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House of Representatives
COMMITTEE ON ENERGY AND COMMERCE
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MEMORANDUM

May 25, 2010

To: Members of the Committee on Energy and Commerce

Fr: Health Subcommittee Staff

Re: Hearing on Synthetic Genomics

On Thursday, May 27, 2010, at 10:00 a.m. in room 2123 of the Rayburn House Office Building, the Committee on Energy and Commerce will hold a hearing titled "Effects of Developments in Synthetic Genomics." Humans have been modifying the genetic characteristics of plants and animals for millennia by breeding plant and animal species to promote certain traits and reduce others. In the last several decades, researchers have been able to work directly with DNA to genetically engineer changes in cells; this research has led to advances such as safe and affordable insulin. In recent years, scientists have developed techniques to synthesize or modify larger segments of DNA more effectively. This hearing will review the current state of such research, explore potential applications in the fields of health and energy, and discuss the relevant ethical and regulatory frameworks.

I. BACKGROUND

What is DNA?

DNA, or deoxyribonucleic acid, makes up the "biological instructions" for the cells of all living organisms. Adults pass copies of their DNA to their offspring during reproduction.[1]

DNA is made up of an "alphabet" of just four molecules or "bases": adenine, thymine, guanine, and cytosine. In cells, DNA consists of two complementary strands, with adenine pairing with thymine, and guanine pairing with cytosine in what are called "base pairs." Cells contain structures that "transcribe and translate" the DNA instructions into proteins, which

[1] National Human Genome Institute, National Institutes of Health, "Deoxyribonucleic Acid (DNA)" (accessed May 24, 2010) (online at http://www.genome.gov/25520880).

perform the activities of the cell. Each section of DNA that directs the cell to produce a protein is known as a "gene." An organism's full set of DNA is called a "genome." [2]

The human genome is significantly more complex than most other species, with over 3 billion base pairs and about 20,000 genes in 23 tightly wrapped DNA structures known as chromosomes, all contained in a nucleus within the cell.[3] For comparison, viruses generally have genomes which are thousands to hundreds of thousands of base pairs, and average bacteria has a genome of approximately 5 million base pairs.

Genetic Engineering

Humans have indirectly altered the genes of organisms for centuries by selecting offspring with desired traits. Modern genetic engineering uses laboratory techniques to directly manipulate one or more genes.

This research commenced in the 1970s, when scientists developed the ability to cut a section of DNA out of a cell and recombine that DNA segment with others in a desired sequence. Eventually, scientists were able to place these new DNA segments into another cell and stimulate that cell to manufacture proteins based on the inserted instructions.

This "recombinant DNA" (rDNA) technology has led to important and fundamental advances in drug development and other areas. In the 1980s, human insulin became the first medicine made with rDNA technology. The "instructions" for human insulin were inserted into *Escherichia coli* cells, and these bacteria in turn produced the human protein. Many more medicines utilizing this technology have now been approved by the FDA.

The technology is also now widely used in U.S. agriculture. Most corn, soybean, canola and cotton crops grown in the U.S. have been modified with rDNA technology to tolerate certain herbicides or to produce an insecticidal protein that kills caterpillars. All these crops have gone through review by the Department of Agriculture, and those that produce the insecticidal protein have also been reviewed by the Environmental Protection Agency. Food from these crops has also gone through an FDA evaluation.[4]

II. SYNTHETIC BIOLOGY

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[2] *See* http://www.genome.gov/glossary/index.cfm?id=173. This useful glossary of terms can provide further details on much of the terminology. The Genetics Home Reference, maintained by the National Institutes of Health's National Library of Medicine, contains another useful glossary, at http://ghr.nlm.nih.gov.

[3] By way of contrast, *Mycoplasma mycoides*, the cell that was the focus of the May 20 Science paper, contains about 1.1 million bases and roughly 1000 genes in a single circular chromosome, and has no nucleus (online at cmr.jcvi.org/cgi-bin/CMR/GenomePage.cgi?org=ntmm02).

[4] *See* http://usbiotechreg.nbii.gov/; Food and Drug Administration, "Plant Biotechnology for Food and Feed," (accessed May 25, 2010) (available at http://www.fda.gov/Food/Biotechnology/default.htm.)

While the term "synthetic biology" has been used in various ways, it is generally understood to describe techniques to construct or adapt existing DNA, cells, or other biological structures.[5] "Synthetic genomics" describes the subset of this research that focuses on genes and DNA.

Science has had the ability to manipulate and engineer DNA for decades, with the recombinant DNA research described above as a major example. Until the past decade, the work was often painstakingly slow, and able to address only relatively straightforward challenges such as using one gene to produce one protein. More novel or complex compounds would be extraordinarily difficult or impossible to engineer using traditional rDNA techniques.

However, in recent years, new strategies combining engineering and biological techniques have enhanced researchers' abilities to work with genetic, cellular or even tissue-level biology. These new synthetic techniques allow for genes and long chains of DNA to be designed and manufactured from scratch using a computer and relevant chemical compounds, rather than manipulating pieces of existing genes from living cells.

The *Science* paper[6] that the J. Craig Venter Institute[7] published on May 20, 2010, describes the results of one such technological leap. [For comments on the significance of the paper, see http://www.nature.com/nature/journal/vaop/ncurrent/pdf/465422a.pdf.] As Dr. Venter will testify at the hearing, scientists have been manufacturing DNA segments for some time, but the sheer size of even the smallest chromosome has made synthesis of a full genome impossible to date. The team at the Institute successfully tackled two challenges: they (1) synthesized the full 1.1 million base pair genome of the bacteria *Mycoplasma mycoides;* and (2) inserted this genome into a recipient cell of a different type of bacteria. This recipient cell then replicated into new cells, which followed the instructions of the synthesized *Mycoplasma mycoides* genome. The team has discussed applications ranging from vaccines to energy production.

Synthetic biologist Dr. Jay Keasling[8] -- who is also scheduled to testify at Thursday's hearing -- is developing new methods to produce artemisinin, among other products. Artemisinin is a critical anti-malarial drug that is currently derived from the sweet wormwood

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[5] The Synthetic Biology Project, Woodrow Wilson International Center for Scholars, "Synthetic Biology 101" (accessed May 24, 2010) (online at http://www.synbioproject.org/topics/synbio101). A number of current definitions for synthetic biology are referenced here.

[6] Gibson, D. G., et al., "Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome," *Science express* (May 20, 2010) (online at http://www.sciencemag.org/cgi/rapidpdf/science.1190719v1.pdf)

[7] *See* http://www.jcvi.org/.

[8] Keasling Lab Website (online at keaslinglab.lbl.gov/wiki/index.php/Main_Page).

plant.[9] While relatively inexpensive by Western standards, this drug is still too expensive for the people in developing countries who need it most. Expanding on standard recombinant DNA techniques, in which only one of a few genes are introduced into an organism at a time, Dr. Keasling inserted multiple genes into yeast cells, and created yeast that can produce synthetic artemisinin. His work has been funded by the Gates Foundation, and he is in a partnership to manufacture the drug at an industrial scale to make it broadly available in the developing world, with the goal of reducing the cost of this key anti-malarial drug by an order of magnitude. Dr. Keasling is also using this technology to develop biofuel energy production.

Other researchers have focused on developing the foundations of synthetic biology. Among them is Dr. Drew Endy,[10] who founded the BioBricks Foundation, an initiative to develop and catalogue a set of standardized DNA tools that can effectively direct the cellular machinery. BioBrick parts are designed to be used interchangeably to produce the same result in different types of cells. For example, some of these BioBrick parts may turn a gene on or off, while other BioBrick parts will allow researchers to measure concentration of a gene product.[11] Dr. Endy will be testifying on Thursday as well.

The National Institutes of Health have extensive experience in research performed using rDNA and synthetic biology. Dr. Anthony Fauci,[12] Director of the National Institute of Allergy and Infectious Diseases, will discuss the role of NIH in this area.

III. POTENTIAL APPLICATIONS

Synthetic biology holds promise for a wide range of applications for health, energy and the environment. Microbes are already being engineered to produce useful medicines such as artemisinin and the same techniques can be applied to more easily produce other drugs. Other possible applications include biological sensors to detect infections, fine tuning existing drugs, and techniques to improve tissue reconstruction.

The same techniques can also be used to help reduce greenhouse gas emissions and our reliance on imported oil. For example, researchers are developing synthetic enzymes that can break down plant waste and convert it into biofuels more efficiently than their conventional counterparts. Others are pursuing microbes that can remove carbon dioxide from the air and excrete hydrocarbons which could be refined into gasoline that is nearly carbon-neutral. Microbes are also being developed to synthesize compounds for use in photovoltaic solar cells.

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[9] The Synthetic Biology Project, Woodrow Wilson International Center for Scholars, "Ethical Issues in Synthetic Biology: An overview of the debates" (accessed May 24, 2010) (online at www.synbioproject.org/process/assets/files/6334/synbio3.pdf).

[10] *See* http://openwetware.org/wiki/Endy_Lab

[11] The Synthetic Biology Project, Woodrow Wilson International Center for Scholars, "Ethical Issues in Synthetic Biology: An overview of the debates" (accessed May 24, 2010) (online at http://www.synbioproject.org/process/assets/files/6334/synbio3.pdf).

[12] *See* http://www.niaid.nih.gov/about/directors/biography/pages/biography.aspx

Potential environmental applications include custom-designed microbes that can detect soil or water contamination, break down pollution such as oil spills, or produce enzymes that allow more efficient and less polluting industrial processes.

Synthetic biology may allow for faster or easier production of enzymes and other cells than could be achieved using conventional technologies. Commercial deployment of some of these technologies may be years or decades into the future while other areas, like drug development and fuels, are areas of active commercialization today.[13]

IV. ETHICAL AND REGULATORY ISSUES

Virtually any new developments in biology raise moral or ethical issues, as well as public health and safety issues. Synthetic biology raises many of the same or similar issues as raised with recombinant DNA technology and nanotechnology. Academicians, researchers and the federal government are evaluating these issues and the extent to which existing regulatory frameworks address them or need modifications.[14] The testimony of Dr. Gregory Kaebnick, a bioethicist at The Hastings Center, will focus on the moral or ethical issues raised by synthetic biology.

With the advent of recombinant DNA technology in the early 1970s, scientists working in the field became concerned that researchers might unknowingly develop organisms that posed human health or other risks. They convened a meeting in Asilomar, California in 1975, which concluded with recommendations for the development of safety guidelines and a process for reviewing the safety of rDNA experiments.[15] This led to the establishment of the Recombinant DNA Advisory Committee (RAC) at the National Institutes of Health (NIH) to oversee the safety of rDNA research, including the establishment of containment standards for research with various kinds of microorganisms.

As the technology advanced out of the laboratory, the White House Office of Science and Technology Policy (OSTP) published in the Federal Register a proposed Coordinated

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[13] Royal Academy of Engineering, Synthetic Biology, (May 2009) (online at www.raeng.org.uk/news/publications/list/reports/Synthetic_biology.pdf); Rodemeyer, M., "New Life, Old Bottles: Regulating First-Generation Products of Synthetic Biology," report for The Synthetic Biology Project, Woodrow Wilson International Center for Scholars, (accessed May 24, 2010) (online at http://www.synbioproject.org/library/publications/archive/synbio2/).

[14] Rodemeyer, M., "New Life, Old Bottles: Regulating First-Generation Products of Synthetic Biology," report for The Synthetic Biology Project, Woodrow Wilson International Center for Scholars, (accessed May 24, 2010) (online at http://www.synbioproject.org/library/publications/archive/synbio2/); Garfinkel, M. S. et al. "Synthetic Genomics: Options for Governance" (October 2007) (accessed may 24, 2010) (online at http://www.jcvi.org/cms/fileadmin/site/research/projects/synthetic-genomics-report/synthetic-genomics-report.pdf).

[15] Berg, P. et al., "Asilomar Conference on Recombinant DNA Molecules. *Science* 188, 991-994.

Framework for Regulation of Biotechnology in 1984, with a final version released in 1986.[16] In essence, it concluded that there was no scientific basis to create a new regulatory oversight regime for biotechnology. Rather, it found that the existing federal regulatory framework should apply to products developed using biotechnology. Thus, for example, pesticides would continue to be regulated by the Environmental Protection Agency (EPA) under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA), and foods and drugs would continue to be regulated by the Food and Drug Administration (FDA) under the FFDCA, irrespective of whether such products were made using biotechnology or other processes. The policy statement also included sections by the relevant regulatory agencies describing their regulatory policies and procedures for the biotechnology products that fell within their purview. For example, EPA noted that under its Toxic Substances Control Act authority, it would review the safety of "intergeneric" rDNA microbes (microbes with genetic material from more than one species) before allowing their release into the environment.

Developments in synthetic biology have spurred some actions by the federal government, including those listed here. The President asked the Presidential Commission for the Study of Bioethical Issues to conduct a study of the potential medical, environmental, security and other benefits of this field of research, as well as any potential health, security or other risks.[17] NIH has recently proposed an update of its rDNA guidelines to clarify that they apply to synthetic DNA as well as recombinant DNA.[18] The Department of Health and Human Services has published recommendations for a screening framework to be used by producers of synthetic DNA products to prevent inappropriate development of select agents.[19]

V. WITNESSES

The following witnesses have been invited to testify:

J. Craig Venter, Ph.D.
Founder, Chairman, and President
J. Craig Venter Institute

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[16] 51 FR 23302; June 26, 1986.

[17] Letter to Dr. Amy Guttman, President and Christopher H. Browne Distinguished Professor of Political Science, University of Pennsylvania, from President Barack Obama (May 20, 2010) (accessed May 25, 2010) (accessible at http://news.sciencemag.org/scienceinsider/assets/2010/05/20/Gutmann.pdf).

[18] Department of Health and Human Services, National Institutes of Health, Office of Biotechnology Activities, "Recombinant DNS Research Under the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)," 74 FR 9411 (March 4, 2009) (accessible at http://oba.od.nih.gov/oba/rac/ProposeRevisionsNIHGuidelines-March-4-2009.pdf).

[19] Department of Health and Human Services, "Screening Framework Guidance for Synthetic Double-Stranded DNA Providers," 74 FR 62,319 (Nov. 27, 2009) (accessible at http://www.gpo.gov/fdsys/pkg/FR-2009-11-27/pdf/E9-28328.pdf).

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