Harnessing Transformational Technologies Symposia Series

2022 TOPIC: Synthetic Biology

SUMMARY
Introduction

Our July 2022 symposium, “Synthetic Biology,” was hosted through a partnership between Los Alamos National Laboratory and the National Academies of Sciences, Engineering, and Medicine’s Committee on Science, Technology, and Law. The symposium is part of a broader initiative focusing on harnessing transformative technologies and builds on our September 2020 symposium titled “COVID-19: Harnessing a Transformational Pandemic” and our July 2021 symposium, “How Artificial Intelligence and Machine Learning Transform the Human Condition.” Each topic in the series represents not only compelling frontiers of research, but also highlights their national security challenges and social, ethical, and legal implications.

Los Alamos is a natural choice of institutions to lead such discussions. Since its creation in 1943, the Laboratory has been at the forefront of scientific innovation. The Lab helped usher in the atomic age, drove development in high-performance computing and advanced materials, and contributed to the kickoff the human genome project. Such transformational technologies underpin the United States’ national security mission and economic competitiveness. Hosting this symposium is a part of the Lab’s obligation and responsibility to engage the broader community in these emerging technological challenges and opportunities, and we benefit from public wisdom and perspectives in shaping Lab strategy. We look forward to the next event in this series, “Climate Change and International Security,” in 2024. For this symposium we intend to continue to leverage the dual benefits of in-person interaction with broader inclusive engagement through online participation.

We thank our speakers, discussion leaders, and the many colleagues who participated in the 2022 symposium and enriched the conversations and subsequent dialogues. We acknowledge and thank the planning committee members and our partners in this Harnessing Transformative Technologies initiative, including the National Academies of Sciences, Engineering, and Medicine’s Committee on Science, Technology, and Law, as well as the University of California and Texas A&M University systems. Their contributions have been essential in making this symposia series a success.
Executive Summary

The Los Alamos National Laboratory and the Committee on Science, Technology, and Law of the National Academies of Sciences, Engineering, and Medicine partnered to develop a series of symposia that explore emerging technologies and their ability to transform society, emphasizing novel science, national security, ethics, and both national and international law. The third symposium in this Harnessing Transformational Technologies series was held on July 17, 2022, and explored the topic of synthetic biology. Today, the world is experiencing a fundamental change in the perception of what defines life as scientists develop the tools to alter the genetic code itself. On one hand, synthetic biology has the potential to cure genetic disorders, offer personalized medicine, enhance crop resistance and yields, improve food security, address climate change, and provide sustainable environmental remediation. On the other hand, the technology behind these innovations could also have unintended consequences or even be misused, leading to negative global impacts.

The field of genetic engineering, which uses laboratory-based technology to directly modify DNA makeup, has made rapid progress in the fifty years since its inception. The production of biosynthetic human insulin was one of its first successes and received U.S. Food and Drug Administration approval in 1982. Since the 1950s, progress has included mapping the human genome, synthesizing RNA and DNA, and inserting synthesized DNA into the genetic makeup of an organism. Even among these discoveries, the development of the CRISPR-Cas9 system (clustered regularly interspaced short palindromic repeats associated protein 9) by J. Doudna and E. Charpentier in 2012 stands out. This technique provided scientists the ability to edit and alter the genome of almost any organism easily and specifically. Not surprisingly, the field of genetic engineering has grown hugely since the development of CRISPR-Cas9 and is already transforming human welfare. Along with the many benefits of this technology, the specter of catastrophe has also grown; individuals working anonymously with minimal equipment now have the knowledge and the tools to alter life. Ethicists, policy makers, and regulators are struggling with how best to facilitate scientific innovation, discovery, and application while preventing harm and ensuring long-term human welfare.

Given the complexity of that challenge, kaleidoscopic public perception and concern, and tremendous scientific opportunity, the Laboratory brought together six experts to expand on current applications and risks, for an audience of scientists, law- and policymakers, government agencies, and the public. The 2022 symposium featured talks by Drew Endy (Stanford University), Kolea Zimmerman (Ginkgo Bioworks), Fyodor Urnov (University of California, Berkeley), Megan Sykes (Columbia University), Alison Van Eenennaam (University of California, Davis) and T. Greg McKelvey (Executive Office of the President/White House Office of Science and Technology Policy). Discussions and questions were moderated by session chairs Hank Greely (Stanford University) and June Yu (Associate Vice President for the University of California National Laboratories).

In the opening talk, Drew Endy underscored the magnitude of the transformational change that synthetic biology could bring about—humans could potentially “design life” and thus escape from what he calls the gravitational well of lineage and reproduction. The construction of life from scratch would obviate the constraint of lineage, opening the door to tremendous opportunities. Readily available genetic information and technology could make synthetic biology “local” (available everywhere) and thus democratic. However, to ensure scientific progress remains firmly in the service of all life requires a farsighted, positive vision, as opposed to a status quo, competition-based mindset.

To bring the promise of synthetic biology to the global market and to all people, companies such as Ginkgo Bioworks have developed an end-to-end bioproduction platform comprised of design, build, test, and grow cycles. Kolea Zimmerman explained Ginkgo’s mission: to make biology easier to engineer. Starting with a customer’s idea and requirements, Ginkgo leverages its extensive database; computational tools; and synthesis, test, and fermentation facilities to deliver a scalable bioproduction process. The goal of biotechnology companies such as Ginkgo is to solve society’s most pressing problems through synthetic biology.

The ability of tools such as CRISPR-Cas9 to edit and alter the genome of almost any organism easily and specifically has opened the door to curing the many genetic disorders that appear in humans, especially in children. While highlighting the many successes (cures for sickle cell disease, beta thalassemia, and amyloidosis), in the short
period since human gene editing began in 2019, Fyodor Urnov cautioned that unless funding models other than free market and for-profit are created, the potential to transform modern medicine could be squandered, leaving 300 million individuals with rare genetic diseases unable to benefit from gene editing treatments. To address this challenge, he described the creation of the Innovative Genomics Institute, whose goal is therapeutic development solely through academic and non-profit entities to expand the unparalleled promise of CRISPR gene editing treatments from N=1 to N=ALL those who need it.

Every year, thousands of patients requiring organ transplants succumb to their disease while waiting for a human donor. One solution to the growing organ shortage is to use xenografts, whole organs or tissues from another species that are transplanted into humans, to supplement the supply of allografts, organs or tissues transplanted from one human into another. If the challenge of evading the immune response to donated organs can be solved, xenotransplantation offers a potentially unlimited supply of organs uniform in size, age, and quality. Megan Sykes described the advances in the three-fold strategy—immunosuppression, genetic engineering, and immune tolerance—to provide a solution to immune barriers to transplantation, particularly xenotransplantation, thereby profoundly impacting the field of medicine and the lives of those waiting for organ transplants.

Alison Van Eenennaam reminded us that food security remains an urgent global concern. Over the last seventy years, the growth in yield of livestock through selective breeding and artificial insemination has been impressive and helped to prevent mass starvation and malnutrition worldwide, however, the job is nowhere near complete. Genetic modifications in the germline could, for example, provide more disease- and drought-resistant crops, more productive livestock, and lead to a more secure and environmentally benign food supply. She gave examples of her work in selective breeding for improvements in livestock welfare and how advances in genetic engineering could contribute to disease resistance and product quality and yield. Her parting message stressed that for synthetic biology to improve the sustainability of animal-source food production, the highly varied international regulatory environment needs to move from putting up barriers to offering incentives to rapidly bring the benefits of carefully reviewed research to the market.

As the final speaker, Greg McKelvey envisioned a regulatory framework in which emerging technologies can safely and securely enhance national security and human welfare. He cited past examples of how predictions by the best minds of the time regarding the potential of a new technology and its impact have often been wrong. He then posed two questions: How should a regulatory body proceed to safeguard against unrecoverable catastrophe or irreversible proliferation of catastrophic capability, given that the technology of increasing power and accessibility is dual use? How should we change the antagonistic relationship portrayed between science driving forward with safety and security as brakes on its progress? Dr. McKelvey concluded that the best option is gathering data and developing rigorous risk assessment so that regulations are based on defensible determination of the probability of capability intersecting malintent and of long-term catastrophic outcomes.
The emerging field of synthetic biology has reached a juncture in which near-term strategy and policy decisions will shape its long-term societal impact. Because of the complexity of the field and the magnitude of its potential disruption to society, such strategy and policy decisions must be deliberately crafted using a positive, progressive vision that strengthens democracy and provides all citizens with optionality and access. In his talk, Drew Endy described how synthetic biology can reinvigorate democracy using the following four questions: (1) Does synthetic biology offer anything new to the advancement of science and society? (2) Will the societal changes imparted by synthetic biology be solely quantitative, or are qualitative disruptions likely? (3) What strategic opportunities exist or could emerge? and (4) Can democracies guide the field of synthetic biology to our advantage?

Myriad successes in synthesis-by-biology, enabled by advances in both synthetic biology and other technologies, have improved the production of medicines, foods, and materials. Only 15 years ago, engineering a 3-enzyme pathway in yeast to produce medicinal natural products from cheap abundant carbon sources like glucose required a team of bioengineers and approximately 100 combined years of expert labor. Today, a single graduate student can engineer a 30-enzyme pathway in the same organism in roughly a year. The onset of the SARS-CoV-2 pandemic further illustrates recent advances in synthetic biology. For example, researchers in Switzerland synthesized and began studying the SARS-CoV-2 virus in the laboratory using genome sequences shared by Chinese scientists two weeks before the first case of infection was reported in Switzerland.

Future successes in synthetic biology are increasingly difficult to conceptualize because they will not necessarily adhere to the natural constraints of life on Earth. These constraints include lineage (all new life flows from life that came before), evolvability (the adaptation of a population to a changing environment), and the requirement of physical reproduction. Analogous to the gravity well that keeps objects grounded on Earth, Dr. Endy proposes the concept of a life well to describe the natural constraints of biology. Just as scientists in the 1960s escaped the gravity well to begin space exploration, the synthetic biologists of today are on the threshold of escaping the life well to unlock “life beyond lineage,” or life beyond the natural constraints of biology.

The removal of the requirement of an organism to reproduce or evolve has been demonstrated in recently published research. For example, alteration of the genetic code in engineered organisms has led to viral resistance or generated genetic fail-safes in which those organisms are unable to evolve, and thus intrinsically contained. Going a step further, the construction of life from scratch would remove the constraint of lineage. Efforts are ongoing to combine the necessary molecules under controlled laboratory settings to synthesize protocells that grow and evolve with their own DNA. Dr. Endy speculates that with proper resource allocation, labor coordination, and scaling, this endeavor is achievable by the end of the 2020s.

The profound societal impacts of advances in synthetic biology that would enable escape from the life well present an opportunity and a responsibility to institutionalize the policies that will govern synthetic biology research and usage. Historically, the regimes along which life promulgates (natural, domesticated, edited, and synthetic) are governed by institutional arrangements.

Drew Endy
Stanford University

Drew Endy is a bioengineer at Stanford University who studies synthetic biology. His goals are civilization-scale flourishing and a renewal of liberal democracy. Prof. Endy helped launch new undergraduate majors in bioengineering at both MIT and Stanford and also the iGEM—a global genetic-engineering “Olympics” enabling thousands of students annually. His past students lead companies like Ginkgo Bioworks and Octant. He is married to Christina Smolke, CEO of Antheia, the essential medicine company. Endy served on the US National Science Advisory Board for Biosecurity (NSABB), the Committee on Science Technology & Law (CSTL), the International Union for the Conservation of Nature’s (IUCN) Synthetic Biology Task Force, and the Pentagon’s Defense Innovation Board (DIB). He currently serves on the World Health Organization’s (WHO) Smallpox Advisory Committee. Esquire magazine recognized Drew as one of the 75 most influential people of the 21st century.
by their own sets of policies. Clustered regularly interspaced short palindromic repeats (CRISPR) gene editing has garnered significant attention in recent years and driven many political discussions; however, its use as a gene editing mechanism falls under policies institutionalized fifty years ago. Synthetic biology, on the other hand, encompasses the interconversion of genetic material and genetic information. In this synthetic regime, most of the policies have yet to be decided or institutionalized, particularly those concerning the elimination of evolutionary or reproductive constraints.

Advancements in the field of synthetic biology will require researchers not only to face the conventional urgency of competition under models of exponential growth (Moore's law), but also to confront the power of networks that grow as the square of the number of nodes in the network (Metcalfe's law) and the challenge of accessing information that lies outside one's domain of control (Joy's law). Thus, interactions between researchers will become important because network strategies can result in a "winner take all" entrenchment of coordination solutions. Once entrenched, displacement of such solutions can be very challenging.

In addition, the public narrative surrounding synthetic biology is often framed using proxy words, such as bioeconomy, to relate the policies and management of the field to economics. While this narrative is adequate for quantitative analysis of the field (e.g., incremental growth), it does not address the qualitative changes and potential disruptions of synthetic biology as an emerging technology. For example, an economic analysis of synthetic biology might focus on the cost of centralized manufacturing versus localized manufacturing, with the market favoring the option of lower cost. This analysis, however, ignores the inherent localization of biology. Because it is restricted to a particular place, biology is the ultimate distributed manufacturing platform. Each biological "product" is generated locally from photons and molecules in the environment. Harnessing this localization represents a qualitative advancement.

Further probing the notion of localized production, Dr. Endy introduces the concept of the bionet and its potential application to a personal biomaker. The bionet improves the manufacturing resiliency of synthetic biology by harnessing the communication resiliency of the internet (i.e., the ability to decouple and recouple information across spacetime). In the bionet, advances in synthetic biology are communicated globally and instituted locally. For example, combining recent advances in electrocatalysis and bioengineering, electricity can be used to power carbon fixation from CO₂ into feedstock for microbial production of a desired product. In theory, this process could produce food or other valuable commodities that are currently derived from biomass, even in areas where plants cannot grow, using electricity and the bionet. Such electro-biosynthesis is just one potential process that could be scaled down to be used in a personal biomaker, representing a "design anywhere, grow everywhere" future of production.

The United States is not alone in imagining this future. Other countries, particularly China, are devoting substantial resources to the realization of such a bioeconomy. This has great disruptive potential, and the ongoing narrative surrounding bioeconomy emergence must prioritize how it benefits all citizens and sustains the values and goals of modern civilization as a whole. A distinctly American bioeconomy would encompass not only technological advancement, but also shared cultural values of liberty and the pursuit of happiness. As a result, the US leadership of the bioeconomy is an opportunity to reinforce democratic principles.

Returning to his four guiding questions, Dr. Endy asserts that synthetic biology offers something new: the potential for networked biotechnology and the ability to engineer life beyond lineage. Qualitative disruptions from synthetic biology are already underway and more are foreseeable, including supply chain impacts and fully biotic technologies. Advances in synthetic biology present numerous strategic opportunities. However, democracies cannot take full advantage of these opportunities without a farsighted, collaborative vision, as opposed to a myopic, competition-based mindset. This can be accomplished through US leadership in coordinated network-based solutions and sustained investments in fundamental science that enable and secure a bioeconomy that offers not only goods and services, but also optionality for all.
Technologies for Transformation: Harnessing Microbial Diversity for Industrial Applications

Kolea Zimmerman

From biosynthesis to the production of chemicals, materials, and medicines, to biodefense, the field of synthetic biology is currently poised to transform all industries. Many of the biggest problems facing humankind have the potential to be solved using synthetic biology. In his talk, Kolea Zimmerman expounded on the transformative potential of biotechnology enabled by the transformation of organisms with DNA. He highlighted the role of biotechnology firms, in particular of Ginkgo Bioworks, in solving society’s most pressing problems by exploiting microbial diversity for industrial applications.

Ginkgo’s mission—to make biology easier to engineer—is actualized through its end-to-end design platform. Notably, Ginkgo does not manufacture its own line of products. Instead, it uses its platform to design products and scale production for customers. The platform takes the idea and requirements of the customer through iterative test phases to deliver a scalable bioproduction process. This is made possible through Ginkgo’s extensive biological codebase, advanced software tools, high-throughput screening and evaluation capabilities, and automated fermentation facilities, placing them at the forefront of the biotechnology revolution. Ginkgo is accelerating innovation across industries by ensuring industrial scalability and lowering the barriers to biological manufacturing and research and development.

The Ginkgo platform consists of iterative design, build, and test phases followed by a grow phase. Through this process the platform identifies the most promising engineered microbial strains and then optimizes fermentation conditions for strain growth to meet customer specifications at industrial scale. First, the design phase combines computational design and protein engineering. Leveraging Ginkgo’s advanced computational tools, extensive codebase of over 5.7 billion protein sequences, and suite of proprietary chassis, promoters, and cellular components, the optimal proteins, pathways, and cells to meet a customer’s needs are identified.

In the build phase, custom DNA sequences are synthesized, and thousands of strain candidates are constructed. As one of the largest users of synthetic DNA in the world, Ginkgo annually synthesizes thousands of artificially designed DNA segments used to incorporate genetic material into a target microbe. These sequences, called constructs, are introduced into Ginkgo’s proprietary chassis strains: microbial cells engineered to execute implanted functions. Then testing begins.

The test phase employs laboratory automation to screen each constructed variant for the highest titer or yield of the desired product and characterize the best-performing variants. Multiplex assays allow tens of thousands of genes to be screened at a time, and approximately 70 million strains are evaluated annually. Testing is conducted by integrated robotic workcells designed for high-throughput screening and advanced analytics. The large output of data is fed back into the design phase software to iteratively improve
the constructs for that particular project, and to improve the software's predictive engineering capability for future projects. Ginkgo deploys small-scale bioreactors to predict the strain performance and scalability of the highest-performing candidates, with thousands of small-scale fermentations performed annually.

The most promising engineered microbes proceed to the grow phase, in which the production process is refined. Ginkgo utilizes its automated Foundry space, with up to 50,000 liters of fermentation capacity and more than 300 robots, to ensure the stability of the strain at industrial scale and optimize the yield of the desired product. Once these quality assurances are met, the organism and technology are transferred to the customer for deployment.

A great example of the potential of this process is the $100 million joint venture between Bayer AG and Ginkgo. The goal of this venture is to circumvent the need to apply fertilizer to non-legume crops by instead treating crop roots with engineered nitrogen-fixing soil microbes. While atmospheric nitrogen is abundant, it cannot be used directly by plants. Currently, such crops require manufactured fertilizers containing ammonia, a usable form of nitrogen for plant growth. Ammonia production contributes to the global consumption of fossil fuels. If instead the roots of such crops could be symbiotically colonized by microbes containing enzymes that convert nitrogen into ammonia, the need for fertilizer would be eliminated.

Challenges in engineering such a microbe are further compounded by additional requirements. The microbe, ideally, must be able to colonize the roots of the plant, continue to produce ammonia even when exogenous nitrogen is present in the environment, and persist in the soil to prevent the need for reapplication. Microbial nitrogen fixation as a means of providing nitrogen to crops would greatly reduce fossil fuel consumption and its contribution to climate change.

Robust biotechnology platforms like Ginkgo’s are poised to tackle many such multifaceted challenges, transforming not only the agricultural industry, but also society. Ginkgo’s foundry of services for designing, building, and testing organisms; codebase of DNA; and team of experts comprise its platform to discover, develop, and optimize the biology needed for microbial products. Ginkgo can readily onboard new chassis strains to develop an engineered microbe for a customer, in addition to performing conventional biosynthesis in which the product is a small molecule. The extensive automation in the foundry facility combined with the accumulated knowledge of the codebase enables Ginkgo’s scientists to work faster and more efficiently than would be possible in a traditional laboratory setting.

As discussed earlier, continuously adding more chassis strains to Ginkgo’s platform enables rapid improvement of existing traits and the addition of new functionalities, especially for microbial products where complex traits are needed. Developing a microbe with complex traits requires high-throughput culturing, transformation, and assaying to identify the best traits, which can then be stacked into a single strain. Appropriate chassis are critical to ensure that expression of target pathways is highly regulated and occurs, ideally, during only the production phase of the cell lifecycle. This allows microbial resources to be devoted solely to biomass production during the growth phase of the lifecycle and optimizes the production phase for more efficient target yield.

Multiplex assay screening approaches are also crucial to engineering new organisms. This is because of the large number of genetic parts that comprise a synthetic DNA promoter circuit. Each part has its own set of variants that can be optimized for the process under development. For example, a synthetic promoter circuit undergoes combinatorial screening, whereby all combinations of variants for each genetic part are synthesized and evaluated. Production is further optimized by ensuring that promoters, regions of DNA occurring before a gene that instructs the production of proteins, are expressed most strongly at the appropriate time during fermentation.

As biotechnology continues to advance, it should move beyond conventional biosynthetic production of small molecules. Instead, creating engineered microorganisms will enable better solutions to today’s most intractable problems by exploiting the complex existing traits within microbial organisms. To address multiple challenges simultaneously, such as engineering microbes for nitrogen fixation, myraid desired traits must be incorporated into a single microbe. Ginkgo’s synthetic biology design platform highlights the scale and efficiency emerging and needed to engineer microbial products for a vast array of high-impact global applications. ■
CRISPR Gene Editing as Medicine: from N=1 to N=all

Fyodor Urnov

A decade ago, Jennifer Doudna and Emmanuelle Charpentier revolutionized the field of gene editing with the discovery of how to use clustered regularly interspaced short palindromic repeats (CRISPR) to create a technique called CRISPR-Cas9 that uses the Cas9 protein to cleave DNA at a specific location. In the intervening years, this technology has migrated from the research bench to the bedside, including its use in life-changing therapeutics for patients with genetic disorders. In his talk, Fyodor Urnov explained how CRISPR-Cas9’s applicability comes from its simplicity, versatility, and scalability; it can safely and accurately create permanent changes in the genome by cleaving DNA at any desired location, priming the DNA for gene editing. However, the current economic model of individualized therapeutic development for genetic disease, also called N=1 or N=rare gene therapy, is not financially viable. Therefore, its potential to transform medicine could be squandered, leaving 300 million individuals with rare genetic diseases unable to benefit from gene-editing treatments.

CRISPR-Cas9 has simplified the process of gene editing by repurposing the Cas9 protein that evolved in bacteria. The Cas9 protein cuts DNA wherever it finds a match to an RNA molecule that it carries. In its natural setting, this RNA molecule harbors a short segment matching the genome of, for instance, a phage. With CRISPR-Cas9, researchers design and deliver a short RNA sequence to guide the Cas9 protein to their desired DNA sequence, where the Cas9 enzyme creates a double-strand break in the DNA. Surprisingly, the CRISPR-Cas9 system was readily transferred from prokaryotes to use in humans. In addition, the CRISPR guide can be paired with other enzymes to carry out a variety of genetic modifications, such as editing a single point in the DNA, adding to the versatility of this system.

CRISPR editing in humans began in 2019 and has already demonstrated early-stage clinical success. Initial work investigated the use of CRISPR to treat hemoglobinopathies, which include the blood disorders sickle cell disease and beta thalassemia. These disorders affect millions of people globally and drastically reduce the life expectancy of those afflicted. In patients with beta thalassemia who were treated with CRISPR gene editing, 42 out of 44 no longer need blood transfusions. Similarly, in the three years since the trial
began, all 31 CRISPR-treated patients with sickle cell disease are free of pain and no longer need blood transfusions. These treatments were conducted ex vivo, with blood stem cells removed from the patient, edited, and returned to the patient.

In 2020, an in vivo CRISPR treatment for amyloidosis, a degenerative disease caused by the accumulation of amyloid proteins in organs, was demonstrated. In this treatment, the CRISPR-Cas9 system was enveloped in lipid nanoparticles and injected into the patient for delivery to the liver. The therapeutic successfully knocked out a gene for amyloid protein production and demonstrated clinical efficacy. Remarkably, the study also showed that the treatment edited the entire liver, one of the body’s biggest organs, and the genetic modifications persisted after a single dose.

CRISPR-based therapeutics for those genetically predisposed to atherosclerotic cardiovascular (coronary artery) disease are also in development. Just this year, a clinical trial began for a gene editing therapeutic to reduce cholesterol, and thus the risk of heart disease. This therapeutic uses a new modality of gene editing, called a base editor. Instead of creating a double-stranded break in the DNA, the Cas9 base editor specifies a permanent chemical change at a single DNA site.

The efficacy of CRISPR-Cas9 treatments and the emergence of new modalities of gene editing are ushering in a remarkable era of human genome engineering to cure disease. Moreover, the safety of these treatments has been so strong that the U.S. Food and Drug Administration (FDA) has signaled support for additional trials, even under conditions of a somewhat high risk-to-reward ratio. For example, pediatric patients, a population considered high-risk for adverse effects, were allowed by the FDA to participate in a trial for CRISPR-based treatment of Leber’s congenital amaurosis, a rare genetic condition which causes vision loss. Similarly, the FDA approved a clinical trial for a curative treatment for HIV in which CRISPR is used to fully excise the HIV genome from that of the patient’s. If successful, the patient could discontinue use of HIV medications, many of which have significant side effects. Regulatory approvals were awarded even with the knowledge that this therapeutic may not increase patient life expectancy over existing drug therapies but will nonetheless improve quality of life.

The initial CRISPR-based clinical trials have been a considerable success, demonstrating the versatility, safety, and most importantly, durability of CRISPR; because the gene editing process is permanent, so is the cure. Despite these clinical successes, the viability of scaling CRISPR technology to treat the over six thousand known genetic disorders remains elusive. These diseases are often degenerative, debilitating, and deadly, and disproportionately affect children.

While the umbrella of rare diseases includes a formidable patient population in the United States, even the most common of these diseases affects relatively few patients. As a result, there is little financial incentive for pharmaceutical companies to pursue curative rare disease research. Thus, the millions of patients who could be cured by CRISPR-based gene editing may be left without such a treatment.

A clear example of this market-based failure is the current treatment of the hundreds of known, editable diseases that cause dysfunction of the immune system. While over 112,000 patients suffer from these diseases and CRISPR could treat a formidable fraction, there are currently no open clinical trials for genome-editing-based therapeutics because they are not commercially viable. Even when the cure is already known and licensed, it may be abandoned. For example, a pre-CRISPR gene editing therapy called a lentivirus therapeutic cured each of its fifty pediatric patients during clinical trial but was not further pursued after licensing to a for-profit company because it was not profitable to produce. Fortunately, this clinical trial has been restarted through the California Institute for Regenerative Medicine.

The few gene therapies that are on the market are exorbitantly expensive, with some as costly as $2-3 million for a single treatment. Furthermore, the current regulatory structure is incompatible with the promise of CRISPR to revolutionize personalized medicine. Preclinical development operates on a long timescale of three to five years, and is expensive (> $6 million); further, this process is configured for clinical trials where multiple patients receive identical treatment, a problematic condition for patients who may have unique mutations in the gene of interest. The FDA approval process cannot be scaled down to meet the needs of just a few patients; therefore, a new process must be established to allow personalized treatment for genetic diseases without sacrificing safety or efficacy.

The Innovative Genomics Institute (IGI) is developing a new model of delivering gene therapy to people languishing without treatment options. Its approach to therapeutic development is solely through academic and non-profit entities, an unprecedented shift in the economics of drug development. IGI has assembled diverse teams of bioen-
engineers, computational biologists, drug delivery experts, clinicians, and regulatory specialists to innovate and deploy life-changing CRISPR-based therapies. Its first project is a treatment for sickle cell disease, with plans in the works to address other challenging conditions as well, including neurodegeneration, ovarian cancer, and autoimmune diseases. A key follow-up effort is to develop a CRISPR treatment to cure Artemis-deficient severe combined immunodeficiency, which disproportionately affects children of the Navajo Nation. This effort will demonstrate IGI’s platform approach that is explicitly designed to be affordable and scalable by using CRISPR in place of more expensive viral delivery systems. The IGI mission is not only to cure genetic diseases, but also to provide an example in equitable health justice; it will show the world that its framework will expand the unparalleled promise of CRISPR gene editing treatments from N=1 to N=ALL those who need it.
Harnessing the Immune Response to Xenografts

Megan Sykes

Since the 1990s, the demand for organ transplants has greatly outpaced the supply of organs, despite an increase in the number of annual transplants. Because donor tissue availability is low, many patients succumb to their illnesses while waiting for a transplant. One solution to the growing organ shortage is to use xenografts, whole organs or tissues from another species that are transplanted into humans, to supplement the supply of allografts, organs or tissues transplanted from one human into another. Xenografts, particularly those from pigs, offer a potentially unlimited supply of organs, uniform in terms of size, age, and quality. An abundant xenograft supply would allow transplants to become elective surgical procedures, eliminating the organ waitlist. It would also improve patient outcomes because transplants would occur at the optimal time for the patient instead of when an organ becomes available. However, to use xenografts, scientists and clinicians must still overcome significant challenges in evading the immune responses that lead to xenograft rejection. In her talk, Megan Sykes detailed how advances in genetic engineering have concurrently advanced the field of xenotransplantation.

Following an organ transplant, the body mounts a formidable immune response using the innate and adaptive immune systems. Thus, transplant rejection is a challenge with both xenografts and allografts. The innate immune system is responsible for hyperacute rejection (HAR), which occurs on the timescale of minutes to days after transplantation. The adaptive immune system causes acute cellular rejection and chronic rejection. These types of rejection occur in weeks to months, and months to years after transplantation, respectively. Both the innate and adaptive immune systems may contribute to delayed xenograft rejection (DXR), which occurs on the order of days to months. All types of rejection are more prevalent in xenografts than in allografts and initiate vascular processes that obstruct blood flow to the transplanted organ, eventually causing its death.

Three strategies to overcome the immune barriers to transplantation, particularly xenotransplantation, are genetic engineering, immunosuppression, and immune tolerance. Genetic engineering for improving xenotransplantation began in the 1990s, first enabled by cloning technology, and has accelerated exponentially with the advent of clustered regularly interspaced short palindromic repeats (CRISPR) gene editing. Improvements in immunosuppressive drugs have contributed significantly to recent advances in overcoming immune responses. These strategies are not mutually exclusive, and the most beneficial treatments will likely use them in combination. Immune tolerance, described in the following paragraphs, provides a promising avenue for increasing the longevity of xenografts.

One of the biggest impediments to xenotransplantation was identified in the 1990s: the lack of a functional α1,3-Gal
transferring enzyme in humans and their ancestors, old world monkeys. Most other species, including microbes, express α1,3-Gal transferase and thus produce α1,3-Gal carbohydrates. Because this carbohydrate is not found in humans, it is a target for our immune systems; as a result, the most abundant natural antibodies in humans are anti-Gal antibodies, which target α1,3-Gal epitopes (the region of the target that a particular antibody binds to). These anti-Gal antibodies contribute to both HAR and DXR, and many attempts to weaken xenograft rejection have focused on anti-Gal processes. Early methods to combat HAR in pig xenografts included adsorption of anti-Gal antibodies and the introduction of human complement regulatory protein transgenes into pigs.

The knockout of α1,3-Gal transferase in genetically engineered pigs in the early 2000s was a major advance in xenotransplantation and successfully overcame the problem of HAR. In the ensuing years, technological advances enabled additional genetic engineering of xenograft source pigs. These include transgenic strategies to introduce human complement inhibition and coagulation inhibition proteins, anti-inflammatory genes and immunosuppressive molecules, and expression of human major histocompatibility complex (MHC) genes for natural killer cell inhibition, as well as gene knockout strategies for additional carbohydrate-generating enzymes in addition to α1,3-Gal transferase.

Non-human primates have been used to investigate xenotransplantation of porcine organs in humans because of the similarities in their organ rejection mechanisms. Studies in the 2010s that combined genetic engineering and immunosuppressive therapies demonstrated varying degrees of xenograft survival. This culminated in orthotopic, or life-supporting, heart grafts surviving over six months and orthotopic kidneys surviving more than a year; however, lungs and livers, which are more challenging, survived less than a month. More recent orthotopic heart transplant studies in non-human primates further improved xenograft survival by limiting the growth of grafted tissues, using either the immunosuppressive drug sirolimus in the recipient or growth hormone receptor knockout porcine donors. Miniature swine donors are likely to be of an appropriate size to bypass this growth problem in human recipients.

To date, the use of Gal knockout and human complement receptor transgenic pigs has prevented HAR and eliminated the need for antibody adsorption in non-human primates, but only in recipients with low non-Gal antibodies. In these recipients, the lack of non-Gal antibodies was critical to xenograft survival because additional non-Gal antibody specificities contribute to xenograft rejection. Two such epitopes have been identified (β4-Gal and NeuGc) and removed from pig donors in knockout studies. However, these genetic modifications might generate new non-Gal specificities as non-terminal carbohydrates are exposed. In addition, further removal of carbohydrates from donor pigs may have unintended deleterious consequences for their health, thereby altering their suitability as donors.

In 2022, xenograft research achieved a remarkable breakthrough when a heart xenograft was transplanted into a human patient for the first time at the University of Maryland Medical Center. The heart of the genetically engineered pig donor, which contained 10 different genetic modifications, sustained the recipient’s life for 7 weeks before death. Additionally, a series of short (< 3 days) preclinical experiments in deceased patients on life support who received ex vivo or in vivo kidney xenografts showed no signs of immediate antibody-mediated transplant rejection.

Advanced immunosuppressive therapies and genetic engineering to knockout donor-Gal and non-Gal epitopes have extended xenograft survival, but survival is still not indefinite. The upper limit of increases to xenograft survival from the knockout of non-Gal specificities has likely been reached. Thus, additional advances in survival will likely come from immune tolerance that weakens T cell- and B cell-mediated rejection.

Two strategies to induce T cell and B cell tolerance to xenografts are mixed chimerism and thymic transplantation. In mixed chimerism, platelet and blood cell production of the donor coexists with that of the recipient, tolerizing the T cells, B cells, and NK cells of the recipient’s immune system to the donor. Mixed chimerism has induced tolerance in mouse to rat, pig to human, and pig to non-human primate models, although additional genetic engineering was required for mixed chimerism in the last model. Thymic transplantation, in which the thymus of the donor is transplanted into the recipient, provides only tolerized T cells in the recipient. This strategy is a complement to mixed chimerism and has induced tolerance in pig to mice, pig to human, and pig to non-human primate models.

In conclusion, Dr. Sykes showcased how combining the strategies of mixed chimerism, thymic transplantation, and genetic engineering in donor pigs has the potential to achieve safe xenotolerance, profoundly impacting the field of medicine and the lives of those waiting for organ transplants.
Gene Editing in Livestock: Science and Policy
Alison Van Eenennaam

Despite the lack of media attention, food security remains an urgent global concern. While COVID-19 has claimed roughly 6.7 million lives since the start of the pandemic, some nine million people die of starvation annually, a rate of approximately twenty-five thousand deaths per day. Genetic engineering for agricultural applications has the potential to improve food security and significantly reduce the environmental footprint of food production. In her talk, Alison Van Eenennaam described recent advances in agricultural applications of genetic engineering and highlighted the policy differences in transgenic animals for biomedical and food applications.

For centuries, selective breeding in domesticated animals has been employed to achieve a desired phenotype. The variety of dog breeds and their marked divergence from their wolf ancestors is one such example. In recent decades, this process of developing new traits and removing undesirable traits from a livestock population has brought about tremendous change. For example, poultry farmers have seen a considerable increase in livestock growth rate since the 1950s; chickens raised under similar conditions and consuming the same amount of feed have quadrupled in size over the last seventy years.

The cattle industry has achieved similar results. A combination of selective breeding and artificial insemination has quadrupled the milk produced per cow since the 1940s. As a result, fewer dairy cows are needed to sustain milk production in the United States, and the greenhouse gas emissions associated with the production of a glass of milk are two-thirds the level they were eighty years ago. These examples illustrate the direct impact of selective breeding, and more broadly genetics, on the sustainability and environmental impact of food production.

Advances in gene editing will enable breeders to further drive genetic improvement in their livestock. Clustered regularly interspaced short palindromic repeats (CRISPR) and other gene editing techniques are powerful, precise tools that allow the modification of specific genes, either through insertion, modification, or deletion of DNA bases. When these editing techniques are used for animal breeding programs, the edited gene must persist generationally, and thus is introduced into the germline (the cells that pass on genetic material to offspring). In contrast, gene editing for biomedical applications generally occurs in somatic (non-reproductive) cells, where genetic changes are not passed on to offspring. Genetic modifications in the germline are accomplished either by somatic cell nuclear cloning of an edited cell, or by microinjection of editing reagents into a single-cell zygote (a fertilized ovum). The ideal result is a homozygous non-mosaic edited animal, where edits have been incorporated into both copies of the targeted gene.

Looking specifically at cattle breeding programs, gene editing can be used to improve a variety of traits, such as animal welfare, disease resistance, and product quality and yield. For example, in dairy cattle, knockout of the gene for beta-lactoglobulin protein, a major milk allergen, enabled the production of hypoallergenic milk. Modification of coat color from black and white to lighter shades of brown and white can increase heat tolerance and better adapt animals to live in warmer climates. Disease resistance, such as reduced susceptibility to the zoonotic disease tuberculosis, can significantly reduce illness and suffering. Currently, approximately twenty percent of animal production is lost to various diseases. Notably, Dr. Van Eenennaam contends that while livestock diseases can be mitigated with antibiotics and chemicals, genetic improvement is the superior and more sustainable solution, because it is permanent and cumulative.

Alison Van Eenennaam
University of California, Davis

Dr. Alison Van Eenennaam is a professor of cooperative extension in the field of animal genomics and biotechnology in the Department of Animal Science at the University of California, Davis. She received a bachelor of agricultural science from the University of Melbourne in Australia, and both an MS in animal science, and a PhD in genetics from University of California, Davis. Her publicly-funded research and outreach program focuses on the use of animal genomics and biotechnology in livestock production systems. Her current research projects include the development of genome editing approaches for cattle. She has given over 700 invited presentations to audiences globally, and uses a variety of media to inform general public audiences about science and technology. A passionate advocate of science, Dr. Van Eenennaam was the recipient of the Council for Agricultural Science and Technology 2014 Borlaug Communication Award and the American Society of Animal Science 2019 Rockefeller Prentice Award in Animal Breeding and Genetics. Twitter: @BioBeef.
In her work at the University of California (UCD), Davis, Dr. Van Eenennaam collaborated with a company called Recombinetics that produced a genetically hornless dairy bull using gene editing. By introducing a naturally occurring dominant bovine allele at the polled locus of chromosome 1, the bull displayed the polled, or hornless, phenotype. Horns on cattle in dairy production systems are typically removed to prevent horn-related injury to handlers and other cattle. Farmers remove horn buds or dehorn livestock physically, both of which are painful procedures for the animals. While polled dairy cattle can be produced with conventional breeding from polled sires, these sires have inferior genetic merit and data demonstrates that their daughters will produce less milk over their lifetimes. Furthermore, the available polled sires are all closely genetically related, so exclusively breeding to produce polled offspring would create a genetic bottleneck. Therefore, farmers are preferentially breeding their cows to elite horned sires. Advances in gene editing now provide an alternative to dehorning livestock while also preserving the high genetic merit associated with horned sires.

The gene-edited hornless bull produced by Recombinetics was used to sire six heterozygous hornless offspring. Dr. Van Eenennaam analyzed the offspring for several years at UCD. As part of the evaluation, the six animals were studied to ensure that their hornless phenotype persisted due to the transmission of the dominant polled allele from the gene-edited sire, and that the composition of their milk and meat were substantially equivalent to that of the offspring of a control, unedited sire.

Genome editing is not a complete catch-all solution, but rather a tool that can be incorporated into existing breeding programs. Thus, it should be viewed as the “cherry on top” of a metaphorical breeding sundae that includes the association of like-minded breeders, development of breeding goals, performance recording, progeny testing, artificial insemination, embryo transfer, genomic selection, and somatic cell nuclear transfer cloning. Genome editing will allow breeders to incorporate useful alleles into their breeding programs without linkage drag, in which deleterious genes are sometimes inherited along with the gene of interest, and potentially bring in novel genetic variation from different breeds. The success of this breeding strategy, however, is predicated on the regulatory environment and whether it allows such advancements.

Guidance released in 2017 by the Federal Drug Administration’s Center for Veterinary Medicine (FDA-CVM), which regulates livestock veterinary drugs in the US, states that any intentionally introduced DNA alteration, whether an insertion, substitution, or deletion, in the genome of an animal is considered an unapproved new animal drug. New animal drugs must undergo a lengthy evaluation and approval process. In contrast, the U.S. Department of Agriculture’s Animal & Plant Health Inspection Service, which regulates genome editing in plants, stipulates that if a genetic modification can be achieved by traditional breeding techniques, then that edited plant is not regulated as a genetically engineered organism. The regulatory environment is even more complicated when viewed globally, as regulations for agricultural genome editing in crops and animals vary dramatically from country to country. For example, Argentina treats any gene-edited product that does not incorporate “foreign” DNA from another species as a conventional product with no additional regulations, whereas the European Union mostly regulates all products of “modern biotechnology” as genetically modified organisms (GMOs) and has approved less than a handful for cultivation in that economic region over the past 30 years.

In an unexpected decision in 2022, the FDA-CVM granted enforcement discretion for the products from two gene-edited bulls to enter commerce. In these gene-edited bulls, the prolactin receptor was modified, resulting in a short-hair phenotype with improved heat tolerance. The intentional genomic alteration gave the same “slick” coat phenotype that is seen in some conventionally bred cattle, leading to a low-risk determination by the FDA. Enforcement discretion is extended to products that are evaluated as low risk. This is not an approval or exemption from new animal drug regulations, but rather a determination that the products were insufficiently risky to be a regulatory priority.

The current drug-centric regulatory policies for bioengineered animals in the United States make laboratory successes difficult to bring to the market and disincentivize investment. However, advances in genetic engineering have the potential to contribute to the genetic improvement of livestock, which is a key driver in improving the sustainability of animal-source food production. As a result, the United States is starting to lag behind the rest of the world when it comes to the approval of genetically engineered livestock and subsequent adoption of these innovations by farmers and ranchers. At a time of increasing concern regarding the environmental footprint of animal agriculture, it’s important to consider the impact of gene-edited livestock not just on food production, but also on our world.
Synthetic biology is profoundly impacting national security. Rather than focus on any specific development in synthetic biology and how it might imperil national security, Dr. Greg McKelvey reframed the relationship between emerging technologies and national security. Drawing on the 1959 Rede Lecture by Charles Percy Snow, which characterized the rift in communication between scientists and literary intellectuals, Dr. McKelvey defined a similar “gulf of mutual incomprehension” between the national security and life science communities. By finding common ground between these two fields, he posits that we can work toward better policy solutions, optimizing the ratio of benefits to risks that new technologies offer society.

The tasks of the Office of Science and Technology Policy (OSTP) and the National Academy of Sciences (NAS) are similar; to maximize the benefits of science and technology and to stimulate scientific research in service of national defense and public welfare, respectively. If we look back 100 years and imagine these organizations having a similar meeting on emerging technology and national security, presenters may have included chemists discussing the nitrate supply for high explosives from the First World War or engineers proposing practical applications of radio waves for the Second.

However, the discipline with perhaps the most significant implications for national security, nuclear physics, may not have been discussed with sufficient consideration of its ultimate potential, if at all. Consider Nobel laureate Robert Andrews Millikan, who in 1929 cautioned against nuclear energy, asserting: “There is no appreciable energy available to man through atomic disintegration and no reason to live in dread of the day when some unscrupulous or careless Dr. Faustus may touch off the stupendous sub-atomic powder magazine and blow this comfortable world of ours into stardust,” adding, “the Creator has realized the wisdom of introducing some fool-proof features into his machine.”

It may seem that if Nobel laureates in the prime of their scientific careers can so misjudge emerging technology, there is no hope for bureaucratic foresight. However, considering the national security implications of new technologies from first principles, at a slight distance from technical details, may have been more fruitful. In contrast to Millikan, in 1924 Winston Churchill questioned, “May there not be methods of using explosive energy incomparably more intense than anything heretofore discovered? Might not a bomb no bigger than an orange be found to possess a secret power to destroy a whole block of buildings—nay, to concentrate the force of a thousand tons of cordite and blast a township at a stroke?”

While the fields of nuclear security and biosecurity may ultimately be more dissimilar than similar, three general trends identified by John Von Neumann at the

dawn of nuclear security also typify synthetic biology: (1) technology evolution is accelerating, (2) the most powerful technologies are intrinsically dual use, and (3) the effects of such technologies are projected globally.4 Developments in synthetic biology pose a unique threat, as growing numbers of states and non-state entities gain access to technologies that can interface with the vital atoms of any organism on the planet. The once highly proprietary code of life is fast becoming open source.

Moreover, while the pace of technological change is exponential, the pace of political change is incremental5—except perhaps in occasional post-crisis scenarios.6 The larger the bureaucracy, the longer it takes for technology change to be detected and understood by policy makers. In addition, policy responses must contend with the Collingridge dilemma: as the impacts of a technology become increasingly apparent, the proliferation of the technology becomes increasingly difficult to control.7

Technological capability arriving before policy can develop expands the opportunity for hazard. As Herman Kahn postulated in his provocative 1965 book On Escalation, a sufficiently powerful capability, made sufficiently accessible, entails eventual catastrophe.8 Synthetic biology is not Kahn’s hypothetical ‘$10 doomsday machine,’ but because of its increasing power, accessibility, and dual-use nature, it lends itself to one of two end states unless sufficient boundaries can be drawn: an unrecoverable catastrophe or irreversible proliferation of catastrophic capability.

Catastrophic outcomes hinge on the possibility of sufficiently powerful capabilities intersecting with negligent or malicious intentions. In the absence of impossibility proofs, disagreements about the plausibility of this intersection skew philosophical discussion. Ironically, Churchill’s posture of skeptical inquiry into the potential for extreme risk is far more scientifically minded than Dr. Millikan’s dogmatic assertion of faith in safety. We are right to question the reflexive denial of the possibility of catastrophic risk—especially in light of the asymmetries in play. According to Clarke’s first law of technology, when a distinguished scientist states something is possible, she is almost certainly right. When she states something is impossible, she is very probably wrong.9 Additionally, history has thus far demonstrated there are no infallible control regimes, and that defense must succeed constantly, while offense needs to succeed only once.10

Therefore, the risk of unacceptable outcomes from technology is better framed by probability; empirically exploring how and when capability might converge with intent by comparing threat models and base rates. Unfortunately, sufficient data and scientific attention to model these probabilities appear lacking. Instead, a profound imbalance exists between the many forces laboring blindly forward to expand the frontier of capability, and the few working backwards from acceptable end states. There is missed opportunity to truly maximize the benefits of science and technology through the rational application of science to technology.

One example is the dearth of epidemiologists studying the digital transmission of pathogens. Scientists and epidemiologists have a long history of evaluating and analyzing the in vivo host-pathogen-reservoir models of disease transmission and containment. However, in vitro and in silico life cycles of pathogen-database-laboratory are emerging, as seen in the reconstruction of SARS-CoV-2 in a laboratory in Switzerland from its digital sequence transmitted by internet, prior to its detection in the local populace as transmitted by aerosol. Such dynamics seem to be acknowledged only grudgingly, rather than embraced as novel scientific and humanitarian opportunities.

Another missed opportunity is the relative lack of analysis regarding the potential health utility impacts of technology threats. In this case, it is instructive to consider the steady decline in mortality rates because of advances in public health and medicine over the last century. Yet there was a sudden, massive increase in mortality during the 1918 influenza pandemic and another in 2020 from

the COVID-19 pandemic—arguably equivalent to erasing decades of hard-won gains in healthy life years through population health improvements. Any new technology pursued to incrementally augment future health should be weighed against its potential to vitiate the accumulated gains from all past efforts—including through low-probability yet extreme-consequence instances of misuse. We must better ask and answer the questions: what are the risks of a new technology if misapplied, and how much technology risk are we willing to accept for potentially marginal gains in public health?

If the only safeguards for progress are Von Neumann’s “day-to-day opportunistic measures” or a “long sequence of small, correct decisions,” how can we ensure that we arrive at those required to maximize the benefits of science and technology in the long run? Dr. McKelvey concludes that a partial answer lies in bridging the two cultures of national security and biological science and launching a movement to bring rigorous inquiry into devising and executing technology strategy. Lowering the barriers between the national security and science communities can cultivate a culture of responsibility and allow for the gathering of data and expertise to address fundamental questions of probability, capability, intent, and rational action.

For too long, the model of science policy has been predominantly two-dimensional and antagonistic; as science drives forward, safety and security are portrayed as impediments to its progress. This model yields the corollary conceit that science must remain rudderless—adrift on extra-rational faith in the “usefulness of useless knowledge.”

Instead, we must create a new framework that harnesses rigorous assessment of risk to steer technology development towards maximum net benefit and away from catastrophic outcomes.

Dr. McKelvey closed by exhorting us to address the fundamental question:

If science is to remain the means to a more secure, prosperous, and salubrious future, how will we augment our wisdom at a rate commensurate with our growing technological power?


Conclusion

The symposium “Synthetic Biology” presented five views on the tremendous potential of gene editing, including the transfer and easy access of genetic information over the internet and ready availability of gene editing tools for local use, to revolutionize human health and welfare, treat and prevent diseases, provide a sustainable food supply, address environmental challenges, and provide cost-effective clean energy. The field of synthetic biology, as well as that of artificial intelligence and machine learning, is in an explosive growth phase, outpacing our ability to assess the probability of unrecoverable catastrophe or irreversible proliferation of catastrophic capability. With the potential emergence of the ability to create life without the constraint of lineage, it is imperative that humankind simultaneously develop the prudence to use the unstoppable advances in science for the betterment and benefit of all. To even begin to answer the question—how can and should we devise robust tools to safeguard against negative impacts—it is appropriate to ponder Dr. McKelvey’s closing question: If science is to remain the means to a more secure, prosperous, and salubrious future, how will we augment our wisdom at a rate commensurate with our growing technological power?

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