Shanghai United International School

Science and Biotechnology

For the Young and Innovative Minds

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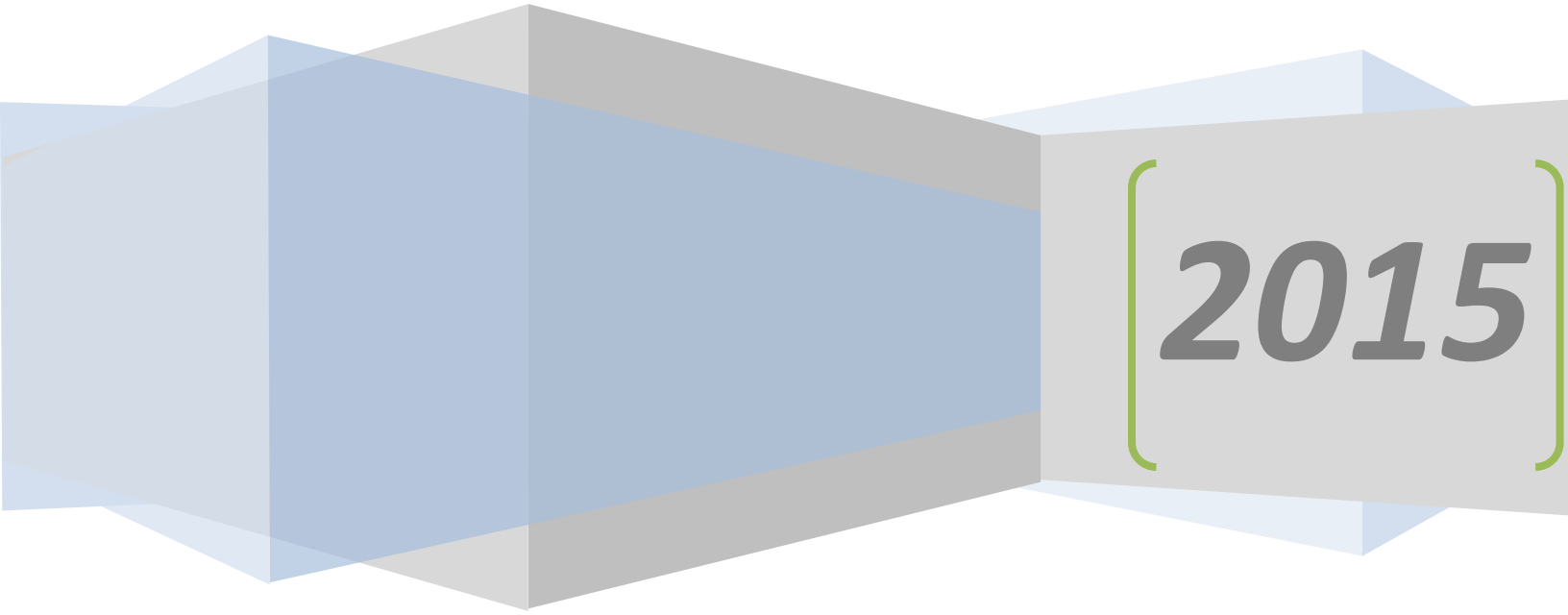

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Introduction

Figure 1 The Earth

This e-Book will show you most of the major and recent discoveries in modern science and technology. Biotechnology is any technological application that uses biological systems, living organisms, or derivatives thereofore, to make or modify products or processes for specific use. It will become your bridge to see the brand new world. In this book there are not only the interesting histories of science but also the innovation yet to be made that will one day change the world.With this book, you can have the world in your hand. Enjoy your journey in science and technology!

Chapter 1: Discovery of Cells and the Development of Cell Theory

1. The Beginning

The study of cells started about 330 years ago. Before that time cells escaped notice because of their small size. With the invention of the microscope and its subsequent improvement, cells became visible and many new discoveries were made about them. Even today the study of cells reveals more detail, and its secrets, which are in fact the secrets of life itself, are revealed with ever increasing clarity.

2. Microscopist Robert Hooke

Discovery

1665: English Scientist and Microscopist Robert Hooke described a honeycomb-like network of cellulae (Latin for little storage rooms) in cork slice using his primitive compound microscope. Robert Hooke used the term cells to describe units in plant tissue (thick cell walls could be observed). Of course he saw only cell walls because cork cells are dead and without protoplasm. He drew the cells he saw and also coined the word cell. The word cell is derived from the latin word cellula which means smallcompartment. Hooke published his findings in his famous work, *Micrographia*[1].

Background

Hooke was born on the Isle of Wight and educated at the University of Oxford. He served as assistant to the English physicist Robert Boyle and assisted him in the construction of the air pump. In 1662 Hooke was appointed curator of experiments of the Royal Society and served in this position until his death. He was elected a fellow of the Royal Society in 1663 and was appointed Gresham Professor of Geometry at Oxford in 1665. After the Great Fire of London in 1666, he was appointed surveyor of London, and he designed many buildings, including Montague House and Dethlehem Hospital.

Connections with Others

Figure 2 Isaac Newton

Hooke anticipated some of the most important discoveries and inventions of his time but failed to carry many of them through to completion. He formulated the theory of planetary motion as a problem in mechanics, and grasped, but did not develop mathematically, the fundamental theoryon which the English physicist Sir Isaac Newton formulated the law of gravitation[i]. Hooke's most important contributions include the correct formulation of the theory of elasticity[2], which

[1]A historic book by Robert Hooke, detailing the then thirty-year-old Hooke's observations through various lenses.
[2]A theory for isotropic, linearly elastic materials subjected to small deformations.

states that an elastic body stretches in proportion to the force that acts upon it; and analysis of the nature of combustion. He was the first to use the balance spring for the regulation of watches, and devised improvements in pendulum clocks. Hooke was also a pioneer in microscopic research and published his observations, which included the discovery of plant cells.

3. Matthias JakobSchleiden

Discovery

1838: Matthias JakobSchleiden, a German botanist, concluded that all plant tissues are composed of cells and that an embryonic plant arose from a single cell. He declared that the cell is the *basic building block* of all plant matter. This statement of Schleiden was the first generalizations[3] concerning cells.

Figure 3 Matthias Schleiden

Background

Born in Hamburg and educated in law at Heidelberg, Schleiden left law practice to study botany, which he then taught at the University of Jena from 1839 to 1862. A man of disputatious nature he scorned the botanists of his day who limited themselves to merely naming and describing plants. Schlieden investigated plants microscopically and conceived that plants were made up of recognizable units, or cells. Plant growth, he stated in 1837, came about through the production of new cells, which, he speculated, where prophagates from the nuclei of old cells. Although later discoveries proved him wrong about the role of the nucleus in mitosis[4], or cell division, his conception of the cell as the common structural unit of plants had the profound effect of shifting scientific attention to living processes as they happened on the cellular level-a change that initiated the field of embryology. A year after Schleiden published his cell

[3] The act or process of generalizing.

[4] The usual method of cell division, characterized typically by the resolving of the chromatin of the nucleus into a threadlike form, which condenses into chromosomes.

theory on plants, his friend Schwann extended it to animals, thereby bringing botany and zoology together under one unifying theory.

4. Theodor Schwann

Discovery

1839: Theodor Schwann, a German biologist, reached the same conclusion as Schleiden about animal tissue being composed of cells, ending speculations that plants and animals were fundamentally different in structure. Schwann described cellular structures in animal cartilage (rigid extracellular matrix). He pulled existing observations together into theory that stated: 1. Cells are organisms and all organisms consist of one or more cells. 2. The cell is the basic unit of structure for all organisms and that plants and animals consist of combinations of these organisms which are arranged in accordance with definite rules. In other words, the cell is the basic unit of life. This statement was the second generalization concerning cells and is the most important in the development of biology. It became known as the cell theory.

Background

Figure 4 Schwann Theodor

Schwann, Theodor (1810-82), German physiologist, generally considered the founder of modern histology, the study of the structure of plant and animal tissues. Schwann was born in Neuss and educated at the universities of Bonn, Warzburg, and Berlin. He was (1838-48) professor of anatomy at the University of Leuven in Belgium; thereafter until his death he was associated with the University of Libge, also in Belgium, serving as professor of anatomy from 1848 to 1858, when he became professor of physiology. Schwann achieved the physiochemical nature of life by applying the cell theory of the German botanist Matthias Jakob Schleiden to the evolution of animal life. He also demonstrated that the mature tissues of all animals are traceable to embryonic

cells. While assisting the German physiologist Johannes Miller in the Anatomical Museum of Berlin, Schwann discovered pepsin, the digestive enzyme, in the stomach epithelium, or membrane tissues, of animals. He also conducted valuable research on the processes of fermentation[5], putrefaction, and muscular and arterial contraction.

5. Rudolf Virchow

1855: Taking Brown's original description of nuclei and observations by Karl on cell division, the German physiologist, physician, pathologist, and anthropologist Rudolf Virchow was able to add a third tenet to the cell theory: Omnis cellula e cellula, or all cells develop only from existing cells.

Discovery

Virchow was the first to demonstrate that the cell theory applies to diseased tissue as well as to healthy tissue-that is, that diseased cells derive from the healthy cells of normal tissue. He did not, however, accept Louis Pasteur's germ theory of disease. He is best known for his text Cellular Pathology as Based on Histology (1850-1860). He engaged also in extensive research in the fields of archaeology and anthropology, producing numerous writings, among them Crania Ethnica Americana (1892). Other publications include discussions of topical political and social questions. Virchow was influential in German politics and from 1880 to 1893 served as a Liberal in the German Reichstag, where he opposed the policies of the German chancellor Prince Otto von Bismarck. He was instrumental in the establishment of the Pathological Institute and Museum in Berlin.

[5] A change brought about by a ferment, as yeast enzymes, which convert grape sugar into ethyl alcohol.

Background

Virchow, Rudolf (1821-1902), German pathologist, archaeologist, and anthropologist, the founder of cellularpathology. Virchow was born in Schivelbein, Pomerania[6], and educated at the University of Berlin. In 1843 he became prosecutor at the Charite Hospital in Berlin, and in 1847 a university lecturer. In 1849 he was invited to the medical school of Wurzburg as professor of pathological anatomy, having been dismissed from his Berlin posts because of revolutionary activities. In 1856 he returned to Berlin as professor and director of the university's pathological institute.

Chapter 2: Top 5 Innovations

1. MyCell Services

Shinya Yamanaka shared the 2012 Nobel Prize in Physiology or Medicine for his discovery that injecting a few transcription factors into a differentiated adult cell can render that cell pluripotent once again. The technology revolutionized biomedical research, allowing scientists to create induced pluripotent stem cell (iPSC) models for a variety of diseases. Now, Cellular Dynamics International (CDI) is utilizing that technology to offer, via the company's MyCell Services, iPSC lines from any patient of interest, as well as differentiated cell lines derived from the iPSCs.

Figure 5 MyCell Services

[6] Now Swidwin, Poland.

"Customers don't have to be stem-cell biologists to leverage this technology," says Chris Parker, CDI's chief commercial officer. "They can simply be interested in a disease state and get the human cells they need to answer appropriate questions."

Paul Watkins, for example, director of The Hamner–University of North Carolina Institute for Drug Safety Sciences, is using MyCell Services to create iPSC-derived hepatocytes from patients who have survived severe liver reactions to drugs, comparing them to iPSC-derived hepatocytes from healthy donors. Ultimately, he says, the goal is to identify specific genetic profiles that indicate susceptibility[7] to adverse drug reactions. "We have the whole exome sequence [for these patients], and we will have the whole genome sequence, so we know the variations that exist and have various hypotheses," Watkins says. "But this technology will allow us to test, directly, those hypotheses."

The iPSC lines are derived from CD34 cells in blood samples sent in by customers, and returned as 96-well plates of a cell type of interest. To create an iPSC line from a patient sample costs $15,000 and takes about 6 months, Parker says, but once the iPSC lines are established, it takes just 1 to 2 months to order more specific cell types derived from that line. The cost per plate for differentiated cells is approximately $1,500, with a minimum order of 20 plates.

CHANDLER: The ability to produce induced pluripotent stem cells "on demand" with high quality and purity has high potential to transform both numerous fields of life sciences research and open the door to potential medical applications.

2. NanoLuc Luciferase Technology

Figure 6 NanoLuc Luciferase

Luminescence reporter assays have become indispensable tools for immunologists, cell and molecular biologists, geneticists, and

[7] state or character of being susceptible

other researchers seeking to shine a light on the molecular dynamics of a cell. Into the mix of luminescence options, which includes firefly luciferase and green fluorescent protein (GFP), Promega has now introduced a new fluorescent[8] reporter enzyme called NanoLuc Luciferase, derived from an enzyme found in a deep-sea shrimp of genus Oplophorus.

The new tool offers several improvements over other luminescent reporters. Its small size—about 2/3 as large as GFP—makes NanoLuc less likely to disrupt the cellular processes researchers are using it to probe. It can also shine up to 240 times as brightly as firefly luciferase. "Bioluminescence has become one of the fundamental measurement technologies used in life science," says Promega head of research Keith Wood. "We think with NanoLuc we've advanced that technology in a number of ways."

NanoLuc user Samuel Hasson, a pharmacology research fellow at the National Institute of Neurological Disease and Stroke, agrees. Without the small size and brighter glow of NanoLuc, Hasson says that his in vitro studies of mitochondrial dysfunction's role in Parkinson's disease would not even be possible. "The signal that you get from the NanoLuc is much brighter," he says. "So when you have cases of low gene expression, the level of signal you get is much higher" than with a firefly luciferase. Plus, "you perturb the natural process less when you have a smaller reporter tagged onto the mitochondrial protein."

The DNA plasmid containing the genetic content needed to produce NanoLuc runs about $320, and the substrate used to detect the molecule's glow is another $125, according to Kevin Kopish, global product manager for NanoLuc. Researchers can expect to pay recurring reagent costs.

[8] Strikingly bright, vivid, or glowing.

3. Photo-Morpholinos

Figure 7 Photo-Morpholinos

Morpholino oligomers (oligos) are molecules that bind to RNA and are commonly used to disrupt gene expression. To have better control over when and where target RNAs are knocked down, biotech company Gene Tools devised Photo-Morpholinos, photo-cleavable morpholinos that can be used to turn gene expression on and off in an organism or tissue culture at particular times using light. When sense Photo-Morpholinos bind to antisense morpholinooligos, the Photo-Morpholino acts as a cage to prevent the antisense morpholinooligo from interacting with its target RNA and reducing gene expression. But shine a little UV light on the system, and the Photo-Morpholino pops off, initiating gene knockdown. Or, antisense Photo-Morpholinos can directly bind the sense RNA target, but the knockdown is reversible with illumination, which cleaves and inactivates the morpholinooligo.

The technique allows researchers to look at the effects of genes in specific tissues of an organism or during different periods of development. George Eisenhoffer, a postdoc in Jody Rosenblatt's lab at the University of Utah's Huntsman Cancer Institute, and his colleagues used Photo-Morpholinos to knock down the gene for Piezo1[9], which they hypothesized to play a role in the extrusion of live cells from epithelial membranes as cells become overcrowded. When Eisenhoffer used a traditional morpholino for Piezo1, zebrafish embryos died very early in development. But with Photo-Morpholinos, he was able "to bypass those defects early in development," knocking down Piezo1 only after it was not lethal to the animals. Sure enough, inhibiting Piezo1 expression later in development led to cell masses on the zebrafish's sides, indicating their membranes had failed to properly extrude epithelial cells (Nature, 484:546-49, 2012).

The company, located in Philomath, Oregon, has sold about 30 custom-made Photo-Morpholinos since the product was launched this past summer, says Jon Moulton, a

[9] A stretch-activated channel.

researcher at Gene Tools. At $700 for 300 nanomoles—enough to inject more than 1,000 zebrafish, for example—the product is not a blockbuster, but "we never saw this one as a big moneymaker," he says. "It was one that our customers really, really wanted."

4. HubioGEM + the Wiggler


Figure 8 BioWigger

For scientists researching new therapies and conducting toxicity screening, biologically realistic 3-D cell constructs are important. But they're also tricky. Enter HubioGEM, a product jointly developed by Vivo Biosciences (which makes HuBiogel, a human-derived biogel matrix) and GlobalCell Solutions (which makes the GEM magnetic microcarrier).

Unlike animal-derived matrices, the biogel supports cells in an environment that approximates human tissue biology. Meanwhile, the microcarriers—made up of a semi-porous hydrogel filled with magnetic particles—provide magnetic control of cell clusters during collection or media exchange without interfering with analysis or screening. Together in a single mixture, they offer a better way to generate and manage 3-D tumor or stem-cell constructs that accurately mimic in vivo metabolic function.

Throw in the Wiggler—a bioreactor system from Global Cell Solutions designed to grow and maintain more robust cultures than conventional multiwell plate or mixing-flask methods, launched this October—and you have a new platform for predictive bioassays. "We've stacked several advantageous traits into a single solution," says Uday Gupta, CEO of Global Cell Solutions. "The end result is healthier, longer-lasting, more manageable, and physiologically relevant cell cultures."Such qualities have proven "extremely valuable" for Eric Murphy[10]. "We do a lot of our drug combination screens in this format now, and we're seeing a lot of therapeutics you would have skipped over in our traditional screens," he says. "I think it's getting us closer to predicting what will happen in vivo."

[10] A scientist who works on cancer pharmacology at the Genomics Institute of the Novartis Foundation in San Diego, California

5. BioFab

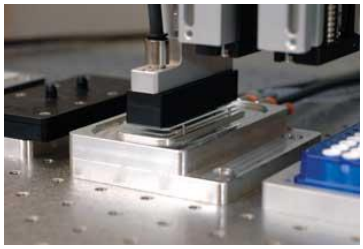

Figure 8 BioFab

Modern pharmaceutical, chemical, and fuel companies increasingly depend on synthetic biology to produce DNA[ii] tailor-made to suit their production needs. Making synthetic genes to program microorganisms used to require a lot of time, in addition to expensive robots and other equipment, but Gen9 has developed BioFab, a new system that can quickly and cheaply produce tens of thousands of double-stranded DNA fragments of between 500 and 1,000 base pairs in length. The company's system for "biological fabrication[11]" couples inexpensively made small DNA fragments with patented or patent-pending chemical processes that accurately assemble them into larger DNA strands, which the platform can do in bulk.

Though pricing varies with the amount of synthetic DNA and the modifications a customer needs, the cost can be less than 10 cents per base pair, which is as little as 1/5 of what some competitors charge, according to Gen9 President and CEO Kevin Munnelly. "The ability to synthesize large numbers of genes in parallel at low cost could transform the field of computational protein design," says molecular engineer David Baker of the University of Washington, who is a customer and a member of the Gen9 advisory board.

The company, which launched this summer, currently has about 20 customers—half from industry, half from academia. Gen9's high-throughput manufacturing process allows the company to reduce both the cost and the production time of synthetic DNA. By 2013, Gen9 hopes to singlehandedly surpass the world's current capacity to manufacture synthetic DNA.

[11] The act or process of fabricating; manufacture.

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[i] **Sir Isaac Newton** was an English physicist and mathematician (described in his own day as a "natural philosopher") who is widely recognized as one of the most influential scientists of all time and as a key figure in the scientific revolution.

[ii] **DNA**) is a molecule that encodes the genetic instructions used in the development and functioning of all known living organisms and many viruses.