



Presidential Commission  
*for the* Study of Bioethical Issues

## **TRANSCRIPT**

Overview and Context of the Science and Technology of  
Synthetic Biology

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

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

Robert Carlson, Ph.D.  
Principal, Biodesic

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**Amy Gutmann:**

Our first speaker is Dr. Drew Endy. He is an Assistant Professor of Bio-Engineering at Stanford University. Dr. Endy is the director of BIOFAB, an open facility advancing biotechnology and he is the President of the BioBricks Foundation as well as being a member of the National Academies' Committee on Science, Technology, and Law. Dr. Endy, we are happy to have you here with us today. Why don't you begin?

**Drew Endy:**

Thank you, Chairwoman Gutmann, Vice Chairman Wagner, and members of the commission.

Given the limited time, I prepared nine slides, which I'd like to share and quickly go through. I've been asked to speak on the overview and context of the technology of synthetic biology. And in framing my remarks, I'd like to recognize that the technology is changing.

Stewart Brand has noted that if we think of this century, the 21st Century, as a century of biology, it must also be a century of bioethics. Let me express my gratitude to you and to the commission for investing your life energy in starting the process here in the early stages of synthetic biology.

This is a cover, or derived version of the cover, from The Economist in response to the article coming from the team at the Venter Institute in Science. It follows in the tradition of press coverage of biotechnology. About 100 years ago, when Jacques Loeb and his team were working on artificial parthenogenesis, the initiation of development in the absence of a sperm, that achievement received similar tremendous popular attention. And it creates many questions in the minds of diverse publics, such as "Is life being created from scratch?" "Are we recapitulating in the laboratory, spontaneous generation?" And so on and so forth.

I want to simply acknowledge this at the outset of my technical remarks and express my own opinions that at this point life has not now been created from inanimate matter. I believe this is a subject for a lot of discussion, but I want to share this so that I can move on to what I consider to be very important practical technical matters and

the ethics associated with them.

I believe that the capacity to synthesize genomes and to install them in replicating cells is what an engineer, which is what I am, would call a BTD: a big technical deal. I think Dan Gibson and Carole Lartigue, the doctors who are the first authors of the work at the Venter Institute, deserve high praise for their accomplishments. I can only now imagine some of the reasons I think this is a big deal. And so what I'd like to do is give you an abstract framework in addition to some examples for this. so that in your work, you might find the gaps in my own thinking.

This little cartoon I drew shows how life works. Natural living systems exist via this process of direct descent and replication from our parents to ourselves to our children if we are so fortunate. So, we are familiar with this. It's how we inherit and are part of the living world.

The technologies within synthetic biology including synthetic genomics allow for a very interesting alternative path. You can take an organism and sequence it. And that converts the physical genetic material into information that can be stored on a database and a computer network, which means that we can change it and edit it as information. And then the technology of synthesis of DNA, which I'll come back to, allows for the genetic material to be recompiled. If that can be established in a cellular chassis and replication initiated, off life goes again.

So these two tools, reading and writing of DNA allow part of the material of life, the genetic material to be decoupled from the physical process of replication. And this decoupling then allows for synthetic living systems, which are derived from natural systems and based on their designs, to be implemented.

This means that the selections don't have to be natural selections. They can be fashioned selections for solving important problems. This decoupling has been demonstrated for some viruses and now with the work from the Venter Institute, a microbe.

Why is this a big deal? Well, stresses can arise when material and information become inter-convertible. For example, you might be

familiar with music and entertainment and video. When music was available on compact disks, the distribution of the material as matter — as compact disks — is how the markets were defined, how sharing and ownership were defined, and so on. But as soon as the information encoding the music was separated from the compact disk and was available as MP3 files or digital music files over a network, that created a tremendous number of changes. You had Napster as a music sharing service and, as a President of a university, all of a sudden copyright violations by your students might become a problem. You see the iTunes store today and so on.

It also challenges safety and security frameworks where if you want to limit access to a gene encoding a toxin by only having experts working with that, what if you make that sequence available on the Internet and now somebody could print the gene or a pathogen, and so on. Being able to go from material to information and back to material can stress and change current practices and relationships. It's part of the reason this capacity of construct and reinstall and initiate replication of a genome is a big deal. I'll come back to this.

Let me go into the technology just a bit. These four bottles show the basis of DNA in a form known as phosphoramidites, and this is based on the work of Marvin Caruthers and his colleagues in Colorado decades ago. So, the four bases are A, T, C, and G, the nucleotides of DNA. The bottles cost about \$250 each. The materials are derived from sugar cane.

What happens with this material is: you hook it up to a machine. This is a very outdated picture. This machine is called a DNA synthesizer. You can see the bottles of chemicals hooked up to that machine. And what this machine will do is take information coming in over a computer network and organize the dispensing of the chemicals in a particular order, the order that you want. And so if you would like to print from scratch a particular sequence of DNA, you enter that into the machine and the machine will dispense the chemicals in that order and to the degree that the machine can successfully construct what's call an oligonucleotide, you will get that physical piece of genetic material out.

So, this is the essence of one of the directions or dimensions of the

technologies in synthetic biology: the ability to go from information that describes the DNA sequence to physical genetic material.

Here's my limited opinion: I believe that the capacity to synthesize and construct DNA is the most currently the number one and most important technology of the 21st Century. The only thing I could imagine that would trump this would be some source of clean renewable fuel. This is equivalent in importance, in my opinion, to the ability to manufacture silicon wafers and computing. I think our manufacturing economy, our security, and our ethical leadership will be depend on our prowess at being able to compile genetic material.

We go from abstract information to physical living design. I want to talk a little bit about where we have come and where this might go because, again, I think the change of capacity here is very important and means that the committee is unlikely, in my opinion, to find sufficient all of the existing and past bioethics work in the subject. I think there is new stuff happening that warrants additional attention.

To be specific, about six years ago, the longest fragment of genetic material that had been constructed from scratch was 10,000 base pairs, small bacterial viruses. Today, with Dan Gibson and colleagues and their work at the Venter Institute, we have now seen published a megabase, a million base pairs of DNA constructed from scratch. That's a 100-fold improvement in six years.

Where should we expect to be six years from now? Well, the simple extrapolation, which may not come true and is worth discussion, would be 100 times greater. That's 100 million base pairs of genetic material. 100 million base pairs of genetic material is interesting. It's most known microbes (all the ones I know about), it's Baker's yeast and almost as big as the worm *c-elegans* or the fly, *drosophila*. And it's just below the average length of a human chromosome. This doesn't mean we're going to know how to weave a worm, or fly a fly, or hammer out a human, but it means we're going to have the capacity to tinker, at the level of genetics. That is new.

Here's the more technical context: Shown here is a gap. This gap is about 4 meters. We have a much bigger gap in synthetic biology down in the technical weeds of the work. On the left, I'm trying to

capture what I believe to be the case today, that 99% of all genetic engineering projects can be encoded by less than 20,000 base pairs of designer DNA, which is about a dozen or so functional genetic components. So the biotech industry that we are familiar with is not today making engineered genomes and delivering products to market.

On the right, we now see that we have the capacity to construct from scratch a million base pairs of DNA, and researchers in Japan have reassembled from natural fragments 8 million base pairs of DNA. These are not designer genomes. These are recapitulations of natural sequences. But the magnitude of these construction projects is significant. You could encode thousands of components here. I don't know how to put together a thousand different DNA components. Maybe others here can teach me, and that would be fantastic. But in that context, what we find as engineers or would-be engineers of biology, we have a 400 fold bio-integration gap. That is, we could, right now, with the construction technologies that exist, we could struggle and try to hope to get 400 times better at putting together the pieces of DNA in order to do useful things.

It's very early, and it's going to be a long haul, I think, to get better at putting this stuff back into place. Let me try and give you some context from a different area: So, 20,000 characters, that gets you things like "The Gettysburg Address," which is around 1500 characters. It gets you an editorial in the New York Times, and it almost gets you Dan Gibson's paper, which is about 34,000 characters.

What would be, you know, the sort of stuff you could write with 8 million characters? Well, you certainly get one-act plays like "No Exit." You get The Color Purple which is not even a million characters. You even get War and Peace as a novel. One of the things to think through and imagine as a future in genomics and empowers synthetic biology, what do we do to write genomes, either to learn or do useful things. That's one of the exciting pulls here.

Let me put this in context. Here are some teenagers who when they first encountered biotechnology didn't like how it smelled, literally the odor. So they wanted to write a simple four-line genetic program. If the cells are growing, smell like wintergreen; otherwise, smell like bananas. You can do this by getting cells to manufacture methyl sa-

licylate, which smells like wintergreen or isoamyl acetate, the chemical odor that smells like bananas. Just because we can construct the genome, doesn't make it easy to compile the DNA that implements a simple four-line genetic program. What would the letters be? Do you start with a "T" an "A" or "C" or "G"?

So, one of the challenges of technologies beyond the tools for building, we're also going to need to invent and develop the languages and grammars that allow us to write DNA programs or poems: a big research puzzle.

Shown here are three of the core technologies that powered the first generation of genetic engineering: Recombinant DNA for cutting and pasting, polymerase chain reaction for amplifying materials, and DNA sequencing for reading out the code. In synthetic biology, we see with the leadership of synthetic genomics a technology platform for building DNA and genomes. This allows some people to become experts as designers and other people to become experts as builders, like an architect and a contractor. That's very different from current practice where today people need to be expert in both activities oftentimes.

We may have some other technologies coming online. Abstraction that leads to languages and grammars, and standards that allow people to define genetic elements in a way that makes sharing easier. Whatever ends up being the case, I believe that to have a chance at being ethical, we must leave the future development of the biotechnology tools. Sometimes ethical matters are go/no-go. But, I think, oftentimes they are gray, and very practically to resolve and lead the resolution of ethical questions, you have to have a stake in the game. So, that's my belief.

Last slide. I want to make some couplings as an engineer speaking practically to ethical matters I encounter. We often learn best by tinkering. I can't overstate how little we know about biology and how much we stand to learn by trying new things out. It's one thing to take a car apart and see what all the pieces are. And you sort of understand how a car works. But if you put the car back together and you have left some things out, when you turn the key, that's a big deal if it starts or not — because you have learned something new about

the car.

Just our capacity to build DNA is going to let all sorts of students and researchers learn more and become better engineers of biology. That's a value, an innate value that must not be overlooked, in my opinion.

Freedom of the press — in this case I mean the DNA press — the ability to synthesize DNA in genomes is like a printing press but it's for the material that encodes much of life. If one publisher controlled all the presses, that would give a publisher tremendous leverage over what's said.

It's very interesting to me that so far as I know, there are no sustained public investments at getting better at building DNA printing presses, which means that the public input into the discussion, beyond commissions such as this and other venues, is practically limited. Institutions and individuals, hackers are community. So I'm an engineer, a civil engineer by training. I like to build stuff. I worked for Amtrak one summer fixing bridges between here and Manhattan. Biology is the most compelling manufacturing technology I have ever seen. I'm not the only person who thinks that. Most of the people are coming after me. They are much younger. They see a nanotechnology that works, that's taken over the planet. It's life. It's constructive. And we can imagine being inspired to get better at programming it with DNA.

The tools of synthetic biology then find these communities and empower them because they are accessible technologies oftentimes. We have a very significant responsibility as leaders in ethics in technology and science to enable and partner with or ostracize these communities. Do we invent a world of “do-it-together” biotechnology? Which I think is what we're trying to do. Or do we push people out to the margins and cut them off and create the consequences of that sort of framing?

Lastly, preparedness and reconciliation. Biosafety. Accidents will happen. We have the gene therapy experiences from Penn. More misuses will occur. We have the anthrax attacks from 2001. Nature is not the same as a representative liberal democracy and that creates a tension between our expectations and duties to protect the rights of the indi-

vidual in a world that oftentimes can be cruel. How do we recognize this and not make such truths intolerable?

Thank you very much.

**Amy Gutmann:**

Thank you very much.

I don't know how many of you recognize this, but I think it does not go without saying: Dr. Endy, you did a truly extraordinary job of synthesizing succinctly the science and your perspective on it. So, thank you very much for that.

And there will be more in time for questions.

Moving on, our next speaker is Dr. Bonnie Bassler. Dr. Bassler is a Howard Hughes Medical Institute Investigator. She is the Squibb Professor of Molecular Biology at Princeton University. Dr. Bassler is also the President of the American Society for Microbiology. She's the 2008 winner of the Princeton University President's Award for Distinguished Teaching and the 2009 recipient of the Wiley Prize in Biomedical Science.

I could go on with Dr. Bassler's honors, but, instead, I will simply welcome somebody I have known for more years than I'd like to admit. She's much younger than I am, however.

Welcome, Dr. Bassler.

**Bonnie Bassler:**

Thank you, Dr. Gutmann. So, I'm pleased that the commission has been asked by the President to consider the benefits, risks, and ethical issues related to the field of synthetic biology. I have been asked to compare and contrast the engineering perspective with that of the biological and genetic sciences and to explain approaches represented by synthetic biology and how they differ from other approaches to biological manipulation. In addition, I will cover what has been accomplished in the field and what I think are important obstacles to the advancement of synthetic biology.

Every living organism, including earth's simplest life form, the bacterium, is loaded with molecular devices that are mind-boggling in their design, complexity, and efficiency even to our most gifted engineers and physicists. As a microbiologist, I offer a few examples from the bacteria. Bacteria have miniature motors that operate like boat engines, complete with propellers. The motors use a molecule called ATP as fuel. This contraption allows cells to swim through liquid at a pace that, given their size, would make Michael Phelps envious.

When bacteria settle out of their liquid world on to a surface — for example, in the ocean when they find themselves in the sediments or perhaps when they encounter a droplet of oil — they sense that they have; they sense that they need another form of transportation. They sprout thousands of appendages like spider legs to crawl across surfaces. When they leave the surface to return to the liquid environment, these legs fall off and the boat propeller reengages. They are the perfect amphibious vehicles.

Turning to information flow, inheritance, and cellular reproduction, bacteria have similar equipment, multi-part machines are constructed from component proteins. One such apparatus can rapidly copy the nucleotide base that constitutes the genome. In the process, it proof-reads every letter. How accurate is the proofreader? If the human being typed at a reasonable rate, say 40 words per minute, and that human being typed continuously for eight hours a day, five days a week, it would be as if he or she made one mistake every 40 years.

Copying the genetic code or the DNA is not sufficient. For life to happen, the biological machinery of a cell must convert the one-dimensional information embedded in the DNA molecule into a complete three-dimensional organism.

Take our best understood bacterium: *e.coli*. There are thousands of elements that the proteins synthesize or allow the cell to acquire from the environment that are essential for life. To name a few, lipids are required to build the membrane that encapsulates and protect the contents of the cell. Nutrients must be consumed to remake parts that wear out. ATP, NADP, and phosphate are a must for supplying energy. The list goes on and on. I repeat that none of these cellular components are made directly from DNA or directly from genes.

Lastly, these cellular components are not swishing around willy-nilly. Rather, there is precise spatial organization to each part, and this provides asymmetry, another feature we understand is essential for life, even in bacteria. Without asymmetry, no embryo could develop, our neurons could not process information, our intestines could not absorb nutrients, and bacteria could neither swim nor crawl. Indeed, all cells, even bacterial cells, possess sub-cellular architectures in which the component parts are put in specific places at specific times.

Biologists have a natural desire to pick apart and analyze these amazing life processes to understand how the natural world works. Engineers have a natural desire to exploit these living structures, to build increasingly useful apparatuses. Thus, the biology-engineering intersection: the synthetic biology field is born.

Synthetic biology builds on traditional genetic engineering methods, but there's a fundamental difference. Traditional biologists do research at the Petri-plate scale. Synthetic biologists promise to take the foundational knowledge acquired by traditional biologists and, using principles from engineering refine, excel and apply it at scales that could achieve unprecedented good for the public. We now have the hope of efficiently applying biological solutions to some of the grandest problems facing the world.

Synthetic biology is taking the natural course one expects when excellent scientists from two disciplines combine their talents. We see this happening all over in science today — especially in biology, biophysics, chemical biology, computational biology, and systems biology. So why, right now, do we need a series of ethics hearings on synthetic biology? What are the benchmark questions that arise in synthetic biology that do not arise in these other burgeoning interdisciplinary fields?

The catalyst for convening these hearings was the publication in Science magazine of a manuscript entitled “Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome”? Why does this manuscript cause unease? To address this, I examined what was accomplished in this publication. The authors have, to their great credit, assembled the largest piece of DNA to date.

However, to replicate the synthesized DNA, the authors required a living cell, complete with the requisite thousands of pre-existing components. All of the biological machines required were already assembled and functioning. Every cellular component was sitting in exactly the correct place in the cell and primed for operation. The membrane was present to house both the introduced DNA and its encoded functions so that the second round of replication could occur. The authors used a bacterial genome that had gone through 4 billion years of refinement to which they made only modest changes. This DNA included all of the instructions for assembling working machines for the precisely timed production and destruction of each component and for spatial localization of each bit.

To put the present work into context, I remind the commission that in 1967, Arthur Kornberg, a Nobel Prize winning scientist and his colleagues synthesized and replicated the virus CX174 genome in *E.coli* exploiting the bacterial component housed in a living cell. Today's accomplishment is strikingly similar.

The genome replicated in 2010 is significantly larger than the genome from 1967. That is no surprise given 43 years of technological advance. Also, between then and now, there have been thousands of experiments in labs all across the world in which sequences of DNA have been synthesized and introduced into cells and the cells dutifully carried out the instructions provided in the DNA. Thus, the recent paper provides us an incremental technical step forward in DNA synthesis and assembly. What the work does not do is provide information or insight about the nature of life.

Is there any technology or finding in this manuscript that should give us ethical unease? My answer is no. Any anxiety I have regarding this work stems from the author's use of a misleading title claiming creation of a bacterial cell and some ensuing sensationalist reports that occurred in the popular press.

The authors did not create. They cloned. Given the title and some of the news coverage of this paper, it is understandable that policy makers and the public are concerned. The title does not represent the scientific findings in the paper. The title has unnecessarily alarmed

people.

Scientists are committed to performing research that is in the public interest and they have a responsibility to articulate accurately their findings and the implications of their research. I hope through these hearings and the work of the commission we can move past the publicity and focus on the future of this field and any genuine ethical concerns it faces.

To finish, I go back to the science of synthetic biology. There is wonderful news ahead for this field. Even with our limited understanding of life's complexity, we do understand many things. We are now able to logically string together pre-existing biological units and get them to perform new functions. We can engineer organisms to do or to produce useful things. We can build entirely new functions that do not, to our knowledge, occur in nature. Such research holds tremendous promise for the future of renewable energy, new material synthesis, a sustainable environment, food and medicine.

Synthetic biology is, however, a young field and it faces hurdles. The first one concerns reliable function. Even when scientists believe they know the components in a particular pathway, when we put them together using synthetic biology, they often fail to mimic the natural performance of the device. Natural systems do not fail when the conditions change, rather they adjust to new environments. We do not understand why synthetic circuits are flimsy and natural circuits are sturdy.

There are three components in the circadian clock that give the oscillations associated with the 24-hour day-night cycle. The circadian clock is exceptionally precise. The period is exactly 24 hours and it lasts the lifetime of the organism. When synthetic oscillators, first built by MacArthur Fellow and Cal Tech professor Michael Elowitz and his colleagues, are introduced into bacteria, they oscillate. However, synthetic oscillators only function in a subset of cells. They exhibit extreme variation between cells. After a handful of oscillations, the synthetic machines stop ticking.

What is important is that we are learning how to build these gadgets and we now have some early synthetic machines in hand. Side-by-side

studies of sturdy natural systems and their brittle synthetic counterparts will provide us two things: a deeper understanding of robustness in natural systems and the ability to synthesize increasingly precise and reliable biological machines.

Another challenge facing the synthetic biology field concerns fitness. Typically, when we introduce nonnative parts into micro-organisms and compel them to carry out new jobs, we weaken them. These tasks come with a fitness price. At present at the test tube level, many synthetic processes work reliably in micro-organisms. However, at larger scales or in competitive arrangements, micro-organisms either get rid of the engineered pieces, or they are outcompeted by their natural rivals: when the forces of natural selection provide new traits, the bugs exhibit enhanced vigor; when human engineer synthetic parts into micro-organisms, we make them wimps.

In summary, the promise of synthetic biology is great, but the notorious complexity and context-dependency of biological systems and the delicate balance that needs to be struck for these systems to be viable makes the engineering approach extremely challenging. But we are only in the early days.

We need to move these studies forward, and we need to keep our focus on the bacteria. Bacteria provide humanity a virtually untapped reservoir of spectacular devices and ingenious pathways. Their diversity surpasses everything else on the planet. We know there are millions and millions of genes in the microbial world and we have no clues as to their functions. That means there already exist millions of unknown molecules of medical, industrial, and agricultural relevance. There exist millions of biological devices awaiting discovery in uses prototypes for constructing real machines. Bacteria are our planet's only limitless renewable resource, and scientists have only studied a few of them. As a nation, we have to take this resource seriously as a significant part of our future. We certainly need ethical oversight and regulation, but we need it applied in a practical and creative way that balances the merits and concerns of scientific achievement and resists over-reacting to sensationalism in the media. If we can have that, all scientists, but especially in this case, biologists and engineers, can continue to work to enhance human well-being by understanding and appropriately harnessing the power and diversity of the awe-

inspiring natural world.

Thank you.

**Amy Gutmann:**

Thank you very much, Dr. Bassler. I think you get a glimpse here of how important it is to bring engineering and biology together and both the different perspectives, but also the interaction and very importantly interconnected perspectives. So, thank you very much for that important window.

We now turn to our last speaker for this session, Dr. Rob Carlson. Dr. Rob Carlson is a principal with Biodesic, a Seattle-based engineering and design firm. Dr. Carlson is the author of a very recently accomplished important book, “Biology is Technology, The Promise, Peril and New Business of Engineering Life.” Dr. Carlson writes on pandemic preparedness, on synthetic vaccines, and other topics.

**Robert Carlson:**

Okay. Well, first, Chairman Gutmann and members of the committee, thank you very much for the invitation. I’m honored to be here today.

I am also in the fortunate position of following two excellent introductions, so I’m going to take a very different perspective here and go into sort of higher level context for how the world is changing. And as synthetic biology is itself a conglomeration of tools, it is a tool in itself to be used in producing systems that have particular defined behaviors, hopefully.

I am going to take a step outside of the immediate context and actually show you a car commercial to start with. And the audio here is not so important, but this is my favorite car commercial of all time. It is a beautiful synopsis of what we mean by the word “Engineering” in our modern day.

What you see here is a Honda Element slowly coming together from Lego-like bricks. And the very end of this piece, there’s a very smooth voice-over that says, “Every piece has its purpose.” This commercial works, in my opinion, because it brings together our expectations

about how engineering functions. All these individual pieces have defined functions. They are understood. We combine them together in a larger system and then we understand how that system works, too. The important piece that's missing from this is that, of course, there are human hands and human intent in engineering. And that's where the ethical issues come in.

The reason I start with this commercial is that its understanding of engineering drives our economy today. This is how we build almost everything in our world today. We have computer models. We have computer manufacturing. And stuff gets moved around the world. We have this march from consumer electronics and the speed with which that comes to the world is due to the facility we have in designing and building objects today.

Of course, we have none of that for biology. Nonetheless, in this hierarchy of engineering and economic complexities starting with a single cell and recombinant DNA, we can make enzymes, drugs, some materials. We're starting to build systems that have multiple genes in a single cell type. Someday down the road, we may be relying on synthetic single cells or maybe something that's a chassis, a stripped-down cell that will provide the metabolic products for synthetic circuits to make more complex materials. Somewhere down the road, we'll have multiple cells contributing to growth and differentiation of everything from tissues, new tissues in our bodies, perhaps larger objects. Someday we may grow houses.

I would note that it's not the case, however, that all of this is somehow off in the future somewhere. The top corner, there's a picture of a woman, Claudia Castrilla, who two years ago had her esophagus replaced by an semi-autologous transplant. There was a donor esophagus whose stem cells were stripped from it and her cells were seeded onto it. It was differentiated in the lab and transported. She's doing very well today.

Last week, we had the first announcement of induced pluripotent stem cells made from peripheral blood and the first announcement of tissue transplant that was designed to differentiate inside the body of a young boy it was put into. It doesn't look anything like stem cells today in that they are different technologies but it can't be too long

before they come together. And that has to be on your radar as well.

Nonetheless, despite the fact that we are very early in this game, we're just barely beginning to get ahold of how to build things using biological systems, in the U.S. today we derive the equivalent of 2% of our GDP from genetically modified stuff. That's a big number. That's about the same as we derive from mining today. That's broken into three areas: genetically modified crops in the U.S., market revenues from those crops are about \$80 billion a year. That's a low estimate and only includes cotton, soy and corn. If you include alfalfa, and if genetically modified sugar beets come back, that's another 10 billion or so. Genetic drugs are about \$70 billion. The biggest part is industrial biotechnology — fuels, enzymes, and materials growing faster and much less regulated and much closer to the consumer. I think that economic activity is going to drive a lot of the uptake and development of biological technologies, especially synthetic biology.

So, the next important thing to note is that we're not the only ones who are going down this road. The numbers for other countries are sort of hard to come by. These are the best estimates from my firm so far. And we continue to refine these. China supposedly is at about 2.5% of their GDP already from biotech, and they have a target of 8% in 10 years. Malaysia claims 2.5% this year, and they have a target of 10% of GDP by 2020. I don't know that I really believe either of those numbers, but that's what's published. India and Pakistan each have substantially smaller numbers. Pakistan is interesting because almost all of that until this year was unapproved genome cotton made by somebody else but pirated essentially and brought into the country. Europe basically looks like the U.S., except, of course, they don't have much in the way of genome crops.

And the definition of biotechnology is very different all over the world. Different agencies in the U.S. Government use different definitions. The OECD has a particular definition that includes things other than genetically modified products so it's hard to sort out exactly what's going on here but these are my best estimates so far. I'm not going to spend a lot of time going through the slide. The point is there are all kinds of different drivers for people to adopt and develop biological technologies. It has particular technologies and a set of technologies.

This set of technologies is international and distributed already and looks like brewing beer than it does like oil production. We might have “open source” biology at some point here in the future if we can sort out the legal issues. And there are many uncertainties as to how this goes forward to have mostly to do with investment and how fast we really want to go.

We heard earlier about the importance of reading and writing DNA. Those are both improving exponentially. That is, the productivity of both reading DNA and writing DNA have been improving exponentially for more than two decades now. The cost of reading DNA and of writing genes in particular from scratch has been falling exponentially. That hasn't had an important impact on our economy yet because it's been too expensive.

So to really get ahold of it, and to really use broadly: that 2% number I showed you doesn't have any synthetic biology in it. That's all recombinant DNA techniques. It is coming. Revenues from synthetic biology are maybe a couple of million dollars a year at this point, that's all — re-agents and instruments and what not.

So, now we're on to what do you do with that DNA. You can stick it together, the little pieces you can make using DNA synthesis and stick them together and make genomes. The longest accomplished synthetic DNAs over the last 30 years and it isn't clear how much longer the game will go on. Once we get another order magnitude, we are at the level of human chromosomes and building a human chromosome from scratch is an extremely complex endeavor and it isn't clear that just making DNA gets you anywhere. But all that said, it seems like — this is from a publication I helped write a few years ago. We have had a particular rate of increase and penetration into the economy and we have all kinds of new tools coming online that can radically change the rate at which we make progress both building these systems for trial and error, for learning, what not and building components of the economy.

Again, I'm not going to go through all this. But this is one version of a chart of how we might make all kinds of different biofuels. And in my opinion, we're going to need all these different energy sources if

we truly want to have renewable energy in this country. We need all of this stuff. There are some industrial chemistry on here and a whole lot of biology on this chart. We can't accomplish the goal of energy independence, particularly if we're using biological sources of energy, unless we get all of this.

Similarly, I won't go into details. This is a timeline from the SARS outbreak. Essentially, what I have done is look at the important diagnostic and sort of action events. In the SARS outbreak, what you find is we were technologically unprepared for this and we're still unprepared for natural outbreaks. We need much better technology to identify threats, to understand threats, and to respond to them, whether they are natural or, as is inevitably the case, artificial threats. The only way we're going to get there, in my opinion, is to have innovation everywhere and anywhere as fast as we can go.

And that's the way technology development has always worked in fact. This is the U.S. Small Business Administration list of transformative technologies that spent some of their time in the garage in their development cycle. And I think biology has to be the same way in order for us to get where we're going to go, where we need to go.

It's briefly instructive to think about aviation in our context. The beginning of aviation, there was in fact no government investment, just like there's no government investment now in synthetic biology, in the U.S. anyway. And there were distributed innovators. They talked to each other and each had different ways of going about their innovation strategy and met with different results. One was making flights in Berlin and had the story of air foils. Those happened to be unstable and he died in a resulting crash. Samuel Langley had a particular law, a particular mathematic duration, called Langley's law which said the faster you go, the lower the air resistance, so that led to a design strategy and led to his airplanes often folding up as soon as they were launched.

My point there is that we're going to see all kinds of different innovation and most of it's not going to work out. Eventually, the Wright brothers' talking to Octave Chanute (or whoever else is out there), they are going to get biological technologies working, but it's going to take a long time.

Aviation took almost 100 years before it became truly important in our economy. That said, biology is already distributed. This is a 2007 map of gene synthesis foundries. These are companies selling gene synthesis services since 2007. There's been a lot of consolidation. There are four major providers of mail-order gene synthesis service. You send them a sequence and a credit card and they FedEx you the DNA two weeks later. There are only four now driven by economics but I can't see there are any technical barriers to additional participants. That is, if you want to set up shop anywhere in the world with a new DNA technology, you don't need any special environment. You don't need any special infrastructure.

Drew mentioned students building genetically modified systems for iGEMs. This is a 2006 map of countries from iGEM. The competition has increased every year. I am fortunate to be a judge and the students usually surprise me. Sometimes they scare me.

This year there are 128 teams registered so far, Drew? Is that right?

**Drew Endy:**  
150.

**Robert Carlson:**  
150 now. International teams have won in the past. This is by no means an activity that's dominated by the United States or by Europe. High school students and undergraduates get together every year and try to build systems that have defined behaviors.

How many genes are enough? Well, so this is the sort of economic, technical perspective on the comments we just heard. The artemisinin project, Jay Keasling's work at Berkeley, at Amyris, to make a malaria drug in yeast, that's 12 genes from four organisms. It's way north of \$40 million if you include the biofuels spinoff. It's not a portable hack. You'd have to rebuild it in a different organism and spend the same amount of money, but we'll get biofuels out of it.

Twelve genes. The Gibson paper describes roughly 1,000 genes. Like Drew, I have no idea how to do anything with 1,000 genes. And it took a whole bunch of really skilled people to do something interest-

ing with 12 genes for this project.

The last thing I want to do is say something about regulation. It's not your remit necessarily to think about prescription regulation but I think the impacts of regulating are important to think about here. So I think drugs are — illicit drugs are — an important model to think about.

So, most of the cocaine that comes into the U.S. or 30% to 70% of the cocaine that comes into the U.S., depending on whether you believe the U.S. Navy or U.S. Coast Guard comes in some point of its journey in on semi-submersibles. Those cost a couple of million at best to build and carry 200 million in cargo. The drug smugglers may have moved on to fully submersible submarines. One was discovered last week.

I'll finish in just a moment. And that's a focus of technological development effort that was prompted by an attempt to restrict production and distribution technologies. The same thing happened in methamphetamines. The DEA's own reporting on what happened when they tried to crack down on domestic methamphetamine production is that they created a bigger, blacker market that is much harder for them to penetrate and understand.

I'm not asserting exactly the same thing will happen in synthetic biology if some attempt is made to regulate DNA synthesis, but I do think the same thing would happen because DNA synthesis is a production technology. The DNA you make with DNA synthesis has some value, but it's not very large. DNA is everywhere in our world. It's not very expensive. But the products that you hope to make using that DNA are much more valuable — many billions of dollars where the DNA itself is thousands of dollars at this point in time.

So, if you attempt to restrict access to the inexpensive thing that's easy to make, I suspect what's going to happen is there will be a very broadly distributed black market that's very hard to see into. And that's all I wanted to say.

Thank you.

## Q & A

**Amy Gutmann:**

Thank you very much, Dr. Carlson. We have ample time now for questions. I ask both the commission member and the public to keep questions, and any comments preceding questions, brief, so we can give ourselves time to hear more and probe our three presenters. I will actually turn to my vice chair for the first question.

**Jim Wagner:**

I appreciate the privilege.

Given the structure that we imagined and the flow of the commission, I don't know when again we will have an opportunity to have an assembly of scientists, folks who are as knowledgeable as you. I'd like to ask several questions, but I'll start with a naive question about the science.

Dr. Bassler, you spoke about differentiating between genetic engineering and synthetic biology, largely as a matter of scale. I wonder, also — and again, it's a very naive question: We've been focusing on synthetic biology as our ability to synthesize gene sequences, base pair sequences. But we haven't spoken about the need — or maybe there is no need — or the possibility that synthetic biology might ultimately address some of the machinery that you have talked about, the protoplasmic chassis that would be operated by the DNA software. Is synthetic biology — do we anticipate it going in that direction? Or is it strictly focused on the genome?

**Bonnie Bassler:**

Well, I think that there are sort of a few kinds of synthetic biology. I think there's people, like we're talking around this paper, that are really interested in being able to make bigger pieces of DNA — bigger pieces of DNA means more genes that we can put together, hopefully in logical ways.

I think there is a second kind of synthetic biology that likes gizmos. Engineers who like to think about, as Drew said, or Dr. Carlson, how cars work, right? So they would like to take genes with known functions. If these could be modular, each function, could you put them

together and make some new contraption — or a better contraption than already exists?

And I think the third kind of synthetic biologist that actually hasn't been talked about today are people who are trying to think about, how did life actually arise on earth? I think Jack Szostak, Ph.D., is the best example of this. Their approach is orthogonal. They take the littlest bits they can — not nitrogen and carbons, but lipids and nucleotides — and try to get them to self-replicate to understand how that could have happened.

So, I think all three of those things are in our future. I think all three of those things will be working together. If we can make bigger pieces of DNA, then the gizmo guys can string more genes together and hopefully make more interesting self-replicating organisms.

I will finish by saying that the premise of all of this is that we have to know what those genes do. These are not just “A,” “T,” “G” and “C” put together. Evolution did that for us. Biologists have provided us knowledge about some of these functions. And that is a real part of synthetic biology if you want to go beyond just making longer DNA.

**Amy Gutmann:**

Great. I open it up. Nita.

**Nita Farahany:**

Thank you for these presentations. They were terrifically informative.

**Amy Gutmann:**

I ask everybody to project into the mics because I think people in the back of the room would appreciate hearing as clearly as we around the table can. So, project out. Get close. Bring the mic close.

**Nita Farahany:**

I'm going to project a little bit more. Thank you. I just started by saying thank you for these presentations in case you didn't hear that.

I want to jump to some of the recommendations that each of you have made, both in your published work and here today about regulations.

So, Dr. Carlson, you suggest that methamphetamines might be a good analogy. And Dr. Endy I know you have been quoted and suggest that perhaps regulation would be difficult and it would create more drives toward other countries or other resources. But I wonder if you are thinking of a particular model of regulation, like methamphetamine and restricting access rather than something like licensing or registration requirements.

I'm wondering with something like biobricks, is there some sort of registration requirement for do-it-yourselfers to track what they are doing and — more like gun licensing laws — to know where the different products were going and to be able to know what the likely outcome of these things would be?

**Amy Gutmann:**

Drew, do you want to start?

**Drew Endy:**

I think if you can bring forward a conversation about regulation, an immediate question becomes, to what end? Or to what challenge is it being focused and addressed?

And so it could be in the case of something like the BioBricks project, International Genetically Engineered Machines (iGEM), and the competition like Rob mentioned where we have genetically engineered machines, an olympics around the world, the regulation would be doe safety. Are these students in their work in schools and universities, high schools and schools and colleges being safe? Are they being safe and keeping the public safe and the environment safe to the best we know how?

What we have done at iGEM as synthetic biology has grown out of genetic engineering is to leverage and take advantage of the past practical successes in that area. For example, the Recombinant DNA Advisory Committee (RAC) and The Office of Biotechnology Assessment at the NIH (OBA) here in the United States, both provide biosafety guidelines for the engineering of genetic material. The iGEM teams, in order to participate in the competition and be judged, have to answer four questions with their submission: Do you have a bio-

safety committee at your institution? Yes or no. What do they think of your project, if yes? Do you have any safety concerns about your project? Are any of the biobrick parts you are contributing back to share with the community, do they have safety concerns with them?

What we see by this mechanism is we are practically promulgating best practices as they exist around the topic of biosafety. Where we run into puzzles on this one particular topic of governance is when the technology platforms begin to move beyond an institutional oversight framework. So we don't have iGEM teams right now — although there are some who would like to participate — coming from outside research universities, community colleges, or even a high school, on a few occasions.

If you think about a future where you go from information to material, your genetic engineering design suite can be a phone on a school bus. Where you can move the information around and email the sequence.

So, what are the challenges in biosafety governance? I'll keep my remarks limited to that for now.

It's going to be to figure out how to deal with an increased scope of genetic engineering work, an increased pace of the work, where it might not be the case that every new design can go through the exact same deep review. And that's dealt with practically already at institutional levels. But we now need to figure out how to promulgate that or to disallow outright such work beyond, you know, relatively rich institutional bounds that can afford to have an established and well-functioning biosafety committee.

**Nita Farahany:**

Can I have a follow-up to this? I'm interested in the do-it-yourselfers that all of you reference in your work. And I know that with the iGEM competition, they are excluded from the competition itself.

I'm wondering if BioBricks would actually sell directly to an individual who wished to purchase to construct in their garage and be one of the small organization inventors that Dr. Carlson refers to in synthetic biology. And if so, given that iGEM excludes them, what types

of biosafety concerns should we have about the do-it-yourselfers? Is there any way to track what they are purchasing and what the product and development course would be from those individuals?

**Drew Endy:**

I think that's a good question that brings up two dimensions of governance. One is biosafety, and second is property rights.

In the same way that I'm very enthusiastic about the technology of synthetic genomics, but we've heard concern about its representation, I'm equally enthusiastic about individuals who are compelled to explore and learn about biology and to tinker with it for useful purposes — the so-called DIY-BIO community.

I think it's unfortunate that it's represented with that label, to be honest. I would prefer it to be represented with a "do-it-together" label.

If you look at the success of iGEM, for example, very specifically, the team that won last year from the University of Cambridge in England implemented seven biosynthetic pathways in different strains of E.coli to make a rainbow of colors. (E-chromi, they called it.)

This is a feat of genetic engineering that makes Jay Keasling's work for \$25 million seem really great, but now they can do it for \$25 thousand.

How did they succeed? They did it together. Half of the genetic parts that went into the project came from the pre-existing collection and they got that for free. The gene synthesis company in Menlo Park, DNA 2.0, gave them free gene synthesis because its President is a graduate of the university. And DuPont gave the students free access to a specially strain of E.coli that overproduced the precursor chemicals. So, the successes in synthetic biology at the level of young people are not do-it-yourself. They are "do-it-together."

I think it (DIY) is an unfortunate misrepresentation. What we have to work through in terms of the biosafety is: Can we expand beyond our institutional biosafety framework boundaries? Can we take an example from amateur radio, for example, and establish a citizen-based bio-review process? Many exciting things to explore.

A second challenge then, to say this very briefly, comes back to property rights. The BioBricks Foundation is a public benefit organization. It doesn't own the BioBrick parts. We haven't cleared freedom to operate on the uses of the genetic components. In 2008, 1500 new biobrick parts came into the competition, contributions from all over the world. If we wanted to be upstanding citizens in the world of property rights, we'd have to try and get claims on those and play within the patent-based system.

I'm not for or against patents per se. But in this context, doing that for 1500 uses of genetic functions would cost about \$25,000 per each one, which adds up to \$37.5 million. The budget for this student and educational event distributed worldwide is \$3.5 million. So the scale and pace of work in the technology is, in this case, outstripped and created not a governance challenge but I think an ownership, sharing, and innovation challenge.

**Amy Gutmann:**

Thank you. Yes, Raju.

**Raju Kucherlapati:**

Great presentations, thank you!

Can you compare and contrast what is happening technically in synthetic biology to what happened in recombinant DNA technology in the 1970s? Some people argue this is no different and there is absolutely nothing new in synthetic biology than what we have been doing for the last 30 or 40 years.

**Amy Gutmann:**

Bonnie, you want to begin?

**Bonnie Bassler:**

Yeah. I think the difference is slight. I think there is DNA synthesis, right? And then there is the stringing together of known functions, and it is genetic engineering.

We have been doing this, biologists, for 50 years. Right? We call it cloning.

I think that the fundamental difference, is that biologists don't typically think about optimization of the process. Like can you get this to work? If it works in a Petri dish, we've won.

But if you really want to make industrial-level products, you know, medicines, vaccines, we have to take this engineering view where they think about, you know, how to get these components to work better together, how to get these to work reliably in a large scale, you know. What actual parts do we need, and what can you do away with? This is how engineers think about building machines.

So, I really do believe that the difference is the perspective of optimization and scale that traditional biologists haven't had.

**Amy Gutmann:**

Let me just follow up on Raju's question...

**Jim Wagner:**

Let's see if the others agree.

**Amy Gutmann:**

...and I'm going to open it to the others as well: If you would, please answer Raju's question about the past and also project forward.

Because part of our charge is to think about answers to this question before, as one reporter asked me, "is the cat already out of the box?" Right? Before things happen that we aren't prepared for.

So, how different is what synthetic biology is doing now and how different is it likely to be moving forward?

And this is a triple-barreled question: What do you anticipate most likely the developments here moving forward?

Rob, you want to start?

**Rob Carlson:**

Gee, thanks.

So, first, I mostly agree with what Dr. Bassler said. I think that the

effort to bring engineering practices in is new and brings power. The attempt to actually go — instead of to a science paper — to a product that has revenue is an important step. And it isn't clear to me that you get there without the engineering component. And I don't know that it's going to be totally successful.

We should be clear that iGEM is kind of an experiment. And the parts agenda that came out of MIT, the ability to snap these parts together like Legos, and there's a lot in there that's good and a lot like an experiment.

It's unclear that you can qualify these parts carefully enough to use them in this way. We're actually not very good at measuring most of the components that we want to use well enough to use them in the way we'd like to use them.

And what do I think is coming? Boy, that's hard.

I think the cat was out of the bag decades ago. I think it is too late. I don't think there's anything we can do about this at this point in time to go back to the previous question or two questions ago.

**Amy Gutmann:**

You are very consistent, Rob.

**Rob Carlson:**

The issue is could you possibly limit access? Is it possible to proscribe these technologies in any way? I don't see there's a physical ability to limit access to the technology. So there's one kind of regulation that I think is off the table already.

**Amy Gutmann:**

What about knowing what's happening? We are a public deliberative body in part because we, as a nation, are committed to actually bringing things out in the open, except when privacy concerns arise — a very important exception, but that's not really relevant here.

So, what about access to knowledge?

**Rob Carlson:**

So, I think that's our only tool in fact. I think that trying to keep track of what people are doing, trying to have people volunteer and do it together, that's great.

Speaking for myself, my own company started in my garage. It was a garage biology company. And do-it-yourself is really, really, really hard. It would have been easier had I had the resources of a university or a larger company. And we are probably going to succeed, but I'm not saying we are going to with a particular project.

Nonetheless, I don't think there's any way you could have stopped me from doing what I wanted to do in my garage. There's nothing illegal. There's no regulation covering what I was up to. And I was actually very careful to only do things that I was sure were without question.

**Amy Gutmann:**

And you're here to prove it.

**Rob Carlson:**

I'm here. The FBI did not come knocking.

And so, going forward, if you are worried about threats, if you are worried about mistakes, I think the only way we can deal with this issue is to try to make sure everyone is open about what they are up to.

And one way to help enforce that is to not enforce it, but to encourage it.

It's to set up some sort of framework where people can ask questions. So, every day, if you are in the lab, you stumble over something that doesn't work. You stumble over some bit of a recipe from some company or kit that doesn't work the way it's supposed to. You want to ask someone about that. We should help people ask that question, in part to make sure that they aren't putting it to some use that is questionable.

Years ago — it doesn't happen to me so much these days — years ago, I used to receive interesting emails from people saying, "What do you think if I do this? What should I do about that?" Most of the time I would say, "Well, it's not such a big deal. You can try that. I

don't think it's going to work." Every once in a while, I get an email that says, "I want to play with this immune system gene and this viral gene." And I say, "That's really a bad idea. Please, don't do that." And we want that to be common, right? We want those kinds of questions to come up so that there's some kind of interaction.

That's the best I think we can do.

**Amy Gutmann:**

Thank you.

Drew.

**Drew Endy:**

I'd agree technically, scientifically, that synthetic biology represents an outgrowth of genetic engineering. But I would equally, if not more strongly, urge you to recognize that changes in process, pace, and scope can lead to very significant transitions.

So, for example, when Carper Mead and Lynn Conway backed off on limits on design on the computer chip in the early 1970s, if you followed their rules, the chips wouldn't be as powerful because they used more silicon, but they'd all have regular layouts. What this led to was you could get your designs fabricated on any different available silicon wafer manufacturing facility because it didn't matter if the masks lined up exactly right. And the significance of that one process difference was that, now, all of a sudden, many people, including students, could design what became micro processors and have them fabricated.

Researchers that had bad internal policies could outsource through an external service, getting access to their own company's fab lines. The first iGEM class — before iGEM existed — all we wanted to do was keep our students out of the lab. We wanted them to spend a month just designing DNA based on everything we knew from the biology that the biologists gave to us. At the end of the month, we're going to ship the DNA over the Internet to a company. The company will print the DNA. The students get it back and they try it out.

Nothing worked that year, except we learned how to decouple the design of genetic material from its fabrication. And so that means a

biological engineering student who is a sophomore today in a laboratory course has a very different experience. And just, last spring, they are quite literally, designing new genes, sending them to a synthesis company, and getting it back and testing it out in a couple of weeks. You index the capacity to the genome scale and it makes a big difference. You combine that with component libraries that aren't 100% broken, meaning they sometimes sort of work — which is better than nothing — which is where we are. And all of a sudden, new things happen.

Please don't underestimate the consequences of changes in process, even if the technology is an incremental development path.

**Amy Gutmann:**

Thank you.

Dan.

**Dan Sulmasy:**

This will be a question, again, about the future of the field. And somewhere in this pile of things I read, maybe it was one of you who said it: Engineers abhor complexity. Maybe one of the two of you, maybe somebody else. But it seems to me that what we heard from Professor Bassler is that the organism-issues are very complex. Gene interactions, gene chromatin interactions, gene membrane interactions, etc.

As far as the future of the field, I'm wondering whether there are, from an engineering perspective, advantages of pursuing the complexity, which would lead you in the direction of eukaryotes, multicellular organisms versus the engineering perspective that pushes toward utility, keeping to smaller, simple organisms that can produce products which would be very useful to people.

Is there a push or a pull in one direction towards the simplicity or towards the complexity?

**Drew Endy:**

Quick answer: both.

Engineers are not always devoted to a model system as a geneticist or biologist might be. They like to solve problems or realize opportunities. And so, you know, Professor Ron Weiss in the Biological Engineering Department at MIT would be someone who moved from engineering in bacteria to yeast and now stem cells. And his interest in engineering biological systems in mammalian cells has to do with implementing a synthetic program that would, inside a person's body, detect levels of insulin and sugar and coordinate the production of insulin within a living body and provide a living therapy for diabetes.

So I don't think it would be wise to expect that — although microbes are the most amazing things and I agree 100% with everything professor Bassler is saying — the engineering community is unlikely to stay just there and isn't already.

In terms of complexity, what you see in synthetic biology from the naive engineer's perspective, is we are scrambling. We are trying to look at the history of technological development and engineering and distill anything to the challenge of how do we get better at engineering biology.

I could talk about telegraph technology in Britain in the 1800s and Roman aqueducts and from the end of past experiences we find lessons interesting to us as engineers. One hallmark of biology is its complexity. And it would be a mistake of the highest order to expect that as we go into this challenge of getting better at engineering biology, we will not learn tremendous new engineering from the biology.

My hope is that, as engineers, biology will teach us how to better work with complexity, how to better integrate artificial systems with a much richer environment in a way that leads to increased flourishing and a sustainable civilization. Where that all plays out and when it plays out, you know, we can't predict. But it seems like a very compelling opportunity.

**Amy Gutmann:**

Since we have this great opportunity for the conversation between engineer and biology, Bonnie, you want to give the biologist perspective?

**Bonnie Bassler:**

I want to be clear. Complexity is the goal. And I don't mean to think that the engineers want to avoid that. They would love that. Biologists, we would love to understand complexity. That's what we try to do. But we can't yet.

You know, we get 12 genes for 40 million bucks to work together. That's where we are today.

So I think the focus and the goal would be to move this to more and more and more complicated organisms. But just the way biology has happened in the last 100 years, we start with bacteria because they are simpler. Right.? They have fewer bits, fewer wires, right. But the truth is, at least currently, is that even with our best understood bacteria, you know, we can't do it yet. So what we find right now, the overwhelming beautiful complexity of these organisms is humbling. So it's hubris to think you can do this in a human now.

I think the focus on bacteria, very often we learn the principles, we learn the rules from studying these bacterial systems and then we get to apply that to ever more complicated organisms. But we need to be clear. We don't even understand E.coli yet. So that I think is a much bigger sort of hurdle than our ability to make DNA, to clone genes. That we can't yet put complicated systems by any means together, even with parts that we think we understand deeply. But that's the — we need jobs, you know.

That's the beauty of it, too, right. It's that it's there and it's there in the bacteria.

**Amy Gutmann:**

Barbara.

**Barbara Atkinson:**

I wanted to put together a couple of your previous comments and ask you a real specific question about the commission and if this is really a strategic priority for our country, synthetic biology. And I want to talk about the value side of it.

What recommendations could this commission make that might

really support that value? Where do you think the areas are that we need the most help? And I have to say that I was caught by your freedom of DNA writing, if you will, if that's one of the areas specifically that might need a recommendation. Or are there other areas that you would suggest?

**Rob Carlson:**

All right. I'll give it a whirl.

So, as Drew noted, there's very little public funding of gene assembly technologies. All of that is in the private sector for the most part.

It's a very different story in DNA sequencing. So that has been the benefit of substantial government support, prizes, commercialization awards, contracts for purchasing instruments, what not.

And that's actually very similar to the way integrated circuits worked. So Intel was able to fund its fabrication facilities in large part because it had contracts to sell chips to the U.S. Government for a variety of purposes — as has happened in DNA sequencing.

But in my conversations with people in the gene synthesis industry, the U.S. Government funds at most 10% of their activities by purchases. So that's professors who have grants who buy genes or occasionally the NIH or some organization funded by the NIH will have a bunch of vaccines essentially written from scratch by DNA synthesis to see how they work.

But, other than that, there's not a lot of support. There is very little support.

Drew, correct me if I'm wrong, on the engineering side of things or the ability to actually build DNA circuits with defined function. There is some support from the NSF, maybe some support from the NIH but it's not so great. It's unclear how much work in industry can be said to be supporting that kind of activity, as opposed to just trying to get something to work to put on the market as soon as possible.

I think that one of the benefits of the U.S. Government investment

in better understanding how to build biological systems that have defined functions is that it will help us sort out the inevitable mistakes that come out of the commercial world. So, one of Monsanto's first cotton products — I forget which one it was in the late 1990s. They tested in the field many years and it looked to be okay. Then, a couple of years after it was released to farmers, in some fraction of the plants, all cotton balls fell off, I think 40% of the plants.

The New York Times reported on that for a couple of months and then there was no longer reporting. It appears what happened was some sort of non-disclosure agreement was signed and farmers received some payments and nobody explored, at least publicly, what went wrong with that crop that had made it through the regulatory process and had been planted.

And I think it would be nice if we had some trouble-shooting capability that we don't have now. That same capability would help us understand pandemics and help us build better biofuels.

**Amy Gutmann:**

Thank you.

Nita.

**Anita Allen:**

Thank you. I had three questions, and, in some form or another, all three have been answered.

I had a question about regulation, and it's pointed out not all regulation is prohibition and might have to look at licensing or registration or even what kind of adjudicatory role government might play in the fields.

The other is cloning versus creation. I guess I kind of want to go there a little bit with you because on the one hand, I think you are quite right there's a strong sense in which Dr. Venter's research is more sort of a cloning than a creation kind of research, yet it's not as if the public is as comfortable as biologists are with the concept of cloning. So I want you to say a little bit about why, if the research that Dr. Venter has come out with is more like traditional cloning than creation, why

we shouldn't be worried about that, too. Because, as we know, some kinds of cloning still invoke a kind of anxiety in the mind of the public. Why is this sort of a benign continuation of benign cloning?

And the third question is about the public investment issue. I was struck by both of the comments from engineers about how there's no public investment in synthetic biology. And yet I remember in the 1990s the government putting lots and lots of money into DNA sequencing and mapping. And that was a huge public investment. But without that investment, a lot of what's happening in the synthetic biology field wouldn't be possible.

Those are my questions.

**Bonnie Bassler:**

So, I agree with you that cloning is a hot word. And I think that, unfortunately, I think the cloning that the public is most worried about is what we would call human reproductive cloning. But that's used synonymously with what molecular biologists have done for almost 100 years, which is to move genes around in bacteria, to cut and put pieces of DNA together.

This paper is about molecular biology and cloning in the context of what we have done since the discovery of DNA almost. It isn't making — I think what the public fears is that we're going to make this designer organism person, right, from scratch. And that we have no ability to do. These were genes that evolution worked on for billions of years. To me, this finding would be like if Shakespeare writes this perfect play and I put the play on the Xerox machine and then get Hamlet, I don't think that the Xerox machine wrote Hamlet, right? So that's what this is.

It is traditional cloning in the sense of what molecular biologists have done, except it's a lot bigger piece of DNA. And that is hugely important for our future and our ability to synthesize useful products at industrial skill. We have to be able to make bigger and bigger pieces of DNA in order to make more interesting products.

And I think the problem is that the public misunderstands what the word cloning means when it has this very negative connotation that

has to do with I think human biology and stem cells. And that's not what this is.

**Anita Allen:**

Could you reframe your wonderful point about it's creation and not cloning without using the word cloning?

**Bonnie Bassler:**

It's a DNA synthesis on a machine of a known genome.

**Anita Allen:**

It works for me.

I have a question of the funding and so forth. Can we be more positive about the role of government? It has been a huge government investment in the foundations of genetic and genomic science.

**Drew Endy:**

Yeah, thank you very much. Let me try and be careful.

So, absolutely, everything that's happening depends on the successes of the genome projects, the successes of molecular biology, genetics. We can acknowledge Warren Weaver, and the Rockefeller Foundation, and Mendel before him, and the patronage of the scientists in the 19th Century and so forth.

Let me turn it to synthetic biology very specifically and use the example of DNA synthesis:

So without naming the federal agency... In 2003, there was the only public funding for an advanced DNA synthesis program in place. The goal of this program was to be able to construct 10,000 base pairs of synthetic DNA in 24 hours. The purpose of the program was to allow rapid response vaccination which I'm sure we'll hear about later this morning. The program was shut down. The reason why gets us back to Dr. Atkinson's question and perhaps a comment from you about the role of the committee.

The program was shut down because it was put through the Washington Post drill. The Washington Post asked, "What is the worst case

scenario associated with this public investment?” And the program manager answered honestly. “Not content to synthesize polio virus in 18 months, our agency can do it in 24 hours.” And leadership of that agency was not in the political position to defend that. And the reason they weren’t in a political position to defend that is that they had no framing, no public framing from an ethics perspective, from a government perspective, from a safety perspective, or from a security perspective, or you name it, that would give them comfort that it’s okay to explore developing tools that will make the engineering of biology easier without putting their careers on the line.

I think if you were to look throughout the federal funding agencies, we see many agencies that are chomping at the bit to try and figure out how to provide significant public support for this important area. But they are hampered by the fact that there’s not been an “okay” to say we have to explore, we have to discuss.

I think this commission, which I recognize as being the first executive-level public venue for considering this has a very important role to play because it makes it okay to talk about this. It makes it okay to try and make the next step because you know you’re going to have a place to work it out and discuss and learn. So I really do thank you both for the questions.

In closing, I should also acknowledge that we do have very important essential, modest, and sustained support from National Science Foundation and from the National Institutes of Health. But these funding amounts are in small numbers of millions of dollars which is a lot of taxpayer money, but not compared to the genome projects. And it is more reflective of a very scrappy, very innovative grassroots research community.

**Amy Gutmann:**  
Thank you, Drew.

Nelson.

**Nelson Michael:**  
Let me move back to the first question that Nita asked about limitations on the technology and perhaps go to someone with my bias,

someone who cloned his first pieces of DNA when I was an undergrad in 1978. And now I struggle with a virus that can change every base part of 10KB genome in one day in one patient. I have always been humbled by the way natural selection that frankly can sweep aside every thing we think we can intelligently do in the laboratory because of that's the way that Mother Nature has done things for billions of years.

I was struck by some of your comments in that sense by the fitness arguments that you have made. And I was wondering if the three of you could briefly expand on what you think might be the ultimate limitation on this technology, which is just the fact that we're so ham-fisted as being able to do it.

**Amy Gutmann:**

One of you can take it. And then I'm going to go to the public for questions.

**Bonnie Bassler:**

Right. I think that nature is awe-inspiring. And I think that the sort of beauty of this commission and the problem is it's the beginning of this field. And our knowledge and understanding is so limited. But this is how all scientific fields have started. It's by this grassroots people, you know. We're scientists and engineers. We're so curious about how things work. We do these little bits. We hope we learn something that makes, you know, 10 years from now we can do it a little bit better.

And I think that the future that the public is really worried about is really far in the future. That does not mean you guys should not be trying to manage or think about that. But I think that the reality of what we are able to do in the lab as opposed to the publicity of what we are able to do in the lab are strikingly different.

And so I think, of course, this is how science happens, right. So I think it's totally a wonderful and forward-looking and it's an amazing field to have the engineers helping the biologists to learn and then the biologists giving the engineers fodder to work with. I think at least right now, what you said, we are bad at it because we don't understand complexity. But that's okay.

**Amy Gutmann:**

Drew.

**Drew Endy:**

Very quickly. Regarding, does the fact that these are highly selected, evolved systems — how does that limit what our capacity to deliver? I don't know. I don't have any experience engineering machines that replicate. In engineers really do for approximation. All our artifacts we make are disposable artifacts. The thing then to say about that is, you know, a lesson from Francis Arnold at Cal Tech and others.

Evolution becomes an editor, a partner with us. It's not something we're fighting against and it becomes, as I suspect we'll hear later today from some of the leaders in the field, you know, thinking about how to take forward engineering and synthesis and every other idea that us naive would-be-engineers of biology have and couple that to the power of evolution to make more complicated systems, that's an incredible opportunity.

**Amy Gutmann:**

I'm going to — oh, yes, Rob, why don't you chime in?

And then I'm going to ask if anybody would like to ask a question.

**Rob Carlson:**

The thing I would add to that is that it took about 100 years to go from Octave Chanute sort of falling off a hill in Berlin to the first 777 which was the first airplane designed and built entirely on a computer, using computer-aided manufacturing.

The pioneers of flight didn't try to build geese and today we still can't build a goose. We have no idea really how a goose can manage to do what it does. The aerodynamics involved are extremely complex. The energy management is extremely complex. And all we can do is take one step at a time and see how far we get. And it's in that same frame that I think all of this has to go. There's complexity out there. We have seen and acknowledge that nature can do marvelous things. And we hope to accomplish a very small fraction are be able to emulate a small fraction of that beautiful synthesis.

**Amy Gutmann:**  
Thank you.

Yes. Would you introduce yourself and then ask your question?

**Robert Donahue:**  
Yes. I am Dr. Robert Donahue with the National Institutes of Health. And my question is to Dr. Bassler.

I would be interested in your comments dealing with — it seems that synthetic biology is heading towards bacteria. And you are the expert on intercommunication between bacteria. What impact is this going to have on that intercommunication?

**Amy Gutmann:**  
Thank you very much. A model question I would say.

**Bonnie Bassler:**  
I'll try to give a model answer. So I think synthetic biology is focused on bacteria now because they are simple, right. So I think that's the beginning. And what this gentleman is asking is we know the bacteria work in groups. They communicate with each other with chemicals and that allows them to carry out collective behaviors. Even our simplest organisms have group behaviors.

There's a paper in 2010 where synthetic biologists have put together a communication circuit and got groups of cells to do things together, that tried to mimic what natural cells do. So I think understanding that, again it's the next step in being able to take one cell and make a synthetic circuit in it. Now we can do it in groups of cells and get them to act coordinately. I think that's a beautiful and natural extension of synthetic biology.

**Amy Gutmann:**  
Thank you. Yes.

**Steve McGill:**  
My name is Steve McGill, a student at the University of Pennsylvania. I was wondering, I guess, what the current state of the intellectual

property environment is there for these genes, these parts. And what do you think it should be going forward with synthetic biology?  
Thank you.

**Amy Gutmann:**  
Thank you.

Drew.

**Drew Endy:**  
You are asking about the property right situation on the uses of genetic functions.

So, for example, Columbia University from Marty Chalthy's work holds the patent on green fluorescent DNA . There's a separate category, equally if not more important, around the tools of synthetic biology and the property rights around doing things.

In terms of the uses around the component libraries, you know, you can find available analysis for how many patents have been filed around uses of genetic functions in the United States, in Europe and Japan and how that sort of tapers off throughout the world.

We're operating practically right now in what the lawyers would recommend me describe as "legal limbo" in that we sort of have an operational research exemption at universities in the United States. It's better in Switzerland and better in other places.

So, that allows what Randy Redburg, the director of iGEM calls a "give and get" system to work for students and organizations. It immediately then creates boundaries beyond research organizations. So if a company like Genencor would like to use Biobricks, clearing to work around the component libraries is a mess. We really do need to grow up and figure out who to scale and define best available practice around clearing freedom to operate and perhaps consider the development of a property right that is better optimized to the future of biotechnology that doesn't have the capital costs and latencies as we see present in the patent system.

**Amy Gutmann:**

The question, the uncertainty is probably the worst situation to be in. Rob, would you like to address this?

**Rob Carlson:**

Speaking from experience in the academic and commercial world, I'm pretty unhappy with the way patents are being applied to biotechnology simply because it's so complicated, it's so expensive. It makes it hard to do anything.

Specifically, from the commercial perspective, one of our projects, if you look into the costs we put into developing the actual molecules and the costs we put into getting a patent, the patent costs are running at about 10 times the capital costs of the actual project. And 90% of those costs are lawyers' fees. So the transaction costs for us to try to secure some sort of property right as it's called, are enormous. They totally outweigh what we spend on the actual project itself.

And that represents a barrier to innovation. And I know you guys aren't going to fix that, but you could at least recommend that you could think about other ways to secure property right for DNA. The Constitution enables Congress to spin up that kind of thing. And what we have right now are trademarks, patents, copyrights, what not. You can patent DNA but you can't copyright DNA. And it would be worth examining whether extending copyright to cover DNA or creating some other kind of property right to cover DNA would be a useful thing to do.

**Amy Gutmann:**

Thank you. Yes.

**David Clayman:**

My name is David Clayman, a current student at the University of Pennsylvania. I'd like to ask what role private industry or government may play in providing a robust error checking mechanism for perhaps DIY bioenthusiasts prior to the introduction of tools at such cheap prices that problems may arise.

**Rob Carlson:**

Do you have specific suggestions?

**David Clayman:**

I think to the analogy of the software development community, which developed very robust algorithms for error checking and error handling prior to the facilitation of the distribution of software development tools of great power and flexibility and ease that amateurs could use.

**Rob Carlson:**

Great. Thank you. I think the private industry has some initial success that's quite significant around trying to coordinate the screening of sequence going into gene synthesis processes. It's not the solution to all the biosecurity problems, but it's the example where leadership with the technology allows you to get a little bit ahead of the curve.

Now, if you want to search for examples from other technology developments, the Moses facility that powered the micro processor revolution in part is a wonderful thing to think about. This is the facility that coordinates access to silicon wafer fabrication and defines the standards of defining chips and placing orders. It then places the orders that come in from a very diverse set of communities, including individuals, gets the chips built and redistributes them.

And so if a combination of public and private — public-private partnership basically — could provide this sort of node, you might be able to complement what individuals can do with the strengthening of community and governance and best practices through clearing houses, basically, that provide access to the technologies in a way that advises them be used for overwhelming constructive processes.

**Amy Gutmann:**

I am aware of the clock. And we are in danger of running over. We have another very important session. But before we close, we're going to take a 10-minute break. Reconvene in 10 minutes. I just want on behalf of all of us on the commission to thank Drew, Bonnie, and Rob, for a truly great beginning.

[AUDIENCE APPLAUSE]