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Industry Study

Final Report
Biotechnology

The Dwight D. Eisenhower School for National Security and Resource Strategy

National Defense University
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BIOTECHNOLOGY 2017

ABSTRACT: A comprehensive US National Security Strategy must recognize the underlying drivers of instability and conflict and fully leverage the US biotechnology industry in applying innovative solutions. As a pillar of national security, a strong, innovative and growing economy is an enduring national interest. The biotechnology industry's impact on the national economy is significant and growing; in 2014 it contributed 2.2% of GDP with revenues predicted to increase 29% by 2019. Investment in biotechnology will drive innovation and shape the future workforce while improving our health and controlling the fastest growing US liability – rising healthcare costs. As the world population increases, bio-agriculture is already helping with food and water insecurity. The United States can harness the full potential of biofuels and biomaterials to end fossil fuel reliance and make America the world's leader of renewable fuels. Lastly, innovative biotechnical solutions will improve our military and protect our population from harm. With proper resourcing and regulation, the biotechnology sector will be a vital component in our National Security Strategy.

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PLACES VISITED

Domestic:

California
Amyris Biotechnologies, Inc. (Emeryville)
Arcadia Biosciences, Inc. (Davis)
BioCurious (Sunnyville)
Bolt Threads, Inc. (Emeryville)
Joint BioEnergy Institute (Emeryville)
Monsanto Company (Woodland)
Sandia National Laboratories (Livermore)
University of California, Davis, Seed Biotechnology Center (Davis)
Zymergen (Emeryville)

District of Columbia
Biotechnology Industry Organization
BioEthics Panel at the Eisenhower School (Fort McNair, Washington DC)
BioFuels Panel at the Eisenhower School (Fort McNair, Washington DC)
BioEntrepreneurship at the Eisenhower School (Fort McNair, Washington DC)
BioSecurity, Center for the Study of Weapons of Mass Destruction, National Defense University at the Eisenhower School (Fort McNair, Washington DC)
Defense Advanced Research Projects Agency, Biological Technology Office at the Eisenhower School (Fort McNair, Washington DC)
Japanese Agency for Medical Research & Development - Washington DC Office
Office of the Surgeon General, Healthcare Delivery Directorate at the Eisenhower School (Fort McNair, Washington DC)
US Patent & Trademark Office, Biotechnology & Organic Chemistry Technology Center at the Eisenhower School (Fort McNair, Washington DC)
US State Department - Japan Desk Office

Maryland
Emergent BioSolutions (Gaithersburg)
Environmental Protection Agency (Silver Spring)
Intrexon Corporation (Germantown)
Montgomery College (Germantown)
National Human Genome Research Institute (Silver Spring)
National Institutes of Health (Bethesda)
US Food and Drug Administration (Silver Spring)
US Department of Agriculture (Silver Spring)
USDA, Animal and Plant Health Inspection Service (Silver Spring)

Massachusetts
Addgene (Cambridge)
Broad Institute of Massachusetts Institute of Technology & Harvard University (Cambridge)
Draper Laboratory (Cambridge)

Ginkgo Bioworks (Boston)
Manus Bio (Cambridge)
Massachusetts Biotechnology Council (Cambridge)
Massachusetts Institute of Technology Lincoln Laboratory (Lexington)
MIT Technology Review (Cambridge)
Scholar Rock Corporation (Cambridge)
Takeda Pharmaceutical Corporation (Cambridge)
Visterra, Inc. (Cambridge)

North Carolina
bioMASON, Inc. (Research Triangle Park)
Medicago, Inc. USA (Durham)
North Carolina Biotechnology Center (Durham)
NC State University BioManufacturing Training & Education Center (Raleigh)
Precision BioSciences (Durham)
Syngenta (Research Triangle Park)

International:

Japan
American Chamber of Commerce in Japan (Tokyo)
Euglena (Tokyo)
Green Earth Institute Company (Chiba)
Innovation Center for NanoMedicine (Kawasaki City)
Japan BioIndustry Association (Tokyo)
Japanese Agency for Medical Research & Development (Tokyo)
Japanese Ministry for Economy, Trade, & Industry (Tokyo)
Takeda Pharmaceutical Corporation (Fujisawa)
US Embassy, Environment, Science, Technology & Health Unit (Tokyo)
US Embassy, Economic & Scientific Affairs Section (Tokyo)
US Embassy, Commerce Office (Tokyo)

Introduction

In January 2017, the US Office of the Director of National Intelligence coordinated multiple intelligence entities to collectively assess world dynamics that will shape the next twenty years of US national security.[1] In the assessment—*Global Trends: Paradox of Progress*—the intelligence community posits that some critical underlying drivers of conflict are climate change, population growth and migration, food and water security, competition around energy resources, and global health.[2]

A comprehensive US National Security Strategy (NSS) must recognize and address the underlying drivers of instability and conflict and fully leverage the idea that US "leadership in science and technology" and its position as the world's leading economy have "been the foundation of American national security since World War II."[3] With these fundamental tenets in mind, national security requires more than military advantage to protect American interests in a dynamic and challenging world. Simply stated, US national security strategy must employ a whole-of-nation approach which leverages the many facets of American strength and leadership to effectively combat underlying drivers of conflict and instability that threaten the interests of the US and its allies.

Accordingly, the field of biotechnology (termed "biotech" for purposes of this paper) presents solutions to many of the underlying problems driving instability and friction in the world. The biotech industry is by no means a panacea. However, it offers viable means to augment a comprehensive future NSS—a strategy that does more than address symptoms of underlying problems, and seeks lasting and potentially curative solutions to global problems.

As part of the Eisenhower School's Industry Studies Program (ISP), a seminar group comprised of sixteen US and international military and civilian interagency students conducted a semester-long study of the biotech industry. The objective was to explore the "national and global resource base," and specifically, to assess the national security nexus within the biotech industry.[4] Through the course of study, the seminar group visited an array of US government regulatory bodies, biotech industry associations, biotech firms, and non-profits in both the United States and Japan.

This paper reflects the group's collective analysis of the opportunities to leverage biotech industry potential as a component of national security strategy. The analysis includes a brief examination of the science and industry of biotech, and then links the strategic problems facing US national security to advancements in the biotech field. The analysis concludes with a set recommendations to leverage the inherent capabilities of the biotech industry and enhance US national security.

Biotech—*Both a Science and an Industry*

Biotech – *The Science*

Biotech is "the use of a cell, a molecule derived from a cell, or the information contained in a cell to solve a problem or to make a product."[5] The science of molecular biology that underpins biotech gives rise to a diverse industry that "harnesses cellular and biomolecular processes to develop technologies" used in research, development, or the modification of products or processes for use in a broad spectrum of applications including agriculture, medicine and health, fuels and materials.[6]

The data derived from biotech is immense, and ever-increasing. Projections show the field of biotechnology will soon become the world's greatest data source, producing up to 40 exabytes of annual data by 2025, more than 400 times YouTube's annual data volume, and surpassing particle physics as the world's largest data generator.[7] The imperative to use this data effectively is driving the convergence of biotechnology, information technology and computational analysis. Simply stated, biotechnology is no longer limited to the lifesciences.

Biotech – *The Industry*

"Bioeconomy," a term coined in 2009 by the Organization for Economic Cooperation and Development (OECD),[8] captures the tremendous economic potential of the biotech industry. It recognizes biotech's diverse applications and how they have "brought [the US] closer to the threshold of a previously unimaginable future"[9] providing potential "solutions to [its] most demanding scientific and societal challenges."[10]

Defining the biotech industry is challenging because of its broad applications and growing numbers of companies entering the market. While typically divided into three sub-sectors of agricultural, industrial, and medical biotech, there is no consensus on the actual scope of the industry. For instance, IBISWorld considers biotech an industry with five segments including: human health technologies (72.0%), agriculture and aquaculture technologies (13.4%), industrial technologies (6.3%), animal health, marine and terrestrial microbial technologies (4.2%), and environmental remediation and natural resource recovery (4.1%) with over 2,000 firms and contributing approximately $100 billion to the US economy.[11] Other experts believe the total number of firms is likely much higher due to the industry's rapid growth and evolution, and the emergence of related industries, such as bio-informatics and bio-chemicals. Additionally, the economic contributions of biotech to the US and global economy are likely significantly underappreciated and predicted to become a major contributor to economic growth in the coming decade.[12]

Five large companies dominate the biotech industry with a combined 78.1% share of the market.[13] However, monopolistic competition, rather than oligopoly, best captures the competitive structure of the industry.[14] With competitive advantage achieved through specialization rather than integration,[15] over 2,000 firms compete in "basic research and target discovery; applied research and lead refinement; clinical and prototype research; manufacturing; and, sales and distribution."[16] This focus on specialization fuels the industry's continued growth as small, highly-focused firms enter the market. It also creates an environment in which large firms achieve innovation via acquisition, providing economic incentive for continued entry.

Though the industry continues to grow and possesses great potential, it faces key challenges in all sectors. The industry requires substantial capital investment while also carrying significant risk.[17] Biotech firms often attempt to address these challenges through cost- and risk-sharing relationships with their supported companies. However, cost- and risk- sharing cannot address the overarching challenge of the industry: research and development continues to push the limits of scientific knowledge, causing it to be a high failure environment. Young companies must pass through the "Valley of Death"[18] to successfully bring a product to market, and many do not make it. The high failure rate for young biotech companies favors serial entrepreneurs and requires significant venture capital and other funding to achieve success. The industry is also challenged by heavy regulatory oversight, particularly in health and agriculture sub-

sectors,[19] with products potentially regulated by more than one agency depending on intended use.[20]

Biotech and a Strong US Economy

As a pillar of national security, a strong, innovative and growing economy is an enduring national interest.[21] Though estimates vary, the biotech industry contributed $353 billion towards US gross domestic product in 2014, representing 2.2% of the nation's production.[22] With revenues predicted to increase 29% by 2019[23] and nearly doubling by 2024[24], the industry's impact on the national economy is significant and growing. This rapid growth allows the US to lead the global biotech industry with 32% of the market[25]; however, the nation's ability to maintain its dominance is not guaranteed. With national competitors increasing biotech investment[26], the US must leverage its lead in the industry to drive innovation, shape its workforce for the future and control the economic drag of health care costs.

Driving Innovation

Scientific discovery and technological innovation deliver a competitive edge for the US economy.[27] Innovation is not an accident; it is the result of deliberate and coordinated action by the "triple helix" of government, industry and academia. The relationships and synergies between these organizations play a critical role in fostering innovation and has led to the establishment and development of several highly productive biotech clusters.

The first biotech clusters emerged in 1980 following congressional passage of the Bayh-Dole Act, which established a means to translate academic research to commercial products. The legislation allowed universities to retain licensing rights to discoveries made through federally funded research, incentivizing academia to pursue commercially relevant research. It also codified the process of technology transfer from academia to industry, establishing a framework for academic-industrial engagement.

Accelerated by Bayh-Dole, encouraged by incentives from state and local governments, and supported by public-private partnerships and development-minded non-profit organizations, major biotech clusters emerged in Research Triangle Park, North Carolina; Cambridge, Massachusetts; and San Francisco, California. These areas are unique in attracting human talent, have access to significant financial capital, are home to top-quality universities and promote cross-disciplinary interaction.[28] The density of the "triple helix" network in these areas allow ideas to travel across the network quickly, build on each other and accelerate products from research concept to commercialization. The success engendered by this network perpetuates the cluster's draw and sustains the momentum of innovation and growth.

Shaping the Workforce

The biotech industry is at a tipping point. The maturation of automation, emergence of artificial intelligence (AI) and their convergence are poised to revolutionize the industry, causing tectonic shifts in the industry's bedrock—its highly skilled and well-trained workforce. A strategy of targeted investment from the "triple helix" will ensure the workforce of tomorrow can secure the US position as a global biotech leader and help sustain the nation's economic power.

Over the past two decades, the slow process of scientific discovery and the early stages of process engineering determined the speed of the industry's design-build-test-learn (DBTL) cycle for creating new biological products.[29] Automation and AI promise to revolutionize the DBTL

cycle by accelerating the pace of discovery, increasing process efficiency, and shifting tasks from people to machines – all changes that will alter the composition and qualifications of the workforce.

Previously limited to a supply-constrained[30] workforce of bioscience-related professionals and technicians, automation and AI will drive the addition of computational analysis, machine learning and machine operations into biotech. The industry's ability to capitalize on these additions will depend on its incorporation of automation- and AI- driven processes and practices across the DBTL cycle. Partnerships between government, industry and academia can promote the growth of the workforce and create a framework to foster the acquisition of necessary skills.

Controlling Health Care Costs

The vibrancy of the US economy is threatened by ever-increasing long-term national debt, which is primarily driven by rising health care program spending. The Congressional Budget Office reported in 2015, health care spending by the federal government surpassed social security expenditures for the first time.[31] By 2046, the debt-to-GDP ratio will rise to approximately 141%[32], nearly five times pre-Great Recession levels (Figure 1[33]). It is, as noted by Secretary of Defense James Mattis, the greatest threat to national security.[34]

As a nation, the United States spent $3.2 trillion on health care in 2015 with a projected increase to $3.35 trillion in 2016, roughly twice as much per capita as any other industrialized nation.[35] If current laws and trends are unchanged, within three decades, federal health care spending will grow to almost 10% of GDP and exceed the entire discretionary budget.[36]

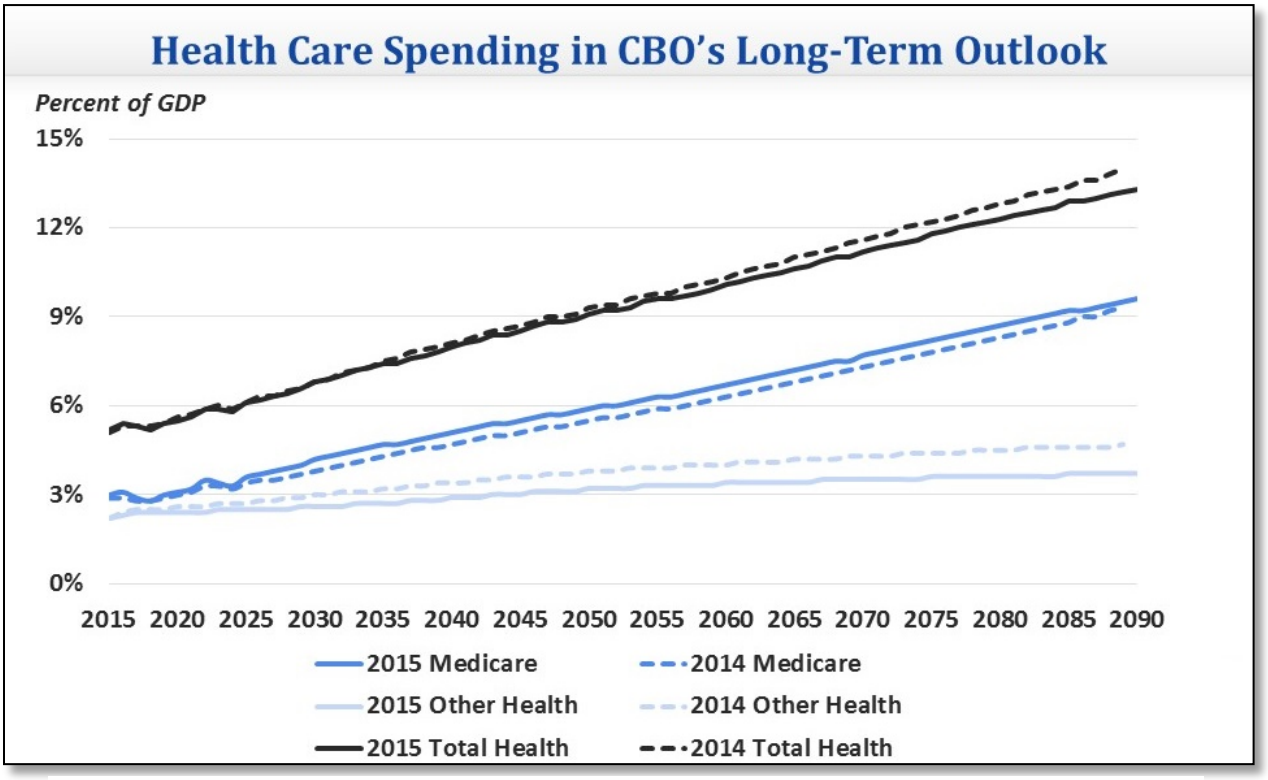


Figure 1 – Congressional Budget Office's Total Health Care Spending Forecast 2015 - 2090

A significant component of total health care expenditures are pharmaceutical costs, which are the fastest growing component.[37] Advances in biotech and the introduction of biologic drugs and therapies could significantly improve or cure targeted diseases and conditions, rather than just treating symptoms. In turn, health care costs could be reduced and mitigate the threat to funding national security requirements posed by cost growth and the national debt burden. Unfortunately, the cost of most FDA-approved biologic drugs is much higher than traditional small molecule pharmaceuticals.

However, the cost of biologic drugs is only a portion of the equation; the other part of the equation is the potential savings/cost avoidance realized by treating or curing the targeted disease/condition. Unfortunately, the few fielded biologics also provide mixed results in this regard. Biologics for treating Hepatitis C[38,39] and certain breast cancers[40] carry high upfront costs that are more than compensated for by long-term cost avoidance, while biologics used to treat colorectal cancer[41] may actually provide little longevity benefit and significantly increase the costs of care.

The true economic value of biologic therapies exists in the largely untapped realm of gene therapies. Gene therapies differ from other biologics as they alter the DNA structures, potentially curing genetic conditions permanently. Only two approved, curative gene therapies exist in the world, and they carry price tags ranging from $665,000 to $1 million per treatment course.[42,43] Scientific advances in gene editing technology such as CRISPR/Cas-9[44] and ARCUS[45] energized investment in translational science and biotech startups resulting in over 670 gene or cell-therapy trials, 68 of which are in Phase III clinical trials.[46] CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats and Cas9 is a nuclease that is used with another element to cut a cell's genome and allow editing. ARCUS (from a component called ARC Nuclease), is patented technology belonging to Precision Biosciences. It is a "next-generation genome editing platform derived from a natural genome editing enzyme called a homing endonuclease."[47] While CRISPR can "cut" DNA sequence well, according to Precision Biosciences, ARCUS can efficiently "paste" with minimum off-target activity.[48] If approved, these therapies could shift the economics of health care, eliminating all costs related to managing and treating their targeted long-term conditions. To attain maximum benefit from these new drugs and therapies, the federal government needs to prioritize research and development efforts toward the disease targets with the highest potential cost-benefit and develop a method to influence price setting.

Drivers of Instability—Food and Water Security

By 2050 the world's population will grow 25%[49], and food demand will increase by approximately 70%.[50] As the population increases and climate change impacts arable land and water resources, productivity of available agricultural lands will need to more than double in an environmentally sustainable and economically viable way in order to meet the world's needs. Figure 2 depicts current food production versus future food production in relation to the growing world population over time.[51] The impact of these forces will be compounded by increasing political fragility in underdeveloped regions, often driven by competition for constrained resources. Biotech offers solutions to address food security challenges. Among its benefits are enhanced crop production for food, feed, fiber, and fuel; improved biodiversity; and increased conservation.

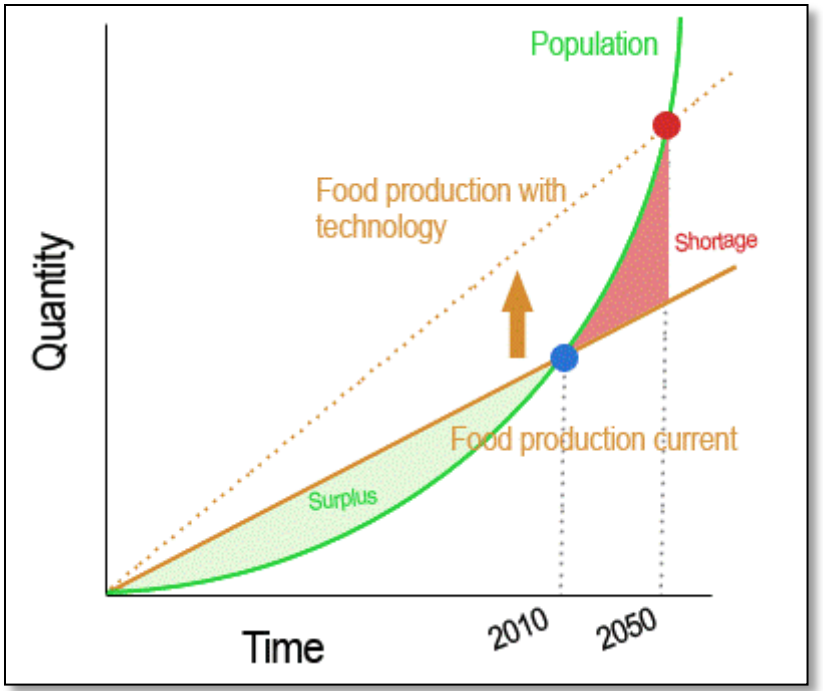


Figure 2 – Food Production In Relation to the Growing Population

Enhanced Crop Production

In the past, crop improvements occurred through traditional breeding techniques, accomplishing genetic modification through selective breeding practices. These techniques, while largely successful, could not produce specific and targeted results. Genetic engineering applies powerful and efficient technology for low-input, high-output agriculture where conventional breeding tools have not been effective. Crops can be engineered to enhance stress tolerance, improve productivity, and increase nutritional value and water efficiency. Though genetic engineering uses the same biological mechanism to accomplish these improvements, crops modified in these ways are commonly identified to the general public as being genetically modified (GM), genetically engineered (GE) or as a genetically modified organism (GMO).

The US GMO industry is regulated by the United States Department of Agriculture (USDA), the Environmental Protection Agency (EPA), and the Food and Drug Administration (FDA). The USDA determines if a GMO is safe to introduce to American agriculture. The FDA determines if a GMO is safe to eat and the EPA evaluates whether a GMO is safe for the environment. These agencies coordinate responsibilities using the Federal Coordinated Framework for the Regulation of Biotechnology. In 2015 President Obama directed the agencies to update the framework and develop a long-term strategy to ensure the regulatory system is prepared for future biotechnology products.

GMO technology has spurred global production of the four main crops of soybeans, corn, cotton, and canola. Since 1996, the amount of land cultivated with GMO crops has increased with yearly double-digit growth rates in 29 GM crop planting countries; 21 developing and 8 industrial. The United States is the biggest producer market followed by Brazil, Argentina, India, and Canada.[52,53] Although most European nations prohibit GMO crop cultivation because of public sentiment, Europe is a big consumer, importing 20 million tons of GMO corn and soybeans annually.[54] In the United States, more than 90% of the soy, cotton, canola, corn and

sugar beets sold have been genetically engineered.[55] Over the past 20 years, the US corn yield increased 38%, proving GMOs are a powerful tool to meet future food security objectives.[56]

Although scientists have highlighted the fact that GMOs are made similarly to traditional crops, lack of public understanding has led to low public acceptance and limited GMO's contribution to food security. This results in a constrained market and inflated prices, driving costs and uncertainty into the sector. Acting on these market influences, firms are reluctant to invest in GMO innovation, stunting the development of next generation crops that could have improved human well-being, enhanced environmental sustainability and made a major contribution toward addressing the challenge of climate change.[57]

The problem in perception originates in skepticism surrounding corporate motivations. Producers, not consumer demand, drove the introduction of GMO crops; and the industry began to claim significant profits. Combined with the public's lack of scientific knowledge, this perception created a suspicion that the firms were willing to sacrifice health and the environment in pursuit of profits. However, of the more than 2,000 studies examining the health and environmental effects of GMOs, none demonstrate significant negative effects. Rather, the studies show GM crops pose no greater risk than conventional crops.[58] Despite such data, a recent survey by the Pew Research Center and the American Association for the Advancement of Science highlighted GMOs struggle for consumer acceptance: 88% of scientists believe GMOs are safe, while only 37% of the US public holds this belief.[59]

This perception issue presents an opportunity for beneficial government intervention in the market. A combined effort of the triple helix may be able to establish a consumer education campaign regarding GMOs, to include follow-through with the GMO labeling law passed in 2016. Industry trade associations are another excellent avenue to advance the dialogue of GMOs and biotechnology in general. The availability of information – both about GMO advantages/ concerns and transparency in GMO inclusion in food products – will enable improved consumer choice. More discussion on ethical barriers and the war on public perception follows later in the report. Additionally, Appendix A explains GMO safety and labeling issues in further detail.

Improved Biodiversity

The last century's climate change and increased industrialization combined with centuries of traditional breeding techniques resulted in a 75% loss of biodiversity in agriculture and domesticated livestock species.[60] Using new technologies such as CRISPR/Cas-9 and ARCUS, biotechnology can halt, and even reverse, this trend through genomic sequencing and the application of diagnostic tools to manage animal health. Access to the livestock genomes are necessary to identify individual genes and proteins that control a host of animal health and welfare functions such as disease resistance and reproduction. Understanding these functions and their respective genes allows for the pragmatic administration of genetic engineering techniques (i.e., transgenic engineering, genome editing, and gene drives) on livestock species and production of commercial and economic benefits.[61] DNA-based diagnostic applications perform disease surveillance and food security screening through the food chain, enhance breeding for desirable traits selection, improve animal production efficiency, and increase the efficacy in the administration of prophylactic and therapeutic measures.

Another opportunity presented through newly developed gene editing technologies is improvement of livestock husbandry and management. With continued high consumption among developed countries, demand is accelerating in developing countries. Without cutting-

edge biotech research and prioritization, development programs would not be able to meet this demand. Additional governmental focus and funding would allow the United States to continue to lead the world in supplying animal food products.

With improved biodiversity comes more nutritious and better tasting foods. Using CRISPR and other technologies, crops with enhanced nutrition profiles are under development. One well-known example is beta-carotene–rich rice called "golden rice." This GMO rice was created to combat malnourished populations in Africa. Biotech companies are also developing allergen reduced foods including varieties of apple, soy, peanut, and milk. None of the examples are yet on the market for two reasons— long and arduous regulatory approval processes and the product may not be lucrative.[62] To fix perception problems, public demand will grow once more nutritious, better tasting GMO foods are in grocery stores.

Water Security

Clean water is an international resource— a critical part of a thriving economy as it supports the health of world populations, the agriculture industry and the manufacturing processes of the industrial base. Using CRISPR and other technologies, bio-agricultural companies are creating drought-tolerant crops. In the future, engineered crops will use less water or salient water to increase global food supplies while dealing with water scarcity.

In addition to the ability to genetically engineer plants that require less water, the biotech industry can contribute significantly to wastewater treatment technologies. Its application has led to water reclamation, nutrient-rich top soil fertilizers, and newly developed energy sources discussed in the next section.

Drivers of Instability—Global Energy Security

Leadership in energy security and technology are critical to national security. The 2015 NSS reiterates that the United States "will apply our distinct advantages in …science and technology… to maximize the strategic effects of our national power."[63] Most energy produced in the United States and the world is non-renewable and petroleum-based. The United States is the world's leader in gas and oil production. Figure 3 depicts the US distribution of five main energy sources and the four main sectors in which they are used. [64]

The global transportation structure remains reliant on petroleum fuels to provide approximately 97% of its energy.[65] US gas and oil consumption has declined. Over the last few years, the United States increased its domestic gas and oil production with burgeoning technologies in hydraulic fracking. Overall US energy security is improving.[66] Regrettably, Europe, Japan and developing countries face significant risks to national security and prosperity due to a lack of sufficient domestic energy capacity. The worldwide distribution of the supply of goods requires a global perspective on energy security.

To decrease risk, countries are investing in industrial biotech. The industry shows significant promise for growth[67] with innovative sub-sectors including biofuels, biomaterials and environmental remediation.[68] The world's leading engineers and companies continue development of energy-conscious solutions such as ethanol, bio-derived materials and wastewater treatment. The power, transportation and heating, ventilation and air conditioning (HVAC) sectors highlight the enormous market opportunities to supplant non-renewable energy

sources with biofuels and better use of resources throughout industrial manufacturing and wastewater treatment. Appendix B highlights challenges for industrial biotech companies.

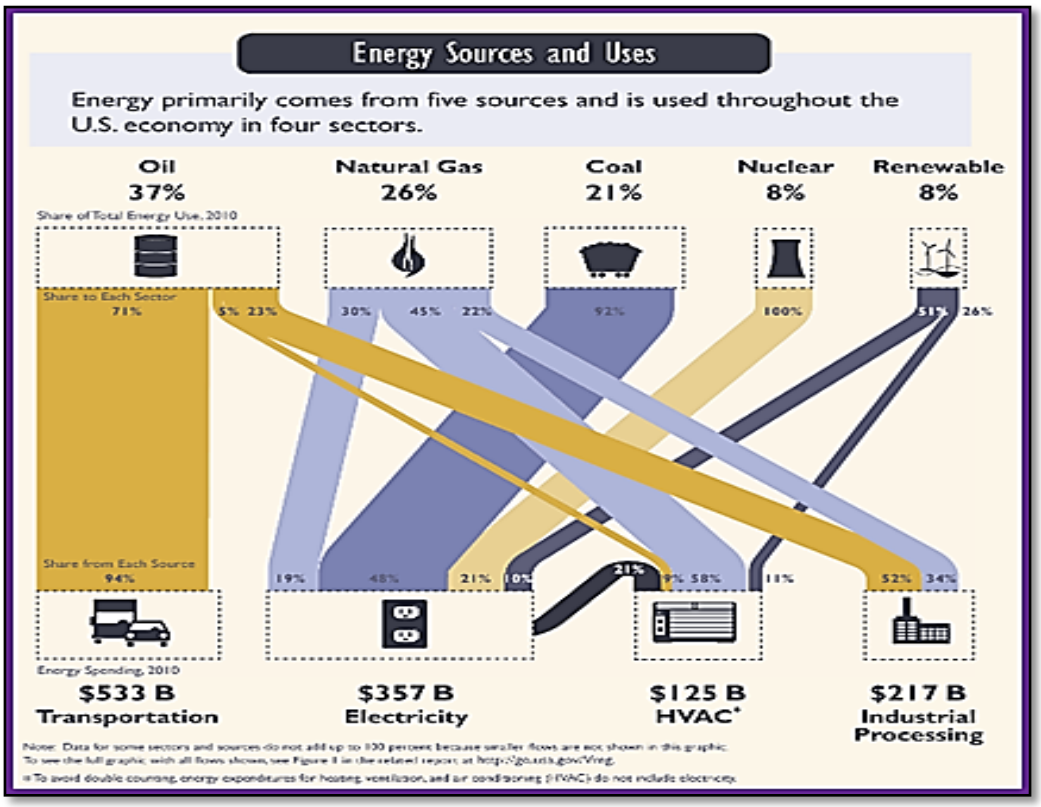


Figure 3 – US Distribution of 5 Main Energy Sources and the 4 Main Energy Sectors

Biofuels

A technological solution to sustainable energy security with prosperous growth potential for the United States and its allies is biologically derived fuels (biofuels). US transportation and storage systems for fuels require "drop-in" solutions. Energy is often traded as a commodity. To compete, biofuels must be chemically similar and cost the same or less than petroleum fuels. The United States must support the biofuels industry in three ways: overhaul energy policy to overcome negative externalities, selectively fund research and development endeavors to get companies through the "valley of death," and require discoverable databases for big data solution methods. The NSS specifically addresses the development of alternative fuels to both lead the global economy and reduce harmful emissions.[69]

Current US policy toward biofuels stems from the Energy Policy Act of 2005. The Energy Independence and Security Act (EISA) of 2007 expanded the policy of the Renewable Fuel Standard (RFS) Program under the Environmental Protection Agency.[70] The RFS Program imposes volumetric renewable fuel requirements to reduce petroleum-based jet fuel, heating oil and transportation fuel. The four RFS categories are: biomass-based diesels, cellulosic biofuels, advanced biofuels and total renewable fuels. The size of the program increased significantly in the 2007 EISA. Long-term renewable fuel goals increased to 36 billion gallons and extended yearly volume requirements through 2022. Qualifying fuels include renewable biomass fuels and grandfathered volumetric allowances.[71] RFS marginally increases the price of traditional fuels to spur industry change but does not significantly hurt domestic fossil-fuel producers.

US policy must maintain the most beneficial biofuel options to advance US energy security and economic prosperity. Currently, three generations of biofuels exist. The complexity of the fuel production process determines classification. Feedstock crops provide the raw material for the first generation of biofuels. Examples are ethanol-based fuels from crops such as corn and sugarcane.[72] The second generation of biofuels use lignocellulosic biomass, residues or waste rather than sugars and vegetable oils from food crops as raw materials. Examples are grasses, waste vegetable oil and municipal waste.[73] In a world with significant poverty, advanced biofuels avoid some of the public discourse on using edible crops for fuel products. Biomass-based biofuels are advancing toward large-scale production and need support to jump from the basic and applied research stages to full-scale, cost competitive production. Third generation biofuels are algal fuels. Algal fuels include organisms from giant kelp to microscopic cyanobacteria.[74] Algae has theoretical productivity between 10 to 100 times that of traditional feedstock.[75] Algal fuels are earlier in the technological stages of development than second generation fuels and require more support and funding during research and development.

Both second and third generation biofuels, also referred to as 'advanced biofuels', have the greatest potential for environmental sustainability and limit impact on world food shortages. Consequently, advanced biofuel options are the most likely candidates for sustainable growth and energy security. US and foreign government policy toward biofuels should address three main areas: countering negative externalities, focusing research funding on the most valuable biofuels and creating discoverable databases to advance basic science. Appendix C discusses biofuels in further detail.

Biomaterials

Bio-materials offer substantial advantages to the United States across a spectrum of NSS priorities. The terms "bio-inspired" and "bio-derived" represent the key areas of interest from a materials perspective. The interest in bio-inspired and bio-derived materials generally stems from the observation that biology and the evolution of natural systems have the potential to provide new and innovative solutions to structural and material challenges. Complex systems in nature have evolved and adapted within their environments to exhibit structural and functional qualities that, when studied carefully and in the right context, "can lead to new design paradigms for engineering materials."[76]

Bio-inspired and bio-derived materials are products that combine biological processes with chemistry and the material sciences of mechanics and engineering to find innovative solutions and alternatives to conventional methods and materials. In the right circumstances, bio-materials present opportunities for resource conservation and independence, along with greater sustainability and superior performance. They also help reduce man's impact on global warming.

Forty percent of carbon dioxide emissions are linked to the construction industry. In North Carolina a biotech company named bioMASON creates masonry bricks using an enzymatic process that simply "eliminates the need for firing by replacing the curing/hardening process with the formation of biologically controlled structural cement."[77] By using this process, bioMASON's construction materials eliminate release of carbon dioxide emissions. Their products include brick, cement and commercial countertop–type applications that can be made from non-potable water, industrial waste streams or even waste treatment water.[78]

Such opportunities have beneficial effects for the national economy and defense interests. Biomaterials offer revolutionary solutions for DoD applications in structural materials (armor and high performance fibers), in functional materials (soft electronics, smart materials and sensors, and power sources), as well as in medical applications (chemical and biological warfare, wound identification and healing, and human performance enhancements).[79] Biomaterial products often perform better than their conventional counterparts; examples include a stronger, lightweight, impact resistant helmet or protective biomaterial that assists in a burn victim's recovery. Appendix D describes bio-inspired and bio-derived materials in greater detail.

While production efficiencies and reduced environmental impacts are the substantial tangible benefits of industrial biotech, it is also clear that this field can be applied to mitigating the effects of limited and/or depleting resources. The United States must continue to resource funding into basic research that supports improvements in biomaterials to maintain technological advantages.

Wastewater Treatment

Like biomaterials, wastewater treatment offers opportunities to conserve energy and improve traditional treatment processes by harnessing the potential biologic and chemical energy of wastewater. Every component of wastewater is a potential resource rather than an unwanted byproduct. Technologies such as aerobic and anaerobic digestion, membrane bioreactors, and fuel cell bio-digesters can power wastewater treatment processes. An interesting aspect of sewage and wastewater is that its latent energy content is two to four times greater than the energy required to process it.[80] However, aerobic processes, such as activated sludge processing, require huge energy inputs and thereby have high costs to facilitate aeration. To create an energy-neutral system, many innovative technologies consider elimination of the aerobic activated sludge process by using anaerobic systems as the first step in biological treatment.

To harness the full potential of novel wastewater treatment technologies, continued government regulation is critical to ensure evolving innovation in the industry. Title 10, Biotech Code 2911(e)(2) requires DoD to achieve 25% renewable energy at its installations by 2025; and DoD is funding significant research to develop energy neutral or energy producing wastewater treatment using biotechnology.[81] In 2013, the EPA published its "Blueprint for Integrating Technology Innovation into the National Water Program," which advocates for the recovery of energy, and other resources like nitrogen and phosphorous from the wastewater treatment process.[82,83]

The US military is also interested in creating net zero systems for its installations and tactical units using biotechnology. One such study focuses on developing a sustainable wastewater treatment system for Forward Operating Bases (FOBs) using anaerobic treatment systems with the capability to remove ammonia and convert methane and hydrogen by-products into electricity.[84] Frequently, waste at FOBs is disposed via burn pits; using a net zero system would protect deployed military personnel from potential health hazards while reducing the military's environmental impact in foreign locations.

US wastewater treatment facilities are also aging and replacements are expensive. The key is to develop US policy, regulations and funding that encourage inexpensive, net zero technology and optimize the system's operations with custom microbes.

Global Health and Biosecurity

As the world's population grows, travel and urban migration will increase interpersonal exposure. Human-animal interfaces will also surge as the human population further invades animals' habitats. Each of these human-human or human-animal interactions is an opportunity for disease transmission and potentially threatens national security, especially with the most feared threat— pandemic influenza.[85] Worse yet, a bioterrorist attack could create a national crisis in the United States. In 2001 the *New York Times* reported on a US Government exercise:

> *Dark Winter, began with a single case of smallpox in Oklahoma City. At the end of the exercise, the imaginary epidemic had spread to 25 states and killed several million people. As it unfolded…the government quickly ran out of the vaccine, forcing officials to make life-and-death decisions.*[86]

Eventually an event like this will occur. The increase in interpersonal interaction combined with the dual-use nature of advances in biotech also provides nefarious state and non-state actors avenues to conduct biological warfare. Controlling and mitigating the natural and man-made threats require effective surveillance, response and prevention.

Threat Surveillance

Surveillance, for both emerging infectious disease and engineered biologic threats, involves monitoring susceptible populations and detecting diseases as they emerge. Done well, surveillance enables rapid disease response, limiting outbreaks to isolated populations while minimizing political, social and economic impacts. Poor surveillance, as was experienced with the swine flu outbreak, enables a disease to grow from a local problem to a global pandemic.[87] Advances in biotech offer opportunities to improve surveillance.

Through MIT-Lincoln Labs and Sandia National Laboratories, both federally funded research centers, the government is developing enhanced biologic sensing systems and dual-use portable, rapid point-of-care devices for surveillance and collection of pre-symptomatic diagnostic information.[88,89] If successful, such systems would significantly enhance surveillance by equipping front-line medical staff with early detection and treatment capabilities well beyond those currently available. However, ever-evolving biological threats demand continued innovation in surveillance, an area in which federal funding plays a critical role.

Threat Response (Treatment)

Once a protective surveillance program detects the presence of an infectious disease or biologic threat, the focus shifts to the response. The relevant public health systems— civilian and/or military— must deliver timely efficacious treatment to minimize the disease's impact and contain transmission. Biotech offers opportunities to improve efficacy and response timelines.

Traditional disease treatments use chemicals as counter-agents to the offending virus or bacteria. These chemicals often produce off-target effects and require higher-than-optimal doses because they rely on non-targeted delivery mechanisms. Biotech, however, allows scientists to design medicines that specifically target the offending cells, using such approaches as designer monoclonal antibodies (mAb) and amino acid modification.[90] Additionally, editing technologies allow the mAbs to be customized to an individual and the antigen, further minimizing the danger of off-target effects.[91]

The ability to tailor mAbs to antigens carries a price— time. The scientific discovery required to identify the susceptible portion of an antigen and generate a functional antibody is substantial. This makes it difficult to create biologic treatments for emerging diseases. However, DARPA's Pandemic Prevention Platform (P3) aims to develop an integrated technology platform to enable public health officials to stop the spread of any viral disease outbreak within 60 days, thereby preventing it from reaching pandemic status.[92]

Prevention

Though advances in surveillance and response will help contain the spread of a previously observed disease, regardless of initial source, immunization remains the best defense. The benefits of immunization through vaccination are multiplicative: for every $1 spent on vaccines, subsequent medical costs are reduced by $6 and yield an overall societal savings of $18.[93] However, traditional methods for producing vaccines carry challenges in development timelines and manufacturing scale.

Biotech advances enable non-traditional approaches to vaccine manufacturing that can address these challenges. For example, freed from the standard egg-based model of flu vaccine production, scientists and researchers in a DARPA-sponsored program successfully used tobacco plants (*Nicotiana benthamiana)* as the manufacturing platform to produce more than 10 million doses of a clinical-grade H1N1 influenza vaccine in a single month, a production rate 85% better than the egg-based model.[94] Further development of such non-traditional vaccine production methods can improve the nation's response to emerging disease by allowing mass immunization before a disease has spread with the potential to alter the economics surrounding vaccine stockpile policies and practices.

Challenges to Biotechnology's National Security Potential – *Counterarguments*

Regardless of the promise biotech holds to mitigate or solve several national security challenges, support for biotech is not universal. The science and industry of biotech have multiple critics who cite lack of commercial viability, the slow pace of scientific advancement and product development, ethical concerns, and public perception as factors that will limit the potential of the biotech industry.

National Security Counter Perspectives and Lack of Delivery on Potential

Though academics often discuss the varied instruments of power— diplomacy, information, military and economic—many political leaders perceive national security as a distinctly hard power enterprise.[95] In such a worldview, military investment carries a high return, while investment in other instruments of power carry uncertain benefits. This perspective can be self-reinforcing via confirmation bias: military investment creates physical products to which success is assigned (e.g. victory or deterrence is due to a military system) while lack of investment drives failures. At the same time, investment in economic growth rarely receives credit for directly influencing complex issues such as climate change and global health. Political leaders often find it easier to allocate resources toward the military rather than instruments of soft power, thus limiting the latter's scale, scope, and impact.[96]

Similarly, the American tradition of belief in the power of markets, Adam Smith's "invisible hand," can hamper the nation's ability to harness the potential of emerging

technologies because markets may resist innovation if it carries a higher cost than existing technologies.[97] Indeed, "the private sector is far more likely to impede technological progress than to advance it" because of the exorbitant costs of innovation.[98] Markets have little patience for the slow and high-risk process of scientific discovery at the heart of emerging technologies. Thus, such innovation must be supported by the governed, often without positive or short-term net gains.

The experience of biotechnology illustrates this market challenge. Despite a consistent federal investment in biotech, commercially viable, cost effective solutions are still not widely available. The initial attempts at creating biologics to cure complex diseases are not cost-effective and first-generation bio-fuels cannot compete with petroleum products in price. These early difficulties continue to cloud the perception of the biotech industry, but they should not determine the industry's fate.

Biotechnology is on the cusp of delivering substantial rewards. Diseases may be eradicated, eliminating long-term costs. Biofuels will be cost-competitive with low-priced petroleum within a few years. In bio-agriculture, crops now require less pesticide, are more nutritious, require less water and deliver increased yields. These achievements directly impact the drivers of instability, thereby enhancing national security.

The magnitude of impact biotechnology will have on national security is limited only by the nation's commitment. Today's advances are driven through disparate investment strategies. If the United States was to apply the full weight of its attention and resources toward rapid, radical advances—as was done in the effort to put a man on the moon—biotechnology could serve as the genesis for the next century's security.

Adoption Barriers and the War of Perception

Some would argue that food scarcity is due to politics, poor distribution of existing food supplies and income inequality. Those critics' points are valid to an extent, however the world's population will be 10 billion by 2050, and to feed a population that large, farmers will have to produce more food in the next fifty years than they have in the past 10,000 years combined.[99] GMO crops (GMC) are benefitting farmers worldwide. Developing countries that produce their own food are more prosperous. GMCs especially benefit poor farmers, 93% of whom are from developing countries such as China, India, the Philippines, and South Africa,[100] directly fighting global income inequality. For example, in 2014 GMCs generated $17.7 billion in direct income.[101] Lastly, locally grown food requires less transportation and less energy. The result is better distribution of less expensive food, saving people money.

Among the most substantial barriers to harnessing the public's full commitment are safety and ethical concerns. People feel more averse toward GM food than other GM applications, such as GM medicine or fuels.[102] As this paper previously discussed, the lack of public acceptance over GMO use is not corroborated by proven scientific evidence. Scientists overwhelmingly state that GMOs will improve food supplies, reduce transportation costs and reduce man's carbon footprint. The biggest sceptics are environmentalists and groups such as Greenpeace and Sierra Club, ironically the groups that point to overwhelming scientific evidence in discussing man's effect on global warming. To sway public opinion, this past summer, more than 100 Nobel laureates called on Greenpeace to end its GMO opposition stating there is a

scientific consensus they are safe and can benefit society.[103] Another important pro-GMO announcement was made by Mark Lynas, a well-known environmental activist who helped to spur the anti-GMO movement in the 1990s. At an Oxford Farming Conference in 2013, Lynas regretted his "anti-science" rhetoric and now fully endorses GMO use. If Lynas and others inside the environmental community advocate GMO use, it may be possible to change overall public perception.

Overcoming ethical concerns is not impossible. A difficult ethical concern that has resolved itself involved stem cell research. Recognizing the entrenched nature of these objections, the industry used scientific discovery to move from embryonic stem cells to induced pluripotent stem cells (IPSC), which are derived from adult skin or blood cells.

The industry has been unable to move beyond the ethical debate regarding the genetic modification of humans. The debate is centered over the conflict between human ability and nature—specifically the skill to manipulate human genetics and the resultant concerns from a modified organism that is no longer human.[104] The fundamental question of the ethical debate is: how much change in the genetic code ultimately creates a new species at the loss of another and what role is man allowed to play in fundamentally changing naturally occurring events?

Perhaps the transhumanist argument is the best response to both the perception and ethical challenges; it argues that the "…essence of being human is not our limitations…it's our ability to reach beyond our limitations."[105] There is simply no magic answer that will placate the dissenting voices and opinions. There is a balance to be found, and it involves a set of ethical boundaries for genomic changes. To ensure research remains ethical, Institutional Review Boards (IRBs) must holistically address the implications of genomic research on the population as a whole and specifically address the topic of what it is to be human.

Regardless of the ethical and perception challenges, biological science is progressing. The true cost of failing to leverage biotech to address the underlying drivers of instability is to cede advantage to those who do—like China. The cost is losing the significant comparative economic and innovative advantage the United States currently enjoys.

Summary of Recommendations

Specific funding recommendations add weight to policy discussions and help with prioritization. Two critical areas preclude this analytic detail. First, biotechnology experts have not come to consensus on defining the industry, which prevents holistic understanding and estimates of current spending. Second, shortfalls in US strategy, policy and implementation piecemeal the benefits of investment, which reduces understanding of causality. On the following page, Table 1 prioritizes the recommendations from the biotech industry study group, and identifies goals, objectives and responsible agencies to address perceived shortfalls. Immediately following are several recommendations; Appendix E contains additional detailed information.

Priority of Effort	Goal / Objective:	Select Recommendations	Lead(s)
1	**Update National Security Strategy (NSS)**	Leverage biotechnology as a means to achieve US strategic objectives	NSC
2	**Develop National Biotech Strategy**	Prioritize and resource biotechnology investments using the design from a *Biotechnology Blueprint*	OSTP
3	**Increase US Biosecurity**	Integrate national biotech R&D strategy and response framework	OSTP (strategy); NIH (response framework)
		Incentivize pandemic flu mitigation	CDC, NIH, DARPA, IRS, international agencies such as WHO
4	**Preserve US lead in biotech (Agriculture, Pharmaceuticals, Industrial Biotech)…Address drivers of instability indirectly**	Fund prioritized S&T	DARPA, BARDA, NIH
		Foster commercialization infrastructure	USPTO, FDA, USDA, EPA, Department of Commerce
		Streamline regulatory burdens	FDA, USDA, EPA
		Target workforce development and convergence	Departments of Labor, Department of Education
		Foster public-private biotech partnerships	OSTP
		Encourage economic development	Congress, FTC, USTR, Department of Commerce
5	**Advance the dialogue of biotech and change negative public perceptions**	Coordinate education program to increase acceptance of GMOs	BIO, USDA
		Explicate biotech ethics to elucidate facts over hyperbole	BIO, Institutional Review Board (IRB), Recombinant DNA Advisory Committee (RAC), presidential bioethics commission
6	**Reduce industrial waste, further energy security, protect water security**	Increase investments in next generation biofuels and industrial chemical development	DOE, EPA
		Incentivize auto industry to develop engines capable of greater ethanol use (E30 & E85) to overcome the "blend wall"	NHTSA, Department of Energy, Department of Transportation
		Maintain RFS standards for energy companies; Enact cap and trade for petroleum fuels and an increased surcharge for companies using hydraulic fracturing techniques	Congress, DOE, EPA

Table 1 – Prioritization of Recommendations

US National Security Strategy

The first step is to develop a national biotech strategy derived from the principles of a US National Security Strategy, which can leverage biotech as a means of achieving, where applicable, US national security objectives. Biotech must be viewed as a science and an industry that can mitigate and potentially solve some of the underlying reasons for conflict and instability.

The second step is to prioritize and resource American competitive advantage via the Office of Science and Technology Policy (OSTP). The executive branch must staff and empower OSTP to establish "clear national goals for Federal science and technology investments in a broad array of areas spanning virtually all the mission areas of the executive branch."[106] This office is also the mechanism to propose appropriate federal regulatory policies that govern the multiple disciplines within biotech.

Specific recommendations for the Economy, Water and Food Security, Energy, Health and Biosecurity follow.

US Economy

The US biotech sector revenue is estimated to have grown on average >10% each year over the past decade—much faster than the rest of the economy which is below 2%.[107] This presents a unique opportunity to increase US government biotechnology funding to a greater level than the current rate, until the rate of biotech growth is equivalent to the rate of general US economy growth. The lag between investment and growth is a complicating factor and biotech funding and causality to economic growth is not established. However, a case can be made to increase funding to biotech as a better option than most other industries with low or negative growth rates. In addition, focused funding on where the biotechnology market does not have sufficient incentive such as education and basic science research should best advance biotechnology's contribution to the US economy, prosperity, and thus, national security.

Funding, targeted by OSTP, to leverage US comparative advantage in the global biotech industry is needed to drive innovation and shape our workforce for the future while simultaneously controlling the costs of health care. Investments in biotech workforce development, especially science and technology, can nurture the spirit and culture of innovation and entrepreneurism resident in the biotech industry. Both the level of funding and what funds are used for are equally important. Continuing current funding of federal institutions enables universities, established industries and small startup companies to assume research and development risks. Of course, just to maintain the US competitive edge in technology requires the federal government to promote investment in basic research and development.

Water and Food Security

Current US public perception of GMOs is generally negative. To improve general education and GMO acceptance, we recommend that Biotechnology Innovation Organization (BIO), the biotech industry's trade association, lead the advertising effort. In coordination with government, BIO needs to change consumer perceptions of GMOs and can start by marketing to key influencers such as high school science teachers and college professors. With the GMO labeling law passed and approved in July 2016, USDA needs to roll out a detailed strategic communication plan and sponsor a public service announcement campaign to be aired on public television and radio including all federally funded college radio stations.

To encourage the next generation of biotech scientists, US policy should fund animal husbandry and life-science programs in support of vocational and college education focused on bioagriculture and technical degree programs.

To streamline GMO development, the US biotechnology regulatory agencies need a more transparent GMO approval process. The Federal Coordinated Framework for the Regulation of Biotechnology revision should include a transformational change in streamlining the approval process as well as clear guidelines that can easily adapt to new technologies. The framework should be formally updated every five years with the ability to spin out yearly rapid revisions between updates.

As part of OSTP's mission, the federal government should use biotech to improve wastewater treatment and address water shortages. The US can support global water security by sharing advances with other nations.

Energy Security

Investments in biofuels should increase to support alternatives to petroleum based fuels. That should include investments in dual use, net zero systems like wastewater treatment, which can produce methane and hydrogen by-products for generation of electricity. Other initiatives could include tax increases on fossil fuels and encouraging the automotive and transportation industry to invest in new engine technologies to take advantage of non-fossil fuels.

Health and Biosecurity

Rising health care spending is a primary driver of the negative debt-to-GDP ratio, threating national security. The federal government can better prioritize spending for research and development toward disease targets with the highest potential cost-benefit, and develop a method to influence price setting.

Increased collaboration with other nations and multi-lateral international organizations for early detection of infectious disease should be encouraged to compile surveillance and diagnostic data, stopping pandemics before they occur in humans, animals or plants. Bio-warfare threats to agriculture and the livestock industry should be considered in prevention efforts.

Finally, steps should be taken to accelerate promotion of genetic constructs and non-traditional approaches to vaccine development to prevent viral disease outbreaks from reaching pandemic status.

Conclusion

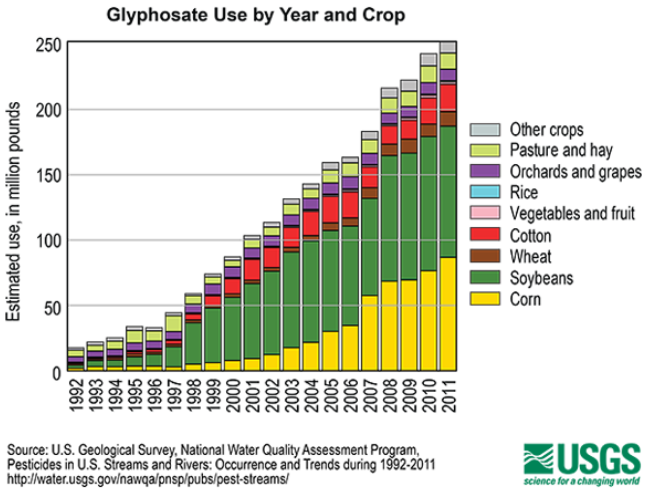
The objective of the Eisenhower School's ISP is to ensure future members of the US national security apparatus are both aware and informed of the strategic implications and opportunities resident in the US industrial base.[108] The biotech industry study group used a series of exploratory visits, both in the United States and Japan, to biotech firms and government regulatory bodies to develop an appreciation for the industry's connections with US national security.

Based on the concept that protecting enduring US and allied interests involves more than maintaining military comparative advantage, the group concluded that the field of biotechnology

offers numerous potential solutions to many underlying problems driving conflict and instability in the world. The group collectively concluded that the field of biotech, with the appropriate federal support and policy, has significant potential to be harnessed as a viable component of a larger, comprehensive US national security strategy.

GMO Safety

Americans have been eating foods containing GMOs for over 15 years and there is no credible evidence to prove they are harmful.[109] Despite this, GMO safety worries most Americans; consumers particularly object to the use of a chemical named glyphosate found in the herbicide brand Roundup®. Around 1990, Monsanto genetically engineered crops to withstand glyphosate treatment, while the chemical kills all other vegetation. Unfortunately, 27 years later, weeds have adapted and many are glyphosate resistant. Farmers now have to spray a lot more glyphosate to achieve the desired results, and it is absorbed into corn, soy, cotton, and other crops. It also enters the water supply and circulates in the air. Several articles have been published recently showing that significant amounts of glyphosate can be found in popular US foods such as Cheerios®, Oreos® and Doritos®.[110]



The USDA reported that in 2010 US farmers applied 91,200 tons of glyphosate.[111] According to the EPA, glyphosate is used in some fashion in the production of over 70 food crops including GMOs and conventional crops such as fruits, nuts, and vegetables.[112] US regulators set an acceptable daily intake (ADI) for glyphosate at much higher levels than other countries. For example, the United States has set the ADI for glyphosate at 1.75 milligrams per kilogram of bodyweight per day, almost six times higher than the European Union's standard of 0.3.[113]

So is glyphosate dangerous? In 2015 the International Agency for Research on Cancer (IARC), part of the World Health Organization (WHO), declared glyphosate a "probable human carcinogen."[114] The IARC classified it as a category 2A risk, the same category as red meat.[115] However, the American Association for the Advancement of Science stated that the European Union has invested more than €300 million in research of GMO safety, including those using glyphosate. After 130 research projects, covering a period of more than 25 years and involving over 500 independent research groups, it has concluded that GMOs are no more harmful than traditional plan breeding technologies.[116] Monsanto's position is that based on overwhelming contradictory evidence, the WHO is wrong. They state,

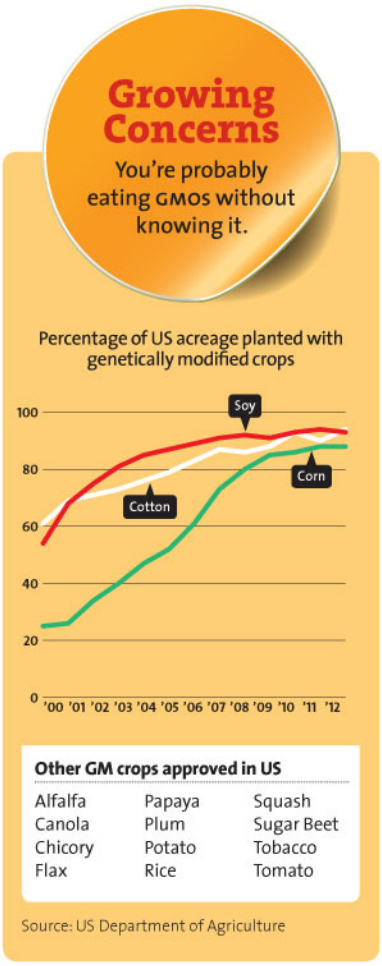
> *In fact, since IARC classified glyphosate, regulatory authorities in the United States, Europe, Canada, Japan, New Zealand and Australia have publicly reaffirmed that glyphosate does not cause cancer. Additionally, in May 2016, the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) concluded that "glyphosate is unlikely to pose a carcinogenic risk to humans from exposure through the diet."*[117]

Clearly glyphosate use is controversial and needs more long-term research to determine its safety.

Labeling

GMO labeling is mandatory in more than 60 countries including the United States.[118] Americans are overwhelmingly supportive of labeling foods that have been genetically modified. In a *New York Times* poll, 93% of respondents supported labeling.[119] In 2009, the FDA stated to the WHO and the Food and Agriculture Organization of the United Nations that it was hesitant to recommend labeling foods made with GMOs. In written correspondence, the FDA stated,

> *Inherently Misleading Labelling – Moreover, mandatory method-of-production GM/GE labelling would likely be inherently misleading. A mandatory method-of-production GM/GE labelling regime creates the impression that the labelled food is in some way different from or less safe than a comparable, unlabeled non-GM/GE food (for example, no requirements exist that all food be labelled to indicate the breeding technique used to produce it).*[120]



A decade ago, Monsanto supported mandatory GMO food labeling in Europe. Many GMC opponents claim that Monsanto does not support similar US legislation. However, the BioAg industry is not against federal labeling legislation; on the contrary, Monsanto helped pass the Safe and Accurate Food Labeling Act of 2015.[121] Signed into law by President Obama on July 29, 2016, GMO food will be required to have a label indicating it contains genetically engineered ingredients and a GMO logo. This law will override any legislated state laws and force one US solution. The new requirement will force food companies to reveal whether products contain GMO ingredients, but the new US law does not mandate that specific information be printed directly on package labels. Instead, consumers can look up the information via a QR code or phone number printed on the label.[122] Industry advocates contend that this single labeling system is manageable and prevents the proliferation of many individual state mandates. Monsanto did not want every state to pass its own labeling laws because it would be expensive and logistically impossible to implement.[123] With the new GMO labeling law, there will be one federal standard. Interestingly, the USDA will be responsible for implementing the new law within two years with assistance from the FDA.

Insect Health

There is growing concern about the environmental impact of pesticides on traditional crops and GMCs. Along with human safety concerns, glyphosate is blamed for an 80% decline in monarch butterflies. Glyphosate has killed the milkweed plant population where monarch butterflies lay their eggs. Dr. Karen Oberhauser, a researcher from the University of Minnesota, is one of many scientists who believe that the adoption of Roundup Ready® and corn and soybean GMCs is the main cause of the butterflies' steep decline.[124]

Pesticides from the neonicotinoid family of chemicals also have a fatal effect on the bee population. Monsanto, Bayer, and Syngenta all manufacture and use neonicotinoid pesticides on their GMC fields. The European Union temporarily banned some neonicotinoids in 2013 and is attempting to pass legislation to completely ban neonicotinoid field use this year.[125] On January 12, 2017, the EPA published a finding that neonicotinoids are hazardous to the bee population when used in some spray applications.[126]

Companies like Monsanto are concerned about bee populations. They are vital to pollinating transgenic crops. But Monsanto doesn't believe neonicotinoids are the culprit. They and many researchers believe the varroa mite is quickly killing off colonies.[127] And they are correct. The varroa mite is an external parasitic that attacks honey bees. Scientists have proven the deadly link between the worldwide collapse of honeybee colonies and the varroa parasite. Originating in Asia, the parasite and its associated virus have spread worldwide over the past 50 years. Scientists stated the mite's arrival in Hawaii in 2007 gave them a unique opportunity to track its deadly spread. "Within a year of varroa arrival, 274 of 419 bee colonies on Oahu Island (65%) were wiped out, with the mites going on to wreak destruction across the Big Island the following year."[128] As a result, Monsanto, Syngenta, and other BioAg companies are assisting in eradicating the varroa, while maintaining neonicotinoids are safe. Going forward, the NIH and EPA need to conduct further long-term studies on neonicotinoids and their effect on humans as well as insects and native plants.

*Bee image from Sierra Club, Canada, http://www.sierraclub.ca/sites/sierraclub.ca/files/images/hb3.jpg
**Tomato image from: https://www.farmtoconsumer.org/wp-content/uploads/2012/08/GMO-Tomato.jpg

To evaluate the most viable options, a case must be made for the reasons so much industrial biotechnology never makes it to market. Getting from basic research through to commercialization of a product is a difficult road. Failure modes for many biotechnology businesses often stem from the mismatch of science and business disciplines. Gary Pisano argues the root of challenges to science-based businesses are:

1. Uncertainty of the science requires significant risk reward and risk management.
2. Highly complex and heterogeneous nature of the scientific knowledge base requires mechanisms for integration across functional areas.
3. Rapid scientific progress requires mechanisms for cumulative learning.[129]

Handling Uncertainty

A successful business strategy to gain funding through venture capitalists or angel funding revolves around the platform and pipeline for the bio-product. The platform is the cell or organism used as a host for product lines. A product pipeline is a suite of potentially viable metabolic processes to obtain product from the cell or organism. The pipeline demonstrates to investors a stream of off-ramp possibilities that represent a future return on invested capital.

Extreme uncertainty in proving out new technologies exacerbates opportunities for failure throughout the biotechnology business cycle. One way biotechnology companies tackle uncertainty is through intellectual property (IP) protection. The main options for protecting IP are the platform and the pipeline. If the platform is difficult to replicate, a company doesn't need to protect the intellectual property (IP) with a patent.[130] Biotechnology platforms are often kept at the trade secret level along with other traditional trade secret processes. The product lines of the platforms are often patented as they are more easily reverse-engineered or copied. In this way, a company can keep the platform technology for a lot longer than the 20 years that US patent law traditionally protects ideas. The downside is that if IP is stolen or reproduced and patented, the company loses both IP protection and current and future revenue streams.

Integration Across Functional Areas

The nature of scientific research requires mechanisms that integrate the scientific knowledge base across disciplines. The development of an industrial application follows a similar process to drug development, without the high level of regulatory gates. The three main phases are discovery, development and commercialization. In discovery, the company must find and refine leads and determine commercial appeal to the market.[131] During this phase, a company is heavily reliant on its biology and chemistry talent. Marketing talent does not exist in many small companies, so a start-up company's ability to determine commercial appeal may be severely limited by its lack of business talent. In development, a company develops the formula and begins pilot production line.[132] Biologists and chemists are the main actors during formulation; biological and chemical engineers become more important as the product is scaled for production. In commercialization, a company scales-up manufacturing, distributes and sells the product.[133] In this phase, manufacturing engineers and a company's business acumen come to the forefront. Throughout, a company's ability to use data is a discriminator.

Mechanisms for Cumulative Learning

Industrial biotechnology research consists of three broad categories: basic research, translational research and applied research.[134] In basic research, government and academic labs

work toward gaining fundamental knowledge of biological processes. Not-for-profits and companies with research divisions also perform basic research. The same organizations perform translational research, which tests prototypes for industrial applications. Applied research develops marketable products and is generally performed by industrial biotechnology companies.[135] Both successes and failure require discoverability for cumulative learning breakthroughs. One method for enhancing discoverability is access to data. Data is an important component of advancing science and technology. Recommendations should incorporate access and sharing of basic science data.

Biofuels and biotechnology companies illustrate the struggles of a business based on science and technology. They provide insights for future policy recommendations for the United States. A look at US biotech companies offers one perspective. An alternative ally perspective branches from Japan's biofuels companies.

Domestic Perspective

The US biofuels industry includes a number of examples at various stages of technological development. Of note, biofuels companies outside of first generation ethanol companies are not producing biofuels as a primary product. The main reason advanced biofuels are not currently a viable alternative for fossil fuels has been the introduction of hydraulic fracturing, or fracking, to access petroleum-based fuels.[136] Fracking becomes a profitable venture as oil prices climb over $60 per barrel. Challenges from fracking companies incentivized the Organization of the Petroleum Exporting Countries (OPEC) to keep prices well below this mark.[137] For the current state of advanced biofuel technology, oil prices of $75 per barrel is the price point of profitability. Biofuels companies moved from marketing fuels to marketing higher margin products to remain viable in the market.

Three US companies with the capability to produce biofuels highlight the threats to the US biofuel industry: Amyris, Manus Bio and Zymergen. Amyris began as a company by producing an anti-malarial through plant-sugar conversion. The company then focused its yeast platform to produce a renewable farnesene for fuels. When the price of oil dropped, Amyris shifted to high margin goods such as emollients and fragrances in a business to business (B2B) model. To capture higher percentage of sales, the company leapt into a business to consumer (B2C) model with solvents and essential oils.[138] Each of the shifts in strategy came from a change in market economics for the company's products or a lack of sufficient funding to get to the next stage of research and development.

Manus Bio uses a different approach to research opportunities and a more diversified business strategy. Figure C1 illustrates the simplified process that Manus Bio uses for production and depicts some product uses.

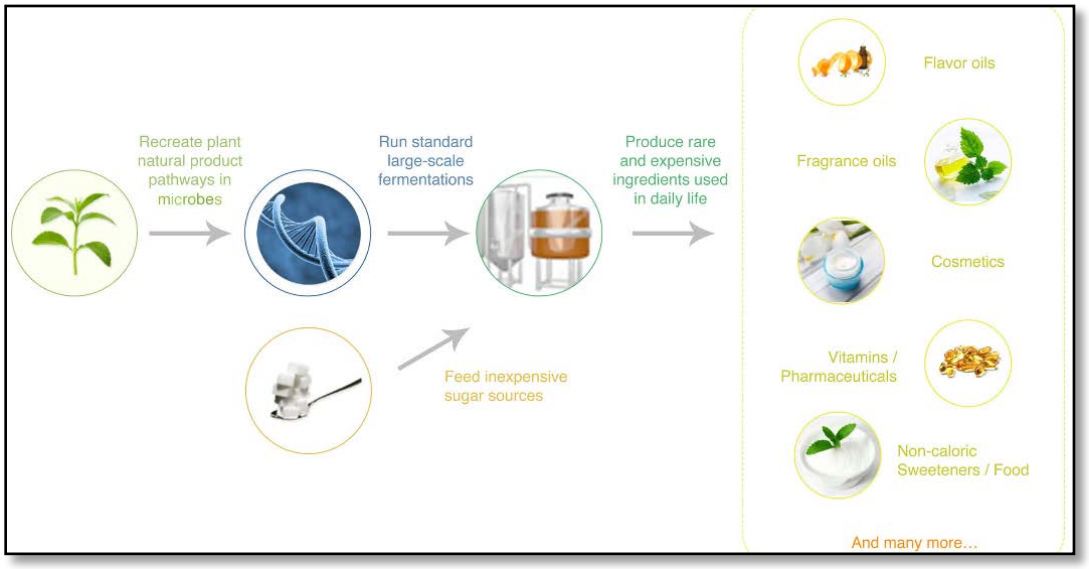


Figure C1 – Manus Bio's process overview to produce pipeline products.[139]

Manus Bio does not focus its platform on one molecule at a time. Manus Bio recreates metabolic pathways necessary to produce rare and expensive ingredients for multiple products.[140] Because Manus Bio focuses on high margin products through a robust platform, it has sidestepped traditional challenges of biofuel companies. Manus Bio diversified itself out of biofuels, which tend to have low margins.

Zymergen approaches biotechnology in a unique manner. The company leverages biology, automation and data science for what each discipline does best. Fully automating laboratories and collecting experimental big data, Zymergen pits its data scientists against its biologists through prescriptive modeling for the best molecules going forward.[141]

Federal funding is important to keep companies that can produce biofuels in business, even if they aren't producing biofuels. Along with the Massachusetts Institute of Technology,[142] Zymergen and Amyris received funding from the Department of Defense (DoD) through the Defense Advanced Research Projects Agency (DARPA) to develop "first-of-its-kind biotechnology infrastructure to provide new materials, flexible capabilities, and manufacturing paradigms for national security and public health."[143] DARPA funding has been important for both Zymergen and Amyris to upgrade laboratory technology and equipment.[144] Both Zymergen and Amyris representatives noted that DARPA only requests the product molecule and not most of the significant data that industry customers require. This is an opportunity for DoD to improve its data repository.

International Perspective

In Japan, the biofuels industrial base faces a similar challenge in oil price and the ability to produce biofuels at a competitive price. However, Japan is in a more difficult energy security position as Japan must import almost all its fuel. Two companies that portray Japan's challenges in the biofuels industry are the Euglena Corporation and the Green Earth Institute.

Euglena is a third generation algal fuel company. Its focuses on the commercialization process starting with the highest value-added production down to the lowest added value.

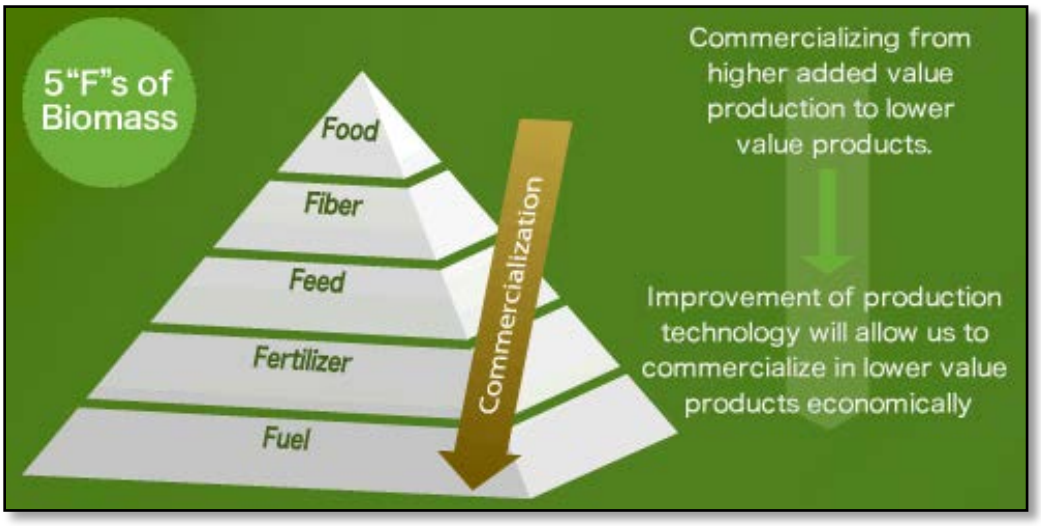


Figure C2 – Euglena's 5 "F"s of Biomass.[145]

Euglena uses this model to capture the most value in the product chain at the top of the pyramid.[146] Of course, fuel is at the bottom of the pyramid and provides the least added value. Euglena will probably not produce biofuels for Japan without significant incentive.

Japan's Green Earth Institute (GEI) has a business strategy similar to Amyris. They have a biotechnology platform that can produce isobutaol with significant downstream processing effort. However, the company has significant effort focused on amino acids. GEI's current cost to produce biofuels is equivalent to a non-competitive price point of $75/barrel of oil.[147] GEI requires significant external funding to reduce costs further. Until GEI gets to scaling production at higher levels, it is difficult to determine the viability of their products in the market.

Friedman defines industrial biotechnology as "the application of molecular biology techniques to improve efficiency and reduce the environmental impacts of industrial processes,"[148] which includes the development of bio-based products and materials. He further indicates that biocatalysts, such as enzymes, are the focus of many industrial biotechnology companies because of their role enabling biochemical reactions and their multi-functionality in various conditions.[149] Other applications include genetic engineering of plants and animals for increased production of material products through molecular farming, the production of bio-fuels and lubricants, bio-plastics, adhesives, and even mining and treatment applications.[150]

Despite the positive emphasis created by the 2009 OECD Report or the *National Bioeconomy Blueprint*, key issues surrounding biotechnology remain. They include: the stigma associated with biotechnologies, funding difficulties and regulatory oversight issues. Regulatory burden is far less so for industrial biotechnology than it is for others such as medical and agriculture.[151] Recent visits to such companies as Bolt Threads, a California based company, confirm this last statement yet also highlight that market regulations, such as those qualifying textiles by the Federal Trade Commission (FTC), exist as barriers.[152] In essence, the production and performance of bio-derived materials represent gaps in certain federal classification systems ultimately affecting their market position/value. This is important because, for bio-derived materials, their acceptance in the market place and market prices become the drivers. In other words, a product needs a demand that differentiates it from other similar products at a production cost providing for a viable revenue.

Bio-Inspired Materials

In *Materials Research to Meet 21st Century Defense Needs*, the National Research Council defines bio-inspired materials as those for which "biological design rules and principles" are considered, leveraged, and applied.[153] "Biomimetic" is another term used synonymously with bio-inspired, which translates to the mimicking of biology. An example of research in this area can be seen at McGill University's Laboratory for Advanced Materials and Bioinspiration in Montreal, Canada, which studies "the structure, performance, and mechanics of biologic materials" through modeling, fabrication, and testing for the purpose of producing new materials with enhanced performance.[154] This laboratory has created a deformable glass that was inspired by seashells with substantially superior impact resistance (700 times that of regular glass), protective skins that are light and flexible, as well as bone graft material.[155] Clearly, the potential applications range from protection to health care.

Bio-Derived Materials

Alternatively, the National Research Council defines bio-derived materials as those new materials obtained through biological routes.[156] For example, Bolt Threads has developed proteins based on a study of natural silks which they ferment to create high performance fibers.[157] Zymergen, another California based company, provides an additional example: "[they] look to nature for inspiration and are building capabilities to engineer any molecule from any microbe [because they] believe harnessing biology is the next wave of innovation that will fuel the real economy over the next century."[158]

Discussion

Despite its relevant title, "Materials Research to Meet 21st Century Defense Needs", the National Research Council's 2003 publication appears somewhat dated. However, it was used purposefully in this discussion to illustrate how slowly bio-inspired and bio-derived materials have progressed over the last decade. It specifically outlines the potential for Department of Defense applications in structural materials (armor and high performance fibers), in functional materials (soft electronics, smart materials and sensors, and power sources), as well as in medical applications (chemical and biological warfare, wound identification and healing, and human performance enhancements). Yet each of these domains are emerging areas of research and technology.[159] This is not intended to be disparaging of the efforts across government or industry but rather a reinforcement of the issues discussed in Part I regarding the lengthy timelines and inherent failures associated with biotechnology research and development. Constant and incremental improvements in these fields combined with a persistent interest/importance related to these technologies may also explain why these domains are still focused on.

National interest and support also remains strong as demonstrated by the Army Research Office partnership with the Institute for Collaborative Biotechnologies mentioned in Part I and the key engagements of the Defense Advanced Research Projects Agency (DARPA).[160] Currently, DARPA has invested in three research portfolios directly related to industrial/materials biotechnology. The first, Biological Robustness in Complex Systems (BRICS) "seeks to develop the fundamental understanding and component technologies needed to engineer biosystems that function reliably in changing environments…where they can achieve greater biomedical, industrial, and strategic potential."[161] The second, Engineered Living Materials (ELM), seeks "to develop living materials that combine the structural properties of traditional building materials with attributes of living systems, including the ability to rapidly grow, self-repair, and adapt to the environment."[162] And the third, Living Foundries, "seeks to transform biology into an engineering practice…expect[ing] to enable the rapid and scalable development of transformative products and systems that are currently inaccessible" with its process and the development of 1000 molecules.[163] Each of these initiatives aims to support the overall national bioeconomy as well as defense interests.

Recommendations

Below is a more detailed list of recommendations by topic.

US National Security

The ability to leverage biotechnology as a means of achieving US national security objectives begins with the development of a comprehensive, whole-of-nation, national security strategy that addresses the underlying drivers of conflict and instability in the world. This is by no means a novel concept. The 2015 NSS and the DNI's Global Trends assessment clearly articulate the major threats to US enduring interests and national security objectives. As a new US administration grapples with these enduring challenges, it must diagnose the underlying drivers of instability and identify the opportunities to leverage the entirety of US capability. The National Security Council must lead this process to catalyze understanding and efforts.

The second US national security recommendation is to continue to prioritize and resource American competitive advantage via the Office of Science and Technology Policy (OSTP). The president must quickly nominate and Congress should quickly confirm a director for OSTP. The director must staff and empower executive committees through the president to establish "clear national goals for Federal science and technology investments in a broad array of domains spanning virtually all the mission areas of the executive branch." Through this strategy and policy generation vehicle, the president can ensure that the nation maintains its competitive edge through funding "research and development strategies that are coordinated across Federal agencies," and are integral to a comprehensive national strategy. This office is also the mechanism to propose appropriate federal regulatory policies that govern the multiple disciplines within biotech. Regarding global climate change, population migration, food and water security, we have multiple recommendations.

US Economy

Growing the US economy includes retraining the nation's workforce to better support biotechnology. Recommendations fall into several areas, spanning from industry to academia and government. The biotechnology industry, through national and regional trade groups and associations, should partner with academia to provide students operationally relevant educational experiences. Additionally, we should adapt the NSF's I/UCRC program to promote convergence and collaboration between centers. Academic institutions with strong science foundations, from the community college level to the doctorate level, should partner with industry to provide professors and students exposure to large scale, high throughput operations. The federal government should develop and deploy a regular update on workforce requirements to education/training program providers.

Another policy recommendation is to maintain current levels of investment in the US competitive advantage in science and technology by nurturing the spirit and culture of innovation and entrepreneurism resident in the biotech science and industry. Continued funding of federal institutions enables universities, established industries, and small startup companies to assume research and development risks. Organizations like the National Institutes of Health, the Biomedical Advanced Research and Development Authority, and the multiple interagency Applied Research Agencies play a significant role in translating ideas into reality.

Government agencies need to focus on economic outcomes through products and technologies instead of regulatory compliance. Once safety is confirmed, getting a

technology/product into use is critical to fully exploiting its potential. DoD can help the biotechnology industry understand DoD business processes. At times, it is difficult and confusing for industry to maneuver within the acquisition and research and development space. DoD should engage with industry through trade associations and other network opportunities to better educate the industry.

Food and Water Security

Regarding food security, recommendations cross several areas. Because it costs a lot of time and money to bring a new biotech trait to market, bio-agricultural companies are not motivated to research non-profitable, yet essential, food modifications. The US biotechnology regulatory agencies need a more transparent GMO crop approval process to cut research and development costs. The new revision of the Federal Coordinated Framework for the Regulation of Biotechnology should include a transformational change in streamlining the approval process between the three agencies as well as clear guidelines that can easily adapt to new technologies. Specifically, if a genetic modification is done to one variety of plant, when the same modification is done to another variety, US policy should dictate that extensive testing is not required for subsequent similar modifications and the approval process can be abbreviated. The framework should be formally updated every five years with the ability to spin out yearly rapid revisions between updates.

The US government, academia, and industry are more likely to favor GMOs than individual consumers. Therefore, it would provide great benefit and promotion of GMO products if this collective body versus individual entities formulate a campaign and work together to consistently educate the consumer on GMOs. Industry trade associations are an excellent avenue to advance the dialogue of GMOs and biotechnology in general. The Biotechnology Innovation Organization (BIO), the biotech industry's trade association, should lead the change in consumer perception of GMOs in collaboration with USDA, FDA, EPA, academia and industry.

USDA should develop an information and education campaign on GMO products and ensure there is a consistent message being shared globally. USDA should create a detailed strategic communication plan and sponsor a public service announcement campaign to be aired on public television and radio including all federally funded college radio stations. This will mitigate any misperceptions consumers may have about GMOs and assist in narrowing the gap of individuals and organizations who are for and against GMOs.

Important factors that influence consumer attitudes are perceptions of risks and benefits, knowledge, and personal values.[164] It is vital that consumers gain trust in government, academia and the private sector, all of which play a significant role in the GMO industry. The GMO labeling law passed during the Obama administration in July 2016 should be fully implemented and not overturned. GMO labeling will provide transparency, disclose information, and educate consumers on whether GMO traits are in their food products. This change in disclosure of GMO ingredients will allow the consumer to have the "choice" on whether to purchase a GMO based product or not versus feeling mislead without any options based on lack of information available. This approach will also help minimize the GMO controversy.

Lastly, US government regulatory agencies should continue to be draconian on mergers in oligopolistic markets as well as pass regulations that encourage competition. This will ensure that the American innovative spirit survives in the bio-agricultural industry while keeping prices

in check. As part of global trade deals, the United States should seek uniform GMC labeling requirements and share its research with trade partners. The United States should apply its instruments of national power to persuade Europe and United Nations allies, in alignment with the WHO (World Health Organization), that GMCs are a safe and indispensable tool to solve world hunger and achieve food security. Multiple avenues for collaboration, including state-to-state and multi-lateral agreements, are available to achieve such goals quickly.

In another area regarding food security, we need to meet the particular demands of growing populations. Especially in the developing countries, it is recommended that a concentrated budgetary focus be on increasing funding to the US Agency for International Development's livestock and agriculture programs. These programs have historically demonstrated progress in building agricultural capacity in developing countries. Domestically, both the US government and livestock industry partners need to re-invest in agriculture infrastructure, vocational training, and college education programs in animal scientific research. To boost the animal husbandry and life-science programs, government grants, scholarships and tax deductions in support of vocational and college education should focus on agriculture and technical degree programs in science, technology, engineering and mathematics (STEM). This is necessary to maintain the US economic edge in both agriculture (including animal livestock sectors) and biotechnology at large.

Global Energy Security

US and foreign government policy toward energy security should address three main areas: (1) countering negative externalities in the environment, (2) funding campaigns and partnership awareness toward the most valuable platform and products, and (3) creating discoverable databases to advance basic science. Industrial biotechnology areas such as biofuels, industrial biotechnology and wastewater treatment offer specific opportunities to shape policy to positively affect global energy security.

Biofuels

Carbon pollution from the energy industry is a significant negative externality. US and foreign governments should continue tax reductions for producers to improve biofuel technology. Globally, tax reductions amounted to $22 billion in 2011 for biofuels,[165] mostly in the United States and European Union. With increased fracking, negative externalities such as the impact on water security will grow, and governments should expand tax reductions to biofuels companies. A viable solution would be to tax fracking companies or impose a federal biofuel excise tax on each gallon of gasoline or diesel. This would raise the price of oil while funding federal biofuel research.

Funding research and subsidizing new alternative energy technologies will promote future prosperity and energy security. Since barriers to entry and capital intensity in biomass power are high,[166] the government should continue to use tax breaks on the production side. It is important to highlight that tax reductions on first generation biofuels are in some ways counterproductive. For example, corn is used for both human and animal consumption as well as bio-ethanol. Subsidizing bio-ethanol prioritizes energy over food and has an unexpected negative externality, as when there is a global food shortage.[167] Therefore, shifting from biofuel to biomass power helps to counter the negative carbon externality and continue technology growth. The United States should revamp its Renewable Fuel Standard Program[168] to emphasize biomass over ethanol production.

Data is critical to advancing technological research, but most data is compartmentalized. Often basic research data is not shared well within a company or across the biofuels industry. In the information age, governments have a responsibility to encourage the sharing of information that is not proprietary. Governments must make best use of contracts to require comprehensive data packages along with specific products to promote shared understanding of biofuel basic science as well as enhance the reproducibility of results. Non-profit organizations, trade associations and communities of practice are avenues ripe for collaboration and access to information. Sharing basic science information best practices should be a priority of OSTP and DARPA within DoD. Governments are advised to refrain from requiring data that provides proprietary knowledge that would limit marketability and the competitive advantage of companies in the market.

Industrial Biotechnology

Greater education and public awareness can meet many challenges. The popular misunderstanding and stigma of the biotechnology industry and its potential can be addressed through clear, transparent and targeted awareness campaigns that reinforce the viability of biotechnology as well as dispel the fears and myths associated with it. Notwithstanding the value of recent national efforts such as "The National Bioeconomy Blueprint" (2012), or even the more recent releases of the "Update to the Coordinated Framework for the Regulation of Biotechnology"[169] (2017) and the accompanying "National Strategy for Modernizing the Regulatory System for Biotechnology" (2016),[170] public education and media strategies still fall short. The recommendations previously presented for a comprehensive Ad Council campaign remain valid.[171] Such awareness campaigns may also serve as platforms for cross-government agency collaboration in other important regulatory functions such as those by the FTC or the US Census Bureau which affect industry classification, trade, and markets. Further, a greater understanding of the industry's dynamics, such as long development timelines, may enhance funding opportunities from external agencies. While increased awareness is good for the industry as a whole, distinguishing industrial biotechnology and biomaterials may further reinforce their overall value to the bioeconomy.

As highlighted throughout "The National Bioeconomy Blueprint", the fostering of public-private partnerships with enduring government support is also critical.[172] The change in administration from President Obama to President Trump presents a concern for enduring relationships. As of April 2017, President Trump has not appointed a Science Advisor/Director of the Office of Science Technology Policy (OSTP) and some have even argued that this function has been minimized.[173,174] OSTP "serves as a source of scientific and technological analysis and judgment for the President with respect to major policies"[175] in coordinating research efforts, and more to the point, in linking the bioeconomy. This must not be undervalued. Staffing, funding and enabling the OSTP needs to be a priority so that the benefits of biotechnology partnerships described above can not only survive but flourish.

Wastewater Treatment

A significant policy recommendation relates to the aging wastewater infrastructure. As President Trump said in his "An America First Energy Plan," stewardship of the environment goes hand in hand with our need for energy, and clean water is a priority.[176] To jump-start biotechnology innovations in wastewater treatment, one of the first priorities for infrastructure investment by the Trump administration should be in support of clean water. The Department of

Energy should lead this endeavor by thoroughly doing a cost-benefit analysis of the newest technologies (including biotech) to understand next steps.

Health and Biosecurity

In the global health area, two recommendations were developed. The first priority is to provide incentives to researchers and commercial industry to focus on developing the drugs with the greatest potential payoff to health outcomes. This could be done by providing federal funds through NIH, DARPA or the National Science Foundation for research that focuses on high payoff drugs, and offering tax incentives or extended patent protection to biotechnology companies that focus on developing drugs with the highest cost-benefit. Focus funding for research and incentives for development on drugs and therapies that will have a positive net benefit (i.e., an overall reduction of health care costs) — this will primarily be in the area of gene therapies that cure conditions for significant numbers of people — not ultra-rare orphan diseases. This reduces expected health care expenditures over time and leaves more money for discretionary funding like national defense. The second priority is to repeal the legislation prohibiting the Centers for Medicare and Medicaid Services (CMS) from negotiating drug prices with pharmaceutical companies and to formally adopt drug value assessment methods currently used and publicized by third parties such as the Institute for Clinical and Economic Review (ICER), Memorial Sloan Kettering (MSK), the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN). Adopting such practices consistent with those in nations such as Japan and Great Britain could result in significant reductions to total health care expenditures in the United States.

For biosecurity, the US government should redouble both internal and external activities to facilitate early detection of pandemic influenza, comprehensive surveillance, identification of transmission pathways and preparedness as steps toward the prevention of pandemic influenza. Additionally, it should create tax incentives for private companies that include additional funding for increased innovation, research, and development, as well as cooperation between the Centers for Disease Control and Prevention, NIH, DARPA and the private sector to develop nucleic-acid based approaches to limiting the spread of infection. A subpart of this recommendation should be to increase international collaboration in pandemic surveillance, research and development and response among relevant US government departments and agencies with international organizations such as the World Health Organization, UN Food and Agricultural Organization, World Food Program and others as well as with key partner nations to accelerate technological advancements to contain and mitigate pandemic influenza. While currently there is limited collaboration, specific joint goals and objectives for collaboration should be identified and adopted.

Additional biosecurity recommendations revolve around the need for the DoD medical community to determine the appropriate biometric data to collect, identify how to properly aggregate the data to represent an exposure to an agent, and developing robust sensors that have a combination of sensitivity and accuracy while withstanding battlefield conditions. Adopting new and innovative technologies by decreasing the time to market, experienced federal contractors such as Nanotherapeutics and Battelle could help advance biotechnology innovations and incentivize companies to support DoD. This example demonstrates DoD's commitment to minimizing the time to market while supporting biotechnology businesses and the warfighter. DoD recognizes this need and is working with the FDA to accelerate the review process facilitating pathways to market when relevant targets (CBRN) are the focus of research areas.

This is a necessary step to ensure the protection of not only the warfighter but civilian populations as well.

Finally, we have recommendations regarding Human Performance Enhancement (HPE). To best leverage the civilian R&D market for military use, DoD or DARPA should have a dedicated office that networks with biotechnology academic-industry clusters to support HPE. It is also imperative the government strengthen transparency and public accountability in the area of biotechnology research associated with HPE. Moreover, to ensure HPE use remains ethical, the US military must adapt and follow the models laid out in the community Institutional Review Board (IRB), the Recombinant DNA Advisory Committee (RAC), and the presidential bioethics commission as local IRB-like committees are not enough. The military IRBs should be networked and linked to additional oversight bodies such as the RAC and the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research to provide a broader public input and concentrated ethical analysis. Additional research into the link between ethical concerns and GMC perception is warranted.

The Next Level of Specificity – Start with Education

At the risk of applying details without a holistic strategy, policy and implementation mechanisms, we offer initial steps to spur on biotechnology's next steps while the US government adjusts its biotech strategy and policy. We start with education of the workforce and government-industry partnerships:

- NSF: Issue "Dear Colleague Letter" (DCL) requesting applied research driving convergence of biological and data/computational sciences. The DCL acts as the formal mechanism for NSF to request research it wants to fund. A DCL is equivalent to a Request for Proposal in DoD.

- NSF: Increase funding for those Industry-University Cooperative Research Centers incorporating exploitation of data in biotechnology. Begin with $3M in single year funding with increasing commitment to $10M per year after 4 years.

- OSTP/Department of Education: Increase biotech Innovation for Learning II-Corps Program to $5M (FY17 request for all bio-related funding was $1M). Increase will enhance incentive for college/university development of commercially-relevant biotech.

- Department of Labor: Expand biotechnology-focused Trade Adjustment Assistance Community College & Career Training (TAACCCT) program to include high-tech areas such as Salt Lake City, UT and Austin, TX to encourage field convergence. Set initial funding at $8M per year. If necessary, divert some funding from lower-performing programs.

- Department of Education: Work through National Governors Association to develop minimum secondary education standards to expose all students to foundation of biotechnology. Provide $1M as seed money to get the initiative started and determine future cost-benefit.

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