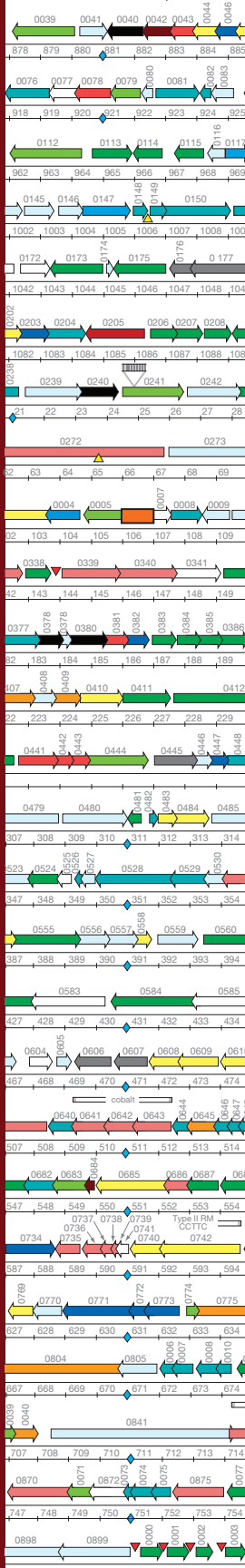
NEW DIRECTIONS

The Ethics of Synthetic Biology and Emerging Technologies



Presidential Commission for the Study of Bioethical Issues

December 2010

NEW DIRECTIONS

The Ethics of Synthetic Biology and Emerging Technologies

Presidential Commission
for the Study of Bioethical Issues

Washington, D.C.
December 2010

www.bioethics.gov

ABOUT THE PRESIDENTIAL COMMISSION FOR THE STUDY OF BIOETHICAL ISSUES

The Presidential Commission for the Study of Bioethical Issues (PCSBI) is an advisory panel of the nation's leaders in medicine, science, ethics, religion, law, and engineering. PCSBI advises the President on bioethical issues arising from advances in biomedicine and related areas of science and technology. The Commission seeks to identify and promote policies and practices that ensure scientific research, health care delivery, and technological innovation are conducted in a socially and ethically responsible manner.

For more information about PCSBI, please see www.bioethics.gov.

On the front cover: Portion of the genome map of *M. mycoides* JCVI-syn1.0. From Gibson, D.G., et al. (2010). Creation of a bacterial cell controlled by a chemically synthesized genome. *Science* 329(5987):52-56.

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PRESIDENTIAL COMMISSION FOR THE STUDY OF BIOETHICAL ISSUES

President Barack Obama
The White House
1600 Pennsylvania Avenue, NW
Washington, DC 20500

Dear Mr. President:

We are pleased to present to you this report, *New Directions: The Ethics of Synthetic Biology and Emerging Technologies*. In response to your request of May 20, 2010, this first report of the Presidential Commission for the Study of Bioethical Issues (PCSBI) examines the implications of the emerging science of synthetic biology, including the announcement in May of the successful creation of a self-replicating bacterial cell with a completely synthetically-replicated genome. It offers recommendations to ensure that America reaps the benefits of this developing field within appropriate ethical boundaries.

PCSBI approached this task through inclusive and deliberative engagement with ethicists, scientists, engineers, and individuals in faith, business, and non-profit communities. We held three public meetings, both in and outside of Washington, D.C., created an open forum for dialogue, and heard many diverse voices.

The Commission found that synthetic biology offers extraordinary promise to create new products for clean energy, pollution control, and medicine, to revolutionize chemical production and manufacturing, and to create new economic opportunities. With this promise comes a duty to attend carefully to potential risks, be responsible stewards, and consider thoughtfully the implications for humans, other species, nature, and the environment.

PCSBI concluded that synthetic biology is capable of significant but limited achievements posing limited risks. Future developments may raise further objections, but the Commission found no reason to endorse additional federal regulations or a moratorium on work in this field at this time. Instead, the Commission urges monitoring and dialogue between the private and public sectors to achieve open communication and cooperation.

The Commission recommends that the government, through a coordinated process or body within the Executive Office of the President, lead an ongoing review of developments, risks, opportunities, and oversight as this field grows. This review should be in consultation with relevant scientific, academic, international, and public communities, and whenever possible its results should be made public. We also recommend that reasonable risk assessment should precede any field release of synthetic organisms. We suggest support for public engagement, education, and dialogue to ensure public trust and avoid unnecessary limitations on science and social progress.

You gave the Commission a rare and exceptional opportunity to be proactive and forward looking in this first study. The Commission is grateful for the opportunity to serve you and the nation in this way. We would be happy to brief you if you have any questions about our recommendations.

Sincerely,

Amy Gutmann, Ph.D.
Chair

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THE WHITE HOUSE

WASHINGTON

May 20, 2010

Dr. Amy Gutmann
President and Christopher H. Browne
Distinguished Professor of Political Science
University of Pennsylvania
1 College Hall, Room 100
Philadelphia, Pennsylvania 19104-6380

Dear Dr. Gutmann,

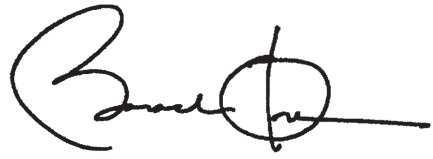
As you know, scientists have announced a milestone in the emerging field of cellular and genetic research known as synthetic biology. While scientists have used DNA to develop genetically modified cells for many years, for the first time, all of the natural genetic material in a bacterial cell has been replaced with a synthetic set of genes. This development raises the prospect of important benefits, such as the ability to accelerate vaccine development. At the same time, it raises genuine concerns, and so we must consider carefully the implications of this research.

I therefore request that the Presidential Commission for the Study of Bioethical Issues undertake, as its first order of business, a study of the implications of this scientific milestone, as well as other advances that may lie ahead in this field of research. In its study, the Commission should consider the potential medical, environmental, security, and other benefits of this field of research, as well as any potential health, security or other risks. Further, the Commission should develop recommendations about any actions the Federal government should take to ensure that America reaps the benefits of this developing field of science while identifying appropriate ethical boundaries and minimizing identified risks. My Science and Technology Advisor, Dr. John P. Holdren, will be in communication with you about the scope and progress of your study.

I ask that the Commission complete its study within six months and provide me with a report with its findings, as well as any recommendations and suggestions for future study that the Commission deems appropriate. Given the importance of this issue, I request that the Commission consult with a range of constituencies, including scientific and medical communities, faith communities, and business and non-profit organizations.

It is vital that we as a society consider, in a thoughtful manner, the significance of this kind of scientific development. With the Commission's collective expertise in the areas of science, policy, and ethical and religious values, I am confident that it will carry out this responsibility with the care and attention it deserves.

Sincerely,



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ACKNOWLEDGEMENTS

The Commission thanks the many scientists and scholars who shared their time, expertise, and insight with the Commission as it completed this work. These include the individuals who participated in its public meetings, listed in the Appendix, and those who contributed their thoughts directly to Commission members and staff.

The Commission is grateful to the members of the public who discussed their views during the public meetings and contributed written comments. The Commission's gratitude extends as well to the agency officials who provided assistance, often on short notice and under tight deadlines. Special thanks go to Alta Charo, Jacqueline Corrigan-Curay, Jason Dietz, Daniel Drell, Michael Firko, Bob Hargrove, Freeda Isaac, Theresa Lawrence, Sally McCammon, Larisa Rudenko, Greg Schweer, Allan Shipp, Deborah Smegal, Jessica Tucker, and Rob Weyandt.

Lastly, the Commission is enormously indebted to its talented staff for their expert work and unwavering commitment throughout this study. Valerie H. Bonham ably led the staff and guided this report to its timely completion. The Commission thanks its other staff members and consultants—Andy Burness, Judith E. Crawford, Alison Faith Davis, John Donnelly, Debbie Forrest, Kathi E. Hanna, Chris Havasy, Holly Fernandez Lynch, David G. Miller, Anne Pierson, Jason L. Schwartz, Kayte Spector-Bagdady, and Esther Yoo—for their many important contributions. The Commission also thanks Diane M. Gianelli for serving as Acting Executive Director and ably guiding the Commission during its formative period.

EXECUTIVE SUMMARY

The 21st century is widely heralded as the century of biology. Building on the fundamental understanding achieved in the second half of the last century, revolutionary advances are expected to improve many aspects of our lives, from clean energy and targeted, safer medicines to new industries. Prominent among emerging technologies is "synthetic biology," which aims to apply standardized engineering techniques to biology and thereby create organisms or biological systems with novel or specialized functions to address countless needs.

The idea of managing or manipulating biology to identify or develop specific characteristics is not new. Scientists have used DNA to create genetically engineered cells and organisms for many years; the entire biotechnology industry has grown around our expanding abilities in this area. The shelves of grocery stores across the United States are stocked with genetically engineered foods. Medical testing for genetically linked diseases is widely used by people across society.

By contrast, the idea of assembling living organisms wholesale from nonliving parts has intrigued human imagination for centuries with no success outside of fiction. For some, that possibility came one step closer last May with the announcement that scientists at the J. Craig Venter Institute had created the world's first self-replicating synthetic (human-made from chemical parts) genome in a bacterial cell of a different species. Intense media coverage followed, and the announcement ricocheted across the globe within hours as proponents and critics made striking claims about potential risks and benefits of this discovery and whether it amounted to an early-stage example of "creating life."

In response, President Barack Obama asked the Presidential Commission for the Study of Bioethical Issues (the Commission) to review the developing field of synthetic biology and identify appropriate ethical boundaries to maximize public benefits and minimize risks. The Commission approached this task through inclusive and deliberative engagement with a wide variety of sources, including scientists, engineers, faith-based and secular ethicists, and others who voiced, as expected, sometimes conflicting views on the science, ethics, and social issues surrounding synthetic biology. Through public meetings

in Washington, D.C., Philadelphia, and Atlanta, the Commission created a forum for open dialogue to hear and assess competing claims about the science, ethics, and public policy relating to synthetic biology.

What the Commission found is that the Venter Institute's research and synthetic biology are in the early stages of a new direction in a long continuum of research in biology and genetics. The announcement last May, although extraordinary in many ways, does not amount to creating life as either a scientific or a moral matter. The scientific evidence before the Commission showed that the research relied on an existing natural host. The technical feat of synthesizing a genome from its chemical parts so that it becomes self-replicating when inserted into a bacterial cell of another species, while a significant accomplishment, does not represent the creation of life from inorganic chemicals alone. It is an indisputable fact that the human-made genome was inserted into an already living cell. The genome that was synthesized was also a variant of the genome of an already existing species. The feat therefore does not constitute the creation of life, the likelihood of which still remains remote for the foreseeable future. What remains realistic is the expectation that over time research in synthetic biology may lead to new products for clean energy, pollution control, and more affordable agricultural products, vaccines, and other medicines. The Commission therefore focused on the measures needed to assure the public that these efforts proceed with appropriate attention to social, environmental, and ethical risks.

President Obama gave the Commission a rare and exceptional opportunity in the world of presidential bioethics commissions to be forward looking instead of reactive. We are ahead of the emerging science, and this unique opportunity underscores the need for the government to act now to ensure a regular, ongoing process of review as the science develops. The Commission calls on the government to make its efforts transparent, to monitor risks, to support (through a peer-review process) the most publicly beneficial research, and to educate and engage with the public as this field progresses. The government must regularly review risk assessment and other issues as the science of synthetic biology progresses. Only through openness and active engagement with all the relevant communities will the government ensure ongoing public support and appropriate oversight. The Commission emphasizes the need to

engage the public over time through improved science education, a publicly accessible fact-checking mechanism for prominent advances in biotechnology, and other efforts promoting clearer communication on the state of science.

Basic Ethical Principles for Assessing Emerging Technologies

To reach its recommendations, the Commission identified five ethical principles relevant to considering the social implications of emerging technologies: (1) public beneficence, (2) responsible stewardship, (3) intellectual freedom and responsibility, (4) democratic deliberation, and (5) justice and fairness. The principles are intended to illuminate and guide public policy choices to ensure that new technologies, including synthetic biology, can be developed in an ethically responsible manner.

The ideal of *public beneficence* is to act to maximize public benefits and minimize public harm. This principle encompasses the duty of a society and its government to promote individual activities and institutional practices, including scientific and biomedical research, that have great potential to improve the public's well-being. Public beneficence requires that when seeking the benefits of synthetic biology, the public and its representatives be vigilant about risks and harms, standing ready to revise policies that pursue potential benefits with insufficient caution.

The principle of *responsible stewardship* reflects a shared obligation among members of the domestic and global communities to act in ways that demonstrate concern for those who are not in a position to represent themselves (e.g., children and future generations) and for the environment in which future generations will flourish or suffer. Responsible stewardship recognizes the importance of citizens and their representatives thinking and acting collectively for the betterment of all. Importantly, it calls for *prudent vigilance*, establishing processes for assessing likely benefits along with assessing safety and security risks both before and after projects are undertaken. A responsible process will continue to assess safety and security as technologies develop and diffuse into public and private sectors. It will also include mechanisms for limiting their use when necessary.

Democracies depend on *intellectual freedom* coupled with the *responsibility* of individuals and institutions to use their creative potential in morally accountable ways. Sustained and dedicated creative intellectual exploration begets much of our scientific and technological progress. While many emerging technologies raise "dual use" concerns—when new technologies intended for good may be used to cause harm—these risks alone are generally insufficient to justify limits on intellectual freedom. As a corollary to the principle of intellectual freedom and responsibility, the Commission endorses a principle of *regulatory parsimony*, recommending only as much oversight as is truly necessary to ensure justice, fairness, security, and safety while pursuing the public good. This is particularly important in emerging technologies, which by their very definition are still in formation and are not well suited for sharply specified limitations. While clear guidelines to protect biosecurity and biosafety are imperative, undue restriction may not only inhibit the distribution of new benefits, but it also may be counterproductive to security and safety by preventing researchers from developing effective safeguards.

The principle of *democratic deliberation* reflects an approach to collaborative decision making that embraces respectful debate of opposing views and active participation by citizens. It calls for individuals and their representatives to work toward agreement whenever possible and to maintain mutual respect when it is not. Public discussion and debate with open interchange among all stakeholders can promote the perceived legitimacy of outcomes, even if those outcomes are unlikely to satisfy all interested parties. An inclusive process of deliberation, informed by relevant facts and sensitive to ethical concerns, promotes an atmosphere for debate and decision making that looks for common ground wherever possible and seeks to cultivate mutual respect where irreconcilable differences remain. It encourages participants to adopt a societal perspective over individual interests.

The principle of *justice and fairness* relates to the distribution of benefits and burdens across society. Biotechnology and emerging technologies such as synthetic biology, for good or ill, affect all persons. Emerging technologies like synthetic biology will have global impacts. For this reason, every nation has a responsibility to champion fair and just systems to promote wide availability of information and fairly distribute the burdens and benefits of new technologies.

Recommendations

With these guiding principles in mind, the Commission considered the array of public policy issues surrounding the emerging science of synthetic biology and makes the following recommendations. The reasons behind each recommendation are provided in the body of the report, and all readers are urged to consider carefully this more comprehensive account. In the cases of recommendations 1, 3, 5, 9, 11, 12, and 17, the Commission recommends ongoing review by the government, in consultation with the relevant scientific, academic, international, and public communities, with initial action completed within 18 months and made public. Some of these actions could easily be completed sooner, and the government is encouraged to do so and make its progress public.

Promoting Public Beneficence

Under the principle of public beneficence, the Commission recommends that the government review and make public findings regarding the scope of its research funding, especially for risk assessment and ethical and social issues raised by synthetic biology. This will promote public engagement and ensure needed transparency regarding federal efforts in the field of synthetic biology.

Recommendation 1: Public Funding Review and Disclosure

Through a central body such as the Executive Office of the President, the federal government should undertake a coordinated evaluation of current public funding for synthetic biology activities, including funding for research on techniques for risk assessment and risk reduction, and for the study of ethical and social issues raised by synthetic biology. This review should be completed within 18 months and the results made public.

Most potential products of synthetic biology are in very early stages of development. Therefore, basic research is critical to further expansion of this science and its effective translation into useful products. Necessary funding decisions should be made with the goal of advancing the public good, whether these decisions support synthetic biology research or other fields. The Commission

does not offer an opinion on the relative merits of particular research directions, but recommends that such decisions receive ongoing evaluation as to the state of the science and its potential applications.

Recommendation 2: Support for Promising Research

Advancing the public good should be the primary determinant of relative public investment in synthetic biology versus other scientific activities. The National Institutes of Health, the Department of Energy, and other federal agencies should continue to evaluate research proposals through peer-review mechanisms and other deliberative processes created to ensure that the most promising scientific research is conducted on behalf of the public.

Information sharing is a critical mechanism for promoting scientific progress and innovation. The principle of public beneficence requires researchers, inventors, patent holders, and others to work together to develop creative strategies to maximize opportunities for innovation. The government should consider best practices and other policy guidance, if needed, to ensure that access to basic research results and tasks is not unduly limited.

Recommendation 3: Innovation Through Sharing

Synthetic biology is at a very early stage of development, and innovation should be encouraged. The Executive Office of the President, as part of the coordinated approach urged in Recommendation 4, should lead an effort to determine whether current research licensing and sharing practices are sufficient to ensure that basic research results involving synthetic biology are available to promote innovation, and, if not, whether additional policies or best practices are needed. This review should be undertaken with input from the National Institutes of Health, other agencies funding synthetic biology research, such as the Department of Energy and the National Aeronautics and Space Administration, the U.S. Patent and Trademark Office, industry, academia, and public civil society groups. The review should be completed within 18 months and the results made public.

Promoting Responsible Stewardship

The Commission endorses neither a moratorium on synthetic biology until all risks are identified and mitigated, nor unfettered freedom for scientific exploration. Instead, the Commission believes that the field of synthetic biology can proceed responsibly by embracing a middle ground—an ongoing process of prudent vigilance that carefully monitors, identifies, and mitigates potential and realized harms over time. Responsible stewardship requires clarity, coordination, and accountability across the government. While new agencies, offices, or authorities are not necessary at this time, the Executive Office of the President should lead an interagency process to identify and clarify, if needed, existing oversight authorities and ensure that the government is informed on an ongoing basis about developments, risks, and opportunities as this field grows. This process must be undertaken by an office with sufficient authority to bring together all parts of the government with a stake in synthetic biology and be sufficiently authoritative to effectively engage or oversee engagement with foreign governments.

Recommendation 4: Coordinated Approach to Synthetic Biology

The Commission sees no need at this time to create additional agencies or oversight bodies focused specifically on synthetic biology. Rather, the Commission urges the Executive Office of the President, in consultation with relevant federal agencies, to develop a clear, defined, and coordinated approach to synthetic biology research and development across the government. A mechanism or body should be identified to: (1) leverage existing resources by providing ongoing and coordinated review of developments in synthetic biology, (2) ensure that regulatory requirements are consistent and non-contradictory, and (3) periodically and on a timely basis inform the public of its findings. Additional activities for this coordinating body or process are described in other recommendations.

Because synthetic biology poses some unusual potential risks, as "amateur" or "do-it-yourself" (DIY) scientists and others outside of traditional research environments explore the field, these risks must be identified and anticipated, as they are for other emerging technologies, with systems and policies to assess and respond to them while supporting work toward potential benefits.

Recommendation 5: Risk Assessment Review and Field Release Gap Analysis

Because of the difficulty of risk analysis in the face of uncertainty—particularly for low-probability, potentially high-impact events in an emerging field—ongoing assessments will be needed as the field progresses. Regulatory processes should be evaluated and updated, as needed, to ensure that regulators have adequate information. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President should convene an interagency process to discuss risk assessment activities, including reasons for differences and strategies for greater harmonization across the government. It should also identify any gaps in current risk assessment practices related to field release of synthetic organisms. These reviews should be completed within 18 months and the results made public.

Coordination and careful risk analysis are essential steps for responsible stewardship, but they are not sufficient. There are several additional approaches, which are known today and continue to evolve as our abilities in this field grow, to limit uncertain risks in synthetic biology. Technology can be harnessed to build in safeguards. A number of safety features can be incorporated into synthetic organisms to control their spread and life span. Surveillance or containment of synthetic organisms is a concrete way to embrace responsible stewardship.

Recommendation 6: Monitoring, Containment, and Control

At this early stage of development, the potential for harm through the inadvertent environmental release of organisms or other bioactive materials produced by synthetic biology requires safeguards and monitoring. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President should direct an ongoing review of the ability of synthetic organisms to multiply in the natural environment and identify, as needed, reliable containment and control mechanisms. For example, "suicide genes" or other types of self-destruction triggers could be considered in order to place a limit on their life spans. Alternatively, engineered organisms could be made to depend on nutritional components absent outside the laboratory, such as novel amino acids, and thereby controlled in the event of release.

The timing of deliberate release of synthesized organisms into the environment and the need to analyze risks prior to release raises special concern. We must proceed carefully, particularly when the probability or magnitude of risks are high or highly uncertain, because biological organisms may evolve or change after release. For any field release, there must be adequate consideration of risk.

Recommendation 7: Risk Assessment Prior to Field Release

Reasonable risk assessment should be carried out, under the National Environmental Policy Act or other applicable law, prior to field release of research organisms or commercial products involving synthetic biology technology. This assessment should include, as appropriate, plans for staging introduction or release from contained laboratory settings. Exceptions in limited cases could be considered, for example, in emergency circumstances or following a finding of substantial equivalence to approved products. The gap analysis described in Recommendation 5 should determine whether field release without any risk assessment is permissible and, if so, when.

Synthetic biology is an international enterprise. Oversight and regulatory mechanisms should adopt an analogous approach, so that the United States is involved in regular discussions with other national and transnational organizations so they may seek coordination and consistency when possible.

Recommendation 8: International Coordination and Dialogue

Recognizing that international coordination is essential for safety and security, the government should act to ensure ongoing dialogue about emerging technologies such as synthetic biology. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President, through the Department of State and other relevant agencies such as the Department of Health and Human Services and the Department of Homeland Security, should continue and expand efforts to collaborate with international governments, the World Health Organization, and other appropriate parties, including international bioethics organizations, to promote ongoing dialogue about emerging technologies such as synthetic biology as the field progresses.

Responsible conduct of synthetic biology research, like all areas of biological research, rests heavily on the behavior of individual scientists. Creating a culture of responsibility in the synthetic biology community could do more to promote responsible stewardship in synthetic biology than any other single strategy. There are actors in the world of synthetic biology, namely engineers, chemists, materials scientists, computer modelers, and others, who practice outside of conventional biological or medical research settings. These groups may not be familiar with the standards for ethics and responsible stewardship that are commonplace for those working in biomedical research. This poses a new challenge regarding the need to educate and inform synthetic biologists in all communities about their responsibilities and obligations, particularly with regard to biosafety and biosecurity.

Recommendation 9: Ethics Education

Because synthetic biology and related research cross traditional disciplinary boundaries, ethics education similar or superior to the training required today in the medical and clinical research communities should be developed and required for all researchers and student-investigators outside the medical setting, including in engineering and materials science. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President, in consultation with the National Academy of Sciences, the National Academy of Engineering, the scientific community, and the public, should convene a panel to consider appropriate and meaningful training requirements and models. This review should be completed within 18 months and the results made public.

Additionally flowing from the principle of responsible stewardship, the Commission observed that careful and deliberate attention should be paid to discussions of potential moral objections as the field advances. Such moral objections include concerns that synthetic biology may conflict with essential conceptions of human agency and life; that its overall impact may be harmful to biodiversity, ecosystems, or food and energy supplies; and that it may fail to respect the proper relationship between humans and nature. The Commission devoted particular time and attention to discussing these possible moral objections during its deliberations. It heard relatively few objections from reli-

gious or secular ethicists concerning the present status of the field. Although the field currently is capable of significant but limited technical achievements, potential developments might raise further moral objections—for example, applications relying on the synthesis of genomes for higher order or complex species. Current objections to synthetic biology on moral grounds are often based on concerns regarding activities that the field is currently incapable of carrying out. However, continued evaluation and efforts to reach and maintain consensus will be needed as this field develops.

Recommendation 10: Ongoing Evaluation of Objections

Discussions of moral objections to synthetic biology should be revisited periodically as research in the field advances in novel directions. Reassessment of concerns regarding the implications of synthetic biology for humans, other species, nature, and the environment should track the ongoing development of the field. An iterative, deliberative process, as described in Recommendation 14, allows for the careful consideration of moral objections to synthetic biology, particularly if fundamental changes occur in the capabilities of this science and its applications.

Promoting Intellectual Freedom and Responsibility

The principle of intellectual freedom and responsibility asserts that restrictions on research, whether by self-regulation by scientists or by government intervention, should limit the free pursuit of knowledge only when the perceived risk is too great to proceed without limit. A moratorium at this time on synthetic biology research would inappropriately limit intellectual freedom. Instead, the scientific community—in academia, government and the private sector—should continue to work together to evaluate and respond to known and potential risks of synthetic biology as this science evolves. This effort may require the government to expand current oversight or engagement activities with non-institutional researchers. National Institutes of Health or the Department of Energy, for example, could be charged to sponsor education programs and workshops that bring together these groups. They could fund training grants or related programs to promote a culture of responsibility among this community. To exercise the appropriate level of oversight, the government will need to monitor the growth and capacity of researchers outside of institutional settings.

Recommendation 11: Fostering Responsibility and Accountability

The government should support a continued culture of individual and corporate responsibility and self-regulation by the research community, including institutional monitoring, enhanced watchfulness, and application of the *National Institutes of Health Guidelines for Recombinant DNA Research*. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President should evaluate, and re-evaluate periodically, the effectiveness of current research oversight mechanisms and determine what, if any, additional steps should be taken to foster accountability at the institutional level without unduly limiting intellectual freedom. Academic and private institutions, the public, the National Institutes of Health, and other federal funders of synthetic biology research should be engaged in this process. An initial assessment should be completed within 18 months and the results made public.

The norms of safe and responsible conduct that have evolved over time for many researchers in institutional settings may not be understood or followed by those new to the field or outside of these settings. It is important to note that presently there appears to be no serious risk of completely novel organisms being constructed in non-institutional settings including in the DIY community. Scrutiny is required to ensure that DIY scientists have an adequate understanding of necessary constraints to protect public safety and security, but at present the Commission sees no need to impose unique limits on this group.

Recommendation 12: Periodic Assessment of Security and Safety Risks

Risks to security and safety can vary depending on the setting in which research occurs. Activities in institutional settings, may, though certainly do not always, pose lower risks than those in non-institutional settings. At this time, the risks posed by synthetic biology activities in both settings appear to be appropriately managed. As the field progresses, however, the government should continue to assess specific security and safety risks of synthetic biology research activities in both institutional and non-institutional settings including, but not limited to, the "do-it-yourself" community. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President, working with the Department of Homeland Security, the

Federal Bureau of Investigation and others, should undertake and periodically update this assessment. An initial review should be completed within 18 months and the results made public to the extent permitted by law.

Certain risks—generally involving national security—often warrant additional protections. Completely free exchange of data and materials might endanger public safety, but unilateral action to limit exchange could damage American research efforts in synthetic biology if U.S. scientists and students are excluded from full collaboration with the international community. Several recent advisory groups have recommended ongoing discussions among research universities, industry, and government on this topic. The Commission agrees that scientists should be actively engaged in these debates.

Recommendation 13: Oversight Controls

If the reviews called for in Recommendation 12 identify significant unmanaged security or safety concerns, the government should consider making compliance with certain oversight or reporting measures mandatory for all researchers, including those in both institutional and non-institutional settings, regardless of funding sources. It may also consider revising the Department of Commerce's export controls. Any such change should be undertaken only after consultation with the scientific, academic, and research communities and relevant science and regulatory agencies such as the National Institutes of Health, the Department of Homeland Security, and the Environmental Protection Agency. Export controls should not unduly restrain the free exchange of information and materials among members of the international scientific community.

Promoting Democratic Deliberation

Through democratic deliberation, questions about synthetic biology can be explored and evaluated on an ongoing basis in a manner that welcomes the respectful exchange of opposing views. This principle yields several opportunities for government and non-government actors alike to work together to ensure that synthetic biology advances in ways that respect divergent views and that avoid some of the misunderstanding and confusion, which at times,

have hampered other scientific endeavors. To enhance democratic deliberation and thereby ensure that the progress in synthetic biology is widely understood and policy choices are thoughtfully considered, the Commission makes the following recommendations.

Recommendation 14: Scientific, Religious, and Civic Engagement

Scientists, policy makers, and religious, secular, and civil society groups are encouraged to maintain an ongoing exchange regarding their views on synthetic biology and related emerging technologies, sharing their perspectives with the public and with policy makers. Scientists and policy makers in turn should respectfully take into account all perspectives relevant to synthetic biology.

Recommendation 15: Information Accuracy

When discussing synthetic biology, individuals and deliberative forums should strive to employ clear and accurate language. The use of sensationalist buzzwords and phrases such as "creating life" or "playing God" may initially increase attention to the underlying science and its implications for society, but ultimately such words impede ongoing understanding of both the scientific and ethical issues at the core of public debates on these topics. To further promote public education and discourse, a mechanism should be created, ideally overseen by a private organization, to fact-check the variety of claims relevant to advances in synthetic biology.

This publicly accessible fact-check mechanism is among the most concrete ways by which public perception and acceptance of emerging technologies could be improved. Education also plays a key role in building public support for otherwise unfamiliar technologies. In light of our Nation's dependence on socially responsible scientific innovation for economic progress and individual well-being, the urgency of expanding effective science and ethics education cannot be exaggerated. Dialogue among individuals and public, private, and community groups demonstrates that science and its oversight do not belong exclusively to experts, highly trained professionals, or government officials. Science is a shared resource, affecting and belonging to all citizens.

Recommendation 16: Public Education

Educational activities related to synthetic biology should be expanded and directed to diverse populations of students at all levels, civil society organizations, communities, and other groups. These activities are most effective when encouraged and supported by various sources, not only government, but also private foundations and grassroots scientific and civic organizations. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President, with input from the scientific community, the public, and relevant private organizations, should identify and widely disseminate strategies to promote overall scientific and ethical literacy, particularly as related to synthetic biology, among all age groups.

Promoting Justice and Fairness

The principle of justice and fairness, at this very early stage of synthetic biology, yields two general recommendations that can be applied to both this technology and other emerging technologies. It directs those in government to consider rules for distribution of risks and benefits in research, and it directs those both in and outside of government to consider processes for just distribution of benefits and risks.

Recommendation 17: Risks in Research

Risks in research should not be unfairly or unnecessarily borne by certain individuals, subgroups, or populations. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President should lead an interagency evaluation of current requirements and alternative models to identify mechanisms that ensure that the risks of research in synthetic biology, including for human subjects and other affected parties, are not unfairly or unnecessarily distributed. Relevant scientific, academic, and research communities, including those in the private sector, should be consulted. This review should be completed within 18 months and the results made public.

Recommendation 18: Risks and Benefits in Commercial Production and Distribution

Risks to communities and the environment should not be unfairly distributed. Manufacturers and others seeking to use synthetic biology for commercial activities should ensure that risks and potential benefits to communities and the environment are assessed and managed so that the most serious risks, including long-term impacts, are not unfairly or unnecessarily borne by certain individuals, subgroups, or populations. These efforts should also aim to ensure that the important advances that may result from this research reach those individuals and populations who could most benefit from them. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President should evaluate current statutory mandates or regulatory requirements for distribution of risks and benefits and consider developing guidance materials and voluntary recommendations to assist manufacturers as appropriate.

In summary, the ability to easily manufacture and manipulate DNA in the laboratory has enhanced scientists' productivity and opened new directions for scientific exploration. In the future, scientists may be able to create entirely new organisms and systems previously unknown in the world today. But breakthroughs such as this raise a host of complex and sometimes controversial issues. They can help humanity in many ways, but they invariably carry some risks and often raise public concerns and fears. With these unprecedented achievements comes an obligation to consider carefully both the promise and potential perils that they could realize.

The recommendations detailed in this report provide a publicly accountable basis for ensuring that the field of synthetic biology advances to improve human health and public welfare with processes in place to identify, assess, monitor, and mitigate risks on an ongoing basis as the field matures. Risk assessment should precede field release of the products of synthetic biology. Ongoing assessment and review is required in several areas to avoid unnecessary limits on science and social progress, and to ensure appropriate restrictions to protect individual safety and our shared environment. Ongoing dialogue about concerns regarding the implications of synthetic biology for

humans, other species, nature, and the environment should continue as synthetic biology develops from its infancy to a fully mature field of scientific inquiry and innovation.

CHAPTER 1
Introduction

On May 20, 2010, the J. Craig Venter Institute announced it had created the world's first self-replicating synthetic genome in a bacterial cell of a different species.[1] Although scientists have used recombinant DNA techniques to engineer pieces of the genetic code for many years, this achievement marked the first time that all of the natural genetic material in a bacterial cell was replaced with a synthetic (i.e., human made or chemically synthesized) copy of the genes necessary for that organism to function. This announcement made headlines around the globe. Reaction was immediate, and it spanned the spectrum from expressions of enthusiasm to cries of alarm. Thoughtful deliberation about the meaning of this achievement was impossible in the hours that elapsed between the breaking news and the initial round of commentaries that ensued.

There is general agreement that this first self-replicating synthetic genome is an exceptional achievement, but there is also vigorous debate about just how momentous the Venter Institute's success is. Some scientists consider it a quantum leap; others see it as an incremental stride.[2] Whether one considers the accomplishment a major advance, a more modest technical step, or some combination of the two, one cannot deny the importance of understanding the potential implications of this and related accomplishments for humankind. The ability to synthesize vaccines, drugs, biofuels, and crops could do much to advance human welfare. At the same time, these innovations raise concerns about what we do not know—that is, whether there are attendant human or environmental risks—and what we perhaps should not know, that is, how to engineer forms of "life" to serve our own purposes.

Rather than offer an immediate opinion on the possible ethical and public policy implications—both positive and negative—of this scientific and technical accomplishment, President Barack Obama asked the Presidential Commission for the Study of Bioethical Issues (the Commission) as its first order of business to recommend how the developing field of synthetic biology and related biotechnologies can best maximize public benefits, minimize risks, and observe appropriate ethical boundaries.[3] He turned to the Commission to conduct "a study of the implications of this scientific milestone, as well as other advances that may lie ahead in this field of research." It was directed to consider the "potential medical, environmental, security, and other

benefits of this field of research, as well as any potential health, security, or other risks." The President charged the Commission to provide recommendations within six months on "any actions the federal government should take to ensure that America reaps the benefits of this developing field of science while identifying appropriate ethical boundaries and minimizing identified risks." Much stands to be gained by the government taking a deliberative and open approach to decision making in this and many other complex scientific and technical areas of public importance.

Recent advances in biotechnology have transformed the life sciences, yielding a level of innovation rarely witnessed in human history. These achievements raise a host of complex and often controversial issues. Breakthroughs can help humankind in many ways, but they invariably carry some risks. Discoveries of new ways of improving or enhancing life raise public hopes and expectations, but they also raise public concerns and, often, fears. Proponents of synthetic biology cite its potential to reduce our reliance on fossil fuels and transform medical care and human health, among other possible benefits. Critics express concerns about "playing God," threatening biodiversity and the organization and natural history of species, demeaning and disrespecting the meaning of life, and threatening longstanding concepts of nature. With these unprecedented opportunities and achievements comes an obligation to consider carefully both the promise and potential perils that they could realize.

Airing these expectations and concerns in a public forum maximizes the potential for public benefit and illuminates risks and possible harms—physical, environmental, and social—that deserve our attention and careful consideration. In addressing the President's charge the Commission therefore attempted to be an inclusive and deliberative body, encouraging the exchange of well-reasoned perspectives with the goal of making recommendations that will serve the public well and will advance the public good. It gathered specific information about the state of synthetic biology, reviewed the findings and recommendations of numerous U.S. and international groups, and listened to sometimes conflicting scientific, ethical, and social perspectives. It sought common ground where possible and generally found it. When common ground was impossible to find, the Commission cultivated mutual respect through active engagement with differing views.

The Commission's Process

In conducting its work, the Commission invited experts and representatives of the public to explore contested territory from multiple perspectives. Some guests presented information about recent and upcoming achievements in the science of synthetic biology, including current and future applications and benefits. Others shared their perspectives on anticipated risks, related regulatory and oversight issues, and ethical considerations. The Commission solicited questions from the public as well as from its own members. This format contributed to highly interactive and valuable sessions. In addition, the Commission encouraged the public to provide written comments throughout its deliberations, and nearly 40 individuals and groups submitted comments. It also consulted with relevant federal agencies and private entities considering similar questions.

Formal deliberations began with an overview of potential benefits. Without any realistic promise of benefits, no risks would be worth taking. Expert panelists cited a host of potential benefits including more efficient and effective drug development; accelerated synthesis of vaccines in response to pandemics; and the ability to engineer algae and other microbes to spur advances in clean-burning fuel, agriculture, bioremediation, and medicine. The Commission also heard about the promise of a robust bio-economy beginning to materialize in the form of novel technological platforms. These and other areas of research in synthetic biology offer significant opportunities for economic growth and job creation.

After discussing the possible benefits of synthetic biology, the Commission considered the current and foreseeable risks posed by this rapidly evolving field. Although the risks at this early stage in the field's development are well managed and relatively small in comparison to the anticipated benefits of the field, they do exist, and several themes emerged in Commission discussions.

First, sheer prudence suggests that we as a society must respect the intricacies of the natural world. Biological systems have developed over billions of years, and their interactions with the environment are astoundingly complex. We are far from being proficient speakers of the language of life, and our capacity

to control synthetic organisms that we design and release into the world is promising but unproven.

Second, understanding our own limitations is an essential prelude to minimizing the risks that will accompany ongoing breakthroughs in synthetic biology and related fields. Like other new technologies, synthetic biology poses uncertain risks. Rapidity of change, both in the field of biology and in the public's understanding of it, as well as accelerating information exchange and technological competence heighten these concerns. Today, predicting cell function from gene sequence alone is very difficult and often impossible.[4] While the successful synthesis of a functional bacterial chromosome is an essential technological step for the development of synthetic biology, it represents a preliminary advance. We remain far from having the scientific and technical expertise required to create truly novel functioning organisms. We must be cognizant, however, of our limited current understanding of what synthetic biology and related technologies may produce in the future and be willing to reassess benefits and harms as the field develops.

Third, ancillary effects and challenges should be recognized and considered. The rise of an economy based on biotechnology may expand jobs and lead to significant financial benefits, but it could also result in economic displacement, excessive demands on already scarce resources, and increased social and economic stratification. Anticipating all of the ramifications of our actions is impossible, but determining how to respond to this uncertainty is the better part of wisdom. The Commission also considered related questions regarding how the U.S. government can best respect intellectual freedom in scientific inquiry and nurture the development of synthetic biology in a way that maximizes its potential benefits while reducing the risks and likelihood of direct and indirect harms.

Critical to all of these themes is the importance of earning public trust in the integrity of both the scientific and engineering communities and the applicable regulatory systems. The Commission therefore focused on the need for greater public education and engagement on these issues as a prerequisite for public acceptance of this new technology and assurance of constructive criticism moving forward.

Basic Ethical Principles for Assessing Emerging Technologies

In approaching its task, the Commission was mindful of the need for an ethical framework for considering the implications of new and emerging technologies like synthetic biology, which itself represents one step in a long continuum of scientific innovation.[5] This is a unique opportunity to consider the ethics of an emerging technology at a very early stage of its development.[6] The Commission found many efforts to shape policy, governance, and regulation related to synthetic biology, but few examples of an ethical framework upon which to gird such proposals. Accordingly, in weighing alternative policy preferences and perspectives, it identified five ethical principles relevant to considering the social implications of synthetic biology as well as all emerging technologies. These principles provide a useful vehicle through which to evaluate the current state of the field and formulate the Commission's recommendations.

The guiding principles are: (1) public beneficence, (2) responsible stewardship, (3) intellectual freedom and responsibility, (4) democratic deliberation, and (5) justice and fairness. These principles should be understood as provisional guideposts. The Commission encourages others to subject these principles, and the recommendations based on them, to further refinements and revisions, as it has done and will continue to do in the future.

Public Beneficence

The ideal of public beneficence is to act to maximize public benefits and minimize public harm. The principle encompasses the duty of a society and its government to promote individual activities and institutional practices, including scientific and biomedical research, that have great potential to improve the public's well-being. In the case of emerging technologies like synthetic biology, this improvement may be by means of providing improved or more widely available forms of medical and health care, food, shelter, transportation, clothing, and eco-friendly fuel, along with other means of improving people's lives. Scientific and technological discovery often have the added potential of increasing economic opportunities, which also redound to the public good.

The *Belmont Report*, a landmark statement of ethical principles for research involving human subjects, defined beneficence to require that "[p]ersons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being."[7] Two general rules stem from this principle: first, do no harm; and second, maximize possible benefits and minimize possible harms.

For synthetic biology and other emerging technologies, we need to apply the principle of beneficence beyond the individual level, the primary emphasis of the *Belmont Report*, to the institutional, community, and public levels, while not overlooking possible harms and benefits to individuals. Policy makers should adopt a societal perspective when deciding whether to pursue particular benefits of synthetic biology research in the face of risks and uncertainty. When deciding whether to restrict these pursuits, a similar consideration of community interests and potential positive and negative impacts is essential.

Public beneficence requires that when seeking the benefits of synthetic biology, the public and its representatives be vigilant about risks and harms, standing ready to revise policies that pursue potential benefits with insufficient caution. The Commission explores the concomitant challenges of meaningful and valuable risk-benefit analysis and potential strategies to address them in the "Responsible Stewardship" section, below.

Responsible Stewardship

Among living beings, humans are in a unique position to be responsible stewards of nature, the earth's bounty, and the world's safety. Human society and governments have a duty to proceed prudently in promoting science and technologies, many of which can improve human welfare but also can harm the environment, create security risks, or otherwise lead to adverse consequences for vulnerable populations or future generations. The principle of responsible stewardship reflects a shared obligation among members of the domestic and global communities to act in ways that demonstrate concern for those who are not in a position to represent themselves (e.g., children and future generations) and for the environment in which future generations will flourish or suffer.

Scientists, policy makers, and the public are tasked with appreciating that the tools of science and technology possess both remarkable potential to enhance future lives and a spectrum of risks capable of causing harm. Both demand attention and action.

Responsible stewardship recognizes the importance of citizens and their representatives thinking and acting collectively for the betterment of all, especially those who cannot represent themselves. These activities must respect the significant impact—both positive and negative—that our decisions have on our world, both today and in the future.

Benefits and risks extend to humans, nonhuman species, and the environment, each with unique needs and vulnerabilities. Emerging technologies present particularly profound challenges for responsible stewardship because our understanding of these potential benefits and risks is largely incomplete, preliminary, and uncertain. The prospect of intentional misuse by malicious actors further complicates efforts to respond adequately to the spectrum of benefits and risks.

Responsible stewardship addresses these varied challenges by calling for actions that embrace potential benefits while mitigating risks over time and across all populations. It calls for broader risk-benefit discussions than what would typically be required based on a concern for public beneficence alone. The principle of responsible stewardship rejects two extreme approaches: an extreme action-oriented approach that pursues technological progress without limits or due regard for public or environmental safety, and an extreme precautionary approach that blocks technological progress until all possible risks are known and neutralized. While the action-oriented approach is irresponsibly brazen, the precautionary approach is overly wary. Both fail to carefully assess the most likely and significant benefits against the most likely and significant harms. Through the development of agile, measured oversight mechanisms, responsible stewardship rejects positions that forsake potential benefits in deference to absolute caution and those that ignore reasonably foreseeable risks to allow unfettered scientific exploration.

This principle is applied to synthetic biology and other emerging technologies through open decision-making processes informed by the best available science. Responsible stewardship calls for *prudent vigilance*, establishing processes for assessing likely benefits along with safety and security risks both before and after projects are undertaken. A responsible process will continue to evaluate safety and security as technologies develop and diffuse into public and private sectors. It will also include mechanisms for limiting their use when indicated.

Prudent vigilance does not demand extreme aversion to all risks. Not all safety and security questions can be definitively answered before projects begin, but prudent vigilance does call for ongoing evaluation of risks along with benefits. The iterative nature of this review is a key feature of responsible stewardship. It recognizes that future developments demand that decisions be revisited and amended as warranted by additional information about risks and potential benefits. The duty to be responsible stewards of nature, the earth's bounty, and the world's safety rests on concern not only for human health and well-being today but also, and importantly, for future generations and the environment looking forward.

Intellectual Freedom and Responsibility

Democracies depend on intellectual freedom coupled with the responsibility of individuals and institutions to use their creative potential in morally responsible ways. Sustained and dedicated creative intellectual exploration begets much of our scientific and technological progress. Without the free marketplace of ideas we would not have many of the scientific discoveries and advancements that have aided us in harnessing energy, sustaining life, and raising our collective standard of living. Intellectual freedom, therefore, is critical for developing innovative technologies that can compete in the global marketplace, and it is a necessary condition for industrial and academic collaborations that yield useful products and tools. While many emerging technologies raise concerns about their potential malevolent use, these risks alone are generally insufficient to justify limits on intellectual freedom. If we as a society stifle intellectual freedom for fear of enabling harm, we will be unprepared and vulnerable if that harm is unleashed upon us. A robust public

policy regarding the responsible conduct of science must promote the creative spirit of scientists and unambiguously protect their intellectual freedom.

At the same time, responsible science should reject the technological imperative: the mere fact that something new can be done does not mean that it ought to be done. The history of science here and abroad is sadly full of examples of intellectual freedom exercised without responsibility that resulted in appalling affronts to vulnerable populations, the environment, and the ideals of the profession of science itself. Scientists who act irresponsibly are capable not only of harming themselves and other individuals, but also of harming their communities, their nations, and international relations. Society as a whole has a stake in what scientists and engineers do, and they must not operate as if their research is totally independent of the groups who will experience both the benefits and burdens of their work. Risks may be especially great when those who provide the means and those who experience benefits are not the same. It is society that collectively provides the means for scientists to do their work and it is to society collectively that scientists bear profound responsibility.

As a corollary to the principle of intellectual freedom and responsibility, the Commission endorses a principle of regulatory parsimony, recommending only as much oversight as is truly necessary to ensure justice, fairness, security, and safety while pursuing the public good. Regulatory parsimony is particularly important in emerging technologies, which by their very definition are still in formation and are not always well-suited for sharply specified limitations. The blunt instruments of statutory and regulatory restraint may not only inhibit the distribution of new benefits, but they can be counterproductive to security and safety by preventing researchers from developing effective safeguards.[8] With sufficient freedom to operate, tomorrow's achievements may render moot the risks of today. Self-regulation also promotes a moral sense of ownership within a professional culture of responsibility.

Democratic Deliberation

The principle of democratic deliberation reflects an approach to collaborative decision making that embraces respectful debate of opposing views and active

participation by citizens. It calls for individuals and their representatives to work toward agreement whenever possible and to maintain mutual respect when it is not.[9]

At the core of democratic deliberation is an ongoing, public exchange of ideas, particularly regarding the many topics—in science and elsewhere—in which competing views are advocated, often passionately. Through formal and informal deliberative processes, decision makers and the people they represent should strive for mutually acceptable reasons to justify the policies that they adopt. These justifications should be expressed in ways that are accessible to those to whom such policies apply.

Citizens, individually and collectively, are active participants in democratic deliberation, engaging in dialogues both among themselves and with their representatives charged with developing policy. Public discussion and debate promote the legitimacy of whatever outcomes are reached, even if those outcomes are unlikely to please all interested parties. A process of active deliberation and justification promotes an atmosphere for debate and decision making that looks for common ground wherever possible and seeks to cultivate mutual respect where irreconcilable differences remain. It encourages participants to adopt a societal perspective over individual interests.

Importantly, democratic deliberation recognizes that while decisions must eventually be reached, those decisions need not (and often should not) be permanent, particularly when subsequent developments warrant additional examination. Democratic deliberation can correct the inevitable mistakes that arise when decisions are made collectively, provided that it is an ongoing, dynamic process. It recognizes the importance of challenging previously reached conclusions in light of new information or perspectives. It therefore requires citizens to take seriously the possibility that the views of one's opponents may be shown to be correct in the future and to be open to changing their own views.

With careful attention to the processes through which decisions are reached and justified, democratic deliberation promotes outcomes that are inclusive, thoughtfully considered, and respectful of competing views.

The principle of democratic deliberation, although a less familiar principle in bioethics than the principles of beneficence and justice, is particularly well-suited to the assessment of emerging technologies, including synthetic biology.[10] These fields offer the promise of remarkable potential benefits to science and society, yet they also raise risks regarding unintended consequences or possible malicious use. Each of these areas is clouded by uncertainty, complicating efforts to promote innovation while minimizing the likelihood of harm. Finding this balance demands careful ongoing review of the science and its applications. It presents an ideal opportunity for broad engagement and dialogue among the scientific community, policy makers, and the public. This active public engagement can enhance the decisions that are reached and the overall public understanding of them, as well as the related issues in science and technology that are central to the future of this new technology, as well as to our Nation and the world.

Justice and Fairness

The principle of justice and fairness relates to the distribution of benefits and burdens across society. Emerging technologies like synthetic biology, for good or ill, affect all persons. Society as a whole has a claim toward reasonable efforts on the part of both individuals and institutions to avoid unjust distributions of the benefits, burdens, and risks that such technologies bring. This same claim extends internationally to all those who may be affected—positively or negatively—by synthetic biology and its applications. As much as possible, and consistent with establishing essential incentives for creating new knowledge and translating it into vibrant markets, a fundamental principle of fairness suggests that society should seek to ensure that the benefits and burdens of new technologies are shared.

A commitment to justice and fairness is a commitment to seek to ensure that individuals and groups receive that to which they are entitled, that is, what they can reasonably and legitimately expect. Identifying, anticipating, and assessing what is reasonable to expect and determining how to measure and compare potential risks and benefits are complex activities, even in the best of circumstances and with the most complete data. They are made more difficult by the uncertainties surrounding scientific advances and the emergence of new technologies. How, for

example, are we to measure and compare the benefits of a technological innovation that leads to an effective medical treatment available on an unprecedented scale at low cost against the costs imposed by the disruption and displacement of previously existing technologies and the people whose livelihoods depends upon them? Advances produced through biotechnology can be highly beneficial but costly. How can and should we ensure that such advances reach those who could benefit most rather than being available only to those who can afford to pay? While such questions are difficult to answer, society must work to provide answers that are both just and fair.

The principle of justice and fairness also suggests that society should seek to ensure that the unavoidable burdens of technological advances do not fall disproportionately on any particular individual or group. Technological innovation benefits from public investment and from societal contribution toward safe and supportive research environments, and so it is reasonable that society expect a return on that investment.

Justice and fairness extend not only from individual societies to their constituents but also from individual societies to the international community overall. Emerging technologies like synthetic biology can and likely will have global impacts. For that reason, every nation has a responsibility to champion fair and just systems to promote the widest availability of information, the broadest distribution of beneficial technologies, and the most expansive culture of responsibility for biosafety and biosecurity.

About This Report

With these guiding principles in mind, the Commission considered the array of ethical public policy issues surrounding the field of synthetic biology. It reviews the science and potential benefits of this field in Chapters 2 and 3. Chapter 4 summarizes the existing oversight framework for new and emerging technologies like synthetic biology. Chapter 5 examines the implications of synthetic biology as viewed through the five principles described above and offers recommendations to ensure that society reaps the benefits of this developing field of science while identifying appropriate ethical boundaries and minimizing identified risks.

[1] Gibson, D.G., et al. (2010). Creation of a bacterial cell controlled by a chemically synthesized genome. *Science* 329(5987):52-56.

[2] *See, e.g.*, Endy, D., Terman Fellow and Assistant Professor of Bioengineering, Stanford University. (2010). Overview and Context of the Science and Technology of Synthetic Biology. Presentation to the Presidential Commission for the Study of Bioethical Issues, July 8, 2010. Available at: http://bioethics.gov/transcripts/synthetic-biology/070810/overview-and-context-of-the-science-and-technology.html; Prather, K., Assistant Professor, Department of Chemical Engineering, Massachusetts Institute of Technology. (2010). Applications of Synthetic Biology. Presentation to the Presidential Commission for the Study of Bioethical Issues, July 8, 2010. Available at: http://bioethics.gov/transcripts/synthetic-biology/070810/applications-of-synthetic-biology.html; Petsko, G.A. (2010). Hand-made biology. *Genome Biology* 11:124.

[3] Letter from President Barack Obama to Dr. Amy Gutmann, Chair, Presidential Commission for the Study of Bioethical Issues, May 20, 2010. Available at: http://bioethics.gov/documents/Letter-from-President-Obama-05.20.10.pdf.

[4] National Academies, Board on Life Sciences. (2010). *Sequence-Based Classification of Select Agents: A Brighter Line*. Washington, D.C.: National Academies Press; National Science Advisory Board for Biosecurity. (2010). *Addressing Biosecurity Concerns Related to Synthetic Biology*. Available at: http://oba.od.nih.gov/biosecurity/biosecurity_documents.html.

[5] *The Belmont Report*, issued in 1979 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, was pathbreaking in the field of bioethics. It articulated and applied a three-pronged ethical framework: respect for persons, beneficence, and justice. These principles have become a widely used tool through which to assess questions in human subjects research and related topics. However, the *Belmont Report's* principles demand refinement in light of new knowledge, different circumstances, and changing experiences. By proactively reflecting on and applying the ethical principles most relevant to our actions, we pursue a practical wisdom—knowledge that aims to produce the best results for society and the world.

[6] The Commission contrasts its work in this respect with that of the National Bioethics Advisory Commission, which was asked by President William Clinton to review ethical issues related to reproductive cloning *after* the successful cloning of an adult sheep. *See* National Bioethics Advisory Commission (1997). *Cloning Human Beings*. Available at: http://bioethics.georgetown.edu/pcbe/reports/past_commissions/nbac_cloning.pdf.

[7] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1979). *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. Available at: http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm.

[8] For example, the "Variola Amendment" to the Intelligence Reform and Terrorism Prevention Act of 2004 made it criminal to produce, engineer, or synthesize the variola virus. The "variola virus" was in turn defined to include "any derivative of the variola major virus that contains more than 85 percent of the gene sequence of the variola major virus or the variola minor virus." 18 U.S.C. § 175c. The broad definition of "variola virus" made it unclear what was actually covered by the statute, and a strict interpretation of the definition would have potentially, and inadvertently, criminalized beneficial research such as production of the smallpox vaccine.

[9] Gutmann, A., and D. Thompson. (1996). *Democracy and Disagreement*. Cambridge, Mass.: Belknap Press; Gutmann, A., and D. Thompson. (1997). Deliberating about bioethics. *The Hastings Center Report* (May/June):38-41; Gutmann, A., and D. Thompson. (2000). Why deliberative democracy is different. *Social Philosophy and Policy* 17:161-180; Gutmann, A., and D. Thompson. (2002). Just deliberation about health care. In *Ethical Dimensions of Health Policy*. M. Danis, C. Clancy, and L. Churchill (eds.). Oxford: Oxford University Press.

[10] Daniels, N. (2008). *Just Health: Meeting Health Needs Fairly*. Cambridge: Cambridge University Press, 103-139; Fleck, L. (2009). *Just Caring: Health Care Rationing and Democratic Deliberation*. Oxford: Oxford University Press.

CHAPTER 2
Science of Synthetic Biology

Synthetic biology is the name given to an emerging field of research that combines elements of biology, engineering, genetics, chemistry, and computer science. The diverse but related endeavors that fall under its umbrella rely on chemically synthesized DNA, along with standardized and automatable processes, to create new biochemical systems or organisms with novel or enhanced characteristics. Whereas standard biology treats the structure and chemistry of living things as natural phenomena to be understood and explained, *synthetic* biology treats biochemical processes, molecules, and structures as raw materials and tools to be used in novel and potentially useful ways, often quite independent of their natural roles. It joins the knowledge and techniques of biology with the practical principles and techniques of engineering. "Bottom-up" synthetic biologists, those in the very earliest stages of research, seek to create novel biochemical systems and organisms from scratch, using nothing but chemical reagents. "Top-down" synthetic biologists, who have been working for several decades, treat existing organisms, genes, enzymes, and other biological materials as parts or tools to be reconfigured for purposes chosen by the investigator.

For the purposes of this report, the Commission focused on the molecular and cellular engineering techniques of synthetic biology and the most foreseeable benefits of this very early field. In time, synthetic biology products for clean energy, pollution control, agriculture, and medicine, may change our lives and our shared environment through the development of novel applications. Because the potential applications of synthetic biology are speculative at this time, and the field is advancing in exciting directions, it is inviting both optimism and unease among scientists and the public.

From Molecular Biology to Synthetic Biology

Synthetic biology is deeply rooted in molecular biology, a field that emerged decades ago with the discovery of the structure and composition of DNA. DNA molecules provide the instructions that direct cell growth, development, and differentiation in every living organism. They contain a sequence of four types of chemical building blocks—adenosine, thymine, cytosine, and guanine (A, T, C, and G)—that combine, ladder-like and in various order, into "base pairs" that are combined into sets called "genes" (see Figure 1).

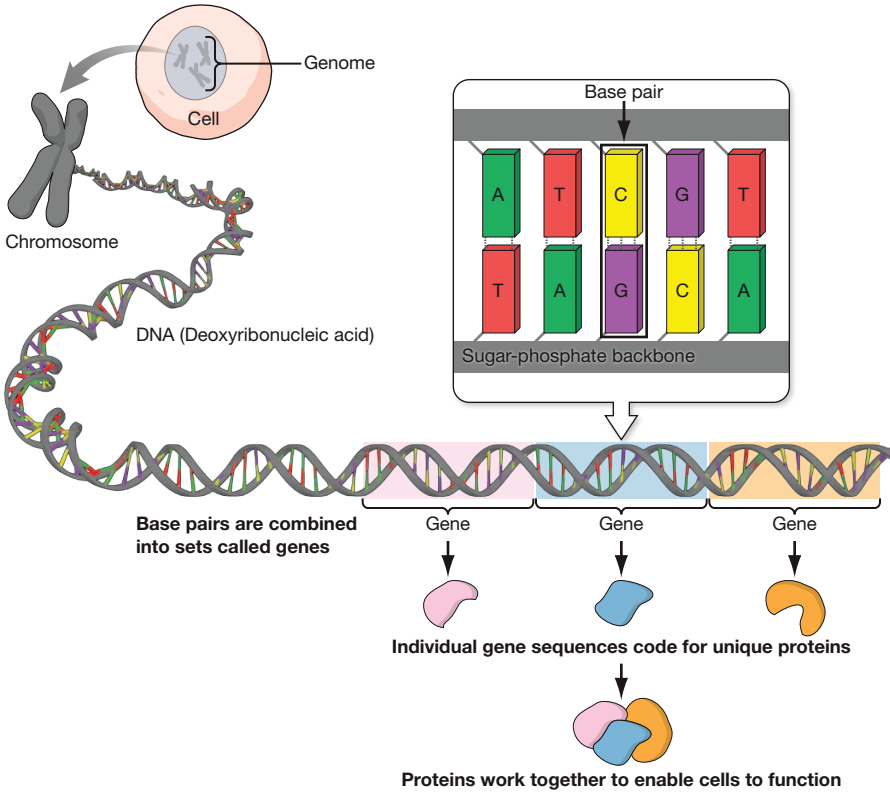

Figure 1: DNA, genes, and proteins.

Individual gene sequences code for particular proteins, which are what enable cells to function. Collectively, the complete DNA sequence of an organism is called its "genome." Genome variation is what makes individual organisms unique.

Though not described as such at the time, the earliest achievements in what is today called synthetic biology can be traced to the birth of genetic engineering in the 1970s. Genetic engineering, sometimes called gene-splicing or recombinant DNA research, is the intentional manipulation of an organism's genetic material using tools that cut, move, and reattach (recombine) DNA segments within and across different organisms.

In 1972, Stanford University biochemist Dr. Paul Berg created the first recombinant DNA molecules by splicing DNA from a bacterial virus into that of a monkey virus, SV40.[1] Two years later, scientists created the first transgenic mammal by introducing foreign DNA into mouse embryos.[2] Today, transgenic mice are a staple of biomedical research. They are used to regulate the expression of individual genes in order to understand how those genes interact with the environment and, in turn, affect human health. Using transgenic mice also enables researchers to increase or decrease specific proteins and better understand their individual roles and functions.[3]

As recombinant DNA technology began to develop in the 1970s, individual scientists, policy makers, and nations undertook profound debate about the safety and permissibility of this research—whether it was too dangerous to proceed at all—in the face of deep uncertainty.[4] Like synthetic biology today, great promise and potential risks were identified.[5] Expert and lay groups intensely debated concerns about possible adverse human health and environmental effects.

In 1974, a group of American scientists called for a moratorium on DNA research and the scientific community voluntarily obliged. To resolve this stalemate, in 1975 scientists from around the world, policy makers, lawyers, and press met together at the Asilomar Conference Center in Pacific Grove, California, to debate safety issues. The deliberations at the Asilomar Conference on Recombinant DNA led to formation of guidelines to ensure safety and a scientific peer review group, today known as the Recombinant DNA Advisory Committee of the National Institutes of Health (NIH). Both the guidelines and the Recombinant DNA Advisory Committee remain as critical components of the genetic engineering research oversight system (see Chapter 4 for further discussion). Many of the processes first proposed at the Asilomar

Conference remain in place, though some have changed in the intervening years as understanding of risks has improved. Scientists and policy makers have pointed to Asilomar as valuable precedent when considering debates regarding research in synthetic biology.

By the end of the 1970s, scientists had created the first commercial product of genetic engineering. An extraordinary benefit for human health, human insulin produced using recombinant DNA technology transformed treatment for diabetes.[6] Following its entrance to the market, public acceptance of this new technology grew and fears decreased significantly.[7]

In the early 1980s, researchers developed another revolutionary technique, called polymerase chain reaction (PCR). The PCR method enabled researchers to amplify and make simple changes to DNA pieces. PCR acts like a molecular copy machine, allowing scientists to enlarge individual DNA sections and manipulate them more easily.

By the early 1990s, automated DNA sequencing became available. This technology considerably accelerated the process of determining the order of individual gene segments, called "nucleotides," or, when very small (typically less than 20 base pairs), "oligonucleotides." Through large-scale genome sequencing efforts, primarily the public and private Human Genome Project, scientists were able identify the complete genetic codes of numerous naturally occurring organisms, including bacteria, viruses, and higher organisms such as mice and humans. The genome of a bacterial cell typically includes 5 to 10 million base pairs, although the synthesized genome of the bacteria in the J. Craig Venter Institute research, described below, contained just over 1 million base pairs.[8] By comparison, a fruit fly genome includes 165 million base pairs, and the human genome includes more than 3 billion base pairs. These significant differences in scale help place the achievement of the Venter Institute team in context. While it represents the first successful synthesis of a complete genome of a single-celled bacterium, it is a relatively small genome compared to those of other species.

After scientists could sequence naturally occurring DNA, they developed techniques to synthesize, or chemically construct, DNA and pieces of DNA.[9]

Figure 2 shows an early DNA synthesis machine and the individual chemicals, including nucleic acids, used to construct sequences. Within the last few years, researchers have developed methods to accurately synthesize increasingly longer segments of DNA and to bring them together into even larger segments of DNA. Stemming from this research, a small industry of commercial DNA synthesis providers has emerged. Five of the main companies, roughly 80 percent of the market, are based in the United States.[10]

Figure 2: Early DNA synthesis machine. (Courtesy of Life Technologies)

The development of DNA synthesis technology has enabled scientists to make entire genes, and, eventually, the complete genome of a microorganism using synthetic methods alone. By synthesizing a complete genome for a bacterial cell and transferring it to a cell with its own genome that was later lost, researchers at the Venter Institute created a self-replicating bacterial cell with entirely chemically constructed DNA (see Figure 3).[11]

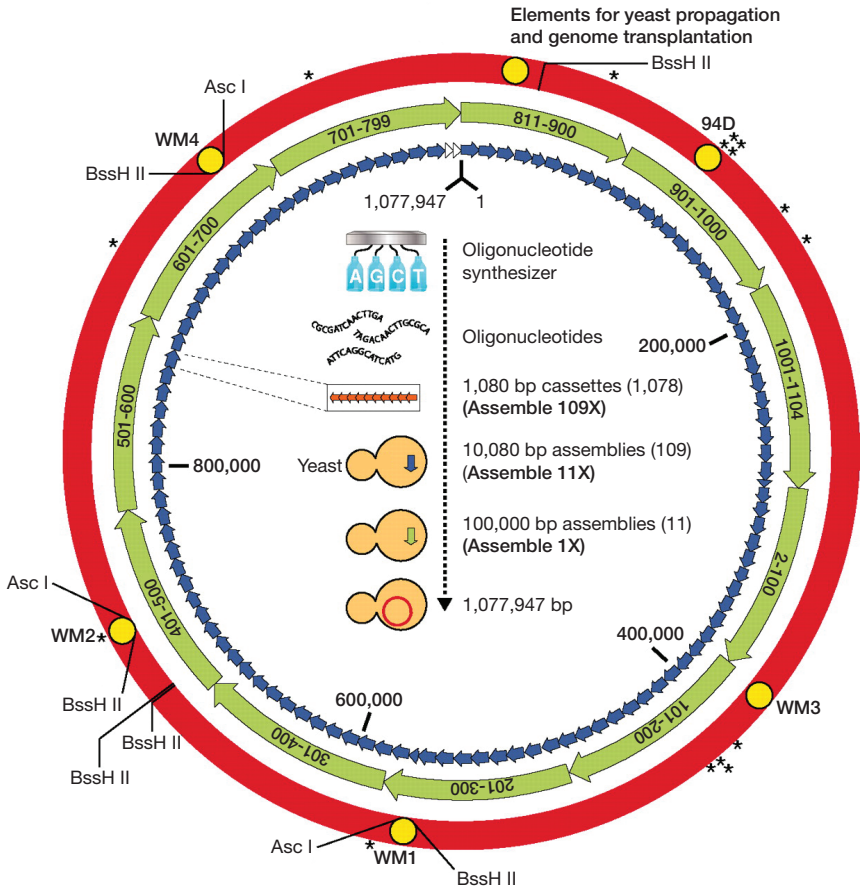

Figure 3: The assembly of a synthetic *M. mycoides* genome in yeast. Source: Gibson, D.G., et al. (2010). Creation of a bacterial cell controlled by a chemically synthesized genome. *Science* 329(5987):52-56.

Of note, many scientists observe that this achievement is not tantamount to "creating life" in a scientific sense because the research required a functioning, naturally occurring host cell to accept the synthesized genome. At the same time, this development should not be undersold. For many, this work represents the "proof of principle" that synthetic biology techniques can be used to construct cells and other organisms with novel characteristics.[12] While this small step does not give us the ability to grow larger-scale organisms, human tissue, or other tools of regenerative medicine, it is an incremental step on which future technical and scientific achievements will build.

THE FIRST SELF-REPLICATING SYNTHETIC BACTERIAL CELL

A May 21, 2010 publication in the journal *Science* by researchers from the Venter Institute announced the design, synthesis, and assembly of the 1.08 million base pair chromosome of a modified *Mycoplasma mycoides* bacterial genome. Beginning with an accurate, digitized genome of the bacteria, the researchers added four watermark sequences to identify the genome more clearly. They then designed more than 1,000 cassettes of DNA including approximately 1,080 base pairs each, with 80 base pair overlaps on each cassette representing adjacent sequences. The fragments were assembled sequentially in yeast. First, 10 cassettes each combined to make 10,000 base pair intermediates. Ten of those intermediates next were assembled to produce eleven 100,000 base pair intermediates, which were then combined into the complete genome. The newly synthesized genome was initially grown in yeast before being isolated and transplanted into cells of another bacterium, *Mycoplasma capricolum*. The genome of the recipient cells were lost as the cells were incubated, resulting in viable, self-replicating *Mycoplasma mycoides* cells containing only DNA from the synthetic genome.

Early molecular biology laid the groundwork for today's synthetic biology, but more recent technological advances have accelerated its development. First, scientists have developed the ability to mechanically synthesize increasingly longer DNA segments accurately and more rapidly than had been possible previously. Second, the costs for DNA synthesis have fallen dramatically over the past decade, dropping from about $30 to well under $1 per base pair.[13]

Computer modeling, not readily available until recently, is also facilitating the design of novel genetically engineered biological systems. As with electrical or civil engineering, modeling is intended to help scientists predict the behavior of a system before it is actually built. Although biological systems are not nearly as easily modeled as an electronic circuit or a bridge, at least at this time, sophisticated simulations, mostly in single-cell systems, are contributing to improved computer modeling of synthetic biological systems.

Synthetic Biology Techniques and Strategies

As discussed previously, to date synthetic biology has been characterized by top-down and bottom-up approaches.[14] The techniques overlap to some extent, and both approaches share a common goal: to engineer specific biological functions with predictability and reliability. In the future, these approaches may come together. For now, it is useful to consider both as illustrative of different experimental methods to reach the same goal.

Top-Down Approach

Through the top-down approach, in use since the 1970s, scientists use synthetic biology to re-design existing organisms or gene sequences with the goal of stripping out unnecessary parts, or replacing or adding specific parts to achieve new or amplified characteristics and functions (see Figure 4). Using this approach, scientists aim to remove parts of an organism or genetic code to create what some have dubbed a "chassis organism" that can then be modified through the addition or subtraction of engineered genetic circuits or metabolic pathways.[15]

One recent example of the top-down approach in synthetic biology is the identification of a "minimal genome."[16] This research provided proof of principle that the total genetic material of a small bacterium, its genome, could be pared down into a functioning unit consisting of only a subset of the organism's original genes.

Top-down synthetic biology is also defined by borrowing properties from one or more living systems to create something new. One example is combining

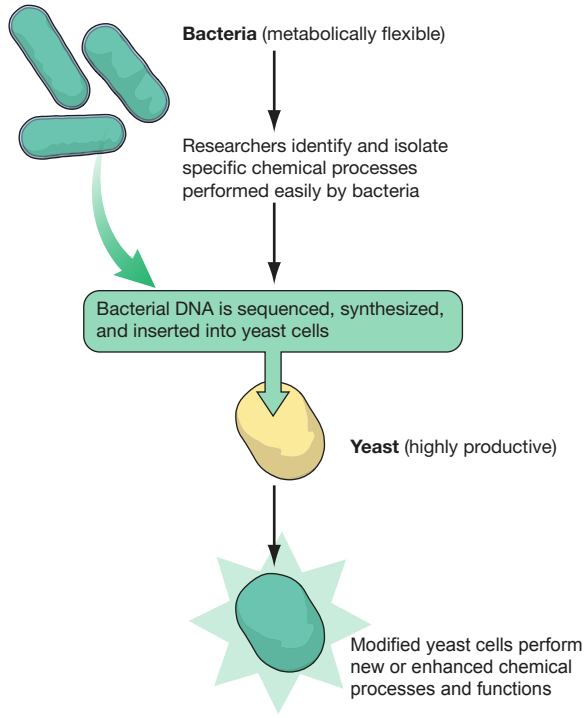

Figure 4: Example of a top-down approach to synthetic biology.

the productivity of yeast cells with the metabolic flexibility of bacteria. In this approach, researchers identify a range of chemical processes performed easily by various types of bacteria and insert these processing abilities into industry-standard yeast cells. In one case, the result was an efficient way to manufacture simple, yet high-value chemicals called methyl halides, used as agricultural fumigants and as fuel ingredients, starting with readily available plant matter such as corn stalks, sugar cane, and switchgrass.[17] Top-down synthetic biology is made easier through the use of increasingly accessible and inexpensive DNA sequencing and DNA synthesis technologies. Scientists can use them to "trawl" for bacterial genes that perform useful tasks and then copy and paste that DNA into yeast, without ever touching (or laboriously culturing) the bacteria, as was once required.[18]

Bottom-Up Approach

In bottom-up synthetic biology, which is relatively new and significantly more challenging, scientists aim to build living systems from raw materials starting with non-living components. For example, a team of scientists is aiming to create completely artificial systems using only non-living materials that mimic the behavior of actual cells. The products of this research are called chemical cells, or "Chells."[19] Bottom-up approaches also include efforts to create genetically engineered circuits and switches to turn specific functions on and off in response to identified stimuli. In some cases, the bottom-up approach could theoretically result in an entirely new organism or material with functions that may be different from currently existing organisms or cells. In other cases, parts with known functions may function differently when assembled into a new material or organism.

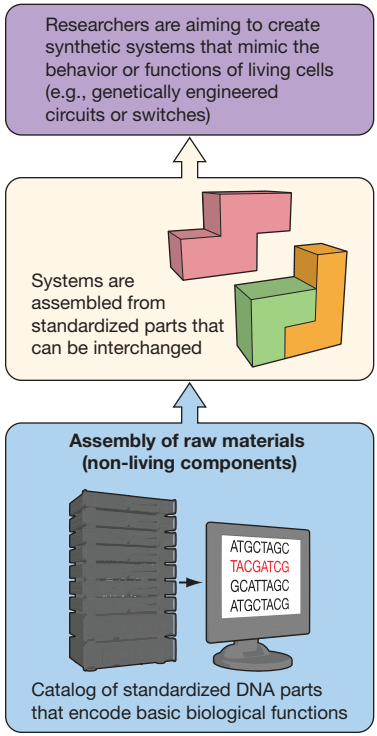

Figure 5: Example of a bottom-up approach to synthetic biology.

Bottom-up approaches are sometimes characterized by their reliance on assembling systems from chemically synthesized standardized parts that perform desired functions in a predictable manner and can be interchanged.[20] Like Legos® or computer components, a goal of this work is to develop a set of basic chemically synthesized pieces with identified and predictable functionality across different platforms. Exemplifying this strategy, the Registry of Standard Biological Parts, or "BioBricks,"™ physically houses an open catalog of standardized DNA parts that encode basic biological functions and can be easily combined and exchanged among

different devices and laboratories.[21] These standardized parts are made available to the public free of charge to further research in this field, and they are central to the annual International Genetically Engineered Machine (iGEM) student competition.

Defining Synthetic Biology

Despite these historical antecedents and complementary methodologies, providing a single definition for synthetic biology is a challenge even to those active in the field. Synthetic biology has attracted interest and investment from a range of different specialties. Biologists, chemists, engineers, and others bring their collective knowledge and expertise to this inherently interdisciplinary science. For this reason, synthetic biology may be viewed from various perspectives, which together help to explain its utility and versatility. A common thread is that synthetic biology is a scientific discipline that relies on chemically synthesized DNA, along with standardized and automatable

iGEM

The iGEM competition resembles a giant science fair for budding synthetic biologists. iGEM is a global synthetic biology competition involving mostly undergraduate students, although non-synthetic biology faculty, and high school students also participate. At the heart of the competition is BioBricks, a repository of standard DNA parts. Several months before the actual competition, competing teams receive a kit of DNA parts. Working at their own schools over a summer, teams design and build synthetic systems that operate in living cells. Examples of recent projects include an arsenic biosensor, wintergreen-scented bacteria, and color-coded microbes. Teams earn medals in a range of categories. Among the more popular of these is "human factors." Here, competitors win points for innovations that directly affect how people work together. Beyond building biological systems, the broader goals of iGEM include growing and supporting a community of science guided by social norms.

processes, to address human needs by the creation of organisms with novel or enhanced characteristics or traits.

To a biologist, synthetic biology is a window through which to understand how living things operate. It provides a direct and compelling means to test, through sequencing, modeling, and reproduction, our current understanding of the life sciences. The ability to model and manipulate living systems using synthetic biology is yielding new knowledge that will better define the functions of genes and physiological systems. In addition to advancing basic science, synthetic biology has important potential applications for medicine, including the design of safe and effective vaccines and targeted approaches to detect and cure diseases like cancer (see pp. 64-68).

From the perspective of a chemist, synthetic biology is a tool for manufacturing novel molecules and molecular systems for various uses. Scientists have used synthetic biology to directly manipulate chemical reactions in living systems, for example, in hopes of making medicines quickly and inexpensively.[22] They have also produced, on a small scale, novel biofuels that can harness energy from plants and the sun.[23] Collectively, these methods could reduce the use and deleterious effects of hazardous chemicals and petroleum-based products.

Synthetic biology viewed through an engineering lens is an opportunity to apply the techniques and tools of engineering to complex living organisms. Many aspects of engineering are based on the principle of standardization, which enables the reliable production of useful commodities. Engineers working in the field of synthetic biology hope to bring a similar level of standardization, predictability, and reproducibility to biology. Examples of engineered biological systems currently under study include synthetic systems that perform sophisticated medical functions—measuring components in body fluids and adjusting them through targeted administration of therapies—as well as biologically engineered "microcleansers" that can clean up oil spills or other forms of industrial waste.[24]

Is Synthetic Biology New?

The answer to this question is complex. Some scientists see synthetic biology as a revolutionary and qualitatively new field of science.[25] Others see current developments in the field as incremental advances in the decades-long growth of molecular biology, genetic engineering, and microbiology.[26] The term synthetic biology itself was first used as early as 1974 by Waclaw Szybalski who saw molecular biology's promise evolving from description to manipulation of genetic systems, heralding a new era of synthetic biology.[27]

One characteristic that distinguishes the synthetic biology of today from the molecular biology of years past is the significant role played by standardized parts, computers, and automation, accelerating a trend prevalent throughout biotechnology. Companion fields like nanotechnology and biomedical imaging share a reliance on automation and reusable, standardized parts.

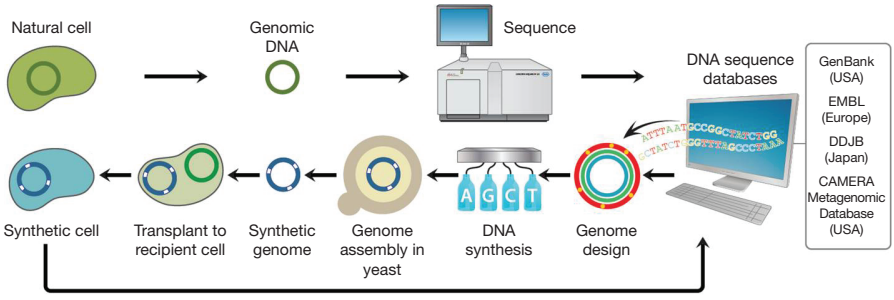

Figure 6: Overview of one process using synthetic biology techniques to produce synthetic cells. (Courtesy of J. Craig Venter Institute)

Recent technological advances and economic efficiencies in DNA synthesis and sequencing permit synthetic biologists to make, move, and manipulate DNA on a much larger scale than was possible only a few years ago. In contrast to conventional research in biology, the quest for predictable functions and standardization lies at the heart of synthetic biology. In this way, the field reflects the influence of engineering on its development.

The Future of Synthetic Biology

Synthetic biology holds great promise as a route to develop novel applications for medicine, agriculture, energy, and other industries. For example, the future may hold microorganisms that are "tailor-made for production of a specific chemical from a specific starting material . . . ." [28] Few of these potential products are anticipated immediately, however, and considerable technical and intellectual challenges remain.

Building a single cell from parts in the laboratory is a vastly different challenge than building an organism that interacts effectively and predictably in nature.[29] The design of synthetic or artificial organisms that can survive in natural environments is likely to be more challenging and unpredictable than doing so in a controlled setting.[30] It is extremely difficult to anticipate with confidence how a synthetic organism will react to and interact with a novel natural environment, adding to concerns about the risks of some applications of this field (see Chapter 3 for further discussion of applications).

Complexity and variation are linked. They both reflect the fact that DNA alone is not sufficient to create the biological functions necessary for the creation of biofuels, vaccines, soil sensors, or any desired product of synthetic biology. DNA can only function if it exists within an environment that provides the cellular components such as ribosomes, proteins, and other structures necessary to read, translate, and implement its genetic code. How any specific DNA sequence functions in a cell is also dependent on secondary modifications in its structure (though methylation) or folding pattern (through changes in histone proteins) that can promote or inhibit the transcription of genes, an area known as *epigenetics*. Much is still unknown

regarding the interactions between and within cells, actual or "artificial," as well as between cells and their environments.

Currently, the behavior of synthetic biological systems remains unpredictable.[31] Function cannot typically be accurately predicted based on DNA sequence alone or by the shape and other characteristics of the proteins and the biological systems for which it codes.[32] Also unknown is how synthetic biological systems will evolve. In most cases, biological systems that have been engineered by scientists quickly revert to "wild type" (i.e., evolve to lose their engineered function rather than gain a new one).[33] Although this notion may be reassuring, it does not rule out the possibility that systems might evolve in unpredictable and harmful ways, particularly if released outside the laboratory.

The potential promise of synthetic biology is immense. Research in synthetic biology has led to the development of genetic circuits and modules with predictable behavior, creation of novel combinations of cells in the laboratory that behave synergistically, and ever-expanding DNA construction capabilities.[34] The field, however, is young. Our understanding of complexity and variation in natural and synthetic parts and systems is far from complete, and the technical tools and skills required for large-scale synthesis and production continue to be refined. If carefully nurtured and guided, however, synthetic biology may provide an opportunity to integrate engineering and the biological sciences into the living world, with potential benefits to national and international security, food and energy supply, public health, and economic well-being.

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CHAPTER 3
Applications, Benefits, and Risks

Synthetic biology offers opportunities to apply biological and engineering principles to benefit humankind in unprecedented ways. Clean energy sources, targeted medicines and more efficient vaccine production, new chemicals, environmental cleansers, and hardy crops are some of the potential applications of this burgeoning field of science. While most of the fruits of synthetic biology remain in early stages of development, some applications are expected to come to market within a few years.[1] Success in these research efforts will yield new jobs as novel products and product streams develop. The pace of acceleration of synthetic biology is likely to increase dramatically in the years ahead.

Despite its promise, synthetic biology raises concerns about risks to human health, the environment, and biosecurity. Some of these potential harms include unanticipated adverse human health effects, negative environmental effects (anticipated or unanticipated) from field release and dual-use concerns when research undertaken for "legitimate scientific purpose…may be misused to pose a biologic threat to public health and/or national security."[2]

This chapter provides an overview of the potential applications, benefits, and risks of synthetic biology. Because renewable energy is expected to yield the first large-scale commercial products of synthetic biology, the Commission discusses this area first. Next, the Commission reviews potential health applications and benefits. Many products remain in research and development, but a few are nearing commercialization. Finally, the Commission provides a summary of potential agricultural, environmental, and biosecurity applications of synthetic biology, all of which are in more preliminary stages of development. Within these discussions the potential health, security, and other risks are examined, as well as anticipated technical challenges.

Renewable Energy Applications of Synthetic Biology

In general, biofuels are renewable energy sources derived from biomass, which includes material derived from plants, animals, and organic waste. Several methods can be used to harvest energy from biomass, including burning, chemical treatment, or biodegradation using the metabolic power of microorganisms. Processing biomass into biofuels or electricity through more complex

chemical and biochemical reactions, as opposed to simple combustion, limits environmental impact by minimizing the production of waste and decreasing net greenhouse emissions. Current practices for farming biomass for energy use employ a range of biological sources including grains, grasses, oil seed crops, trees, sugar, and corn.

Ethanol is the most common biofuel worldwide. It is produced mainly from corn or sugar cane. Biodiesel, another currently used biofuel, is made from vegetable oils, animal fats, or recycled restaurant grease. There are challenges to widespread commercial development of either of these fuels. For ethanol production, challenges include inefficiencies and energy costs for production, as well as concerns about the volume of plant sources needed and possible collateral impact on food prices. Biodiesel also involves significant energy costs for production.

Promise and Potential Benefits

Biofuels and related products produced through synthetic biology offer the potential to reduce global dependence on fossil fuel, cut harmful emissions, and minimize economic and political volatility surrounding fossil fuel reserves. Some biofuels produced with synthetic biology processes are expected to be available commercially within the next few years. Other research may not yield commercial products for a decade or more.

The various synthetic biology alternatives to current biofuel production methods include producing cellulosic ethanol (derived from cell walls rather than corn) and manufacturing other bioalcohols with synthetically manipulated biomass. Biofuel can also be produced from modified algae that use the natural process of photosynthesis to manufacture bio-oils, such as biodiesel, more easily than current chemical processes.[3]

The biochemical conversion of biomass into energy involves chemical reactions performed by biological systems. Enzymes in microorganisms such as bacteria break down biological materials into their component parts, from which energy can be extracted more easily. Perhaps the simplest example of biochemical conversion is a backyard composting bin, in which microorganisms gradually

degrade vegetation in the presence of oxygen. As is apparent from the surge of warm air that emerges upon opening the lid of the bin, this form of bioconversion is an energy-yielding process.

Synthetic biologists aim to improve the speed and efficiency of converting biomass into advanced, second- or third-generation biofuels with cleaner and more favorable energy-usage profiles.[4] This challenge may be met by creating "super-fermenting" yeast and bacteria through synthetic biology. These organisms have the potential to boost the power and potential of current industrially used microorganisms by means of new or altered genes. Synthetic biology also offers new biomass sources, or feedstocks, that are more efficient, reliable, low-cost, and scalable than current sources. These include forest and agriculture residues, some grasses, algae, oilseeds, and potentially sewage.[5]

Aside from biofuels, synthetic biology may also play an important environmental role by harnessing energy in novel, cleaner ways than traditional non-renewable energy production processes. Large global reserves of hydrocarbons, such as oil, gas, shale, and oil sands, might be leveraged with synthetic biology tools. Coal bed methane, for example, is a globally available source of natural gas. Its reserves are vast and largely untapped. Synthetic biology research is underway to harvest this methane through microbial digestion and other processes.[6]

Bioalcohols

Unlike ethanol derived from corn or sugar cane, cellulosic ethanol is made from cellulose fibers, a major component in the cell walls of all plants. Processing plant biomass not used for food, for example, waste corn stalks, straws, grass clippings, prairie grasses, and wood chips, could reduce economic and other pressures imposed by relying on corn for ethanol. However, cellulosic ethanol is a relatively low-yield bioalcohol and, like ethanol fuel derived from more conventional chemistries, still tends to corrode storage and transport equipment.

NEW PRODUCT PIPELINE: BIOALCOHOLS

Amyris (Emeryville, California) is using a synthetic biology platform to convert sugar into a range of products, including yeast-derived cellulosic alcohol fuel. The oil-based fuel is harvested in a similar fashion to the technique used by the Joint Bioenergy Institute (akin to separating cream from milk).[7]

British Petroleum and **DuPont** created a partnership to develop, produce, and market biobutanol.[8]

Gevo (Englewood, Colorado) genetically engineered bacteria to make biobutanol, a promising new biofuel. It also successfully converted cellulosic biomass into isobiobutanol and converted the fuel into jet fuel.[9]

Global Bioenergies (Evry, France) created yeast and bacteria with the capacity to transform sugar into hydrocarbons chemically identical to those distilled from oil. Bio-isobutane is the targeted end product; this hydrocarbon gas can be converted into high-octane gasoline.[10]

The U.S. Department of Energy's **Joint Bioenergy Institute** (Emeryville, California) is using synthetic biology to biodegrade plant biomass into biodiesel, which is skimmed off the top of a fermentation broth.[11]

LS9, Inc. (South San Francisco, California) developed the UltraClean™ product line that employs synthetic biology to produce its DesignerMicrobes™. These microorganisms use sugar cane or cellulosic biomass to create high-energy transportation fuels.[12]

The various commercial products and products presented and described in this report are intended to provide examples of current projects, not to endorse any particular entities.

A potentially more promising bioalcohol made by synthetic biology and used for energy production is butanol. Like ethanol, butanol is produced by the fermentation of sugars and starches or through the breakdown of cellulose. The crude product is then refined to make usable fuel. A particular advantage of butanol (and a similar biofuel called isobutanol) is that it can be used

directly in a traditional gasoline-powered engine. It also has a relatively high-energy density, resulting in better gas mileage than ethanol.[13] Some bacteria have the built-in enzymes to manufacture butanol, but the natural process is not very fast or high-yield. Synthetic biologists have engineered the easy-to-manipulate bacterium *E. coli* to improve this bacterial biochemical reaction to make butanol more industrially useful.[14]

Photosynthetic Algae

Another tool for creating biofuels via synthetic biology is through the use of photosynthetic algae. Algae are low-input, high-yield feedstocks that, under experimental conditions, produce substantially more energy per acre than land crops such as corn or soybeans.[15] To create biofuel from algae, the cells are grown, harvested, and treated chemically or thermally to recover the oil content inside algal cells, the so-called "bio-oil." While experimental yields have not yet been duplicated on a commercial scale, an alternative strategy currently under development with synthetic biology is engineering algal cells to secrete oil continuously through their cell walls and thereby increase yield. This time-saving step may support large-scale industrial operations in the near future.[16]

Proponents of farming algae note that it is biodegradable and therefore relatively harmless to the environment if spilled. Algae can also be grown on land and in water that is otherwise unsuitable for crops and food production. Making bio-oils using algae is expected to be less polluting and more efficient than converting vegetable oils or animal fats into biofuel.[17]

Through its capacity to consume carbon dioxide, algae offer the added benefit of mitigating greenhouse gas emissions. Unlike ethanol, algae-derived bio-oils, such as gasoline, diesel, and jet fuels, have been found to have very similar physical and chemical properties in comparison to currently used petroleum-based products, suggesting that these fuels are likely to be compatible with current transportation technologies and infrastructure.

NEW PRODUCT PIPELINE: PHOTOSYNTHETIC ALGAE

Aurora Algae (Alameda, California and Florida) is growing algae in open-pond systems consisting of readily available seawater. The pilot facility in Florida produces approximately three tons of algal biomass per year, with the ultimate goal of producing 40,000 tons of algal biomass per year.[18]

Joule (Cambridge, Massachusetts) engineers algae to make and secrete liquid hydrocarbons, bioethanol, and other fuel materials from sunlight and waste carbon dioxide (the sole feedstock) in a single-step, continuous process. Pilot operations are currently underway, with commercial development slated for 2012.[19]

Solazyme (South San Francisco, California) uses photosynthetic algae to produce an oil-based fuel, Soladiesel®, at industrial manufacturing scale with production capabilities currently in the tens of thousands of gallons. In July 2010, Solazyme delivered 1,500 gallons of algal-derived jet fuel to the Navy.[20]

Synthetic Genomics Inc. (La Jolla, California) engineered algal strains to create a biocrude oil that can be used as a feedstock in refineries, using a continuous biomanufacturing process that sidesteps the intermittent cycle of growing and harvesting. In July 2009, Synthetic Genomics entered into a $600 million multi-year agreement with ExxonMobil.[21]

The various commercial products and products presented and described in this report are intended to provide examples of current projects, not to endorse any particular entities.

Hydrogen Fuel

Hydrogen fuel is an additional area of focus for commercial applications of synthetic biology. Hydrogen is a highly desirable fuel source because it is clean-burning, producing water as a by-product. Hydrogen also has the second highest energy density per unit of weight of any known fuel.[22]

Several possible routes to generate biohydrogen are under investigation. One method uses engineered *E. coli* as a host organism to produce hydrogen in

addition to other biofuels.[23] Engineered algae are also being examined as sources of biohydrogen.[24] Finally, and perhaps most promisingly, researchers are investigating ways to produce high yields of hydrogen using starch and water via a synthetic enzymatic pathway.[25] The latter system is particularly attractive, as it may enable sugar to be converted into hydrogen fuel inside a vehicle itself. This would mitigate the problem of storage that exists today, as hydrogen takes up inordinate amounts of space at regular atmospheric pressure and compression of the gas requires energy and makes storage both difficult and dangerous.[26]

The synthetic processes being explored, if successful, will differ markedly from the current method of producing hydrogen fuel, which involves converting natural gas using steam. Natural gas techniques are costly, inefficient, and heavily reliant on fossil fuels. The synthetic biology-driven process is expected to cost significantly less while providing substantially higher yields, though research remains early in the developmental pipeline.

Risks and Potential Harms

Synthetic biology offers many potential methods to improve energy production and reduce costs, which deservedly generate attention and enthusiasm. A full assessment of these promising activities requires comparable attention to the current limitations, challenges, and anticipated risks or harms. This assessment is particularly important at this time because renewable energy applications may be the first synthetic biology products to come to market.

Contamination by accidental or intentional release of organisms developed with synthetic biology is among the principal anticipated risks. Unlike synthetically produced chemicals, which generally have well-defined and predictable qualities, biological organisms may be more difficult to control. Unmanaged release could, in theory, lead to undesired cross-breeding with other organisms, uncontrolled proliferation, crowding out of existing species, and threats to biodiversity.[27]

Consider biofuel production systems that employ synthetic biology and pond-grown algae. One hypothetical, worst-case scenario is a newly engineered type of high-yielding blue-green algae cultivated for biofuel production unintentionally leaking from outdoor ponds and out-competing native algal growth.[28] A durable synthetic biology-derived organism might then spread to natural waterways, where it may thrive, displace other species, and rob the ecosystem of vital nutrients, with negative consequences for the environment.

This scenario is theoretical. Considering it and developing appropriate precautions is nevertheless appropriate because of the rapid development of synthetic biology-generated photosynthetic algae for fuel production and the uncertain nature of the harm that may arise from accidental release. One of the advantages of synthetic biology is that many of the tools being developed include strategies to remediate such risks. Some of the approaches proposed include the engineering of so-called "terminator" genes or "suicide" switches that can be inserted into organisms, precluding them from reproducing or surviving outside of a laboratory or other controlled setting in the absence of unique chemical conditions.[29] Some are clearly sufficient to neutralize the risk of release, and others require further study as synthetic biology progresses.

Another risk in the energy sector is harm to ecosystems from the required dedication of land and other natural resources to production of biomass as feedstock for biofuels. If large areas of land were to be dedicated to biofuel development, this could put new and intense pressures on land, potentially affecting food production, communities, and current ecosystems. Because these applications of synthetic biology are still young, the impact of biofuel production on land use remains unknown. Some argue that efforts to develop and grow additional cellulosic biofuel will dramatically change and adversely impact the way land is used in the United States and abroad.[30] Others suggest that biofuel production can proceed safely with only minor adjustments in current land use practices.[31] Existing biodiverse prairie and meadow grasses may actually enhance the growth of feedstock for second-generation biofuels.[32] On balance, many anticipate the potential efficiencies and attendant reduction in reliance on fossil fuels offered by energy production using synthetic biology would offset anticipated risks to the environmental ecosystem as it exists today. But considerable uncertainty remains.

Health Applications of Synthetic Biology

Synthetic biology has the opportunity to advance human health in a variety of ways. Improved production of drugs and vaccines, advanced mechanisms for personalized medicine, and novel, programmable drugs and devices for prevention and healing are among a few of the expected achievements.

Promise and Potential Benefits

There is a long tradition of employing plants and other biological organisms to detect and cure human disease. Genetic engineering technology has been used for more than three decades in medicine to engineer bacteria with the ability to produce commercially relevant molecules like insulin and vaccines for hepatitis B virus and human papillomavirus.[33] Synthetic biology applications related to health build on this history, but most remain early in the research and development pipeline. The quick pace of biomedical research in general, and synthetic biology research in particular, suggests that this could change soon. This research is being conducted at universities and biotechnology or synthetic biology companies in the United States and overseas.[34]

Medicines

Synthetic biologists have refined a chemical technique called metabolic engineering to enhance the production of medicines. Through this process, scientists alter an organism's metabolic pathways—the series of chemical reactions that enable the organism to function at the cellular or organism level—in order to better understand and manage how those pathways work. They can redesign these pathways to produce novel products or augment the production of current products, like drugs. Synthetic biology can also be used to engineer molecules and cells that express proteins or pathways responsible for human disease. At some point these products may be used in efficient, large-scale screening methods to identify novel drugs for disease treatment or prevention.

One well-known example of synthetic biology in medicine is the re-engineering of a microorganism to make the antimalarial drug artemisinin more cheaply and efficiently. Malaria affects approximately two to three hundred million people each year and results in between 700,000-1,000,000 deaths, largely among young children in sub-Saharan Africa.[35] Artemisinin is a naturally occurring chemical derived from the plant artemesia, or sweet wormwood. It is an effective malaria treatment, but is difficult to obtain due to limitations on plant yield and high production costs. To address this problem, synthetic biologists at the University of California genetically engineered *E. coli* bacteria to produce a high volume precursor that can be chemically converted to artemisinin.[36] This semi-synthetic artemisinin is being developed today by the pharmaceutical company Sanofi-Aventis in collaboration with the California researchers and the Institute for OneWorld Health. If successful, these efforts should substantially reduce the drug's production cost and increase and stabilize world supply. Full-scale production is expected to begin shortly, with marketing expected in 2012.[37]

> "Making a few micrograms of artemisinin would have been a neat scientific trick," said Dr. Jay Keasling, whose laboratory originally developed the synthetic biological concept for making artemisinin. "But it doesn't do anybody in Africa any good if all we can do is a cool experiment in a Berkeley lab. We needed to make it on an industrial scale."[38]

Vaccines

Synthetic biology techniques are also being studied and used to accelerate the development of vaccines. Influenza vaccine production is among the key areas of focus. To develop a vaccine, one first needs to identify the virus strain, with its unique genetic code, against which the vaccine will be used. Synthetic biology tools, including rapid, inexpensive DNA sequencing combined with computer modeling, may streamline production time by accelerating this first step.

One industry group is developing a "bank" of synthetically created seed viruses for influenza vaccines that it hopes will enable more rapid vaccine production by reducing virus identification time.[39] DNA-based vaccines created "on-the-spot" to match actual, circulating viral genetic material may be a more efficient process for producing vaccine seed stock in the future.[40] However, these strategies are preliminary and may prove no more efficient or effective than conventional reverse engineering techniques. More research and experience is needed.

Advancing Basic Biology and Personalized Medicine

Twenty years ago, cloning, or replicating, a single gene was enormously time consuming. Today, such a task can be done in minutes by a machine, a development that has fueled rapid advances in synthetic biology. The ability to easily manufacture and manipulate DNA in the laboratory has enhanced scientists' productivity and opened new directions for scientific exploration. Researchers see great potential for synthetic biology to advance knowledge of fundamental biological principles. Expanding the DNA "alphabet" beyond its traditional four nucleotides—A, C, G, and T—to include non-naturally occurring nucleotides also gives synthetic biologists more flexibility in studying, detecting, and treating disease. For example, scientists recently used polymerase chain reaction (PCR) with novel nucleotides, a process that increases DNA's information potential and thus enables the manufacture of proteins with new properties.[41] To this end, researchers have already developed diagnostic tests using these DNA nucleotides to screen for human immunodeficiency virus, cystic fibrosis, and other diseases.[42]

In general, personalized medicine aims to apply the science of genomics to develop individually tailored, and thereby more effective, approaches to disease prevention and health care.[43] Synthetic biology offers useful strategies for advancing this goal. Many current cancer treatments focus on non-selective cell killing or on delivery to specific tissues. A growing body of knowledge supporting a molecular classification of tumors may facilitate the development of specifically designed detection devices matched to individual tumors. A synthetic biology approach currently under study is a cancer treatment that focuses on up to six cellular identifiers rather than one, effectively enabling

the treatment to be targeted more carefully and precisely toward the cells intended to be killed, while sparing healthy ones.[44]

Custom protein and biological circuit design may eventually enable the delivery of "smart proteins" or programmed cells that self-assemble at disease sites. Similarly, synthetic organisms could be developed to create a trigger to deliver or withhold treatment depending upon a local disease environment (such as low levels of oxygen) and provide targeted killing of cancer cells.[45] These and other novel approaches to tailored disease treatment may substantially improve outcomes and reduce the costs and burden of disease across the population.

While the benefits of synthetic biology to health care may prove monumental, significant hurdles remain. With the exception of semi-synthetic artemisinin and potential, near-term improvements in vaccine design, most of the anticipated health benefits of synthetic biology remain in the preliminary research stage. We are unlikely to see commercial applications from much of the biomedically oriented synthetic biology research for many years, although the pace of discovery is unpredictable.

Risks and Potential Harms

In addition to practical challenges, biomedical applications of synthetic biology raise potential risks for humans and the environment that are, in part, similar to those identified in the biofuels discussion and those commonly understood within the biomedical or greater engineering research communities today. Human health risks may arise from adverse effects of intentional or inadvertent release of the organisms engineered using synthetic biology. Infectious diseases may be transmitted to laboratory workers after needle sticks or to family members following airborne transmission of disease agents manipulated using synthetic biology techniques. Risks may also accrue to the wider human community or the environment if organisms proliferate without adequate means to limit reproduction.

Similarly, novel organisms developed with synthetic biology to treat illness may trigger unanticipated adverse effects in patients. The use of cell therapies of bacterial, or potentially, mixed microbial origin may cause infections or

unexpected immune responses. New organisms developed with the emerging technology of synthetic biology may pose unusual, if not unprecedented, risks resulting from their potential as biological organisms to reproduce or evolve.

Many of these risks are qualitatively similar to the risks that arise in horticultural biomedical and biotechnology research. There are well-established mechanisms in place to identify and manage future risks (see Chapter 4). Additionally, as with energy applications, internal mechanisms to reliably contain function and reduce or eliminate these risks are being developed. "Biological isolation," which is also termed "biosafety engineering," aims to build in molecular "brakes" or "seatbelts" that restrain growth or replication of partially or fully synthetic organisms.[46] Synthetic organisms can be engineered to be contained physically or temporally. Additional data are needed to assess how well biologically engineered safeguards, such as "kill switches" that activate after a defined number of generations, will work.

Agricultural, Food, and Environmental Applications of Synthetic Biology

Synthetic biology may also help to shift, if not substantially mitigate, some of the existing threats to our global food supply and environmental health. These potential benefits are in some ways more preliminary than the expectations for energy and health, but research and development in these fields are well underway.

Promise and Potential Benefits

In agriculture, efforts to manipulate crops and breed animals for specific purposes are not new. Many traditional farming practices, from plant breeding to animal husbandry, aim to direct evolution to achieve desired outcomes. Use of recombinant DNA technology, cloning, and other biotechnology tools have enhanced these practices. Taking these activities one step further, synthetic biologists are experimenting with high-yield and disease-resistant plant feedstocks that can be supplemented with efficient and environmentally friendly microorganisms to minimize water use and replace chemical fertilizers.[47] Researchers are altering the properties of plants through methods that combine metabolic components from various organisms in order to gain nutritional benefits, such as higher levels of food-grade protein.[48]

Efforts to remove waste using biological means date to at least 1972, when a researcher at General Electric applied for a patent on a form of *Pseudomonas* bacteria genetically engineered to digest oil slicks.[49] Environmental applications of synthetic biology are generally targeted to pollution control and ecological protection. The impact of naturally occurring oil-devouring microorganisms at the site of the 2010 oil spill off the U.S. Gulf Coast, for example, demonstrated how these organisms could reduce some types of pollution.[50] Synthetic biologists are eager to understand and direct these biological capabilities, or even enhance them, to respond to existing and future waste generated by human activities.

NEW PRODUCT PIPELINE: CROP ENHANCEMENT AND POLLUTION CONTROL

A synthetic biology-produced Pyrethium-grown compound may find use as natural insecticide.[51]

Synthetic biology-produced DNA sensors may be able to perform a range of roles, including detecting food spoilage and monitoring soil nutrition.[52]

Synthetic biology technology has been proposed to control biodegradation of a range of sources including toxic chemical pollutants such as industrial coolants, solvents, explosives, and residues from burning oil, coal, and tar.[53]

Other environmentally relevant examples of synthetic biology applications include laboratory-constructed microbial consortia, known as synthetic biofilms, which are being developed for use as environmental biosensors. These sensors could be used, for example, to monitor soil for nutrient quality or signs of environmental degradation. The design of biological "wetting agents," or biosurfactants, could increase the efficiency of bioremediation efforts and minimize the extent of damage from pollutants.[54] Biosurfactants are naturally produced by bacteria, yeasts, or fungi and are environmentally friendly in freshwater, marine, and terrestrial ecosystems. Synthetic biology may offer the ability to enhance the features of microbially produced biosurfactants to tailor them to specific spills or otherwise polluted areas.

Risks and Potential Harms

Synthetic biology applications in the context of agriculture, food, and the environment raise concerns broadly similar to those raised about genetic engineering in the past and those discussed above with respect to safety, resource management, and biodiversity. In brief, these risks include harms to humans, plants, or animals from, for example:[55]

- uncontrolled environmental escape or release and attendant disruption to ecosystems,
- new or sturdier pests—animal or plant—that may be difficult to control, and
- increased pesticide resistance and growth of invasive species.

As in the discussion of energy and health applications, the risks may be assessed and managed through existing protections long in use for biomedical and greater engineering research. Synthetic biology applications in the context of agriculture, food, and the environment may require more targeted efforts, however, including use of inbred checks, such as "suicide genes" or "kill switches" to ensure that they cannot propagate unintentionally.

Many potential applications of synthetic biology go well beyond the genetic engineering practiced throughout the biotechnology industry today. In the future, the field may be capable of creating entirely new organisms and systems previously unseen in the world today. Synthetic biology's critics and proponents alike worry that creating new organisms that have uncertain or unpredictable functions, interactions, and properties could affect ecosystems and other species in unknown and adverse ways. The associated risks of escape and contamination may be extremely difficult to assess in advance, as such novel entities may have neither an evolutionary nor an ecological history.[56]

Countering these concerns, at least somewhat, is experience showing that synthetic cells and systems in research settings have tended to be short-lived by comparison to those that have evolved in nature. Scientists have observed that synthetic organisms allowed to develop in the laboratory have consistently evolved toward nonfunctionality.[57] These are encouraging preliminary findings, but they do not eliminate the need for precautions in the event that

a future synthetic organism behaves differently than expected outside of the contained laboratory setting.

Another concern related to synthetic biology's impact on natural systems—crops grown for either biofuel or food consumption—is the broader effect on how society views and protects biodiversity. Does a chemically synthesized organism increase or decrease biodiversity, as measured by traditional taxonomy-based classification schemes? This concept becomes important in policy discussions pertaining to the use and potential abuse of land and other natural resources.

Biosecurity

Generally, the term "biosecurity" refers to the efforts needed to prevent misuse or mishandling of biological agents and organisms with the intent to do harm. The National Science Advisory Board for Biosecurity (NSABB), an independent federal advisory committee charged with advising the U.S. government on biosecurity issues and "dual use" research—that which may be used for either good or ill—defines the term as follows: "[b]iosecurity refers to the protection, control of, and accountability for high-consequence biological agents and toxins, and critical relevant biological materials and information, to prevent unauthorized possession, loss, theft, misuse, diversion, or intentional release."[58]

Unlike applications and potential applications of synthetic biology in the energy, health, agricultural, and environmental sectors, possible benefits in the biosecurity arena have not garnered significant public attention. Nor have they received comparable investment from academia, industry, or the government. It is nonetheless easy to anticipate some potential benefits.

Synthetic biology may enhance biosecurity by enabling researchers to identify biological agents of concern that may be developed synthetically or semi-synthetically. In the same way that the J. Craig Venter Institute "branded" the bacterium it synthesized this year with traceable information in the organism's genetic code, researchers may uniquely tag the genetic code of new organisms that they develop. When combined with other measures

to ensure biosecurity, this tagging process may provide an additional and effective deterrent to malicious use.

Similarly, biosecurity may be improved using the techniques discussed above for applications in energy, human health, agriculture, and the environment. As noted, "suicide" genes or terminator technologies built into the genome of a new organism to inhibit growth or survival outside of a contained environment may offer particularly effective means to counter biosecurity threats. Related tools could be crafted to ensure organism death in the face of particular chemicals or contexts. Uncertainties remain, however, with regard to the effectiveness of such strategies.

Concerns about dual use or intentional misuse of synthetic biology to do harm are among the most prominent critiques of this emerging technology. One of the most widely voiced risks attributed to synthetic biology is that it may be used, in the wrong hands, to intentionally create harmful organisms for bioterrorism. Recent examples of virus reconstruction using traditional recombinant DNA techniques fuel these concerns. These examples include the laboratory creation of infectious polio virus, the mycoplasma genome, and the 1918 strain of influenza virus.[59]

Frequently lost in these discussions about synthetic biology risks is recognition that DNA alone is not sufficient to create an independently functioning biological entity, such as a disease-causing virus that could spread. Despite the relative ease of access to known DNA sequences through public databases like GenBank[60] (an annotated collection of all publicly available genetic sequences), and equivalent databases across the globe, most experts in the scientific community agree that mere knowledge of a viral genome is far from sufficient to be able to re-constitute it or create a disease-forming pathogen. Rather, one must have an appropriate host and conditions for a virus to grow. Few individuals or groups today have the financial means or the technical skills to accomplish such ends, even when scientifically feasible. As the many technical challenges in synthetic biology affirm, it is not yet possible to craft functioning biological organisms from synthesized genomic material alone.

Risks and Potential Harms

With regard to biosecurity risks arising from synthetic biology, NSABB has twice issued reports and made recommendations to the federal government—first in 2006 and again in 2010.[61] In 2006, the group focused on synthesis of select agents and toxins, which are defined in law as certain infectious components of identified "select agent viruses," meaning those that the U.S. government has found to pose a severe threat to human health.[62] Following a review of the science at that time, the group made specific recommendations to reduce biosecurity risks, many of which the United States has since implemented, such as the establishment of a screening infrastructure for genetic sequence providers and others.[63]

NSABB's report "Addressing Biosafety Concerns Related to Synthetic Biology," issued in April 2010, offered four specific recommendations to ensure biosecurity in the current field of synthetic biology:

- Synthetic biology should be subject to institutional review and oversight since some aspects of this field pose biosecurity risks.
- Oversight of dual use research should extend beyond the boundaries of life sciences and academia.
- Outreach and education strategies should be developed that address dual use research issues and engage the research communities that are most likely to undertake work under the umbrella of synthetic biology.
- The U.S. government should include advances in synthetic biology and understanding of virulence/pathogenicity in efforts to monitor new scientific findings and technologies.

These recommendations reflect an attempt to balance the considerable potential benefits of synthetic biology with the risks resulting from intentional or unintentional misuse of this technology and its products. Noticeably absent were recommendations to restrict access to genetic sequences separate from those components of Select Agents and toxins already limited by the U.S. Select Agent regulations (see Chapter 4). In large part, this determination appears to reflect the fact, as noted, that sequences alone will not yield, nor often be sufficient to predict, functions.

NSABB's work is not unique. Many experts and interested groups in the United States and abroad have recently devoted considerable time and energy to evaluating the biosecurity risks of advancing synthetic biology practices.[64] This still-young field benefits from a clear consensus among scientists and policymakers that biosecurity risks, while perhaps overstated by some, nevertheless are serious and warrant ongoing and proactive re-examination as technical capacity evolves. The tools used to mitigate these risks may also be the tools to mitigate environmental, health, and other potential risks. The tools to address risk depend on an expanding scientific knowledge base as much as potential benefits do.

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CHAPTER 4
Oversight

A wide array of existing federal laws and regulations apply to the emerging field of synthetic biology. The scope of federal authority depends on whether the activity involves research or production; whether federal funds are involved; the nature of the application (e.g., to generate drugs, food, cosmetics, or fuels); and whether the product is subject to national security or export controls. Applicable also are local institutional, municipal, and state requirements, many of which focus on safety and security.

This chapter presents a brief overview of the components of the U.S. oversight system as it relates to synthetic biology. It is intended to be a descriptive summary of the major regulatory laws and agencies without Commission recommendations or opinion (presented in Chapter 5). It focuses on the exclusive, as well as shared and overlapping, federal authorities governing research, development, and commercialization. Generally, synthetic biology is treated like other comparable areas of science and technology, and the federal government relies, in part, on local institutional-level oversight to identify and reduce risks.

The government's initial efforts at oversight of genetic engineering activities arose in the mid-1970s and focused, consistent with the state of the science at the time, on laboratory-contained research.[1] When the first genetically engineered organisms were being considered for field testing in the mid-1980s, the U.S. government issued a trans-agency guidance document, called "The Coordinated Framework," for regulating the research and development of biotechnology products. Fundamentally, the policy calls for the government to regulate genetically engineered products through existing legal frameworks established for products developed without genetic engineering. For example, drugs developed by means of genetic engineering are regulated under the pre-market review and approval standards of the Food and Drug Administration (FDA) for new drugs.[2] The key to this policy, reflected in regulations across the government, is its focus on risk rather than methodology. Regulation is predicated on a risk-benefit assessment of the characteristics of the final product (i.e., its intrinsic characteristics and features), not the method by which it is made.[3] Products presenting higher risks or greater uncertainty are subject to higher degrees of oversight. This approach enables existing agencies and regulations to serve, with revisions in current rules as technology evolves,

as the oversight framework for emerging biotechnology. Periodic reassessment, ideally through an ongoing process of open public dialogue, is required as new knowledge and new understanding of risks emerge. The Coordinated Framework's standards continue to drive the federal government's approach to oversight of biotechnology, including synthetic biology.

Through this system, some oversight protections apply broadly to anyone working with specific organisms or creating certain environmental effects. Other oversight is more narrowly focused, applying exclusively, for example, to researchers or the research setting. Regulatory programs of the U.S. Department of Agriculture (USDA) or FDA apply case-by-case to particular goods like food or drugs. USDA regulations govern also the interstate movement of certain infectious agents, agricultural pathogens, and pests. The Environmental Protection Agency (EPA) regulates the safety of new chemicals not addressed by other statutes, including industrial chemicals and pesticides, and oversees emergency management programs for the clean up of environmental hazards. The Occupational Safety and Health Administration (OSHA), Department of Transportation (DOT), and Department of Commerce (DOC) play roles as well, setting safety standards respectively for the workplace, interstate transfer of infectious agents, and export of disease-causing organisms or knowledge and technologies that may pose security risks.

The National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) help to ensure the safe and ethical conduct of synthetic biology research through promulgation of risk assessment and containment standards for laboratories and investigators. NIH specifically oversees research involving recombinant DNA molecules and receives advice from the NIH Recombinant DNA Advisory Committee (RAC), a group of non-federal experts governed by the openness and public meeting provisions in the Federal Advisory Committee Act.[4] Biosafety standards and requirements of review are set forth in the *NIH Guidelines for Recombinant DNA Research (NIH Guidelines).* The *NIH Guidelines* require risk-based classification and containment for NIH-funded research involving the construction or use of recombinant DNA molecules, as well as organisms and viruses containing these molecules. Synthetic nucleic acids are addressed to the extent that recombinant methods are used in their assembly.[5] NIH is currently considering a proposal to amend

the *NIH Guidelines* to specifically include research with synthetic nucleic acids, regardless of whether recombinant techniques are used. NIH published this proposal in March 2009,[6] and, in June 2010, after consideration of public comment, RAC recommended that the NIH Director adopt these changes. CDC and NIH also promulgate a widely accepted industry standard, *Biosafety in Microbiological and Biomedical Laboratories (BMBL)*, which establishes specific procedures for laboratory safety.[7]

CDC, USDA, the Department of Health and Human Services (DHHS), and the Federal Bureau of Investigation (FBI) also play specific roles in addressing concerns about biosecurity. The Federal Select Agent Program (FSAP), administered by CDC and USDA with the Animal and Plant Health Inspection Service (APHIS), regulates individuals and entities possessing, using, or transferring "select agents and toxins" within the United States.[8] Select Agents and toxins are pathogens or biological toxins that have been declared by DHHS and USDA to "have the potential to pose a severe threat to public health and safety."[9] The FBI conducts the security risk assessment of individuals requesting access to Select Agents.[10]

Taken together, these provisions form a protective patchwork quilt of regulations and guidance for research, the workplace, environmental risks, and in some cases pre-market review of safety and efficacy for new products. Anticipated advances in synthetic biology, however, raise questions about the capacity of this system to provide effective oversight of the entire field. Concerns about biosafety and biosecurity, for example, are frequently voiced. Biosafety focuses on protecting people, plants, animals, and the environment from accidental exposure to a pathogen or toxin with potential adverse effects. Biosecurity focuses on keeping biological agents and technologies out of the hands of those who might misuse them. For both biosafety and biosecurity, risk assessment—which typically extrapolates from data on known risks to characterize new and uncertain risks—may be particularly complicated for synthetic biology as novel or previously uncharacterized organisms are developed.

Oversight Challenges

The effective oversight of biotechnology relies on the assessment of the risks posed by the products generated and the process used to generate them. These assessments are predicated on understanding the biologic characteristics of the agent, its host, and the environment in which it will function.[11] In synthetic biology, a major concern is whether the scale of manipulation, using *de novo* chemical synthesis instead of conventional recombinant DNA techniques, raises sufficiently new levels of uncertainty about products, such as their characteristics or safety profile, to warrant new levels or forms of oversight.

The first generation of synthetic biology products is, or may likely be, relatively simple and similar to other genetically engineered products.[12] In the short term, agents generated through synthetic biology are unlikely to raise novel risk assessment or risk management issues. One of the biggest challenges in the oversight of synthetic biology, however, is its capacity to create novel entities that are increasingly dissimilar to known agents or organisms, making potential risks harder to assess. As the field begins to develop more complex, novel, and artificial agents and products, assessing the risks posed will be challenging, particularly for those products with the potential to be released into the environment[13] (see also Chapter 2 for a discussion of risks and benefits).

The increasing ease of access to the materials and supplies used to generate synthetic agents poses another unique oversight challenge. Gene and oligonucleotide sequences or parts can be commercially obtained with ease, and reagents and automated equipment for synthesizing nucleic acid sequences are available as well.[14] Deviant uses of synthetic biology could therefore, at least theoretically, occur outside of the scope of existing oversight mechanisms. At this stage, however, technical challenges to creating novel organisms are such that it is difficult to imagine the creation of a substantial threat.

Finally, current federal oversight of biotechnology is, in some cases, limited to entities that are owned or funded by the federal government. This means that research currently being conducted using private funds is not subject to some federal oversight.

Federal Authorities

Many federal agencies have jurisdiction over research and production activities involving synthetic biology. The Coordinated Framework organized lead responsibilities for oversight of intentional, beneficial uses of biotechnology, but did not compartmentalize oversight. The oversight is integrated, and overlap is minimized but necessarily exists as the framework is built to respond flexibly to changing science.

This shared oversight is described below, generally, in terms of the particular sectors discussed earlier in this report, but the discussion should not be understood to suggest silos or pigeonholes in the oversight system.

Biosecurity

Several regulatory schemes and initiatives are focused on reducing biosecurity risks arising from biotechnology. These include FSAP, export and interstate transfer limitations, and the 2010 guidance for synthetic double-stranded DNA providers.[15]

Federal Select Agent Program

FSAP is administered by DHHS/CDC and USDA's APHIS.[16] Congress established FSAP to limit the possession, use, and transfer of biological agents and toxins, designated as "Select Agents," that have the potential to pose a severe threat to public health and safety, animal and plant health, or to the safety of animal or plant products.[17] Facilities that possess, use, or transfer Select Agents, including for use in synthetic biology, must be registered with FSAP, and individuals or entities seeking to use, transfer, or possess Select Agents must apply for registration and approval for these activities. Select Agents that are regulated by both CDC and APHIS are referred to as "overlap" agents and involve threats to both sectors.[18]

The Select Agent regulations extend both to specific agents as well as certain genetic elements, recombinant nucleic acids, and recombinant organisms. Among the regulated genetic components are: (1) nucleic acids that can

produce infectious forms of any of the Select Agent viruses; (2) recombinant nucleic acids that encode for the functional form(s) of Select Agent toxins if the nucleic acids (a) can be expressed in vivo or in vitro, or (b) are in a vector or recombinant host genome and can be expressed in vivo or in vitro; and (3) Select Agents and toxins that have been genetically modified.[19] These regulations are specifically targeted to address scientific advancements such as synthetic biology. The nucleic acid sequence information of Select Agents is not regulated.[20]

Each individual or entity applying for registration must designate a "Responsible Official" who will ensure compliance with the regulations, including conducting annual inspections and overseeing proper disposition of Select Agents.[21] Registration is granted to entities only after a risk assessment is performed for the individuals who have access to, or the ability to gain possession of, a Select Agent or toxin. Additionally, registration is contingent upon a facility inspection by FSAP, and approval of additional documents such as security, biosafety, and incident response plans. Any certificate of registration issued is only valid for three years and for a single physical location, and no individual may access a Select Agent at any time without approval by the DHHS Secretary or the APHIS Administrator.[22] All records relating to Select Agents and toxins must be kept for three years and produced upon request.[23] Any theft, loss, or release of a Select Agent must be reported to the relevant agency immediately and an APHIS/CDC Form 3 must be submitted within seven calendar days.[24] Inspectors may inspect records and premises where Select Agent activities are carried out without prior notification.[25]

APHIS/CDC issued guidance recently for those who create or use synthetic biology and may therefore be subject to the Select Agent regulations.[26] This guidance was partially in response to the National Science Advisory Board for Biosecurity's (NSABB's) report, *Addressing Biosecurity Concerns Related to the Synthesis of Select Agents*, which discusses the regulatory and oversight framework as it relates to synthetic genomics and Select Agents.[27] Elsewhere, the FBI has implemented a "tripwire" initiative in partnership with the U.S. synthetic biology industry to report suspicious requests for genetic sequences. The FBI also has conducted outreach to academia and industry and do-it-yourself (DIY) communities to improve biosecurity for synthetic biology research and uses.[28]

Export Administration Regulations

The Bureau of Industry and Security within DOC administers the Export Administration Regulations.[29] These regulations govern the export and re-export of dual-use commodities, software, and technology from the United States and apply to any individual or entity seeking to export.[30] Included in this group may be researchers collaborating with overseas colleagues, manufacturers with foreign plants, and gene synthesis providers shipping orders outside of the United States. Particularly relevant to the oversight of synthetic biology are provisions designed to restrict access to materials that have dual use applications (i.e., materials with both commercial applications and military or other defense applications).[31]

Items subject to the Bureau of Industry and Security's licensing authority are listed on the Commerce Control List (CCL).[32] Category 1 of the CCL contains "materials, chemicals, 'microorganisms,' and toxins."[33] Products are then classified according to "reasons for control:" (1) national security and dual use; (2) missile technology; (3) nuclear nonproliferation; (4) chemical and biological weapons; and (5) anti-terrorism, crime control, regional stability, short supply, United Nation sanctions, etc.

For each controlled item, detailed licensing requirements and policies for screening potential recipients are imposed. Licenses are provided depending on the nature of the threat. The end user receiving the product must also be screened against lists of proscribed individuals and organizations. Relevant screening lists include: (1) the Entity List (parties who may trigger a license requirement under Export Administration Regulations), (2) the Denied Persons List (parties denied export privileges), (3) the Unverified List (parties where the Bureau of Industry and Security has been unable to identify the end user in prior transactions), (4) the Specially Designated Nationals List (parties barred by the Treasury, Office of Foreign Assets Control), (5) the Debarred List (parties barred by the State Department under International Traffic in Arms Regulations), and (6) Nonproliferation Sanctions (parties that have been sanctioned under various statutes).[34]

Interstate Transfer Regulations

DOT sets rules for the safe and secure transportation of hazardous materials,[35] which may encompass materials necessary for, or created by, synthetic biology. Designated hazardous materials include substances (e.g., wastes and pollutants) that DOT believes are capable of posing an unreasonable risk to health, safety, or property during transport.[36] All persons transporting hazardous waste by air, rail, highway, or water must follow the regulations put out by the Pipeline and Hazardous Materials Safety Administration (PHMSA), an agency within DOT. Specified packaging, labeling, and transport requirements are imposed. For example, packages containing hazardous waste must be able to withstand conditions normally involved in transportation such as changes in pressure, temperature, and humidity, as well as vibrations and shocks.[37] Hazardous materials must also be labeled appropriately to warn transporters (and possible emergency responders) of the type of material contained in the packaging.[38] Hazardous material employees must receive training on PHMSA regulations so they can perform their functions safely.[39]

PHMSA is authorized to conduct inspections and enforce these regulations with civil penalties. Inspectors may send warning letters alerting transporters to probable violations or issue citations if they believe the alleged violation does not have a "direct or substantial impact on safety."[40] Any person who knowingly violates a requirement of these regulations may be liable for a civil penalty up to $55,000 per transportation or shipping violation, and up to $110,000 if the violation results in death, serious illness, serious injury, or substantial destruction of property.[41] In addition, anyone who knowingly, willfully, or recklessly violates the regulations and releases a hazardous material may be imprisoned for up to 10 years for any resulting death or bodily injury.[42] DOT reserves additional authority through the Federal Motor Carrier Safety Administration, the Federal Railroad Administration, the Federal Aviation Administration, and the U.S. Coast Guard.[43]

Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA

In October 2010, DHHS issued guidance for screening orders of synthetic double-stranded DNA. The guidance addresses the potential biosecurity concerns associated with the use of double-stranded DNA synthesis to reconstruct regulated pathogens and toxins. The guidance recommends "baseline standards…regarding the screening of orders so that they are filled in compliance with current U.S. regulations and to encourage best practices in addressing biosecurity concerns associated with the potential misuse of their products to bypass existing regulatory controls."[44] Compliance with the guidance is voluntary, but many of its specific recommendations reflect underlying statutory or regulatory mandates. Meeting its standards will help ensure that synthetic double-stranded DNA provided for use in synthetic biology will be in compliance with applicable federal regulations, namely the Select Agent regulations and the export administration regulations.[45]

The guidance emerged from a multi-year, public engagement process. Designed as "best practices," the intention of the guidance is efficient update as new information and technical skills emerge. The drafters explained: "[t]he target audience for this guidance is the gene and genome synthesis industry, because the technical hurdles for *de novo* synthesis of Select Agents and Toxins from double-stranded DNA are much lower than for *de novo* synthesis of these agents from single-stranded oligonucleotides."[46] This guidance proposes a screening framework for "commercial providers of synthetic double-stranded DNA that is 200 base pairs…or greater in length to address concerns associated with the potential for misuse of their products."[47] The framework includes "customer screening and sequence screening, follow-up screening as necessary, and consultation with U.S. Government contacts, as needed."[48]

Biosafety

Biosecurity and biosafety concerns frequently overlap, as do the oversight strategies employed to address them. In the earliest days of the genetic engineering era, oversight efforts focused on safety concerns shared by the public as well as scientists conducting this novel research. As the field has grown

and matured in the 40 years since then, the tools developed to address these concerns have evolved as well.

NIH Guidelines for Research Involving Recombinant DNA Molecules

NIH established the *NIH Guidelines* in 1976. They were created in light of public concern about emerging techniques for manipulating genetic material, and the 1975 Asilomar Conference on Recombinant DNA in which scientists from academia, industry, and government came together to establish shared principles for containment and safety in such research. The *NIH Guidelines* specify practices for constructing and handling recombinant DNA molecules and organisms and viruses containing recombinant DNA molecules. Compliance with the *NIH Guidelines* is mandatory for investigators at institutions receiving NIH funds for research involving recombinant DNA[49] and would encompass synthetic biology falling within these confines as well. With input from NIH RAC, NIH has modified the *NIH Guidelines* nearly 30 times since their inception in order to keep pace with advances in science and biosafety. Satisfying their terms is a condition of NIH funding, and they are also widely accepted and followed voluntarily by scientists and organizations, both public and private, across the research enterprise. In addition, other government agencies, including DOE, the Department of Veterans Affairs, and USDA, currently have policies in place that state that all recombinant DNA research conducted or funded by those agencies must comply with the *NIH Guidelines*.[50] Through an active process of public engagement and deliberation, they have become a "gold standard" that is cross-referenced by numerous resources, including *Biosafety in Microbiological and Biomedical Laboratories* (*BMBL*) (see discussion below).[51]

The oversight process prescribed in the *NIH Guidelines* begins at the local level. Through the work of Institutional Biosafety Committees (IBCs)—local groups that include experts in safety and scientific practice—individual research plans are reviewed on a regular basis to assure that biosafety protections, including laboratory containment, are appropriate for the risk posed. Minimum containment measures (Biosafety Levels [BSL] 1-4) based on the known and unknown risks of particular experimental agents and designs are set forth in the *NIH Guidelines*, and institutions may impose additional

measures as deemed necessary to comply with their responsibilities under the guidelines.[52] Many IBCs also review other forms of research that entail biosafety risks as part of their institutionally assigned responsibilities.[53] Generally, NIH places primary responsibility on institutions to conduct oversight locally and non-compliance is expected to be self-reported.[54]

Following the advice of NIH RAC and other experts, in 2009 NIH proposed to clarify the scope of the *NIH Guidelines* to specifically cover nucleic acid molecules made solely by synthetic means. The proposed revisions, which are undergoing final review, aim to clarify the applicability of the *NIH Guidelines* to research with synthetic nucleic acids and to provide principles and procedures for risk assessment and management of such research.[55] NIH expects to finalize these amendments this year.

Private work may also interconnect with the federal oversight structure if the institution receives federal research funds. For example, although the work done by the J. Craig Venter Institute on the self-replicating synthetic genome was not federally funded, the Venter Institute is a major federal grant recipient, and thus, is required to adhere to the *NIH Guidelines*, regardless of the source of funding for a particular project.[56] In application, this means that along with IBC review, the Venter Institute followed the corresponding risk group and biosafety measures for the organisms it was working with as prescribed by the *NIH Guidelines*. In addition, the Venter Institute also must follow regulations directed toward private workplaces, such as the OSHA laboratory standards described below.

Biosafety in Microbiological and Biomedical Laboratories (BMBL)

CDC and NIH developed *BMBL* to address the "safe handling and containment of infectious microorganisms and hazardous biological materials,"[57] including those which may be used for synthetic biology. *BMBL* centers on the principles of containment and risk assessment. Containment under *BMBL* includes the "microbiological practices, safety equipment, and facility safeguards" required to protect people who work with biological material, the public, and the environment from exposure. Risk assessment allows the "appropriate selection of microbiological practices, safety equipment, and

facility safeguards" required to prevent what *BMBL* deems "laboratory-associated infections."[58] *BMBL* complements the *NIH Guidelines* and is broader in its focus. Laboratories that receive federal funding for research may be required to comply, if, for example, the agency requires compliance as a policy matter for its intramural labs, or as a term and condition of specific extramural funding. There is no federal law that requires compliance for all researchers regardless of funding. Thus, generally, they set a voluntary standard.[59] Biosafety standards evolve as scientific knowledge progresses, and *BMBL*, like the *NIH Guidelines*, is intended to evolve and adapt.

Workplace Oversight

OSHA regulates working conditions for employees in most private sector and federal government workplaces.[60] In addition, many states (State Plan States) have occupational safety and health programs that have been approved by federal OSHA and cover public sector (state and local government) as well as private industry employers.[61] Therefore, the regulations of OSHA or an equivalent State Plan State program will be relevant to most synthetic biology laboratories or workplaces. Under OSHA, employers must create an environment that is "free from recognized hazards that are causing or are likely to cause death or serious physical harm."[62] The regulations of OSHA or an equivalent State Plan State program lay out safety principles and precautions for working with and disposing of hazardous chemicals as well as toxic and hazardous substances. Particular attention is paid to ventilation, sanitation, protective equipment, machinery, and emergency procedures.[63] Hazardous waste cleanup and first aid procedures are also imposed.[64] Employers must evaluate the hazards of chemicals at their work place and inform employees about potential harms through "comprehensive hazard communication programs" including container labeling, warnings, and safety data sheets.[65]

The regulations of OSHA or an equivalent State Plan State program also protect employees who may be exposed to blood or other potentially infectious materials such as human bodily fluids, human unfixed tissues or organs, and Human Immunodeficiency Virus (HIV)-containing cells or culture medium.[66] Regulations require employers exposing employees to such substances to have exposure control plans, delineated methods of compliance, and special protocols pertaining to the HIV and the Hepatitis B virus.[67]

EPA also plays a role in workplace oversight through the Toxic Substances Control Act (TSCA). Under TSCA, EPA assesses risks to workers from exposure to new intergeneric microorganisms. EPA can impose personal protective equipment requirements and engineering control restrictions to control worker exposure to potentially harmful substances.[68]

Energy

Oversight provisions for synthetic biology in the energy sector include the general security and safety standards described above. They also include specific provisions aimed at various products, for example, biofuels, biosensors (for various applications), and chemical oil dispersants. These provisions may also apply in other sectors, such as health or agriculture as well.

New Chemicals Including Microorganisms

EPA, under TSCA, regulates new chemicals and microorganisms, including those that could be derived from recombinant DNA technologies and synthetic biology.[69] These new chemicals and new microorganisms can have uses in the energy sector but TSCA also addresses other industrial and commercial applications. Under the law, individuals or entities seeking to market or import new chemicals or microorganisms into the United States for commercial purposes must give EPA notice. New microorganisms subject to this requirement include "'intergeneric' microorganisms (including bacteria, fungi, algae, viruses, protozoa, etc.) formed by combining genetic material from organisms in different genera" and "microorganisms formed with synthetic DNA not from the same genus."[70] At least 90 days notice and submission of any known or "reasonably ascertainable" data on the intergeneric microorganism are required.[71] EPA scientists then conduct a risk assessment to ensure that the microorganism will not present an unreasonable risk of injury to health or the environment. EPA reviews the proposed use(s) of the new intergeneric microorganism. It evaluates potential human health and environmental hazards as well as potential environmental, worker, and general population exposures from manufacturing, processing, use, and disposal. EPA may require that additional data be developed by the submitter to enable it to make a reasoned evaluation and may limit or impose restrictions depending on the findings of the risk assessment weighed

against the benefits of the microorganism.[72] The same process applies to proposed commercial research and development testing of new microorganisms that are released into the environment. Individuals or entities seeking to conduct such field trials must also file 60 days notice and data with EPA.[73]

Certain intergeneric microorganisms are exempt from the requirement for full notification if the manufacturer meets specified criteria defining eligible microorganisms and specified use conditions (including conditions relating to containment, inactivation, and a number of criteria on the introduced DNA). The limited set of microorganisms eligible for exemption are those that have undergone categorical risk assessment as a species, or as a group of strains within a species, whereby specific features of the category and the history of safe use of members of the exempt category were reviewed. The criteria used, and list of eligible microorganisms, were subject to public comment at the time of proposal and had significant input from major scientific societies. This exemption is most applicable to the use of microorganisms to manufacture specialty and commodity chemicals. Also exempt are intergeneric microorganisms used for documented research in contained structures or research required to comply with the *NIH Guidelines*. The exemption for research and development conducted in contained structures must also address inactivation controls that take into account considerations such as the organism's ability to survive in the environment, potential routes of release, and procedures for transfer of materials between facilities.[74]

EPA's oversight of synthetic biology under TSCA may be limited in ways that pose particular challenges as synthetic biology evolves. First, the amount of information EPA requires to be submitted with a notification that is useful for assessing the risks of microorganisms is limited.[75] Manufacturers need not test new chemicals for toxicity, pathogenicity, or other harmful effects before they submit a notification to EPA.[76] Therefore, EPA may have limited information on which to base its risk assessment. However, if EPA determines that the available information is insufficient to permit a reasoned evaluation of the health and environmental effects of a new intergeneric microorganism and that the microorganism may pose an unreasonable risk, EPA typically will allow submitters to suspend the notification review period to enable such data to be developed. EPA can also impose restrictions on the manufacture,

processing, distribution in commerce, use, or disposal of a new intergeneric microorganism to limit exposures and releases until sufficient data are developed. However, with the potential for increasing complexity with synthetic biology products, predictability of the properties of microorganisms will be more complicated. Under TSCA, EPA does require immediate reporting by industry of new information on existing substances which reasonably supports the conclusion that the substance presents a substantial risk to human health or the environment.[77]

A second challenge is that the reach of the law is limited to commercial or commercial research and development activities.[78] It is unclear that all potential users or developers of synthetic biology products, for example, noncommercial research efforts by DIY users, are covered.

Human Health

FDA is the primary regulatory agency that exercises specific authority over drugs and devices for human health. Research activities related to such products are also subject to concurrent biosecurity and biosafety protections described above, including the *NIH Guidelines*, *BMBL*, and TSCA rules of EPA, as applicable.

Food and Drug Administration

New drugs and devices must satisfy FDA's safety and effectiveness standards before they can be introduced into the U.S. market.[79] For drugs, these standards require pre-market review and approval. For devices, FDA requires manufacturers to show substantial equivalence to a marketed device. FDA regulated foods, discussed below, and cosmetics generally reach the market without pre-market approval, although food additives and colorings are reviewed.

Synthetic biology potentially may be used in some fashion in all of the products that FDA regulates. For decades in the health care area, FDA has reviewed and approved numerous biotechnology-derived pharmaceuticals and devices, including drugs and devices created from bioengineered organisms.[80] It approved its first recombinant product, human insulin, in 1982.[81] FDA has

issued guidance to explain its thinking about the application of its laws and regulations in the biotechnology sector.[82] It draws no distinction between traditional recombinant techniques and synthetic techniques for genetic engineering. Gene segments "may be obtained from other organisms, or synthesized from scratch in a laboratory."[83]

Before, during, and after approval for clinical testing or marketing, the manufacturer or researcher (e.g., the "sponsor") of a product must work closely with FDA and provide ongoing data about safety and effectiveness.[84] FDA also oversees pre-clinical testing, manufacturing processes, and advertising and promotional labeling.[85] The agency imposes minimum ethical standards on clinical research that it oversees, including requiring the informed consent of research participants, safety and ethics review at the local level, and adverse event reporting.[86]

FDA retains considerable and ongoing authority to monitor safety and protect consumers. It may require manufacturers to submit a "risk evaluation and mitigation strategy," including use of patient registries or screening tests, to manage known or potential risks at the time of approval or after the product has gone to market.[87] It may withdraw approval, urge a voluntary recall, petition a court for injunction or seizure, require label changes, or issue warnings if so warranted.[88] Severe penalties may also be imposed on violators of FDA's requirements. Perpetrators can face civil penalties up to $1,000,000 per violation and criminal sanctions including up to 10 years imprisonment.[89]

As new technologies and applications arise, such as those that may be created by synthetic biology, FDA has responded and clarified its oversight. In 1985, it held that research using recombinant DNA technology should follow safety and containment provisions of the *NIH Guidelines*.[90] Genetically engineered animals, which may be used, for example, to produce pharmaceuticals or food for human and animal consumption, are regulated under FDA's animal drug provisions because the genetically engineered construct (the modified DNA produced by traditional recombinant or synthetic means) itself is an article that meets the definition of a "drug," something "intended to affect the structure or any function of the body of…animals."[91] FDA's new animal drug approval process, similar to the process for human medicines, generally

requires pre-market review and approval. For genetically engineered animals of a species not traditionally consumed as food, and for which animal health and environmental risks are shown to be low, FDA may exercise "enforcement discretion" and decline to require pre-market approval, as it did with aquarium fish engineered to glow in the dark.[92]

Agriculture, Food, and Environment

Many of the laws and regulations discussed above apply to research and commercial activities involving synthetic biology in the agriculture, food, and environment sectors. Under TSCA, for example, EPA undertakes prior review of new chemical substances, like biofertilizers, and other environmental applications of biotechnology, like bioremediation and mineral extraction. In addition, algae developed for chemical production other than energy, when grown in the open, would be construed as a potential environmental release and receive TSCA oversight. Major oversight programs involving plant and animal pests and pesticides are administered concurrently by USDA and EPA respectively. FDA oversees certain food safety and production activities.

Environmental Impact

Under the National Environmental Policy Act (NEPA), all federal agencies undertaking major action must take into account the impact their action may have on the environment.[93] Before reaching a final decision on any proposed action that may have a significant effect, the government must evaluate, through a public process, the anticipated environmental impact of the action along with any reasonable alternatives.[94] Public comment is requested at several points in this process.[95] Pursuant to NEPA and the Clean Air Act, EPA reviews all "environmental impact statements," and makes its comments available to the public. EPA also reviews selected environmental assessments.[96] NEPA does not require agencies to select the alternative with the least environmental impact.[97] The NEPA process, however, helps ensure that agencies are making informed decisions, responding to public concern, and taking into account mitigation of environmental impact. Typically used in situations such as new construction or major changes in federal land use, NEPA requirements may also be applied to laboratory research and scientific advancements. While

the drafting of an environmental impact statement is time consuming, the NEPA process adds an important layer of protection to uncertain or controversial decisions surrounding synthetic biology.

Plant and Animal Pests

USDA's APHIS is responsible for regulating the introduction (importation, interstate movement, and environmental release) of genetically engineered organisms that are known to, or could, pose a plant pest risk.[98] Genetically engineered organisms are considered to be "regulated articles" if the donor organism, recipient organism, vector, or vector agent used in their creation is known to be a plant pest, the plant pest status of that organism is not known, or there is a reason to believe that one of these organisms may be a plant pest, and therefore may encapsulate synthetically created organisms.[99] APHIS derives the authority to regulate the introduction of genetically engineered organisms from the Plant Protection Act of 2000.[100] This act defines a plant pest as a living stage of an organism (such as an insect, bacterium, fungus, or virus) that "may directly or indirectly injure, cause damage to, or cause disease in any plant or plant product."[101] The regulations apply to genetically engineered microorganisms, insects, and other traditional types of plant pests and to any genetically engineered plants if plant pest organisms (bacterial and viral plant pathogens) are the donor organisms and vector agents are used in the creation of these genetically engineered plants.[102]

APHIS currently uses a permit and notification system to authorize the introduction of regulated articles; all regulated articles are eligible for the permitting procedure, and certain regulated genetically engineered plants are eligible for the notification procedure.[103] The notification procedure is an administratively streamlined process. Currently, most regulated genetically engineered plants are introduced under notification, and approximately 10 percent of APHIS authorizations are done under the permitting procedure. A permit may be withdrawn where any permit condition established by APHIS is violated.[104]

In making a regulatory determination for a permit or notification for a regulated article, APHIS bases its determination on whether the actions under notification or permit are unlikely to result in the introduction or dissemination of a plant pest. This determination takes into account various risk factors, including, among other things, a low risk that the genetically engineered organism or its progeny can persist, reproduce, or establish without human assistance.

A person may petition the agency to evaluate submitted data and assess whether a particular regulated article is unlikely to pose a plant pest risk, and, therefore, should no longer be subject to APHIS regulations for genetically engineered organisms.[105] If, based on submitted information, the agency concludes that the article is unlikely to pose a plant pest risk, the agency may make a determination to approve the petition and confer non-regulated status on the regulated article. Thereafter, APHIS would no longer require permits or notification for the introduction of this genetically engineered organism.[106]

For animals and genetically engineered animal products, APHIS controls import, export, and interstate movement through a similar licensing process. To apply for a product license, test reports and research data must be submitted that establish the purity, safety, potency, and efficacy of the product. Product labels, including all claims made on them and in advertisements, must also be submitted.[107] Facility licenses are approved once a USDA administrator has approved the conditions of the production facility and production methods and verified that the applicant is sufficiently qualified.[108] Researchers and sponsors must show that their experimental product will not contaminate any current products and will be carefully disposed of and controlled.[109] Authorization to ship experimental products is allowed only in very strict circumstances and to limited destinations.[110]

No products may be imported into the United States without a permit.[111] Biological product permits can be issued for research and evaluation, distribution and sale, and transit shipment.[112] Strict requirements for containment, disease profile of the shipping country, qualifications of the recipient, and safety of the product, among others, are applied during the application process.[113] Ongoing inspection of production facilities and products may

be undertaken.[114] Manufacturers and importers must keep detailed records of the production process, testing results, and inventory and disposition of the product.[115] These detailed APHIS regulations would therefore add many helpful pieces to the patchwork quilt of protections for different types and uses of synthetic biology.

Pesticides

Before pesticides can be commercialized or used in the United States, they must meet specific health and safety standards under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).[116] FIFRA requires EPA to determine that a pesticide will not pose an unreasonable risk of harm to human health or the environment.[117] Both naturally occurring and genetically engineered microorganisms and plants, including those created by synthetic biology, are regulated in this way.

EPA's pre-market approval and post-market adverse event reporting requirements rely on careful scientific evaluation. The agency must determine "with a reasonable certainty" that "no harm to human health" and no "unreasonable risks to the environment" will occur when the product is used as intended and according to label directions.[118] EPA requires applicants to perform various tests and submit comprehensive data before approval.[119] EPA also sets "tolerances," meaning maximum pesticide residue levels, for the amount of the pesticide that can remain in or on foods or feed crops.[120]

For research on pesticides, EPA's oversight is more limited. It does not require pre-approval for laboratory or contained-setting research.[121] Field testing, which is a prerequisite for commercial marketing approval, usually requires EPA pre-clearance through an experimental use permit or notification.[122] Experimental use permits are granted if, in EPA's view, the experimental use will not yield unreasonable adverse effects on the environment. As with marketing approval, applicants must submit detailed information including safety and pre-field testing data, to support their permit request.

States also regulate pesticides under FIFRA and applicable state laws. Some states impose more restrictive requirements and others defer to EPA's oversight.[123]

Genetically Engineered Foods

All genetically engineered animals, regardless of whether they are intended for food use, are within FDA's jurisdiction, as explained above, because the recombinant DNA constructs that alter the animal's structure or function meet the definition of new animal drugs. FDA oversees the safety and effectiveness of these animals through its pre-market review and approval processes. Applicable law does not require pre-market clearance for "food," whether derived from plant or animal. However, FDA requires evidence that food additives are safe at their intended level of use before they may be added, which is relevant for the products of genetic engineering.[124]

FDA has two main authorities over foods. First, it has post-market authority to seize foods that pose a risk to public health.[125] Second, it may regulate as food additives the substances (e.g., enzymes) added to plants. For example, in 1994 the agency reviewed a genetically engineered tomato with improved ripening qualities and regulated a gene product added to the tomato as a food additive.[126] Where a substance is not "generally recognized as safe" or otherwise exempt, FDA must review and approve the use of the additive before marketing, regardless of the technique used to add it to food.[127]

FDA is authorized to assure that the foods under its purview bear labels that are truthful and not misleading.[128] For foods from genetically engineered plants, FDA policy expressly indicates that name changes are appropriate only if "the resulting GE [genetically engineered] food product" is "materially different from its traditional counterpart," meaning that "the GE food product differs in nutritional quality, taste, etc."[129] In the tomato example cited above, FDA found use of the traditional name "tomato" appropriate because the genetically engineered product did not meaningfully differ in chemical composition from a traditional tomato. In contrast, FDA did require a special label for oil derived from a genetically engineered soybean plant because it contained significantly higher amounts of oleic acid than traditional soybean oil.[130] Production methodology (i.e., whether a product is produced through biotechnology or through conventional breeding) is not considered "material" information, and therefore such information is not required to be disclosed on the food label.[131] FDA follows this same standard for foods from genetically

engineered animals, although no genetically engineered animals have been approved for food at this time.

Environmental Impact and Clean Up

At the far end of the oversight scheme, particularly at this early stage of synthetic biology research and development, are remediation programs. EPA oversees programs for prevention and emergency management of chemical accidents;[132] oil pollution prevention and discharge;[133] and emergency planning and notification.[134] Under EPA, the Office of Solid Waste and Emergency Response also has both emergency and long-term clean up programs under the Comprehensive Environmental Response, Compensation, and Liability Act, as well as the Resource Conservation and Recovery Act. The scientific risk assessment and response strategies employed in these operations are likely to evolve as the field of synthetic biology itself evolves.

Summary

Multiple federal departments and agencies have significant oversight responsibilities for synthetic biology. The scope of these authorities extends from the laboratory to the field, the environment, the workplace, and the market. Some agencies impose specific safety conditions on research funded with federal dollars or at institutions that receive federal funds. Others reach all research, development, and commercial activities that raise specific threats or risks of harm. Generally, there is at least one federal agency—NIH, CDC, FDA, USDA, OSHA, DOT, DOC, or EPA—with specific oversight responsibility for a proposed application and frequently there is overlapping jurisdiction. Where prior experience or the character of the activity warrants heightened scrutiny, like drug and device development or pesticide use, pre-market review or approval is usually required. Genetically engineered animals require approval by FDA prior to entering into commerce.

This patchwork quilt of measures is built on long-standing practices that have adapted to new technologies over time. Risk assessment in this field may be particularly challenging and require both new techniques and new standards. Further adaptation and restructuring may be required as the applications

of synthetic biology grow and their consequences are better understood. As elaborated on in Chapter 5, the Commission's overview has indicated that the government should undertake a more comprehensive review, through a central body such as the Executive Office of the President, to assure that the existing patchwork quilt is indeed affording the U.S. public and the environment with adequate protections as the field of synthetic biology advances.

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[13] Ibid.

[14] Patterson, A., op cit. For example, in 2002 virologist Eckard Wimmer announced that his team had created live poliovirus "from scratch" using DNA they ordered by mail, and a viral genome map on the internet. Ball, P. (2004) Starting from scratch. *Nature* 431:624-626.

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[16] APHIS/CDC. *Applicability of the Select Agent Regulations to Issues of Synthetic Genomics*. Available at: www.selectagents.gov/SyntheticGenomics.html.

[17] 7 C.F.R. Part 331; 9 C.F.R. Part 121; 42 C.F.R. Part 73.

[18] 7 U.S.C. § 8411.

[19] 7 C.F.R. § 331.3(c); 9 C.F.R. §§ 121.3(c), 121.4(c); 42 C.F.R. §§ 73.3(c), 73.4(c).

[20] APHIS/CDC. *Applicability of the Select Agent Regulations to Issues of Synthetic Genomics*, op cit.

[21] 7 C.F.R. § 331.9; 9 C.F.R. § 121.9; 42 C.F.R. § 73.9.

[22] 7 C.F.R. § 331.7; 9 C.F.R. § 121.7; 42 C.F.R. § 73.7.

[23] 7 C.F.R. § 331.17; 9 C.F.R. § 121.17; 42 C.F.R. § 73.17.

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[31] 15 C.F.R. § 730.3.

[32] 15 C.F.R. § 738.1.

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[35] 49 U.S.C. § 5103.

[36] 49 C.F.R. § 171.8.

[37] 49 C.F.R. § 173.24.

[38] 49 C.F.R. Part 172, Subpart E.

[39] 49 C.F.R. Part 172, Subpart H.

[40] 49 C.F.R. §§ 107.309-107.310.

[41] 49 C.F.R. § 107.329.

[42] 49 C.F.R. § 107.333.

[43] 49 C.F.R. §§ 174-177.

[44] Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA (2010), op cit., at 62820.

[45] Ibid.

[46] *Screening Framework Guidance for Synthetic Double-Stranded DNA Providers*, 74 Fed. Reg. 62319, 62319 (Nov. 27, 2009).

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[48] *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA (2010)*, op cit.

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[64] 29 C.F.R. § 1910.120.

[65] 29 C.F.R § 1910.1200.

[66] 29 C.F.R. § 1910.1030(a)-(b).

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[68] 40 C.F.R. Part 721.

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[73] 40 C.F.R. § 725.250.

[74] 40 C.F.R. Part 725.

[75] 15 U.S.C. § 2607(a)(2).

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[106] APHIS. (2010). *Petitions*. Available at: www.aphis.usda.gov/biotechnology/petitions.shtml.

[107] 9 C.F.R. § 102.3(b).

[108] 9 C.F.R. § 102.4.

[109] 9 C.F.R. § 103.2.

[110] 9 C.F.R. § 103.3.

[111] 9 C.F.R. § 104.1(a).

[112] 9 C.F.R. § 104.2(a).

[113] 9 C.F.R. § 104.2.

[114] 9 C.F.R. Part 115.

[115] 9 C.F.R. Part 116.

[116] 7 U.S.C. § 136 *et seq*.

[117] 7 U.S.C. § 136a(c)(5); 7 U.S.C. § 136(bb). *See also* EPA. (2010). *Regulating Pesticides*. Available at: www.epa.gov/pesticides/regulating/index.htm.

[118] EPA. (2010). *Evaluating New Pesticides and Uses*. Available at: www.epa.gov/pesticides/regulating/index.htm#eval.

[119] 40 C.F.R. Parts 152, 158, and 161; EPA. (2010). *Pesticide Registration Program*. Available at: www.epa.gov/pesticides/factsheets/registration.htm#process.

[120] 21 U.S.C. § 346a; EPA. (2010). *Pesticide Tolerances*. Available at: www.epa.gov/pesticides/regulating/tolerances.htm.

[121] 40 C.F.R. § 172.3(b)(1).

[122] 7 U.S.C. § 136c; 40 C.F.R. Part 172, Subpart A; 40 C.F.R. § 172.45.

[123] American Association of Pesticide Control Officials. Available at: http://aapco.ceris.purdue.edu/index.html.

[124] 21 U.S.C. § 348; International Food Information Council and FDA. (2010). *Food Ingredients and Colors*. Available at: www.fda.gov/Food/FoodIngredientsPackaging/ucm094211.htm; FDA. (1992). *Statement of Policy: Foods Derived from New Plant Varieties: Guidance to Industry for Foods Derived from New Plant Varieties*, 57 Fed. Reg. 22984 (May 29, 1992).

[125] 21 U.S.C § 334; 21 U.S.C. § 342.

[126] 21 C.F.R. § 173.170; 21 C.F.R. § 573.130; FDA. (1994). *Agency Summary Memorandum Re: Consultation with Calgene, Inc., Concerning FLAVR SAVR™ Tomatoes*. Available at: www.fda.gov/Food/Biotechnology/Submissions/ucm225043.htm#out38.

[127] Maryanski, J.H., Biotechnology Coordinator, Center for Food Safety and Applied Nutrition, FDA. (1999). *Genetically Engineered Foods*. Statement to the Subcommittee on Basic Research, House Committee on Science, October 19, 1999. Available at: www.fda.gov/newsevents/testimony/ucm115032.htm.

[128] 21 U.S.C. § 343(a).

[129] FDA. (2010). *Background Document: Public Hearing on the Labeling of Food Made from the AquAdvantage Salmon*, Page 4. Available at: www.fda.gov/downloads/Food/LabelingNutrition/FoodLabelingGuidanceRegulatoryInformation/Topic-SpecificLabelingInformation/UCM223913.pdf; FDA Statement of Policy, op cit.; FDA. (2001). *Draft Guidance for Industry: Voluntary Labeling Indicating Whether Foods Have or Have Not Been Developed Using Bioengineering*. Available at: www.fda.gov/food/guidancecomplianceregulatoryinformation/guidancedocuments/foodlabelingnutrition/ucm059098.htm.

[130] FDA Background Document, op cit.

[131] *Alliance for Bio-Integrity v. Shalala*, 116 F. Supp. 2d 166, 178-179 (D.D.C. 2000).

[132] 40 C.F.R. Part 68.

[133] 40 C.F.R. Part 112; 40 C.F.R. Part 110.

[134] 40 C.F.R. Part 68; 40 C.F.R. Part 112; 40 C.F.R. Part 110; 40 C.F.R Part 355.

CHAPTER 5
Analysis and Recommendations

The President asked the Commission to recommend how the developing field of synthetic biology and related technologies can maximize public benefits, minimize risks, and observe appropriate ethical boundaries. A framework of basic ethical principles can provide guidance in the assessment of an emerging technology such as synthetic biology. In this case, as described in Chapter 1, five principles are identified that are most relevant to assessing ethical considerations related to synthetic biology and other emerging technologies:

1. Public Beneficence
2. Responsible Stewardship
3. Intellectual Freedom and Responsibility
4. Democratic Deliberation
5. Justice and Fairness

The Commission relied on these principles to conduct its analyses and build its recommendations, as presented in this chapter. It is the Commission's hope that these principles will be applicable not only to synthetic biology, but also to assessing other emerging technologies.

Public Beneficence

The ideal of public beneficence is to act to maximize public benefits and minimize public harm. This principle encompasses the duty of a society and its government to promote individual activities and institutional practices, including scientific and biomedical research, that have great potential to improve the public's well-being. In the case of emerging technologies like synthetic biology, this improvement may be by means of providing improved or more widely available forms of medical and health care, food, shelter, transportation, clothing, and eco-friendly fuel, along with other means of improving people's lives. Scientific and technological discovery often have the added potential of increasing economic opportunities, which also redound to the public good.

This section focuses on how society and its members—individually and collectively—can provide an environment for synthetic biology to flourish for the benefit of as many people and communities as possible. The Commission observed during its deliberations considerable enthusiasm for the field among scientists, industry representatives, and the public. The anticipated benefits portend dramatic potential improvements in energy production, the economy, health care, and other areas that would enhance public welfare. The development of strategies that will allow the field to continue to grow in ways that offer the greatest potential net benefit to individuals and communities, both in the United States and worldwide, should be a high priority for public policy.

Promoting Public Well-Being and Prioritizing the Public Good

Citizens and their representatives have good reason to be engaged observers in the development of synthetic biology, particularly in light of the potentially transformative benefits to society of potential uses. Chapter 3 presented current examples of synthetic biology applied in research and development programs designed to benefit humankind. Environmentally friendly biofuels and affordable antimalarial drugs are among the near-term products of synthetic biology already receiving significant attention. These are important current examples of how advances in synthetic biology may deliver widespread benefits that promote social welfare. Continued investment in this field

should be directed to these types of applications and others that offer similarly expansive opportunities to address serious problems that affect our collective well-being.

The Commission's deliberations called attention to the diversity of interests and practitioners participating in the synthetic biology community. Despite their range of disciplinary backgrounds, nationalities, and institutions, synthetic biologists appear united in contributing their expertise to the development of novel products that address global needs. Distinguishing between academic, public, and commercial research in synthetic biology is extremely difficult, as many researchers are active contributors in each domain. In many ways, drawing this distinction is unnecessary. The organizational home of an individual practitioner may not limit his or her ability to work with others to accomplish shared research goals.

This intermingling of academic and commercial research—both basic and applied—provides fertile ground for innovation.[1] The development of semi-synthetic artemisinin, an antimalarial drug, is one example that demonstrates how academic, public, non-profit, and industry interests have come together to promote global well-being. In this case, researchers at a public university interested in exploring synthetic biology identified the production of artemisinin, a treatment for malaria, as potentially improvable using synthetic biology techniques. An estimated one million people, primarily children under the age of 5 years, die annually from malaria.[2] Researchers began with public dollars and expanded their work in partnership with a private foundation. The results are being commercialized by a for-profit pharmaceutical manufacturer, and a non-profit foundation is planning for eventual distribution. While the story is not over and initial drug production remains in process, the model shows how collaboration between academia, the private sector, and industry can use synthetic biology to address significant societal problems.

The artemisinin story illustrates one way that a diverse group of interests and funding sources—both public and private—can collaborate on research and development activities involving synthetic biology. As with many emerging technologies at an early stage, however, public information about the amount of public and private investment in this field is minimal.[3]

Public funding of research can bring an enhanced measure of focus, oversight, and accountability to any emerging technology. Absent national security protections, government-funded research in the United States is publicly disclosed. Public funding also promotes transparency and accountability that might not exist in purely private efforts.

Private funds may not be widely available for research into risk assessment practices or the ethical and social safeguards that aim to maximize public benefit while minimizing the risks of new technologies like synthetic biology. In synthetic biology, there are some notable exceptions of private funding for efforts to examine ethical, legal, and social issues, including commendable activities supported directly by the J. Craig Venter Institute and the Alfred P. Sloan Foundation.[4] The scope and impact of these efforts are, however, generally quite limited. In order to understand the possibilities and moral limits of synthetic biology public funding may be necessary to augment such efforts. The products of this work are critical to ongoing efforts to evaluate safety and to promote public acceptance of this emerging field. Research exploring the normative and conceptual issues related to these topics can be a valuable complement to the empirical, quantitative, or qualitative work that typically receives greater support from public funding sources.

To promote public engagement and assure needed transparency regarding federal efforts in the field of synthetic biology, the government should review and make public findings regarding the scope of its research funding at this time.

Recommendation 1: Public Funding Review and Disclosure

Through a central body such as the Executive Office of the President, the federal government should undertake a coordinated evaluation of current public funding for synthetic biology activities, including funding for research on techniques for risk assessment and risk reduction, and for the study of ethical and social issues raised by synthetic biology. This review should be completed within 18 months and the results made public.

The evaluation recommended here would ensure effective use of public funds, promote transparency, develop priorities, and avoid redundancy. This recommendation and the examples below align with the Commission's interest in

justice and fairness. It aims for the potential benefits of synthetic biology to extend to as many individuals and communities as is reasonably possible, addressing this country and the world's most urgent and compelling needs (see pp. 161-166). Public funding can be an important tool in realizing these goals and doing so in ways that are sensitive to ethical and safety concerns.

Most potential products of synthetic biology are in very early stages of development. Basic research is critical to further expansion of this science and its effective translation into useful products. Basic research—work that focuses on enhancing our understanding of fundamental principles of science and the natural world—is also important to the growth of the field. Direct commercial applications are not typically the intended outcomes of basic research, yet this work can also be extremely valuable to society. A commitment to basic research reflects a belief that knowledge is itself a public good.

More practically, scientific fields invariably develop in unanticipated ways. The aggressive pursuit of fundamental research generally results in a broader understanding of a maturing scientific field like synthetic biology than approaches solely focused on developing specific applications to address contemporary needs. This understanding of basic principles may be a particularly valuable way to prepare for the emergence of unanticipated risks that would require rapid identification and creative responses.

At the same time, synthetic biology research is in competition for scarce resources with other areas of science and other societal needs. Decisions will be required regarding which research directions deserve funding over others. These decisions should be driven in part by which strategies offer the most promise based on scientific, technical, and social considerations.

Potential profitability is also a significant motivator of research and development investments. When research is fairly new, as in the emerging field of synthetic biology, the promise is often high but the incentives for investment can be low because of uncertain success or marketability. Some drugs that address asymptomatic risk factors or "lifestyle" issues (e.g., drugs that do not treat life threatening conditions or pain), rather than specific disease processes, have received significant attention from the pharmaceutical industry because

there is a large market and potential for profit in the United States and other developed nations. Some of these drugs can be quite beneficial to patients, such as statins to reduce elevated cholesterol levels. Drug manufacturers frequently devote research resources to the development of very similar versions of competitors' already successful, profitable products instead of pursuing novel research directions with a less certain path to success or profits.

Other more prevalent and deadly diseases lacking therapeutic or preventive options today receive lower investment priority, especially diseases more common in developing nations. Absent a reliable market in the United States or other wealthy countries, manufacturers often choose not to devote significant investment dollars to these diseases, choices reflecting rational responses to the market. Government and others interested in promoting public well-being, such as private foundations, can effect change by re-drawing the financial landscape for research and development in these areas.

Recent congressional and Administration emphasis on "high risk/high reward" research offers one example of how the public good can be promoted when market forces alone may not succeed. The National Institutes of Health (NIH) has created several programs that specifically support creative, highly innovative research approaches that might otherwise be too novel or too risky to receive funding through traditional channels.[5] In 2007, Congress also expressly directed the agency to award research grants for these types of potentially high-impact research projects.[6] In the private sector, the Bill and Melinda Gates Foundation, through its "Grand Challenges in Global Health" program, is changing the financial picture by awarding substantial grants—nearly $500 million dollars in recent years—to stimulate scientific innovation among traditional and nontraditional researchers to treat and prevent diseases most prevalent in developing nations.[7]

The development of novel antibiotics is one example in which incentives could help stimulate research interest toward an important public need that might otherwise not receive sufficient attention.[8] Similarly, funding or incentives to spur research into age-related degenerative diseases of the nervous system (including dementia and gait disorders) may help in the quest for cures for Alzheimer's disease, Parkinson's disease, and related disorders prevalent in aging populations.

The Commission's deliberations focused specifically on synthetic biology, following its charge from President Obama, but alternative research strategies are also appropriately being pursued to address many of the national and global concerns for which synthetic biology may provide solutions. The Commission supports public and private investment in synthetic biology-related research as one important avenue of research among others.

Recommendation 2: Support for Promising Research

Advancing the public good should be the primary determinant of relative public investment in synthetic biology versus other scientific activities. The National Institutes of Health, the Department of Energy, and other federal agencies should continue to evaluate research proposals through peer-review mechanisms and other deliberative processes created to ensure that the most promising scientific research is conducted on behalf of the public.

Synthetic biology is advancing rapidly. Future funding decisions should be made through ongoing evaluation of the state of the science and its potential applications. Policy makers, the scientific community, and the public should continue to assess the adequacy of existing peer review and funding mechanisms to address future advances in synthetic biology-related science and technology. Private interests, including for-profit and nonprofit entities, should likewise consider global public needs that can be uniquely advanced through their efforts.

Realizing Economic Opportunities

Most current attention to the potential benefits of synthetic biology focuses on applications related to health, energy, and the environment. Investment in synthetic biology also can bring economic benefits, both from the direct activities related to research and development and from the eventual commercialization of successful technologies. These benefits have the potential to strengthen communities through the creation of jobs and other opportunities, thereby enhancing citizens' quality of life. Forecasting the potential impact of synthetic biology on job creation and economic growth is difficult, but the Commission received public comments estimating that the use of synthetic

biology in the chemical industry alone could generate global revenue of $1 trillion and create 1.2 million direct jobs.[9] Additional revenue and jobs would be expected from synthetic biology activities related to pharmaceutical and agricultural applications.

Potential economic benefits may be particularly valuable to communities in developing nations, where health, access to resources, and economic stability are closely linked to one another and to disparities in health and welfare. This underscores the importance of adopting a global perspective when considering the potential benefits of synthetic biology.

Although the potential economic benefits cannot be known with precision, this potential should nonetheless be continually assessed as part of activities to promote synthetic biology. Technological solutions alone cannot eliminate the fundamental causes of global inequality, but they can contribute to comprehensive programs to address them. This theme is addressed when considering the principle of justice and fairness.

Intellectual Property and the Sharing of Scientific Knowledge

Information sharing and reasonable access to discoveries and inventions have long fueled the scientific enterprise. These activities enable scientists to leverage each other's work in order to more quickly advance new projects and translate basic research into products. Impediments to innovation and information sharing, some say, arise from the patent and copyright system. These mechanisms afford inventors and authors a time-limited right to prohibit others from using their work or similar work of the same design. One concern consistently raised with regard to biotechnology is the potential limiting effects of intellectual property claims over research results, particularly in basic research.[10] Patents on discoveries and restrictive or exclusive licensing agreements may encourage, but also may deter or increase the development costs of subsequent inventions that build on the basic discovery. Some who provided testimony to the Commission argued that the current system unduly limits scientific advances; others took the opposite view and asserted that the current system works well.

The patent system is designed to encourage innovation and investment by providing incentives to inventors to disclose their discoveries to the public so that others can build on them. In return, the inventor is granted exclusive rights to the invention and control of its development for a limited period of time. Balancing the interests of the inventor and those who wish to use the invention is a challenging task in science generally, and in biotechnology particularly. These concerns have been the focus of numerous studies, for example, in genomics.[11] Ongoing discussions have focused on the roles and responsibilities of government, the academic community, and the private sector in adopting intellectual property practices that foster an environment in which invention and innovation can thrive. Such discussions are likely to continue as patent law and court decisions in this area evolve.[12]

Synthetic biology raises challenging issues in this area as a result of research interest in creating standard biological "parts" that can be combined to build new biological systems or organisms for potential use in health care, agriculture, and energy (see Chapter 3). The field also is particularly dependent on information technology and the need for common standards.[13]

Concerns about the effects of patenting on synthetic biology mirror those expressed about patents involving DNA and genetic tests—that is, whether patents will be granted that are either too narrow or too broad.[14] Overly broad patents could "restrict collaboration and stifle development in the field, and narrow patents may overcomplicate the process, meaning that hundreds of patents have to be negotiated to produce a system from standardized parts."[15] For example, the Venter Institute is seeking a patent on the synthetic cell it described in May 2010 and on processes for making synthetic genomes. For some, these efforts raise questions about the extent to which a patent on synthetic organisms should be issued and whether doing so is in the public interest.[16] Others in the synthetic biology community have taken steps to keep some portion of the "parts" developed with synthetic biology available in an open-source system (e.g., BioBricks and the Registry of Standard Biological Parts) without traditional patent restraints.[17]

In the last 20 years, we have seen increased emphasis on transparency, data sharing, and creative licensing practices for patentable subject matter.

This trend applies especially, though not exclusively, to publicly funded research. Examples of current data sharing requirements include several NIH policies introduced since the late 1990s, most recently the 2007 NIH Public Access Policy, a congressionally mandated provision for public distribution of research results.[18] Similar policies apply to awardees of the Howard Hughes Medical Institute and the Wellcome Trust, private research funding sources in the United States and the United Kingdom, respectively.[19] Public clinical trial disclosure requirements have arisen from the private sector, through research journal publishers, and the public sector, through congressional actions in 1998 and 2007.[20] Demands for licensing inventions to meet social needs, including providing access to medications or enabling more research and technology development, have fueled innovative licensing practices and creative solutions to so-called "patent thickets" and other limitations on scientific exploration.[21]

The principle of public beneficence requires researchers, inventors, patent holders, and others to work together to develop creative strategies to maximize opportunities for innovation. Licensing alternatives could include methods of compulsory or bundled licensing, patent pooling, and broad, non-exclusive licenses for foundational technology. Because synthetic biology is in large part based on the application of engineering principles through the use of standardized, modular parts, access to those standard components could be especially critical to the development of the field.

Intellectual property issues in synthetic biology are evolving. The Commission offers no specific opinion on the effectiveness of current intellectual property practices and policies in synthetic biology. It recognizes that there are important concerns that deserve ongoing attention, especially as this rapidly developing field evolves. Current litigation, such as *Association for Molecular Pathology, et al. v. U.S. Patent and Trademark Office, et al.*, is likely to influence practices and policies in the future. This case presents the question of whether isolated human genes—those with mutations associated with an increased risk of breast cancer—and the comparison of their sequences is patentable.[22] Thus, the government should keep careful watch on this field and consider best practices and other policy guidance, if needed, to ensure that access to basic research results and tasks is not unduly limited.

Recommendation 3: Innovation Through Sharing

Synthetic biology is at a very early stage of development, and innovation should be encouraged. The Executive Office of the President, as part of the coordinated approach urged in Recommendation 4, should lead an effort to determine whether current research licensing and sharing practices are sufficient to ensure that basic research results involving synthetic biology are available to promote innovation, and, if not, whether additional policies or best practices are needed. This review should be undertaken with input from the National Institutes of Health, other agencies funding synthetic biology research, such as the Department of Energy and the National Aeronautics and Space Administration, the U.S. Patent and Trademark Office, industry, academia, and public civil society groups. The review should be completed within 18 months and the results made public.

The Commission urges the government to consider subsequent reviews and coordinated assessment if needed. Information sharing is a critical mechanism for promoting scientific progress and innovation.

Responsible Stewardship

The principle of responsible stewardship calls for prudent vigilance, establishing processes for assessing likely benefits along with assessing safety and security risks both before and after projects are undertaken. A responsible process will continue to assess safety and security as technologies develop and diffuse into public and private sectors. Prudent vigilance does not demand extreme aversion to all risks. Not all safety and security questions can be definitively answered before research begins, but prudent vigilance does call for ongoing evaluation of risks of harm along with benefits. The duty to be responsible stewards of nature, the earth's bounty, and the world's safety rests on concern not only for human health and well-being today but also and importantly for future generations and the environment looking forward.

The principle of responsible stewardship can be interpreted in an operational way to pose the question, "What can and should we, as a society, do in response to the emerging field of synthetic biology to be responsible stewards of nature, the earth's bounty, human health and well-being, and the world's safety, now and into the future?"

Options for action in this area range from doing nothing—that is, allowing the field of synthetic biology to proceed without limits or regard for public or environmental safety—to halting or substantially slowing its progress until risks can be identified and mitigated. One common interpretation of the "precautionary principle" would prescribe the latter approach. There are several definitions of the precautionary principle, but it generally states that if an action or policy has the potential to cause harm but uncertainty exists regarding the likelihood or severity of harm, the responsibility for demonstrating the safety of the approach belongs to those advocating for the policy or action.

The precautionary principle evolved primarily in the context of European debates and resolutions concerning the environment and genetically modified foods, and it is often raised in discussions involving risk and uncertainty in public policy in the United States and internationally.[23] One premise behind the precautionary principle may be that because there is a social responsibility to protect the public or the environment from plausible and avoidable harms,

protections should be relaxed only when science produces evidence that harm is unlikely to result. In some legal systems, such as that of the European Union, the application of the precautionary principle is a statutory requirement.[24]

A contrasting perspective is the "proactionary" principle, which assumes that an emerging biotechnology should be considered "safe, economically desirable and intrinsically good unless and until shown to be otherwise, which means that the burden of proof is on those who want to slow down a given line of research."[25] Advocates of the proactionary principle appeal to a commitment to intellectual freedom, the autonomy of individual decision making, economic growth, national competitiveness, and improved health and well-being. At its most extreme, this principle might allow science and technology to go forward unfettered, but, in general, proponents of this principle have supported some measure of oversight and monitoring.[26]

In order to provide benefits to human conditions and the environment, the Commission thinks it imprudent either to declare a moratorium on synthetic biology until all risks can be determined and mitigated, or to simply "let science rip," regardless of the likely risks. The field of synthetic biology can proceed responsibly by embracing neither the precautionary principle nor the proactionary principle. The Commission instead proposes a middle ground—an ongoing system of *prudent vigilance* that carefully monitors, identifies, and mitigates potential and realized harms over time. It came to this position for several reasons.

First, synthetic biology does not necessarily raise radically new concerns or risks compared to those that have been expressed about other emerging technologies, for example, molecular biology and nanotechnology. In many ways, synthetic biology is an extension of genetic engineering and part of an increasingly interconnected network of scientific disciplines including, among others, nanotechnology and information technology.[27]

Second, many existing oversight mechanisms and bodies (statutory, regulatory, and voluntary) are well situated and in the process of reviewing and monitoring the field of synthetic biology as it develops. The Commission endorses activities aimed at ensuring that those mechanisms and bodies are

sufficiently well coordinated and supported to effectively monitor risks in an ongoing and proactive fashion.

However, synthetic biology does introduce some possible risks that warrant special attention. According to the National Science Advisory Board for Biosecurity (NSABB), synthetic biology poses "varying degrees of uncertainty regarding the predictability of biological properties of partially or completely synthetic agents or materials."[28] It also poses some unusual potential risks, as "amateur" or "do-it-yourself" (DIY) scientists and others outside of traditional research environments explore the field. These risks must be identified and anticipated—as they are for other emerging technologies—with systems and policies to assess and respond to them while supporting work toward potential benefits. In this section, the Commission considers several approaches to promoting responsible stewardship, including oversight mechanisms, establishing safeguards, supporting relevant research, and encouraging and developing a culture of responsibility.

Stewardship through Oversight

Scientists have been conducting biological research that poses risks throughout the history of modern science. Consider Edward Jenner's experiments 200 years ago to develop a smallpox vaccine using cowpox virus, or more recently, gene therapy for rare diseases and studies of pathogens that could kill or sicken thousands through a natural or malevolent environmental release. History tells us that such research has resulted in enormous benefits for society, but it sometimes has had terrible consequences. Over time, safety and security practices and procedures have expanded and evolved to increase the likelihood that risks will be anticipated, mitigated, and monitored and that responses can be activated quickly should harms arise.

In the United States, oversight frameworks already exist for many activities of modern biological science including research involving humans, animals, microorganisms and toxins, and recombinant DNA. Oversight also occurs with regard to laboratory worker safety, use of federal funds in research, and transport and containment of dangerous agents. Oversight is frequently, but not exclusively, tied to public funding or the need to gain regulatory approval in order to market or distribute a product (see Chapter 4).

Long-standing regulatory systems, for example for food, drugs, and chemicals, undergird such approaches, while others developed specifically around the fields of genetic engineering and biotechnology. Some grew out of what were initially, and in some cases remain, voluntary self-policing efforts. These policies tend to be predicated on a risk-benefit assessment that is scaled according to identified risk and that evolves through an ongoing process of open public dialogue.[29] Over time, reflecting principled flexibility, many have been modified as risks, or the lack thereof, became clearer.

Demonstrating the government's increasing attention to this new field, the evolving federal oversight framework for synthetic biology, in the past year alone, includes:

- a proposed revision of the *NIH Guidelines for Research Involving Recombinant DNA Molecules* to address synthetic biology,[30]
- development of a U.S. government *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA*,[31]
- development of an Animal and Plant Health Inspection Service (APHIS)/Centers for Disease Control and Prevention (CDC) guidance on how current Select Agent regulations apply to those who create and use synthetic genomic products,[32] and
- consideration by the NSABB of strategies for conducting outreach to all practitioners of synthetic biology, enhancing the culture of responsibility, and promoting international engagement.[33]

These efforts build on the existing oversight responsibilities exercised by various federal agencies, including the Environmental Protection Agency (EPA) (chemical safety), the Food and Drug Administration (FDA) (food, drugs, and medical devices), the Department of Agriculture (crops and animal feed), and the Department of Homeland Security (biosecurity).

Internationally, the community of scientists working in synthetic biology, as well as policymakers and ethicists, are also focusing on ways to assure responsible stewardship. For example, the European Commission supports SYNBIOSAFE, a collaborative project among public and private parties that is researching the safety and ethics of synthetic biology. Governance and oversight strategies for

synthetic biology research and products are similarly being addressed through multiple efforts at the international level.[34]

To assure responsible stewardship in the field of synthetic biology, clarity, coordination, and accountability must exist across the government. The Commission does not believe that new agencies, offices, or authorities must be developed at this time, if ever. Instead, the Executive Office of the President (EOP) should lead an interagency process to identify and clarify, if needed, existing oversight authorities and to ensure that the government is fully informed on an ongoing basis of developments, risks, and opportunities as this field grows.

Recommendation 4: Coordinated Approach to Synthetic Biology

The Commission sees no need at this time to create additional agencies or oversight bodies focused specifically on synthetic biology. Rather, the Commission urges the Executive Office of the President, in consultation with relevant federal agencies, to develop a clear, defined, and coordinated approach to synthetic biology research and development across the government. A mechanism or body should be identified to: (1) leverage existing resources by providing ongoing and coordinated review of developments in synthetic biology, (2) ensure that regulatory requirements are consistent and non-contradictory, and (3) periodically and on a timely basis inform the public of its findings. Additional activities for this coordinating body or process are described in other recommendations.

These activities might be carried out, for example, under the auspices of the Office of Science and Technology Policy in the EOP, or the Emerging Technologies Interagency Policy Coordination Committee. It is essential that they be coordinated by an office with sufficient authority to bring together all parts of the government with a stake in synthetic biology. It is similarly important that this effort be sufficiently authoritative to effectively engage with, or supervise engagement with, foreign governments. A critical component of this coordinated strategy is to assure both the scientific community and the public that biosafety, biosecurity, and environmental risks of synthetic biology are fully addressed.

In any scientific inquiry, risks must be justified by anticipated benefits. Such balancing of risks and potential benefits is often complicated by uncertainty. Because much of science explores the unknown, policy makers should develop policies that acknowledge uncertainty about both risks and potential benefits. Information, flexibility, and judgment are critical to find the appropriate balance and determine the most responsible way to proceed. The rapid development of the field of synthetic biology makes the challenges of decision making under conditions of uncertainty particularly acute.

Recommendation 5: Risk Assessment Review and Field Release Gap Analysis

Because of the difficulty of risk analysis in the face of uncertainty—particularly for low-probability, potentially high-impact events in an emerging field—ongoing assessments will be needed as the field progresses. Regulatory processes should be evaluated and updated, as needed, to ensure that regulators have adequate information. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President should convene an interagency process to discuss risk assessment activities, including reasons for differences and strategies for greater harmonization across the government. It should also identify any gaps in current risk assessment practices related to field release of synthetic organisms. These reviews should be completed within 18 months and the results made public.

Individual scientists were among the first to raise concerns about the possible risks posed by synthetic biology research. In fact, synthetic biologists have been discussing among themselves the appropriate safety policies for their field since at least 2004. Members of the synthetic biology community have met in a series of meetings over the past 6 years to discuss concerns about both biosafety and biosecurity. They also considered environmental concerns and appropriate tools for risk assessment.[35] Like SYNBIOSAFE in Europe, the Synthetic Biology Engineering Research Center, a collaborative project funded by the National Science Foundation in the United States, is examining safety, security, and preparedness issues.[36] The willingness and initiative of the scientific community to engage in this level of introspection is both reassuring and essential.[37]

Similar to researchers in the early years of recombinant DNA research in the mid-1970s, those closest to this emerging field have exercised caution. While self-governance is not a sufficient means to mitigate all risks, it is likely an effective way to control many of the risks associated with emerging technologies, including synthetic biology, particularly at this early stage.[38] Individual scientists and students typically are the first to notice the laboratory door ajar, the suspicious behavior, or the lack of safety precautions among colleagues.

The activities of nontraditional scientists involving synthetic biology are also noteworthy. Communities of "amateur" scientists are actively working to increase understanding of potential physical and environmental risks posed by synthetic biology activities. As these communities grow, organized efforts to engage this community in discussions of safety and security and to foster a commitment to responsible stewardship will be increasingly important (see pp. 146-148).

Industry, too, has worked collaboratively to enact policies to promote responsible stewardship. For example, both the International Gene Synthesis Consortium and the International Association of Synthetic Biology—whose members include the vast majority of the gene synthesis providers in the United States and worldwide—have developed best practice guidelines for screening orders and customers. These groups are participating actively in public discussions of regulatory options, collaborating on implementing screening practices, and interacting with the Federal Bureau of Investigation (FBI) on training and notification efforts.[39] Moreover, these organizations and their member companies have committed publicly to improve screening protocols and tools and to incorporate recent U.S. government guidance into practice.[40]

Stewardship through Use of Safety Features and Reviews

Coordination and careful risk analysis are essential steps for responsible stewardship, but they are not sufficient. There are several additional approaches, known today and evolving as our abilities in this field grow, to limit uncertain risks in synthetic biology. Technology can be harnessed to build in safeguards, just as cars have brakes and seatbelts, houses have smoke detectors, and computers have anti-virus software. A number of safety features can be incorporated into synthetic organisms to control their spread and life span.

The intentional and unintentional consequences of novel research designs and new products cannot always be predicted. In the case of a newly engineered synthetic organism, for example, lack of history regarding the behavior of the entity, either environmentally or ecologically, requires that there be a means to track or contain it if it can survive outside of the laboratory.

Surveillance or containment of synthetic organisms is a concrete way to embrace responsible stewardship. These safety features may require some combination of public investment and incentives for additional private funding, and they should be implemented only after they undergo rigorous testing and validation.[41] Promoting and supporting efforts to design and employ safeguards will ensure that they are widely adopted and become a standard tool for practitioners of synthetic biology.

As part of the coordinated approach described in Recommendation 4, and on an ongoing basis as the field progresses, the government should specifically monitor the potential risks of organisms with novel synthetic traits or properties surviving or multiplying in the natural environment. As needed, reliable containment and control mechanisms should be identified and required. Among current options, "suicide genes" or other types of self-destruction triggers could be considered in order to limit the life spans of synthetic organisms.[42] Organisms could also be designed to require nutritional components absent outside the laboratory, such as novel amino acids, thereby controlling them in the event of release. These are options only and should be updated as science progresses. The primary consideration is to ensure that concrete protections are inserted into synthetic organisms to assure safety.

Recommendation 6: Monitoring, Containment, and Control

At this early stage of development, the potential for harm through the inadvertent environmental release of organisms or other bioactive materials produced by synthetic biology requires safeguards and monitoring. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President should direct an ongoing review of the ability of synthetic organisms to multiply in the natural environment and identify, as needed, reliable containment and control mechanisms. For example, "suicide genes"

or other types of self-destruction triggers could be considered in order to place a limit on their life spans. Alternatively, engineered organisms could be made to depend on nutritional components absent outside the laboratory, such as novel amino acids, and thereby controlled in the event of release.

The timing of deliberate release of synthesized organisms into the environment and the need to analyze risks prior to release raises special concern. We must proceed carefully, particularly when the probability or magnitude of risks are high or highly uncertain, because biological organisms may evolve or change after release.[43] Generally, the paradigm for risk assessment throughout the scientific community and oversight agencies is to evaluate a new organism in terms of known relatives and to set containment rules or environmental risk mitigation strategies based on the applicable rules for the known relative (see p. 83). This approach appears to have worked effectively and enabled risk assessors to modify methods as science has evolved.[44] Prudent vigilance is required to ensure that this strategy of comparison to known relatives, when they exist, remains effective as synthetic biology advances.

Recommendation 7: Risk Assessment Prior to Field Release

Reasonable risk assessment should be carried out, under the National Environmental Policy Act or other applicable law, prior to field release of research organisms or commercial products involving synthetic biology technology. This assessment should include, as appropriate, plans for staging introduction or release from contained laboratory settings. Exceptions in limited cases could be considered, for example, in emergency circumstances or following a finding of substantial equivalence to approved products. The gap analysis described in Recommendation 5 should determine whether field release without any risk assessment is permissible and, if so, when.

This recommendation is not intended to suggest that a National Environmental Policy Act-style risks evaluation must be conducted in all cases. As noted, there are numerous models and strategies employed across the government for risk assessment, for example, through FDA's premarket and post-market processes, EPA's Toxic Substances Control Act processes, and others. The goal of this recommendation is to ensure that for any field release there is adequate

consideration of risk. Through the suggested inter-agency process, the government may find that for some products—for example, first-generation fruits or vegetables developed with synthetic biology instead of traditional recombinant methods—there is no material need to establish formal risk assessment and premarket approval if not required already under existing law. Because of the uncertainty surrounding this novel technology and the great potential it presents for confusion and public fear, Recommendations 5 directs the government to affirmatively examine current policies for field release, to ensure that they are adequate, and to disclose to the public the results of this review.

The Commission's deliberations also highlighted the degree to which synthetic biology is an international enterprise. From student competitions to commercial gene synthesis companies, the synthetic biology community is an interactive global network. Oversight and regulatory mechanisms should adopt an analogous approach, so that the United States is involved in regular discussions with other national and transnational organizations, together seeking coordination and consistency when possible. These interactions should foster international collaboration as well as provide opportunities for the United States to learn from the positive and negative experiences of other countries similarly striving to promote the safe development of this field. International cooperation to create, maintain, enforce, and periodically update universal safety standards is essential.

Recommendation 8: International Coordination and Dialogue

Recognizing that international coordination is essential for safety and security, the government should act to ensure ongoing dialogue about emerging technologies such as synthetic biology. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President, through the Department of State and other relevant agencies such as the Department of Health and Human Services and the Department of Homeland Security, should continue and expand efforts to collaborate with international governments, the World Health Organization, and other appropriate parties, including international bioethics organizations, to promote ongoing dialogue about emerging technologies such as synthetic biology as the field progresses.

Creating a Culture of Responsible Stewardship

Responsible conduct of synthetic biology research, like all areas of biological research, rests heavily on the behavior of individual scientists. Federal oversight can guide the development of a culture of responsibility and accountability, but it also must be fostered at the local level. Ethical as well as biosafety and biosecurity standards are translated into practice at the laboratory level—and by the institutions that sponsor that laboratory science.[45] As an example, programs focused on homeland and transportation security embrace the message, "if you see something, say something." The same is true for laboratory science. It is at the individual or laboratory level where accidents will occur, material handling and transport issues will be noted, physical security will be enforced, and potential dual use intentions will most likely be detected.

Creating a culture of responsibility in the synthetic biology community could do more to promote responsible stewardship in synthetic biology than any other single strategy. For example, ethics education is required for most federally funded investigators conducting research with human subjects or laboratory animals.[46] Similarly, researchers working with select agents must undergo training in biosafety and biosecurity before having access to select agents and pathogens.[47] Researchers working with recombinant DNA in institutions that receive federal funds for such research know they must undergo review by an institutional biosafety committee (IBC) prior to beginning work.[48] These agreements between scientists and the public are the terms—the social contract, one might say—for conducting "risky" science, and they are well understood by most of the biological and biomedical research community.

Federal funding for engineering research, in contrast to clinical research, generally does not include a requirement for ethics training. Recently, the National Science Foundation began conditioning some research awards on agreements that institutions mentor funded postdoctoral research fellows and implement plans for "appropriate training and oversight in the responsible and ethical conduct of research. . . ."[49] Other federal research sponsors lack even these modest requirements. There is an urgent need more generally for

careful consideration of the education and training necessary to promote ethical conduct in engineering research and practice.

There are new actors in the world of synthetic biology, namely engineers, chemists, materials scientists, computer modelers, and others who practice outside of conventional biological research settings.[50] These groups may not be familiar with the standards for ethics and responsible stewardship that are commonplace for those working in biomedical research. This poses a new challenge regarding the need to educate and inform synthetic biologists in all communities about their responsibilities and obligations, particularly with regard to biosafety and biosecurity.

Recommendation 9: Ethics Education

Because synthetic biology and related research cross traditional disciplinary boundaries, ethics education similar or superior to the training required today in the medical and clinical research communities should be developed and required for all researchers and student-investigators outside the medical setting, including in engineering and materials science. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President, in consultation with the National Academy of Sciences, the National Academy of Engineering, the scientific community, and the public, should convene a panel to consider appropriate and meaningful training requirements and models. This review should be completed within 18 months and the results made public.

Collectively, these recommendations are designed to balance enthusiasm for the potential benefits of synthetic biology with the vigilance required to minimize the risks associated with research in this field and its applications. Through technological and regulatory mechanisms, a spirit of international collaboration, and researcher education, the scientific and policy communities can work together to be responsible stewards for humankind, other species, and our shared environment.

Weighing Moral Objections

The Commission's discussion of synthetic biology thus far has focused on efforts to identify and assess the risks and potential benefits of research and development activities. Significant challenges exist for the scientific and regulatory communities in these areas, and these recommendations aim to strengthen systems to promote activity in this field while protecting against risks. There is a second category of concerns regarding synthetic biology, one that is largely independent of specific risk-benefit analyses related to proposed applications or research directions. These are concerns that synthetic biology is intrinsically objectionable from a moral perspective and should therefore not be allowed to proceed.[51] The term "intrinsically objectionable" is used to express the idea that an activity or practice is "bad in itself." The suggestion of some critics, moreover, is that no amount of vigilance, safeguards, or similar mechanisms could justify the transgression by synthetic biology of an important moral barrier.

Intrinsic objections have led to direct policy consequences in other areas of biomedical science and technology, most notably the restrictions on research related to human reproductive cloning and embryonic stem cell research. These types of concerns have had a long and important place in bioethical discussions and debates. Intrinsic objections to synthetic biology raise important issues deserving ongoing consideration as part of comprehensive efforts to assure that this field progresses within appropriate ethical boundaries.

The Commission learned of several possible intrinsic objections to synthetic biology during its deliberations.[52] In one formulation, synthetic biology is thought to conflict with essential concepts of human agency and life, "promoting a grandiosity about human powers or dismissiveness about the specialness of life."[53] The tools of synthetic biology and the technological capabilities they provide may, according to some critics, accentuate humankind's temptation to hubris, suggesting an expansive, even limitless, ability to shape life and the future. Related to this criticism is the suggestion that advances in synthetic biology demonstrate that life is "nothing more than the sum of its parts" and that there is nothing "unique and unknowable about

life itself."[54] Contrasting synthetic biology with genetic engineering, medical ethicists Joachim Boldt and Oliver Müller write,

> [S]ynthetic biology does not soften edges, but creates life forms that are meant not to have any edges from the start. It does not add value to an existing organism; it brings into existence something that counts as valuable from our point of view. Seen from the perspective of synthetic biology, nature is a blank space to be filled with whatever we wish.[55]

Boldt and Müller argue that the transition from genetic engineering to synthetic biology marks a profound shift from the manipulation of existing species to the creation of new forms of life, a shift having considerable ethical significance. They note that the metaphors commonly used in synthetic biology which describe organisms as physical artifacts—"BioBricks," living machines, hardware and software—"may in the (very) long run lead to a weakening of society's respect for higher forms of life that are usually regarded as worthy of protection."[56]

Other commentators note that some of the potential products of synthetic biology "might fail to fit comfortably into our intuitive dichotomy between the living and the non-living."[57] For example, bacterial "bio-factories" are a potential application of synthetic biology that invokes yet another metaphor describing organisms in terms of physical artifacts. These bio-factories would possess many characteristics regularly associated with life, including a nucleic acid genome and the ability to reproduce. They would also possess features commonly associated with machines—such as modular construction and a rational design developed for specific applications.[58] Some critics of synthetic biology suggest that this amalgam of characteristics, even in single-celled organisms, could adversely affect how we understand and treat other forms of life generally, not simply those produced through synthetic biology.

Another related objection to synthetic biology is that it fails to show adequate respect for nature and the environment.[59] These critics distinguish the products of synthetic biology as unnatural in ways that other interactions between humans and nature are not.[60] Philosopher Christopher Preston writes that genomes assembled through synthetic biology "depart from a core principle

of Darwinian natural selection—descent through modification."[61] He argues that synthetic biology may therefore constitute a "moral 'line in the sand.'"

Civil society organizations such as the ETC Group also express concern about the overall impact of synthetic biology on biodiversity, ecosystems, and food and energy supplies worldwide.[62] These critiques combine intrinsic moral objections to the very nature of the enterprise of synthetic biology with reservations regarding its consequences and the specific harms that may result from continued research in the field. Biodiversity, for example, could be adversely affected by unpredictable outcomes of unintentional or deliberate release of synthetic organisms. Additional harms to biodiversity could result from potential applications of synthetic biology that aim to convert "low-value" forests and agricultural products into feedstocks for energy-producing processes.[63]

Concern for the continued flourishing of plant and animal species derives from the unique ability of humans to serve as responsible stewards of nature (see pp. 25-27). It also acknowledges the complex relationships that exist among species in ecosystems. Unintended consequences could result from potential synthetic biology applications that involve new or modified species in nature or novel uses for existing species.

Concerns for biodiversity are not restricted to wholesale threats to species. The potential of synthetic biology to enhance, add, or remove genes (and, therefore, proteins and their functions) within organisms highlights the potential effects of synthetic biology on genetic and genomic diversity. These impacts potentially extend also to genetic diversity among humans. Gene therapy trials using recombinant DNA in humans are already underway. However, genetic manipulation, as described above, is proceeding in limited and carefully controlled ways to potentially improve human health. The Commission is aware of no active or planned research programs involving synthetic biology applied to human genomes, which are vastly larger and more poorly understood than the bacterial genomes studied thus far.

Throughout its deliberations, the Commission took special efforts to learn the views of major faith-based communities, including those of Christianity, Judaism, and Islam. In other contexts, religious groups have expressed clear

and unqualified opposition to specific scientific activities based on intrinsic arguments, such as the position of the Catholic Church on human embryonic stem cell research. Similar opposition to synthetic biology has not been voiced thus far. Following the publication of the Venter Institute's paper, an official from the Catholic Church praised the development as "a further mark of man's great intelligence, which is God's gift enabling man to better know the created world and therefore to better order it."[64] The statement encouraged continued synthetic biology research, provided that the research proceeded responsibly and did not undercut the sanctity of life.

The Commission did not hear or identify any specific objections to current research efforts in synthetic biology based on the views of organized religions. In response to claims by some commentators that the Venter Institute's research demonstrates that life is merely a manipulable series of chemical reactions without any unknowable mystery or value, the Commission heard compelling rebuttals from several faith-based thinkers and others, including many scientists. Among them, it heard that absolutely nothing accomplished in synthetic biology by way of synthesizing the genome of a self-replicating bacterial cell from its component parts—which is the most striking and specific technical achievement of the Venter Institute team—demonstrates that life is without mystery or value that goes beyond the assembly of its parts. The mystery of life is amply great, as both religious and secular minds can appreciate, to survive even the most masterful scientific feats.[65]

As a scholar from the Christian tradition commented to the Commission during its deliberations,

> The mystery of existence from a Christian theological standpoint is that anything is rather than nothing, that there is something rather than nothing. That life is possible. The dynamism and the energy of matter and being itself are taken as an expression of the very vitality of God. And neither wonder nor mystery it seems to me are vitiated by the fact that we have figured out the biomechanical and bioelectrical and biochemical mechanisms thereof.[66]

Although contemporary synthetic biology is occasionally described as "creating life," (see pp. 155-157) this, as a factual matter, has not happened. The field currently is capable of significant but quite limited technical achievements. Potential developments that would raise further intrinsic concerns—the synthesis of genomes for a higher order or complex species, for example—are not currently possible. There is widespread agreement that this will remain the case for the foreseeable future. Synthetic biology is currently capable of manipulation and duplication of genomes of single-celled organisms. The creation of novel, complex organisms *de novo*, the focus of some opposition to synthetic biology on intrinsic grounds, is a far more difficult technical achievement. The Commission does not find it to be an inevitable consequence of recent and ongoing research activities in synthetic biology.

After careful deliberation, the Commission was not persuaded by concerns that synthetic biology fails to respect the proper relationship between humans and nature. It was reminded during its deliberations of the challenges of defining "nature" or "natural" in this context, particularly in light of humans' long history interacting with and affecting other species, humankind, and the environment.[67] Damaging consequences have resulted from some of this past activity. The Commission believes, however, that opposition to synthetic biology at present on such grounds alone does not adequately reflect the relationship of this technology to previous scientific activities and the current limited capabilities of the field.

These varied concerns are quite valuable, however, in calling attention to fundamental, challenging questions regarding how to best understand interactions among humans, technology, and nature beyond the limited context of synthetic biology. To what extent and in what valuable ways are the many different kinds of life on earth more than the sum of their standardized and non-standardized biological parts? Such discussions and the related attention they direct toward potential objections to synthetic biology will surely continue as the field matures, as well they should. The question relevant to the Commission's present review of synthetic biology is whether this field brings unique concerns that are so novel or serious that special restrictions are warranted at this time. Based on its deliberations, the Commission has concluded that special restrictions are not needed, but that prudent vigilance

can and should be exercised. As this field develops and our ability to engineer higher-order genomes using synthetic biology grows, other deliberative bodies ought to revisit this conclusion. In so doing, it will be critical that future objections are widely sought, clearly defined, and carefully considered within their appropriate context.

Recommendation 10: Ongoing Evaluation of Objections

Discussions of moral objections to synthetic biology should be revisited periodically as research in the field advances in novel directions. Reassessment of concerns regarding the implications of synthetic biology for humans, other species, nature, and the environment should track the ongoing development of the field. An iterative, deliberative process, as described in Recommendation 14, allows for the careful consideration of moral objections to synthetic biology, particularly if fundamental changes occur in the capabilities of this science and its applications.

Intellectual Freedom and Responsibility

Democracies depend on intellectual freedom coupled with the responsibility of individuals and institutions to use their creative potential in morally responsible ways. Sustained and dedicated creative intellectual exploration begets much of our scientific and technological progress. A robust public policy regarding the responsible conduct of science must promote the creative spirit of scientists and unambiguously protect their intellectual freedom. At the same time, responsible science should reject the technological imperative: the mere fact that something new can be done does not mean that it ought to be done.

Society as a whole has a stake in what scientists and engineers do. In turn, scientists and engineers should recognize the potential impact of their research on those who will experience both its benefits and burdens and their responsibility to those who provide the means, directly or indirectly, for their research. As a corollary to the principle of intellectual freedom and responsibility, the Commission endorses a principle of regulatory parsimony, recommending only as much oversight as is truly necessary to ensure justice, fairness, security, and safety while pursuing the public good.

The section on responsible stewardship stressed the importance of regulatory parsimony, recommending limiting regulation to that which is necessary to promote public safety and security, public beneficence, and justice and fairness. In its discussion of democratic deliberation (see pp. 152-155), the Commission recognizes the important part that all citizens can serve in working together for the common good. Responsible stewardship and democratic deliberation are two important components of a framework that promotes intellectual freedom coupled with responsibility. This section examines the central role of this principle in supporting the development of synthetic biology and other emerging technologies.

Intellectual freedom lies at the heart of America's scientific enterprise. Such freedom facilitates the innovation and industry that have fueled its success. History is rife with examples in which ingenuity, hard work, and unfettered creativity have yielded extraordinary, sometimes unexpected, scientific

advances for the betterment of society as a whole. From Benjamin Franklin studying electricity with a kite in a raincloud, to the Wright Brothers testing different aerodynamic control systems and building the first successful airplane, students learn every day about the value of intellectual and scientific freedom and exploration.

Scottish scientist Alexander Fleming famously discovered the antibiotic penicillin by chance in 1928 after observing an area on a mold-contaminated Petri dish where bacteria did not grow. David Hewlett and William Packard started in their backyard garage an electronics revolution that continues to the present, working in the 1930s in what is now described as the "birthplace of Silicon Valley." And the Internet, with its vast reach today, began as a simple idea to share data among U.S. Defense Department researchers in the 1960s. These examples show that the precise outcomes of open scientific exploration and discourse cannot always be predicted, but the value they deliver as the engine of progress, in science and in society overall, is unparalleled.

Intellectual freedom and responsibility can be understood in two senses. First is the special institutional attribute—academic freedom and responsibility—that pertains to the "academy" (broadly speaking, universities and the scholars and researchers whose professional standing carries with it the rights and responsibilities of academic freedom). Some research involving synthetic biology today occurs in this setting, which includes unique institutional structures to promote the responsibility that accompanies intellectual freedom. Second is the right of all individuals to freedom of inquiry. The DIY research communities and other private researchers are exercising such freedom but without the institutional norms and procedures designed to assure responsibility, although these groups often develop their own mechanisms intended to do so.

In academic communities, intellectual freedom is essential. The ability to explore ideas openly and freely—even controversial or unpopular ideas—is fundamental to the mission of education and research. "The common good depends upon the free search for truth and its free exposition," according to one widely endorsed statement on academic freedom.[68] Academic freedom is not to be confused with license; it protects neither socially irresponsible behavior (the abuse of one's academic office) nor research that poses risks to

individuals or institutions without adequate safeguards. Its limitations notwithstanding, the free exchange of ideas is essential to both academic inquiry and to the overall health of societies, and is recognized to be vital in the United States and other modern democracies. Protecting this core freedom—while meeting the corresponding responsibilities—is among the foremost concerns of academic communities.

Certain regulatory and norm-based constraints on academic and intellectual freedom in academic and other settings ensure that scientists act responsibly to protect others. In academic science, universities and other institutions accept the responsibility to abide by safety and security measures in laboratory research. These institutions, government, and most industry research programs employ extensive quality assurance and control processes that satisfy both external mandates and internal needs. In non-academic settings, like some DIY synthetic biology communities, recognition and acceptance of such processes are less common. In some cases, practitioners unaffiliated with an institution are simply unaware of applicable or reasonable restrictions governing scientific research methods intended to promote security and safety.[69]

Research Oversight Policies and Practices

Citizens and their leaders should have a voice in deciding the conditions and direction of research efforts, especially, though not exclusively, when public funds are used. Likewise, scientists have a responsibility to ensure that they use public monies wisely and act in ways consistent with public trust. Recognizing this responsibility, scientists at the early stages of the genetic engineering revolution came together to develop what remains a substantially self-regulated system to protect against physical risks in genetic research. At the historic Asilomar Conference on Recombinant DNA in 1975, scientists developed a set of principles that required containment measures to be an essential consideration in experimental design and that "the effectiveness of the containment should match, as closely as possible, the estimated risk."[70] Although the scientists recognized that it might be difficult to predict the level of risk for any particular experiment given the novel character of the research, the guidelines established graded containment strategies and categorized expected areas of inquiry, setting minimum levels of containment

within the graded system. Like atomic scientists before them, the scientists who participated at Asilomar recognized that the uncertain nature of the risks associated with their efforts demanded that they act cautiously and with utmost attention to the public interest. They agreed to defer types of research that could not be carried out at that time with sufficient safeguards.

Building on this framework, scientists both in and outside government developed a shared culture of responsibility to assure safe conduct of research in the largely uncharted world of genetic engineering. In the 35 years since Asilomar, the then-nascent field of genetic engineering research has flourished. Its safety continues to be governed by a dynamic process of active engagement among scientists in academia, government, and the private sector.

Synthetic biology today finds itself in a position similar to the field of genetic engineering in 1975. Some urge extreme caution and prohibition until safety is proven, and others are perhaps too sanguine, dismissing all efforts that might limit intellectual freedom and scientific exploration. As mentioned in the sections on responsible stewardship and democratic deliberation, the Commission finds neither of these approaches appropriate. The principle of intellectual freedom and responsibility leads us to the conclusion that restrictions on research, whether by self-regulation among scientists or by government intervention, should limit the free pursuit of knowledge only when the perceived risk is too great to proceed without limit. Restrictions can prevent research harms but also can impede innovation and progress that may itself reduce harms.

In 2009, NIH recommended that synthetic biology research should be overseen at this time in the same manner as more traditional genetic engineering research. The Commission agrees. The *NIH Guidelines for Recombinant DNA Research* (the *NIH Guidelines*), discussed in Chapter 4, establish safety conditions based on the risk profile of the end product, for example, a genetically modified virus strain, rather than the techniques used to make it. Risks are assessed and safety precautions imposed based on risks, but research is not limited or restricted in the absence of realistic and identified concerns. This framework is time-tested, familiar to most researchers, and consistent with the principle of intellectual freedom and responsibility.

A moratorium at this time on synthetic biology research generally or in particular areas would inappropriately limit intellectual freedom. Instead, the scientific community—in academia, government and the private sector—should continue to work together to evaluate and respond to known and potential risks of synthetic biology as this science evolves.

Recommendation 11: Fostering Responsibility and Accountability

The government should support a continued culture of individual and corporate responsibility and self-regulation by the research community, including institutional monitoring, enhanced watchfulness, and application of the *NIH Guidelines for Recombinant DNA Research.* As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President should evaluate, and re-evaluate periodically, the effectiveness of current research oversight mechanisms and determine what, if any, additional steps should be taken to foster accountability at the institutional level without unduly limiting intellectual freedom. Academic and private institutions, the public, the National Institutes of Health, and other federal funders of synthetic biology research should be engaged in this process. An initial assessment should be completed within 18 months and the results made public.

This activity may best be undertaken through the coordinated approach chosen to implement Recommendation 4. The Office of Science and Technology Policy or another Executive Branch office could also direct this review. The responsible office must be empowered to bring together all relevant agencies and departments and assure effective engagement with outside groups.

The notion of "enhanced watchfulness" requires the scientific community to recognize the varied risks associated with synthetic biology and develop internal processes to identify and respond to potential threats rapidly and effectively. Enhanced watchfulness reflects a relationship among scientists, citizens, and policy makers built on trust and mutual respect. To earn and preserve public trust, the research community should actively engage in continuing efforts to promote the safe development of synthetic biology and to recognize potential threats before they cause harm.

A culture of responsibility is particularly effective in university settings where academic freedom is an institutionalized right but not an unrestricted license. The responsibilities attendant to this freedom are implemented through practical mechanisms that nurture and support the culture of responsibility. Compliance with the *NIH Guidelines*, for example, is assured through a series of internal checks and balances from the investigator through to local oversight committees (e.g., IBCs) and the institutional signing official responsible for assuring that the institution meets all terms and conditions of research funding.

Researchers in institutions outside the university setting also have an incentive to limit risks and frequently have systems in place to support and sustain the culture of responsibility. Biotechnology companies staffed with scientists trained in academia and accustomed to working with oversight committees like IBCs often volunteer to comply with the *NIH Guidelines* and other standards developed through consensus of the scientific community.[71] Researchers in government agencies are also familiar with IBC review and the *NIH Guidelines*, and often are required to comply with them (see pp. 89-90).

Nurturing this same culture among DIY investigators or others outside of institutional settings is more challenging. The global expansion of DIY synthetic biology raises fears about biosafety and biosecurity. The open access environment underpinning many DIY efforts, as well as the increasing affordability and availability of synthetic biology tools through private gene synthesis companies and others, generates understandable concern about the ongoing effectiveness of self-regulation and the culture of responsibility standard. In partial response, the FBI expanded efforts in the last few years to partner with industry and actively engage the DIY community on safety concerns and risk mitigation strategies.[72]

The principle of intellectual freedom and responsibility, when responsibility is exercised largely by individual rather than institutional actors, requires the government to be particularly vigilant, although perhaps no more limiting of research efforts. To exercise the appropriate level of oversight, the government will need to monitor the growth and capacity of researchers outside of institutional settings. This effort may require the government to expand current

oversight or engagement activities with these non-institutional researchers. NIH or the Department of Energy, for example, could be charged to sponsor education programs and workshops that bring together these groups. They could fund training grants or related programs to promote responsibility among this community.

Recommendation 12: Periodic Assessment of Security and Safety Risks

Risks to security and safety can vary depending on the setting in which research occurs. Activities in institutional settings, may, though certainly do not always, pose lower risks than those in non-institutional settings. At this time, the risks posed by synthetic biology activities in both settings appear to be appropriately managed. As the field progresses, however, the government should continue to assess specific security and safety risks of synthetic biology research activities in both institutional and non-institutional settings including, but not limited to, the "do-it-yourself" community. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President, working with the Department of Homeland Security, the Federal Bureau of Investigation and others, should undertake and periodically update this assessment. An initial review should be completed within 18 months and the results made public to the extent permitted by law.

As above, this activity could be undertaken by a central office implementing Recommendation 4, but it need not be, provided that the implementing office has sufficient authority to accomplish this charge. The analysis recommended here should identify efforts to bring the non-institutional communities into the ongoing culture of responsibility and local accountability that currently exists in many institutional settings.

This recommendation acknowledges that the norms of safe and responsible conduct that have evolved over time for many researchers in institutional settings may not be understood or followed by those new to the field or outside of these settings, but it is not a call for specific restraints upon the DIY community at this time. Synthetic biology is occasionally critiqued as scientists "playing God," (see pp. 155-157), but a more general concern is ensuring that all scientists, particularly DIY scientists, reject a culture of *play* and adopt a

culture of *responsibility* as it relates how they view their own research in a field fraught with risks to themselves, the public, and the environment.

It is important to note that there is presently no serious risk of completely novel organisms being constructed in non-institutional settings such as the DIY community. The research result announced by the Venter Institute in May 2010 was a significant technical achievement, but the synthesis of a self-replicating bacterial cell with a synthetic genome required nearly 15 years of work by a large team of highly experienced scientists and an estimated $40 million in research expenditures. The Commission's deliberations revealed that this combination of technical and financial resources and scientific expertise is not currently available in the DIY community. The potential synthesis of completely novel organisms presents additional, still unresolved technical challenges even for research groups working in institutional settings. While there are known risks related to near-term activities by the DIY community, such as the growth of potentially pathogenic organisms using conventional methods or inadequate waste disposal practices, the risks associated with this group using synthetic biology techniques to create novel organisms are presently quite low.

This recommendation echoes recent conclusions of the NSABB, which also considered issues of education and outreach to all practitioners of synthetic biology and ways to effectively promote a culture of responsibility.[73] Scrutiny is required to assure that DIY scientists have an adequate understanding of necessary constraints to protect public safety and security, but at present the Commission sees no need to impose unique limits on this group.

Assessing Oversight and Export Controls

The culture of responsibility depends, at least in part, on voluntary compliance with the *NIH Guidelines* in institutions without federal research funding, such as private companies. Accordingly, the Commission recommends that the government undertake an ongoing process of review to monitor risks and effectiveness of current oversight systems in these settings and in contexts such as the DIY community.

However, certain risks—generally involving national security—often warrant additional protections. One of the primary concerns about the risks posed by synthetic biology is its dual use potential, defined as the possibility that it will yield information or technologies capable of being misused, thereby endangering public health or national security. The threat of malevolent use of scientific knowledge is not new; however, the global, collaborative, and electronically linked nature of modern biological sciences, such as synthetic biology, complicates efforts to control scientific information and material exchanges across borders.

Where uncertainty exists regarding the danger of specific genetic sequences that potentially code for harmful substances, sequence providers should strive to ensure that customers and end-users have legitimate purposes for their use. Adherence to the government's voluntary *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA* will aid these efforts.[74] Scientists and laboratory technicians should ensure that containment and other safety precautions are in place. The scientific community should take steps to carefully manage both scientific and social risks associated with synthetic biology as this field grows.

Chapter 4 briefly describes the current system of export controls and other measures designed to reduce concerns about malevolent use arising from information exchange. Policy makers in this area face complex challenges. Completely free exchange of data and materials might endanger public safety, but unilateral action to limit exchange could damage American research efforts in synthetic biology if U.S. scientists and students are excluded from full collaboration in the international community. An additional complication for export control efforts in synthetic biology is that much of the "currency" of the field are the sequences of genetic data that are often available in public databases or could be distributed easily and without detection.

Several recent advisory groups have recommended ongoing discussions among research universities, industry, and government on this topic. The National Research Council's 2007 report, *Science and Security in a Post 9/11 World*, expressly calls for more dialogue on export controls. The NSABB in 2010 also recommended expanded outreach and education strategies "that address

dual use research and engage the research communities that are most likely to undertake work under the umbrella of synthetic biology."[75] The Commission agrees that scientists should be actively engaged in these debates.

Recommendation 13: Oversight Controls

If the reviews called for in Recommendation 12 identify significant unmanaged security or safety concerns, the government should consider making compliance with certain oversight or reporting measures mandatory for all researchers, including those in both institutional and non-institutional settings, regardless of funding sources. It may also consider revising the Department of Commerce's export controls. Any such change should be undertaken only after consultation with the scientific, academic, and research communities and relevant science and regulatory agencies such as the National Institutes of Health, the Department of Homeland Security, and the Environmental Protection Agency. Export controls should not unduly restrain the free exchange of information and materials among members of the international scientific community.

Democratic Deliberation

The principle of democratic deliberation reflects an approach to collaborative decision making that embraces respectful debate of opposing views and active participation by citizens. At the core of democratic deliberation is an ongoing, public exchange of ideas, particularly regarding the many topics—in science and elsewhere—in which competing views are advocated, often passionately. A process of active deliberation and justification promotes an atmosphere for debate and decision making that looks for common ground wherever possible, and seeks to cultivate mutual respect where irreconcilable differences remain. It encourages participants to adopt a societal perspective over individual interests. With careful attention to the processes through which decisions are reached and justified, democratic deliberation promotes outcomes that are inclusive, thoughtfully considered, and respectful of competing views.

Biotechnology has the potential to affect everyone, and opportunities for the public to participate in discussion and deliberation about emerging technologies such as synthetic biology are critical. The principle of democratic deliberation highlights the importance of robust public participation in both the development and implementation of specific policies as well as in a broader, ongoing national conversation about science, technology, society, and values.

In its examination of synthetic biology, the Commission saw encouraging examples of ways in which the public has been invited to learn about this emerging field and to share its perspectives. It learned of groups of citizens coming together, sharing their mutual interest and expertise in synthetic biology—biologists and engineers, teachers and students, professionals and amateurs, from nations around the world. These activities provide an important foundation for expanded efforts regarding public engagement and public education that are not only valuable but essential. This section highlights examples of how citizens are already shaping the present and future of synthetic biology and notes several opportunities for how these efforts can be enhanced and strengthened.

Promoting an Ongoing Public Dialogue

Many groups in addition to this Commission have studied and reported on issues related to synthetic biology in the past several years, including U.S. and international government agencies, professional societies, commercial and industry groups, and private organizations. As the Commission did throughout its deliberations, virtually all of these groups consulted broadly among those with interest and expertise regarding the potential impact of synthetic biology on science and society. The Commission commends these efforts, as they embody a belief that policy regarding synthetic biology is best developed when informed by open and ongoing discussions among a diverse group of stakeholders. Policymaking bodies involved in regulation and oversight of synthetic biology are encouraged to continue to actively solicit input from the public regarding their work, ensure that those views receive thoughtful consideration, and make available and accessible to the public the eventual decisions that are reached and the reasoning for them. Public deliberation is particularly valuable while the field is still young, as there is a unique opportunity to shape its development in ways most likely to promote the public good while assuring safety and security.

The Commission understands that not all policymaking activities in this area can be fully transparent to the public, such as those related to some aspects of biosecurity or involving trade secrets in certain commercial applications of synthetic biology. Concerns about biosecurity and proprietary interests ought not, however, justify excessive secrecy such that the development of science and the participation of the public are unduly compromised. Nor should these necessary limitations preclude those with advisory or decision-making responsibilities from viewing the public as active partners in their work. In addition to being a valuable source of good ideas, public participation frequently fosters the perceived political legitimacy of the policies and practices that are ultimately chosen.

A recent survey of public attitudes regarding synthetic biology found that nearly two-thirds of respondents supported continued development of the field, including additional research on its possible effects on humans and the environment.[76] There was a strong correlation between self-reported awareness of

synthetic biology and support for ongoing research, as 80 percent of those who had heard a lot about the field believed it should move forward, compared to only 52 percent of those who had heard nothing about it. Overall, 73 percent of those surveyed reported having heard "just a little" or "nothing at all" about synthetic biology. These data indicate both the need for broader public engagement regarding synthetic biology and the positive impact of such efforts on public support for novel and otherwise unfamiliar technologies.

In many areas of biomedical research, public engagement is an important component of study design and a means to ensure public support. A notable example of this practice is the Framingham Heart Study and its Ethics Advisory Board. The study, which began in 1948, is a federally funded project based in Framingham, Massachusetts that aims to identify and understand the risk factors for heart disease by observing entire families and populations over time. The Framingham Ethics Advisory Board is comprised largely of past and present study participants as well as local clergy and physicians. It serves as a forum for community deliberations and a vehicle to advise the researchers on design and oversight issues.[77]

The development of the NIH policy on Genome-Wide Association Studies demonstrates another type of proactive public engagement to build public understanding and support. In connection with building a large-scale, central database of individual genotype and phenotype information for secondary research studies, NIH published requests for public comment during the policy development process and held meetings with members of the public prior to finalizing its policy.[78] In another example, community engagement is required by law for certain research projects in which individual informed consent is not feasible, such as research conducted in emergency settings.[79] Increasingly, community engagement or consultation is a prerequisite for research with particular populations, such as Native Americans, or research requiring the use of high-containment facilities to control dangerous pathogens.

Other groups have noted the potential value of public engagement specifically for synthetic biology and related topics. In its April 2010 report on synthetic biology, NSABB recommended outreach and education directed toward participating scientific communities, while also stating that more active

engagement of the general public could lead to a better collective understanding of synthetic biology.[80]

An active, dynamic exchange between citizens and government need not be confined to regulatory and legislative processes. During its deliberations the Commission learned of several initiatives in which government agencies such as the FBI are in regular dialogue with members of the synthetic biology community.[81] These activities provide opportunities for citizens and their government to learn from each other, exchange ideas, share concerns, and work collaboratively toward fostering a safe, productive environment in which synthetic biology can develop.

Government bioethics commissions such as this one can be part of national and international conversations regarding synthetic biology and other emerging technologies.[82] While by no means a substitute for robust, ongoing exchanges between citizens and policy makers, the Commission's deliberations on this matter sought to provide an inclusive forum for discussion, with the hope that its recommendations will be a catalyst for future deliberations.

The Commission's interest in democratic deliberation calls for a national and international dialogue on synthetic biology and its implications, a conversation that bridges specific research initiatives and considers how the field as a whole can best move forward safely and beneficially. The Public Engagement with Research Team of the Research Councils UK is one example of an approach that promotes sustained interactions among researchers, students, and the public on major themes related to research and innovation.[83]

Recommendation 14: Scientific, Religious, and Civic Engagement

Scientists, policy makers, and religious, secular, and civil society groups are encouraged to maintain an ongoing exchange regarding their views on synthetic biology and related emerging technologies, sharing their perspectives with the public and with policy makers. Scientists and policy makers in turn should respectfully take into account all perspectives relevant to synthetic biology.

Democratic deliberation encourages respect for a wide range of reasonable perspectives. Positions based directly on personal revelations—whether divine or secular in nature—are unlikely to be accessible to most citizens. However, by carefully attending to the concerns raised by religious traditions, a respectful dialogue can develop that can often lead to positions that are accessible, independent of their source.[84] While the Commission did not observe significant religious concerns related to synthetic biology at this time (see pp. 137-138), the field is young, and future developments may prompt new concerns, underscoring the importance of ongoing deliberation that is responsive to changing circumstances in science and society.

Striving for Accuracy and Understanding

For effective public deliberation on potentially contentious topics such as synthetic biology, participants should endeavor to express their views in ways that are accessible to others. In part, this means striving to convey one's own views and those of others accurately and with as much mutual understanding as possible. Throughout its deliberations, the Commission was impressed by the quality of discourse on synthetic biology from those working in and around the field. It did observe, however, that the media sometimes described synthetic biology in ways more provocative than accurate. This observation may not be surprising to some, but it makes the development of ongoing deliberative forums on science all the more essential to enhancing public understanding.

In the days immediately following the May 20, 2010, announcement of the creation of the first self-replicating cell containing an entirely synthetic genome, some press accounts worldwide declared, "Scientists have created the world's first synthetic life form."[85] Subsequent coverage attempted to place this work in context, particularly regarding whether it could properly be described as truly creating synthetic or artificial life. In its deliberations, the Commission heard that while the May 20 announcement marked a significant technical achievement in demonstrating that a relatively large genome could be accurately synthesized and substituted for another, it did not amount to the "creation of life"[86] (see Chapters 2 and 3 for further discussion).

While this interpretation of the research appears to be widely held among the scientific community, public perceptions of synthetic biology may have been influenced by initial news of "creating life." This language may excite public interest in a potentially transformative field, but it can serve a useful purpose only if it is followed by careful and robust deliberation informed by an accurate understanding of the current state of synthetic biology and the uncertainty regarding its potential benefits and risks. This example illustrates the considerable opportunities and challenges facing science journalists today to excite public interest and convey accurate understanding of developments in science and technology.

Discussions about synthetic biology and related technologies often raise objections that scientists are "playing God." The Commission's deliberations with representatives of a range of religious communities found this language to be unhelpful at best, misleading at worst. It learned that secular critics of the field are more likely to use the phrase "playing God" than are religious groups. While religious thinkers suggested caution regarding the human tendency toward hubris, none expressed concern that synthetic biologists were "playing God."[87] The provocative nature of this phrase does more to obscure rather than to illuminate those important moral concerns regarding synthetic biology that deserve serious consideration (see pp. 135-140).

Recommendation 15: Information Accuracy

When discussing synthetic biology, individuals and deliberative forums should strive to employ clear and accurate language. The use of sensationalist buzzwords and phrases such as "creating life" or "playing God" may initially increase attention to the underlying science and its implications for society, but ultimately such words impede ongoing understanding of both the scientific and ethical issues at the core of public debates on these topics. To further promote public education and discourse, a mechanism should be created, ideally overseen by a private organization, to fact-check the variety of claims relevant to advances in synthetic biology.

Public deliberation about synthetic biology can be hindered both by imprecise language such as "creating life" or "playing God" as well as by scientific claims that fail to convey accurately to the public the current state of the field, the implications of research results, and the limits of scientists' present knowledge and abilities. The fact-check mechanism recommended here is intended to address these concerns by providing an independent venue where scientific claims related to synthetic biology or other emerging technologies are evaluated by impartial, qualified experts. The results of these analyses would be readily accessible to the public, likely through a website. The Commission envisions a program analogous to FactCheck.org, a project that monitors the accuracy of statements made about U.S. politics.[88] It would be interactive, inviting the public to suggest claims for review by project staff, and funded by private sources without real or perceived conflicts of interest.

Improving Scientific and Ethical Literacy

Meaningful citizen participation in deliberations regarding synthetic biology requires familiarity with general concepts in science and particular aspects of this developing field. Collectively, these tools are referred to as "scientific literacy."[89] The National Academy of Sciences has defined scientific literacy as "the knowledge and understanding of scientific concepts and processes required for personal decision making, participation in civic and cultural affairs, and economic productivity."[90]

Making science accessible to the public requires creativity and innovation in public education. The Commission was pleased to learn that in synthetic biology several groups have launched commendable efforts to educate the public about this emerging field. These groups include the Synthetic Biology Project of the Woodrow Wilson International Center for Scholars and the Synthetic Biology Engineering Research Center, which is funded in part by the National Science Foundation.[91] Through online resources, curricula for teachers and students, and events such as the International Genetically Engineered Machine (iGEM) competition (see p. 46), these and other groups are developing innovative programs to increase the public's understanding of synthetic biology.

Public education efforts addressing synthetic biology need to be part of our Nation's expanded attention to an increasingly urgent need to enhance scientific literacy, broadly understood. Scientific literacy must go hand-in-hand with improved ethical literacy, meaning an understanding of moral concepts, traditions, and controversies concerning the responsibilities and rights of individuals and communities toward one another.

Recommendation 16: Public Education

Educational activities related to synthetic biology should be expanded and directed to diverse populations of students at all levels, civil society organizations, communities, and other groups. These activities are most effective when encouraged and supported by various sources, not only government, but also private foundations and grassroots scientific and civic organizations. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President, with input from the scientific community, the public, and relevant private organizations, should identify and widely disseminate strategies to promote overall scientific and ethical literacy, particularly as related to synthetic biology, among all age groups.

This effort could be led by EOP or the relevant science agencies such as NIH or DOE in collaboration with the Department of Education. This group should consider the feasibility of including public education components or the development of school curriculum modules in research funding agreements. These activities could be linked to specific projects or organized at the institutional level among recipients of federal research support. It should also examine other models to promote and enhance scientific and ethical literacy, including activities directed by private organizations or developed by private groups in partnership with the government. The Synthetic Biology Project of the Woodrow Wilson Center may serve as one such model.

Scientific research and public education about science are best approached as mutually related, even mutually dependent, endeavors. The iGEM competition, for example, combines hands-on student exposure to research tools and practices with education on many issues—science, safety, and policy—related to synthetic biology. The Commission commends programs throughout the

scientific community that include educational programs as components of ongoing research projects. One illustrative example is Project BioEYES, which provides classroom-based learning opportunities for students in grades K-12 through the use of live zebrafish.[92] With active participation from scientists committed to making science accessible to young people, over 18,000 students in Philadelphia, Baltimore, and South Bend have encountered science in innovative ways. In particular, this project and others similarly directed to under-resourced schools seek to make science available to all students, particularly those who might otherwise lack access to cutting-edge scientific resources and expertise.

In 1999, the National Bioethics Advisory Commission noted that the need for expanded education is "not simply…the provision of information with the aim of adding to the net store of knowledge by any one person or group; rather, education refers to the ongoing effort to inform, challenge, and engage."[93] Engaging citizens—and particularly young people—in challenging science curricula regarding synthetic biology and other emerging technologies as well as many other issues lies at the intersection of science and citizenship. In light of our Nation's dependence on socially responsible scientific innovation for economic progress and individual well-being, the urgency of expanding effective science and ethics education cannot be exaggerated.

Fostering Grassroots Collaborations

As noted, democratic deliberation is based on ongoing interaction among citizens on topics of common interest. For an emerging technology such as synthetic biology, many of these dialogues will be among scientists or other interested citizens and policy makers or regulators. Such interactions are vital to a democracy, but they are not sufficient. Exchanges among individuals and groups of citizens are also important. In particular, grassroots collaborations have been established around synthetic biology. Groups such as DIYbio are loosely organized networks of self-described "citizen scientists" coming together because of a common interest in the tools, methods, and applications of synthetic biology, rather than shared professional affiliations or policy responsibilities. In this way, the "do-it-yourself" community embodies a "do-it-together" ethos.[94]

These kinds of collaborations are commendable; they strengthen notions of citizenship and community at the core of a democracy. They demonstrate that science and its oversight do not belong exclusively to experts, highly trained professionals, or government officials. Science is a shared resource, affecting and belonging to all citizens.

Through democratic deliberation, questions raised by the emerging science of synthetic biology can be explored and evaluated on an ongoing basis in a manner that welcomes the respectful exchange of opposing views. This deliberation is best positioned to succeed when it includes a diverse set of accessible arguments built upon a foundation of public understanding and engagement with science and technology. In this way, democratic deliberation advocates for an inclusive view of synthetic biology and its oversight. A community-oriented perspective strengthens efforts to ensure that this science develops in ways that will be acceptable to the majority of the population. This perspective also complements activities intended to promote justice and fairness in the development of synthetic biology and its applications.

Justice and Fairness

The principle of justice and fairness relates to the distribution of benefits and burdens across society. Emerging technologies like synthetic biology, for good or ill, affect all persons. Society as a whole has a claim toward reasonable efforts on the part of both individuals and institutions to avoid unjust distributions of the benefits, burdens, and risks that such technologies bring. This same claim extends internationally to all those who may be affected—positively or negatively—by synthetic biology and its applications.

In calling attention to justice and fairness, the Commission highlights the importance of considering not simply *what* the benefits and risks of synthetic biology are, but *to whom and to what* those benefits and risks are directed. Its examination of synthetic biology discussed strategies intended to realize potential benefits and minimize risks by means of thorough, inclusive deliberative processes. These benefits and risks can be specified; they are not abstract concepts. They have the potential to directly and significantly affect individuals and entire populations, species, and environments. The principle of justice and fairness encourages a proactive sensitivity to the distribution of these outcomes.

Justice and fairness are concepts with closely related but distinct meetings. Many definitions exist, but justice is generally the broader concept of the two. One type of justice, distributive justice, refers to concern for the equitable allocation of goods and evils in a society. Fairness provides one specification of justice, as in philosopher John Rawls's principles of equal liberty and equal opportunity among members of communities as two of the primary attributes of "justice as fairness."[95] In its work, the Commission refers to the principles of justice and fairness collectively to refer broadly to concern for how benefits and burdens ought to be shared among communities and nations.

Some of the most exciting potential current applications of synthetic biology involve products with the potential to address major challenges in global health and welfare. Semi-synthetic artemisinin (see p. 65), for example, could offer a valuable treatment for malaria around the globe. Synthetic biofuels could be particularly valuable in nations where energy deficits hinder development and

economic growth. There is great value in striving to pursue these and other applications and to ensure, if successful, that they reach those individuals and communities who would most benefit from them.

As it advances, synthetic biology may also pose a spectrum of risks to human health, other species, ecosystems, and national security (see Chapter 3). The likelihood and severity of most of these risks are difficult to predict at this time, but part of the work of oversight activities, broadly speaking, is to assess where the risks and harms of synthetic biology are most likely to be experienced, if at all, and act to prevent or minimize any adverse impacts. Research-related risks, potential environmental exposures, and social and economic displacement can be unavoidable hazards of science and technology, but these burdens should not fall disproportionately on any particular individual or group. Of great concern are those individuals and groups whose political, economic, or other status makes them particularly vulnerable.

Sensitivity to the fair distribution of the risks and benefits of synthetic biology, like other biotechnologies, is appropriate regardless of the source of funding. Yet fair distribution of the benefits of synthetic biology is an especially important consideration for government-funded research. Government support provides both benefits and obligations. Benefits include the creation of a safe and secure research environment as well as direct funding for particular projects. These benefits come with a corresponding responsibility for beneficiaries to do their part to ensure that return on these investments is justly distributed across society. Concern for justice and fairness should be a central consideration of all aspects of the planning and implementation of research in synthetic biology and its applications.

Just Distribution of Risks, Burdens, and Potential Benefits

With any technological advance come burdens and risks. These burdens can arise both in the research and development process and from the eventual introduction of new technologies and products into the marketplace. Frequently, the risks are unknown or of uncertain magnitude at the early stages

of development of a field. Ongoing and recurring risk assessment is often required to fully understand and respond appropriately.

Chapter 3 discusses the potential benefits and risks of synthetic biology as it is understood today. One set of risks relates to the conduct of synthetic biology research. These include risks to laboratory workers and personnel, risks to research subjects, and risks related to the unintentional or deliberate release of experimental agents into the environment. In the United States, numerous oversight systems are in place to guard against potential harms that may result from these types of risks (see Chapter 4). These include provisions designed to prevent physical harm to workers, study subjects, and the public generally.

For study subjects, specific mechanisms are in place to ensure that volunteers are fully informed about, and agree to accept, the possible risks or harms they may face before they begin. Oversight bodies assess research risks in light of potential benefits to individuals, and in some cases, communities, prior to approval. Many believe also that research should be responsive to the needs of the entire population being studied or affected by the research activities.[96]

Evaluation of research proposals and ongoing review should include consideration of possible environmental exposures or social disruption. These considerations are particularly relevant for synthetic biology. Clinical and observational research in this field is relatively limited at present, but harmful environmental effects or unintended consequences on human health loom as major sources of concern and public anxiety. These concerns need not be addressed by institutional review boards, which are commonly understood to be prohibited by federal regulation from considering such effects beyond their relevance to the protection of human subjects directly participating in the research.[97] To address the uncertain or potentially unique risks that may arise from synthetic biology in light of its extraordinary potential to manipulate and manage living systems, special consideration and safety reviews may be needed. In addition to concerns about possible environmental exposures or social disruption, consideration must also be given to potential hazards to the public posed by synthetic biology consumer products, including medicines.

Recommendation 17: Risks in Research

Risks in research should not be unfairly or unnecessarily borne by certain individuals, subgroups, or populations. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President should lead an interagency evaluation of current requirements and alternative models to identify mechanisms that ensure that the risks of research in synthetic biology, including for human subjects and other affected parties, are not unfairly or unnecessarily distributed. Relevant scientific, academic, and research communities, including those in the private sector, should be consulted. This review should be completed within 18 months and the results made public.

Attention to these concerns is particularly relevant when those participating directly in research or likely to be affected by research activities do not share the nationality, culture, economic status, or political power of those conducting the research.

The introduction of new technologies may also lead to increased risk of harmful environmental exposures in specific locations, and the principles of justice and fairness require vigilant attention to these environmental risks. The arrival of new products or applications of synthetic biology should not compel any particular population to "shoulder a disproportionate burden of the negative human health and environmental impacts of pollution or other environmental hazards."[98] All citizens ought to "enjoy the same degree of protection from environmental and health hazards."[99] Accordingly, the Commission makes the following recommendation as a means to expand attention to the relative burden that some communities or individuals may bear regarding the potentially adverse effects and risks of new technologies.

Recommendation 18: Risks and Benefits in Commercial Production and Distribution

Risks to communities and the environment should not be unfairly distributed. Manufacturers and others seeking to use synthetic biology for commercial activities should ensure that risks and potential benefits to communities and the environment are assessed and managed so that the most

serious risks, including long-term impacts, are not unfairly or unnecessarily borne by certain individuals, subgroups, or populations. These efforts should also aim to ensure that the important advances that may result from this research reach those individuals and populations who could most benefit from them. As part of the coordinated approach urged in Recommendation 4, the Executive Office of the President should evaluate current statutory mandates or regulatory requirements for distribution of risks and benefits and consider developing guidance materials and voluntary recommendations to assist manufacturers as appropriate.

There is considerable enthusiasm among advocates of synthetic biology for the varied benefits that this emerging field may yield for individuals and communities. Some critics have expressed concern, however, that synthetic biology will only exacerbate existing disparities with regard to health, welfare, and socioeconomic status.[100] Similar concerns are often voiced in response to other new technologies.

Much of the optimism surrounding synthetic biology stems directly from its potential to address some of the longstanding, significant problems associated with these disparities. Synthetic biology offers potential applications that may be particularly beneficial to less advantaged populations, including improved quality and access to vaccines against infectious diseases, medications, and fuel sources. A just society recognizes the value of establishing incentives to create new knowledge and to translate it into vibrant markets in ways intended to distribute benefits widely. As new tools arrive and mature, it will be important to identify strategies to responsibly ensure that communities and nations who may most immediately benefit are empowered to do so. Doing so will require ongoing review of how intellectual property and licensing arrangements can best be structured to promote both scientific innovation and the public good (see pp. 119-122).

Stakeholders should work collaboratively, aiming to ensure that advances made possible by synthetic biology reach those who could benefit from them, particularly less advantaged populations. Attention to the just distribution of potential benefits is most effective when continually examined in concert with research and development activities. It encourages an awareness of the

full "life cycle" of a new application of synthetic biology, from initial research through potential global implementation. This holistic perspective recognizes that decisions made even in early stages of development may have consequences—technological, economic, or practical—that can affect the eventual implementation of potential research products positively or negatively. The ongoing development of semi-synthetic artemisinin is an example of a research program that reflects an appreciation for the challenges and importance of ensuring wide access to possible products.[101] Research and development activities throughout synthetic biology would be well served by similar appreciation of the relationships among current activities, potential future implementation concerns, and the concepts of justice and fairness.

[1] Although current levels of public and private investment in synthetic biology are not available, according to the Woodrow Wilson Center, the U.S. Government has spent approximately $430 million on research related to synthetic biology since 2005. By comparison, the European Union and three individual European countries—The Netherlands, U.K., and Germany—spent approximately $160 million during that same period. See: Woodrow Wilson International Center for Scholars. (2010). *Trends in Synthetic Biology Research Funding in the United States and Europe, June 2010, Research Brief 1.* Available at: http://www.synbioproject.org/library/publications/archive/researchfunding/. A few companies' combined spending already far exceeds those public investments. (*See, e.g.*, Dimond, P. (2010). Analysis & Insight: Synthetic biology—the devil is in the financial details. *Genetic Engineering and Biotechnology News* (July 13, 2010). Available at: http://www.genengnews.com/analysis-and-insight/synthetic-biology-the-devil-is-in-the-financial-details/77899331/.)

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APPENDIX
Guest Speakers

Bonnie L. Bassler, Ph.D.
Howard Hughes Medical Institute Investigator; Squibb Professor, Department of Molecular Biology, Princeton University; President, American Society for Microbiology

Jason Bobe, M.S.I.S.
Director of Community, Personal Genome Project, Harvard Medical School; Co-Founder, DIYbio.org

Sydney Brenner, M.D., D.Phil.
Senior Distinguished Fellow of the Crick-Jacobs Center, The Salk Institute

Allen Buchanan, Ph.D.
James B. Duke Professor of Philosophy; Investigator, Institute for Genome Sciences and Policy, Duke University; Distinguished Research Associate, Uehiro Centre for Practical Ethics, University of Oxford

Arthur L. Caplan, Ph.D.
Emmanuel and Robert Hart Director, Center for Bioethics; Sydney D. Caplan Professor of Bioethics, School of Medicine, University of Pennsylvania

Alexander M. Capron, LL.B.
University Professor; Scott H. Bice Chair in Healthcare Law, Policy and Ethics; Professor of Law, Keck School of Medicine; Co-Director, Pacific Center for Health Policy and Ethics, University of Southern California

Robert Carlson, Ph.D.
Principal, Biodesic

George Church, Ph.D.
Professor of Genetics, Harvard Medical School

James J. Collins, Ph.D.
University Professor; William F. Warren Distinguished Professor; Professor of Biomedical Engineering; Co-Director, Center for BioDynamics, Boston University; Investigator, Howard Hughes Medical Institute

Drew Endy, Ph.D.
Terman Fellow & Assistant Professor of Bioengineering, Stanford University; Director, BIOFAB: International Open Facility Advancing Biotechnology; President, The BioBricks Foundation

Ruth R. Faden, Ph.D.
Director, Johns Hopkins Berman Institute of Bioethics; Philip Franklin Wagley Professor of Biomedical Ethics; Professor, Department of Health Policy and Management, Bloomberg School of Public Health; Professor, Department of Medicine, Johns Hopkins University

Gregory Kaebnick, Ph.D.
Research Scholar, The Hastings Center; Editor, The Hastings Center Report

Nancy M.P. King, J.D.
Professor, Department of Social Sciences and Health Policy, Wake Forest University School of Medicine; Co-Director, Wake Forest University Center for Bioethics, Health, and Society

Ingrid Mattson, Ph.D.
Director, Macdonald Center for the Study of Islam and Christian-Muslim Relations; Director, Islamic Chaplaincy Program; Professor of Islamic Studies and Christian-Muslim Relations, Hartford Seminary; President, Islamic Society of North America

Jonathan D. Moreno, Ph.D.
David and Lyn Silfen University Professor; Professor, History and Sociology of Science; Professor, Philosophy; Professor of Medical Ethics, School of Medicine, University of Pennsylvania

Thomas H. Murray, Ph.D.
President, The Hastings Center

Bryan G. Norton, Ph.D.
Distinguished Professor of Philosophy, School of Public Policy, Georgia Institute of Technology

Amy Patterson, M.D.
Acting Director, Office of Science Policy; Director, Office of Biotechnology Activities, National Institutes of Health

Kristala L.J. Prather, Ph.D.
Assistant Professor, Department of Chemical Engineering, Massachusetts Institute of Technology

Arti K. Rai, J.D.
Elvin R. Latty Professor of Law, Duke University School of Law; Member, Institute for Genome Science and Policy, Duke University

David Rejeski
Director, Science and Technology Innovation Program, Woodrow Wilson International Center for Scholars

David A. Relman, M.D.
Thomas M. and Joan C. Merigan Professor of Medicine; Chief, Division of Infectious Diseases, Department of Medicine; Professor, Department of Microbiology and Immunology, Stanford University School of Medicine; Chief of Infectious Diseases, Veterans Administration Palo Alto Health Care System; Chair, Working Group on Synthetic Biology, National Science Advisory Board for Biosecurity

Randy D. Rettberg, M.S.
Director, iGEM and MIT Registry of Standard Biological Parts; Principal Research Engineer, Department of Biological Engineering, and Computer Science and Artificial Intelligence Laboratory, Massachusetts Institute of Technology

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Jim Thomas
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J. Craig Venter, Ph.D.
Founder and President, J. Craig Venter Institute

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Professor, Department of Pathology and Laboratory Medicine; Chair, Therapy and Vaccines Program, CAMB, University of Pennsylvania; Chair, Scientific Advisory Board, Inovio Pharmaceuticals

Ron Weiss, Ph.D.
Associate Professor, Department of Biological Engineering and Department of Electrical Engineering and Computer Science, Massachusetts Institute of Technology

Sondra E. Wheeler, Ph.D.
Martha Ashby Carr Professor of Christian Ethics, Wesley Theological Seminary

Hugh Whittall
Director, Nuffield Council on Bioethics

Paul Root Wolpe, Ph.D.
Asa Griggs Candler Professor of Bioethics; Director, Center for Ethics, Emory University

Edward H. You
Supervisory Special Agent, Federal Bureau of Investigation, Weapons of Mass Destruction Directorate, Countermeasures Unit I, Bioterrorism Prevention Program

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