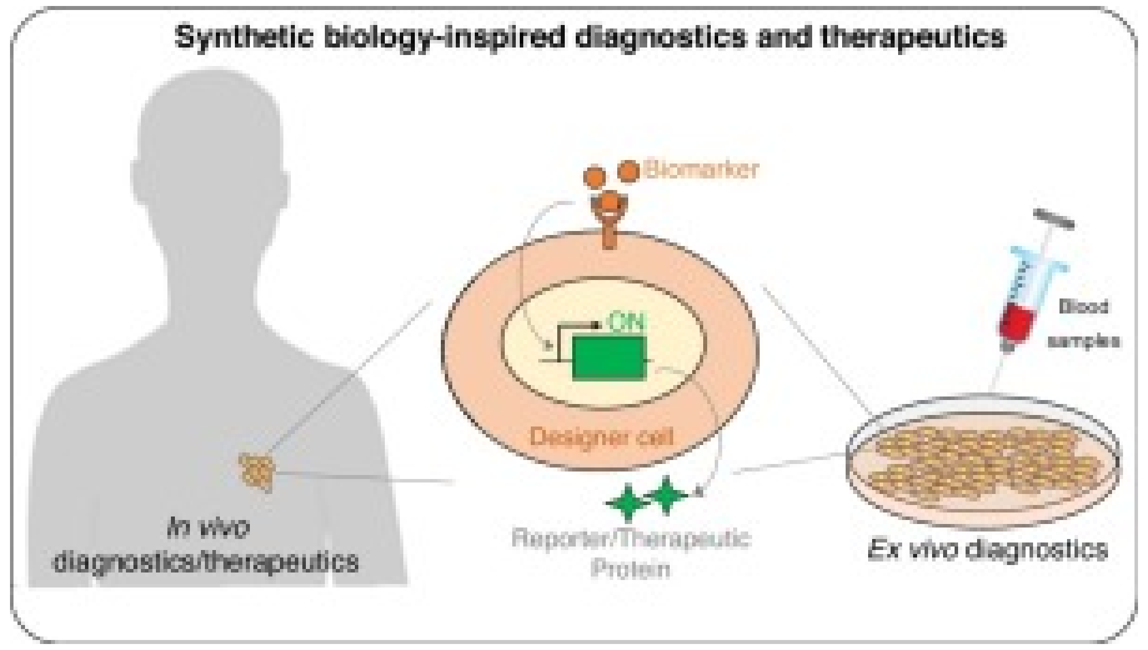
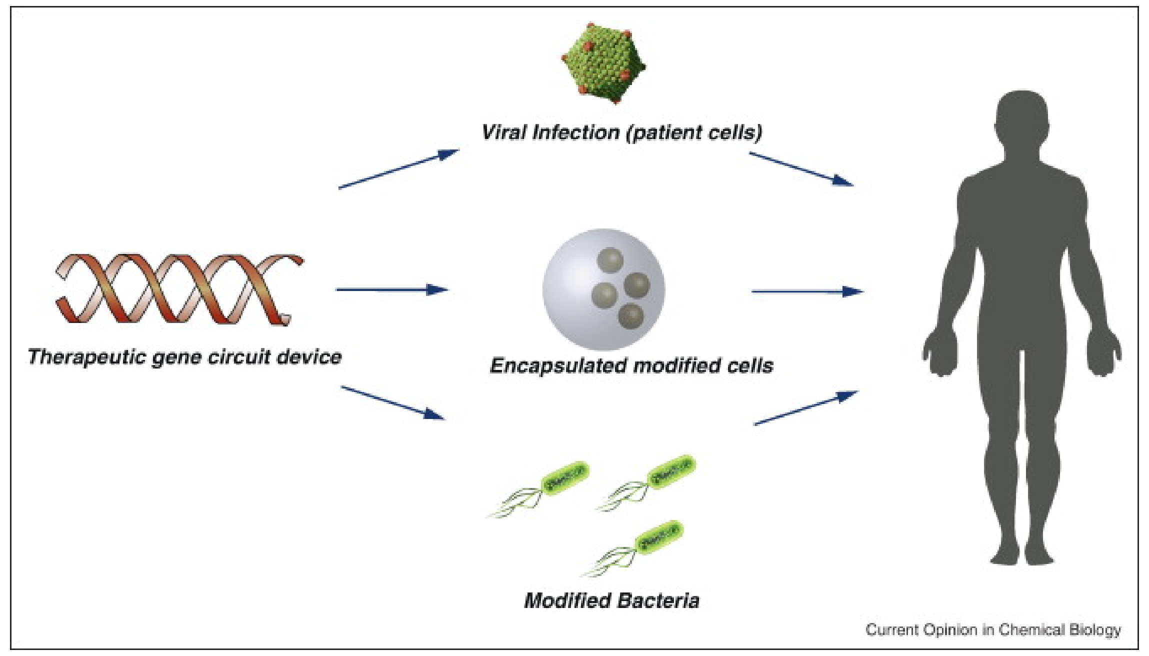


Biomedicine - Diagnostics



Biomedicine - Therapeutics

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Summary

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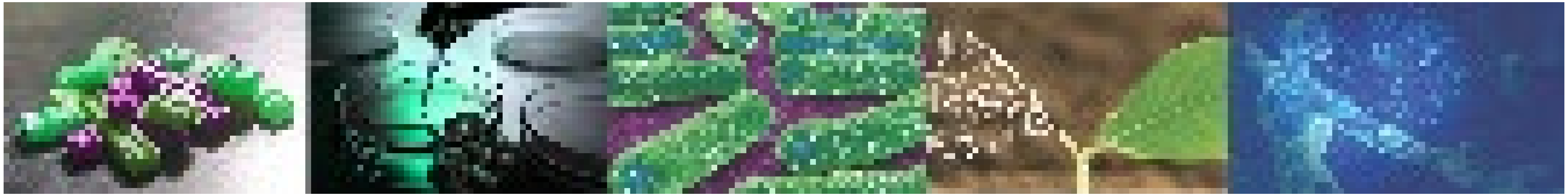
- Synthetic Biology has two motivations: Build to understand/Build to innovate
- Synthetic Biology is an interdisciplinary field emerging from molecular & systems biology, chemistry, physics and computer science; strongly influenced by engineering concepts
- History of founding developments in 5 main areas in the field: Genetic circuit design; Metabolic engineering; Genome engineering; Protocell/minimal cell design; Xenobiology
- Engineering principles underlying Synthetic Biology: Abstraction; Modularity; Standardisation; Design & Modeling
- Uses the Design-Build-Test-Learn cycle as efficient framework for scientific innovation
- Applications of Synthetic Biology aim at solving some of humanity's grand challenges



Thanks for watching!

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