Concept of the Cell:
A Synthetic Biologist's Blueprint for Making a Cell

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Introduction and Background

People have always been intrigued about their own existence and what life is. Throughout history, we have asked many questions about our existence, and those queries span all levels, from philosophical to scientific. You have likely wondered, what does it mean to be alive? What constitutes life as we know it? Robert Hooke likely asked the same questions in 1665, when he looked through his microscope and saw the cell wall remains of oak tree bark cells. And perhaps so too did Antonie van Leeuwenhoek in 1674, when he crafted better lenses to watch live cells through microscopes. In the context of modern biology, we often define life mechanistically as a function of the smallest unit: the cell. But do we really know what constitutes the cell on which life is built? This question has led to an emerging area of science known as synthetic biology.

Synthetic biologists ask big, curiosity-driven questions and attempt to solve the concept-based puzzles that have intrigued humans through the ages. These molecular explorers artificially replicate biological systems by using relatively simple tools and parts in research laboratories. In other words, they view biological systems as machines that can be assembled from simple parts.

Since 1995, two of the biggest questions being asked by synthetic biologists have related to the existence of life: What is a cell? Can a cell be built from scratch, like a machine? This question is applicable to all three categories of cells shown in Figures 1 and 2, since all three types possess a core set of subsystems that allow them to function and to replicate.

LEARNING OBJECTIVES

1. To determine what a typical cell must do at a basic level to function within a natural setting
2. To identify the main features and biosynthetic processes that a typical cell needs to function
3. To assess the biological significance of identified cellular features and biosynthetic processes
4. To identify and assess the functional significance of the relationships between cellular features and biosynthetic processes

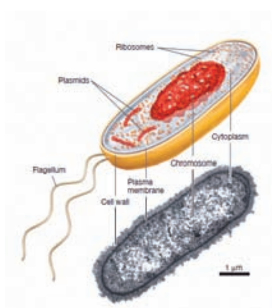

FIGURE 1. Generalized schemes of typical prokaryotic and eukaryotic cells.
The various subcellular compartments or structures are labelled.
Source: Source: Freeman, Scott, Biological Science, *3rd edition, p. 120. © 2008. Printed and Electronically reproduced by permission of Pearson Education, Inc., Upper Saddle River, New Jersey, Dr. Terry Beveridge/Visuals Unlimited, Inc.*

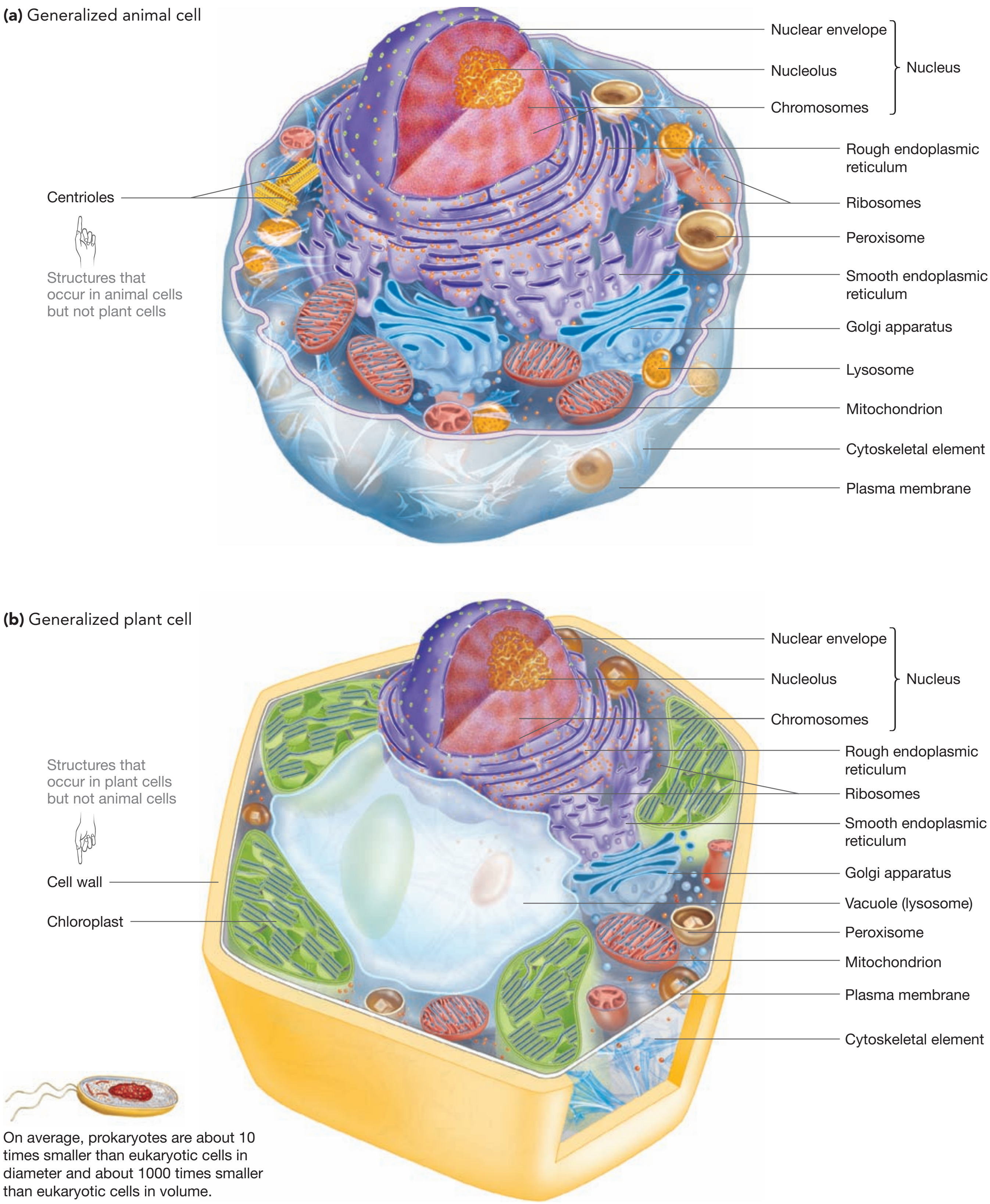

FIGURE 2.
Generalized animal cell and generalized plant cell.
Source: Freeman, Scott, Biological Science, *3rd edition, p. 123. © 2008. Printed and Electronically reproduced by permission of Pearson Education, Inc., Upper Saddle River, New Jersey.*

PHOTO A. Anthony C. Forster, Vanderbilt University.
Source: Anthony C. Forster/ Vanderbilt School of Medicine.

PHOTO B. George M. Church, Harvard Medical School.
Source: George M. Church, Harvard Medical School.

Anthony Forster (see Photo A) of Vanderbilt University and George Church (see Photo B) of the Harvard Medical School, in their 2006 review paper published in the *Molecular Systems Biology Journal*, described the concept of the cell and the need to build a synthetic cell: "Life, like a machine, cannot be understood simply by studying it and its parts; it must also be put together from its parts.... A much simpler purified system based on a real cell would thus be easier to model and understand." Like inventors tinkering with a prototype, Forster and Church proposed a way to build a **minimal synthetic cell.** Figure 3 reproduces that blueprint from Forster and Church's 2006 paper.

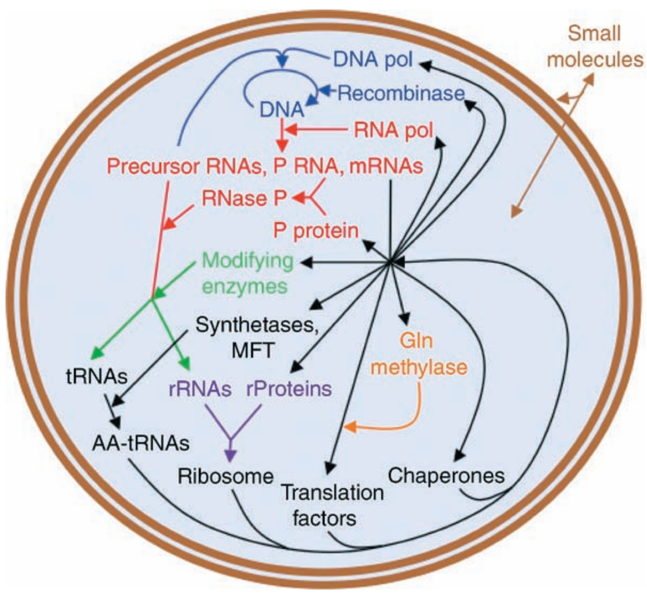

FIGURE 3. A proposed blueprint for a minimal synthetic cell containing biological macromolecules and pathways.
The depicted macromolecules and pathways represent features necessary for a cell to function and to replicate by using small molecule nutrients. The authors of this figure colourized the essential biochemical subsystems: blue for DNA synthesis, red for RNA synthesis and cleavage, green for RNA modification, purple for ribosome assembly, orange for post-translational modification, and black for protein synthesis.
Source: Reprinted by permission by Macmillan Publishers Ltd: Fig. 1 Anthony C Forster and George M Church. 2006. Towards Synthesis of a Minimal Cell. Molecular Systems Biology *2:45. Article 45. doi: 10.1038/msb4100090 www.molecularsystemsbiology.com © 2006 Nature Publishing Group.*

PHOTO C. **Hamilton O. Smith, Nobel Laureate, 1978, Physiology or Medicine, J. Craig Venter Institute.**
Source: J. Craig Venter Institute.

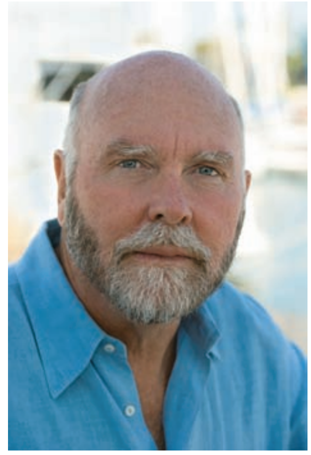

PHOTO D. **J. Craig Venter, J. Craig Venter Institute.**
Source: J. Craig Venter Institute.

To plan and construct a framework for building a minimal synthetic cell, synthetic biologists must identify the foundations underlying a typical cell—the basic design of a cell. What parts are required to satisfy, in the most fundamental way, the simple or basic needs of a cell? As illustrated in Figures 1, 2, and 3, a cell has critical features, organelles, and biosynthetic processes that make up the machinery of a cell. This machinery is crucial in facilitating processes that meet the needs of a cell and allow a cell to live and survive by using small nutrient molecules.

Scientists from around the world developed ways to look at the minimal infrastructure of a synthetic cell. J. Craig Venter Institute scientist Hamilton Smith (see Photo C) used a computer analogy to describe how to make a minimal synthetic cell: a cell's cytoplasm is the hardware and the genome is the operating system. As Smith explains, "A synthetic cell is created by synthesizing a genome and installing it into a recipient cytoplasm." Hamilton and his team at the J. Craig Venter Institute (see Photo D of J. Craig Venter) are working on what needs to go into the genome or operating system of a cell.

Investigation

Designing a Minimal Synthetic Cell

You have been invited to join Hamilton Smith's research team to design a plan for building a minimal synthetic cell. With a minimal operating system in mind, Hamilton's research team set out to use the simplest known operating system as the starting point: the system operating the bacterium *Mycoplasma genitalium*, a tiny bacterium that possesses one of the smallest genomes. The single circular DNA chromosome or molecule of this organism is 580 000 base pairs in circumference. This DNA circle houses 485 protein-coding genes and 43 RNA-coding sequences. The team has already shown through mutation studies that at least 100 genes are not required when tested one gene at a time. The team's next step is to decide which of the remaining genes are to be built into an artificial chromosome: the new, smaller operating system for a synthetic cell. As part of the Hamilton Smith research team, you are to select and use concepts presented in the course and your textbook to develop a blueprint for making a synthetic minimal cell. The engineered cell will need to possess the fundamental qualities of a real cell.

The first question to answer is, what minimal features or abilities should this synthetic cell have to work? Explore the following Critical Thinking Questions when constructing the blueprint for a minimal synthetic cell, decide which basic features and processes underlie a working cell, and then build the machinery that brings a cell to life.

Critical Thinking Questions

1. What do cells need to live in the environment that surrounds a typical cell?
2. What features form the basic design of a simple cell and will address a cell's basic needs?
3. What biosynthetic processes are needed to fulfill a cell's basic needs?
4. What parts are needed to build the minimal machinery of a cell?
5. How do you build this machinery, and how do you tell whether the synthetic cell works?

References and Further Reading

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Some Useful Websites

Cellular visions: the inner life of a cell: http://www.studiodaily.com/main/searchlist/6850.html

This is arguably the coolest animation of what a live cell looks like inside, all set to music. The animation should help you visualize the building of a synthetic cell.

iGEM website at MIT: http://www.igem.org
iGEM is an annual competition for students interested in synthetic biology and making engineered cells do things.

J. Craig Venter Institute website: http://www.jcvi.org
This website has many big research ideas and opportunities for students.

Sixteen-minute talk by Craig Venter: on the verge of creating life: http://www.ted.com/talks/craig_venter_is_on_the_verge_of_creating_synthetic_life.html
This easy-to-follow lecture on creating life is from Craig Venter himself.

Synthetic Biology website: http://syntheticbiology.org
This convenient, centralized website has links to projects, techniques, and researchers studying in area synthetic biology.

Synthetic Biology website at Harvard: http://www.harvardscience.harvard.edu/directory/programs/wyss-institute-biologically-inspired-engineering
Catch up on what's new in synthetic biology at the Wyss Institute for Biologically Inspired Engineering.