



Presidential Commission
for the Study of Bioethical Issues

TRANSCRIPT

Applications

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Jim Wagner:

Could we have our speakers come to the table. And if others could take their chairs, we'll get under way. Thank you.

Commission members, we need you as well, actually. I see them filtering up. I saw Nita out there. And there's Bonnie in the back of the room.

So that there is ample time for our speakers to present and for us to ask questions, let's do get under way.

Really, again, appreciate this morning's conversation and the presentations, helping us to — wow. Helping us to define what is and is not synthetic biology and to understand a little bit more about some of the science involved. This particular session, we are going to focus and we have asked our experts to focus more on applications. We'll try to use a similar format. Have our speakers present for a brief period. You have the timer in front of you. Make sure after all of you have presented the commission has time to ask questions. And then we'll try to throw it open — not try to — we will, certainly, throw it open to the public for other questions they may have.

Our first speaker we have heard all about. Dr. Craig Venter is the founder and Chairman and President of J. Craig Venter Institute, and founder and C.E.O. of Synthetic Genomics, Incorporated.

We have been talking all morning about some of the many feats that his team has accomplished, including the most recent demonstration that a cell of one microbe species with incorporate the genome synthetically assembled from another cell. He is a member of the National Academy of Sciences, a recipient of many awards including the 2008 National Medal of Science by President Obama.

We are delighted to have you here, Dr. Venter, and look forward to your comments.

J. Craig Venter:

Thank you very much. It's certainly a pleasure to be here.

I'd like to start off by thanking President Obama for asking the com-

mission to take on a review of what I think is a very critical topic. In fact, we asked for the first ethical review, your institution, the University of Pennsylvania, in the mid 1990s, before we did the first experiment as soon as we knew we were going in this direction. And the results of that review after two years was published in Science in 1999, and I think that was the first, to my knowledge, scientific ethical review before the science was done.

So, I think we set a precedent in this field, actually going against my usual trend by asking for permission first, rather than asking forgiveness afterwards, for moving things ahead. But that was just the start. And I think this is now the third administration to deal in some way with synthetic genomics.

President Clinton actually had a special session in the White House where myself and others addressed the issues of making synthetic viruses, particularly around the sequencing of the smallpox genome which my team did in the early 1990s and all these issues about public availability of such critical information came up at that time. And the U.S. Government came down on the side of open dissemination of this information. Since then, the Sloan Foundation has funded now a few studies and reports with my institution along with MIT that was published last year.

On publication, in 2003, of the synthetic Phi X 174 virus. Because that work, in fact, in contrast to what you heard, was actually funded by the U.S. Government. It was funded by the Department of Energy. After lots of deliberations within the executive branch of the government, they came down on the side, again, of open publication of this information and the methodology.

And it was announced, as all our studies have been done, in a peer-reviewed scientific publication. Most of these have been in the series of the journal Science, and it was announced publicly with a press conference with the Secretary of Energy.

There has been government involvement almost at every level of this from the beginning. And part of the agreement that was had at that time was the formation of the NSABB to look at dual use research, the National Academy of Sciences, the so-called Fink Report has

looked at dual use research and recently the DOE gave another grant to Bob Friedman and Michelle Garfinkle at my institution to look further at some of the ethical uses and limitations.

So, although we have been discussing this broadly for over a decade and it's been in the world press for well over a decade, I think our recent publication was the first time most people — and probably most of you actually — heard about synthetic genomics. So, I think this commission can take it to the next stage and, as Drew Endy said, this technology is moving very rapidly in a progressive fashion.

Let me help with some definitions because I think there was clearly some confusion that came out of the first panel. The fundamental differences between what we do and what's been done before and how we define synthetic genomics is: we start with digital information in the computer. From all our reading of the genetic code, my team sequenced the first genome of the living organism in 1995. And we went from having the "A," "C," "G" and "T's" to 1's and 0's in the computer. Synthetic genomics as we defined it starts with those 1s and 0s and remakes the software of life and then activating that in cells.

Dr. Bassler was correct about the pioneering work of Kornberg in the 1960s. In fact, President Johnson had a huge announcement on how the first synthetic life had been created at that time. But the difference is Kornberg and team did not know what the sequence of the Phi X genome was. They copied it with DNA polymerase so it was the equivalent of a Xerox piece of DNA. But the important thing is when they put that DNA into E-coli it started producing the viral particles.

The difference is what we did in 2003 is we started with the digital code of the Phi X genome in the computer, made the genome from the four bottles of chemical s that Drew Endy showed you and showed that the molecule could be activated it showing that the synthetic could be activated in the same way that normal DNA or even Xerox copies of DNA could be. The big challenge was going to the next stage and trying to do this with a bacterial cell. Our whole motivation for doing this was trying to understand a minimal cellular life form, trying to get down to minimal the gene sets. The technology in molecular biology tool sets does not exist until we did this work

to be able to do that. So there's many distinctions but the single most important one is we start with digital code in the computer. That was the concern during the Clinton administration about smallpox: if we could regenerate it from the digital code, then destroying the virus had no impact on national security or human health.

That's been an ongoing discussion since. So we scaled up the synthesis abilities over the last decade. First with a 500,000 base pair genome, but we were not able to boot that up in a cell. There were two aspects of this work. One is the chemical synthesis of the DNA and the other is booting it up. DNA is the software of life. The notion that came out of first Kornberg work and then our work with the synthetic Phi X genome is that the DNA software builds its own hardware so it's irrelevant evoking vitalism arguments that were debunked 80 years ago. There are components in the cell and George Church and others will be using those components and we think we will as well to have cell-free systems that can be reconstructed.

I think it's interesting science but it is irrelevant to these arguments of how you boot up a new piece of chemical software. So, one of the most important experiments we did was in 2007 where we isolated the DNA, the chromosome from one species, and transplanted it into another cell, replacing the DNA in that cell. And it converted the cell we transplanted the DNA into, into the species that we isolated the DNA from.

So, it was like putting different DNA in you and converting you to another species. If we can do that at the single cell level, doing it at the multiple cell level, as perhaps decades off, but not centuries away.

So, these are important concepts about starting with digital code and starting with DNA. It is software and it does build its own hardware. I think that's an interesting science question. What do we need? Do we need some ribosomes, a few TRNAs, a few other things, and some lipids and can we get some cells to boot-up from that. I think that's going to be important about understanding origins of life. But we are in fact building upon 3.5 billion years of evolution.

The argument that because we're using genes that we have discovered versus inventing new genes we have not created a cell is a spurious

one. It's like saying Tesla didn't build a new electric car because they used the batteries from one source and they bought an electric motor from another source. They combined those parts to make the Tesla, which is a pretty exciting electric car.

My team has discovered a majority of genes known to science. We're up to 40 million. There were less than 1 million when we started. These are going to be the future design components.

I think biobricks are an important teaching tool. It's great for getting students involved in biotechnology, but the number of genes on this planet I'm sure will top out somewhere over 200 or 300 million. We're dealing with a lot of design components. Nobody is going to patent them. And I think combining those in new ways, now using these tools we had in the proof of concept experiment is what the future of this field is going to be.

We couldn't do any of this until we did the study that was just published in Science. We were able to make these really large pieces of DNA. But until you can boot them up in a cell and get them activated, it was an interesting academic exercise.

So, it's very different from what's happened before in molecular biology. This is a new set of tools starting from a new vantage point. And as Drew said, it changes a lot of the rules.

Scientists sort of controlled who got what, whether they sent them their cell line or their DNA clone for a gene. Now, anybody who has access to the Internet, if that information is in the public databases, you can download it and you can make those genes. Now, any virus sequence that's in the public databases can be pretty readily remade. Fortunately, not in all of them is the DNA infective. Smallpox is one of them. Having the DNA from smallpox on its own can't just boot up readily. But these tools are there. It's a different startling point. All you need is the digital information and a DNA synthesizer. So building the pieces of DNA was an interesting technological challenge. Getting it booted up was straightforward biology and molecular biology.

None of it is cloning. These are totally misuses of terms. Cloning

means everything and anything to biologists. It's sort of a collecting term: It's making copies of cells, making copies of DNA, splicing DNA So we think it's an irrelevant term for what we do.

We use the term synthetic cell because every protein in the cell — all the constructions in the cell — is derived from the synthetic DNA. For the cell that we used as the recipient cell, all its characteristics are 100% gone after a few replications. So, everything in the cell that we have is from that synthetic DNA and, therefore, we define it as a synthetic cell.

It's a cell that never existed before.

Of course, we use copies of existing genomes. I agree with the statement that we're very early on in our knowledge of biology, but we definitely have new tools now to get there.

We're using some of these tools to make new vaccines, so we have a program that is funded by the NIH to make synthetic components of every flu vaccine that we and others have ever sequenced. And we can recombine these and make a new flu vaccine seed candidate in less than 24 hours. We're working with Novartis and it's very possible the flu vaccine you get next year will be from these synthetic DNA, synthetic genomic technologies.

It was announced last year that we have a program with ExxonMobil to try and get cells to capture CO₂ and make basically a bio-crude that can go into refineries. We still have not found any cells that can do this naturally at the levels that are required. So, at the very minimum, it's going to need extensive engineering, but I'm absolutely certain, at least by the time we get to version 2.0 of these cells, they will be completely synthetic as will most things going forward in an industrial environment.

Definitions are important. The definitions can be found in our scientific publication. I think this is an area that Drew Endy's students show we are limited more by our imaginations now than any technological limitations. I think having an intelligent ethical legal framework for this new science to emerge in is absolutely critical.

Thank you very much.

Jim Wagner:

Thank you. We appreciate your views and clarification on the definition. And also impressing upon us the value of the technology coupling with the science.

Dr. George Church is our next presenter, Professor of Genetics at Harvard Medical School. He has pioneered innovations in reading and writing DNA, he directs personal genomes.org with a goal of enabling open access integration of full genome sequences, environmental and trait data goal of working toward 100,000 individuals. Very interesting application. Again, this session being on applications, very eager to hear what you have to say, Dr. Church. Thanks for being here.

George Church:

So, thank you for the time here. As soon as my slides come up, I'm going to talk almost entirely about application. And it's going to be different a little bit from previous talks in that I'm not going to talk about introductory definitions and in particular about what we can't do or have done but what we are doing.

So this is my thank you slide. And my conflict of interest slide.

[AUDIENCE LAUGHTER]

And so as a graduate student, I worked with Greg Sutcliff, another graduate student, to sequence the first semi synthetic plasmid, which we did at a ridiculously high cost even though we were students. This has been used in many recombinant DNA efforts, and some of them are listed here, were really single gene efforts from Biogen and so on.

What's wrong with this picture? This fellow is not using safety goggles.

[AUDIENCE LAUGHTER]

He's not properly grounded for electroporation. But the main thing is we've gone well beyond manual genome engineering that I had in

the last slide. We have gone beyond minimal cells to these fast robust useful cells. We're focusing on lowering costs.

We have talked a lot about scaling up, but not lowering costs. I will focus on that. We look forward to whole genomes, but most of what I'll talk about is doing a little bit less than a whole genome but on a genome scale.

And the question is, why do we do things on a genome scale? And then there's safety and security as the reason for doing things on a genome scale. And evolution is a unique capability that we have that most other fields in engineering do not have. And my major take-home for all this is that we are going much faster than it appears. And we should not be reassured that biology is not capable of engineering and there's no difference between what we're doing and what I did as a graduate student.

Why, genome-wide? This is the big question. You can talk about how to do things genome-wide but we really need to know why. Genetic engineering was one or two genes. Genome engineering as it's commonly used term and is also a couple of genes it's just done in the chromosome rather than on a plasmid. Big deal. Metabolic engineering you might do a pathway or a small network — 30 genes or less. But genetic code offers us multi-virus resistance and safety measures and some use of new amino acids and this is truly genome-wide and one of the few articulated goals that is genome-wide.

The safety component is incredibly important. This is not meant to just be an analogy or images. But we have interoperable parts. These are all from cars but the same thing applies in biological design now: hierarchical design, computer-aided design, cost-effectiveness, standards, and isolation.

We need to – it is not sufficient to have a set of rules and guidelines, if there isn't testing, if there isn't surveillance. You can do licensing as we do driver's license but you have to do surveillance to make sure people are obeying the laws.

And then again evolution is something that's new. There have been recommendations in 2006 and the next slide, 2007, which I think

don't go far enough. We talk about "preferred practices." We pragmatically talk about federal grantees and contractors. There's a lot more out there than federal grantees and contractors.

The Sloan 2007 went a little further than this. But we need to have surveillance and enforcement. And so back to my earlier recommendations on really licensing the entire ecosystem in synthetic biology, I think is important. We need to have surveillance and testing of systems that are proposed to go in. And this is not restricted to bacteria. We have a very active human synthetic biology community and human do-it-yourself community. Some of my undergraduates have gone and sequenced part of their genomes on their own without F.D.A. approval and without really using any special equipment. And this is a whole another subject we're not going to talk about — do-it-yourself or do-it-ourselves biology and bio-weather-map and so on.

We have studied vaccinations. That's another topic for another day.

Genome engineering: some success stories. We already mentioned one for artemisinin, but also bio-propane from DuPont, too, a \$400 million project was very successful, 90% of the theoretical yield. It only involved eight foreign genes plus 13 — I'm sorry 13 down and six up regulations in the E.coli genome. 27 changes was a lot of work back then.

I'm going to talk about hundreds of changes that we have incorporated. These are two other companies that I helped start that are not in the future but are already making thousands of liters of production scale fuels, either from biomass or from carbon dioxide and light, (LS-9 and Joule). These are making alkanes, diesel, and gasoline. Part of this is the success of comparative genomics. You can look through algae and cyano bacteria for those that make trace amounts, as Craig sort of alluded to, just trace amounts of the alkanes by taking fatty acids, reducing and decarbonating the aldehydes. To find those genes, you can look at the genomes that produced and those that didn't produce these trace amounts and then you can identify the genes and overproduce them.

Rob Carlson alluded to this exponential curve. This is actually quite different than his curves, although basically the same. What's different

is that around 2004 or 2005, there was an increase in the rate of this exponential curve from 1.5 to 10 fold. And more importantly, this is a gap between our recent huge increase in second generation or next generation sequencing and synthesis, and we're still stuck in the first generation for gene synthesis in the companies and genome synthesis that we're using first generation sequencing and synthesis for the most part.

There are 21 next generation sequencing technologies and 21 companies that go with it. And I am an advisor for about 16 of them. And similarly, there's a next generation synthesis off of chips that we've been doing since around 2004. This has lagged a little bit behind from making genes and genomes, but it's certainly terrific for making short constructs.

Working in the cells, it's one thing to make DNA but getting the work in the cells, there are many tools. These are protein based specificity tools. And more general tools which are DNA based, homology-based, they don't require specific proteins to put it in precise locations in the genome to make precise changes. But some of these involve single stranded DNA number 3 and number 4 in particular.

And we have automated this in order to bring down the cost and extend our capabilities industrially. One of these is called — or the general term is — multiplex automated genome engineering or MAGE. And this has one particular implementation shown on this slide but there are many others. You can see it's a catch-all phrase. This one uses single strand oligonucleotides that use computer-aided design to optimize secondary structures, optimize the position and length. You have to have a mismatch repair turned off for some of these. And there's a special proteins.

But the key point is in a few years, we move from an efficiency around 10 to -4; 1 in 10,000 to 25% to 100%. And now we can get up to 8 mutations per two-hour cycle and we can just continue the cycle, 8 changes precisely in the genome wherever you want. You can make up to 1 billion different changes in a population. I'll show you an example where we did 100,000.

This is Harris' prototype. A computer aided design of the upgrade.

This is the actual upgrade. This is applying it where we made 100,000 genomes, not one by one, but in a mixture. And it shows the awesome power of accelerated evolution in the laboratory, where we could make these 100,000 genomes focusing all of the changes in the known pathways, including putting in some genes from other organisms. And in three days, we can get the highest yields we have ever seen for this hydrocarbon lycopene which makes tomatoes red is involved on the order of 24 genes.

Another project that we have done which is less binational and less evolutionary and allows new amino acids and has safety features, here we changed all of the codons TAG into TAA genome wide in order to free up that codon and allow us to delete the cellular factor that recognizes it. This can be generalized. There are 64 codons of these triplets and we have targeted nine of them. This allows us to do three things. New amino acids, safety features and multi-virus resistance which itself is a safety feature. We have these nine. We have done one of these nine codons that we're targeting out of 64. We have synthesized all the DNA to do the remaining eight, at least proof of concept on the essential genes.

And another topic that is far beyond what we can talk about today probably is the project where we're making ribosomes and Craig alluded to an in-vitro system which has interesting commercial applications. The key thing here is just changing these nine codons would require changing just 2.7% of the genome, not the whole genome. But if we're making these optimal 90, we have compiled the genome two and a half fold over and we essentially have remade the genome, even though we've only changed 2.7% of it. And that lies in the future, and it remains to be seen which is more efficient. Doing it all synthesis all at once where we'll probably have multiple failures, or doing it one at a time.

And just as a quick last slide or two is this issue of safety in terms of isolation. You can have physical isolation or you can have biological isolation. The changing of the genetic code, the genes can neither go out or come in that are functioning. The critics of the genetically manufactured organisms have wanted it for years. Hopefully we can provide it.

A third way that it's isolated is physical and genetic and it's this metabolic dating back to the early days of recombinant DNA there was this acid that was used by deleting the biosynthetic pathway that you made the bacterium dependent upon that. It's not common in the environment, but it does occur. And that's one of the down sides. Some of these other SACB or tox-antitox pairs are used but as counter selections. But they are ways of having the cell self-destruct but they have the problem that they can be lost just before you need them. So they are not ideal. So we think going forward using the new genetic code to allow us to design multiple essential genes to have multiple dependencies that have been used in Peter Schultz's group.

So, in conclusion, just to remind you, you know, where we think we need genome engineering and synthetic biology, it's in making biology safer than it already is and this involves really using some of the lessons of other engineering disciplines, interoperable parts, hierarchal designs, computer-aided designs, cost effectiveness, standards, isolation, testing, redundant systems, surveillance very important, not just surveillance of government grantees — licensing at every part of the ecosystem. And focusing on this ability to evolve both in the lab and outside the lab.

Thank you.

Jim Wagner:

George, thank you for that. Your message is loud and clear in the face of advancement and technology advancement is astounding. And some near-term applications are very exciting. And also clarifies and I appreciate your last slide. And it was used before to help clarify for us what some engineering challenges are going forward.

Our final speaker in this panel is Kristala Jones Prather. Dr. Prather is an Assistant Professor of Chemical Engineering at MIT and has worked in industry as well as academia. She has been recognized for her work with numerous awards and investments. She is a Research Young Investigator and received Technology Review's TR35 Young Investigator Award. She has also the NSF investing in her through an NSF Career Award. She's an investigator in the multiple institutional Synthetic Biology Engineering Research Center funded by NSF.

Welcome, we're pleased to have you here.

Kristala Prather:

Thank you very much. Let me start by thanking the commission for an opportunity to come and speak to you today.

The title of this panel is "Applications in Synthetic Biology," and what I'm going to do is try to give an overview of what recent accomplishments in the field have been. And I've done this by selecting a few representative papers from the literature. I hope what we can learn by that is both what we have done today and we can start to think about how that may project forward into what potential achievements or applications of synthetic biology might be in the future.

Unlike George, I am going to start with a definition. You have heard a lot of them and you have heard — I think what's clear is there is, I will say lack of universal agreement on what synthetic biology is and how it should be defined. I'm going to give a practical definition, one we use within the SYNBERC research center. It's very simple, goal-oriented definition, and it says that synthetic biology is about making biology easier to engineer.

You have heard some of these things before, particularly this morning. And in the first session about the relationship between biology and engineering and how they interact with each other. For us in particular, it's about applying engineering principles to biological systems, and it involves words like design, modeling, and characterization.

I was trained by Jay Keasling and there's a well-known cartoon that Greg Stephanopoulos at MIT used to show in which there's a group of students in the class and a student raises her hand and says "what's the difference between metabolic engineering and genetic engineering?" And there's a professor who says, "Lots and lots of math." And then there's a picture of the professor and no students.

There is in engineering this idea that we like to have models of systems that are numerical and mathematical. And it's an attempt so we can have this loop back and change your model and see what the new characteristics are. So I think that is a part of synthetic biology, which has traditionally been different from genetic engineering. But

it's not wholly distinct from what you may know as systems biology. Again this effort to include math and the ability to predict and design and what we do. And we'll highlight DNA synthesis as an enabling technology.

You'll see from the first few slides that if we're talking about making biology easier to engineer and we want to get started with that now and based on I thought what Drew gave was a very good slide of the technology gap, if you will, between the ability to write DNA and to know what to write on DNA. Much of what's happening now under the umbrella of synthetic biology is using DNA synthesis at a very minimal level because we have to start with some existing biological substrate. In that vein, if we think of this goal of engineering biology and what is our biological workspace?

We heard about microbes being the substrate of choice because of their relative simplicity and I'll use relative quite intentionally because we're still talking about very complex organisms even though they are less complex than the million cells which you see there and also plants. And if we think about now from an applications perspective, if these are biological substrates that we want work with, then applications may I think become pretty clear in terms of extrapolating from that. We can think of therapeutics that include pharmaceuticals in terms of small-molecule pharmaceuticals as well as biologics or what's referred to as biopharmaceuticals. Essentially protein therapeutics are more complex agents.

Energy, especially fuels, but not exclusively — and I'll give a brief slide on that. Chemicals which may be part of the pharmaceuticals but leading toward thinking of new ways for materials to have renewable materials, things to get rid of other polypropylene bottles which will fill landfills if we can't figure out good ways to recycle.

And agriculture when we think about the biological works of plants and the potential to extend with genetically engineered organisms for agriculture. With this paper here that we have heard about already, which is the work from the Keasling lab from the University of California at Berkeley, producing the antimalarial drug, artemisinin oxide, which can be used for an antimalarial. This was funded as the numbers have come up. I am sure we can all recite them. \$42.5

million from the Gates Foundation as something of a public-private partnership between UC Berkeley and Amyris which was a company founded by folks from the Keasling lab to develop this technology.

One of the unique aspects, intellectual property came up previously. There were lots of issues because the University of California had to agree to make the licenses available essentially free and the commitment by all parties involved is that they would develop this as a remedy for at-cost production. This was to be a non-profit generating venture as far as the company is concerned.

Amyris, if you have been keeping up with the literature, has sort of transitioned this process. It's now in the hands of industrial manufacturing and they have switched their focus almost exclusively to fuels. So it's an example of how the basic technology of these achievements and what we're able to do with engineering of biology with synthetic biology, with metabolic engineering, whatever particular phase you want to use, builds a repository of intellectual information and intellectual property that can be then converted into other downstream applications and in this case from therapeutics to fuel. We have talked a lot about microbes. That work was done in microbes.

There are efforts and achievements in synthetic biology going into increasingly more complex systems. This is a paper from Martin Fussenegger's Group at the ETH in Zurich about developing effectively a circuit to control gene expression for implants. So the idea was they were able to take pieces from microbial cells to put together a regulatory element to respond to a particular molecule that they then put into a skin lotion. They could have subcutaneous implants. If you applied this lotion, you would get gene expression. This notion of a circuit to control expression of a gene from the introduction of a small molecule, this is now an example where we can think about how that actually has potential applications in medicine in terms of being able to activate gene expression perhaps with novel forms of gene therapy that, in a way, would be a subcutaneous implant so you're not talking about trying to modify the genome with more I would say complex perspectives of gene therapy where you're looking at, for example, removing stem cells and reengineering them and putting them back into the cell. This would be a separate implant that would be distinct from the native or the human chromosome.

Moving on to the field, I have already mentioned Amyris work. This is work from Jim Liao at the University of California in Los Angeles that was published in "Nature" a couple of years ago for making higher order branched alcohols as biofuels. This is technology that's been licensed by Genomatic. Dr. Bassler mentioned and if I can paraphrase from going to scale and optimization and getting something industrially viable, this is the case where this work was licensed by a company and they are actively working to commercialize this process. Similar to the work done that we have heard about before, these are pathways to a certain extent are all natural. The molecules being produced were ones being identified as minor products in wine fermentation so the enzymes or the genes needed in order to convert what ends up being intermediate amino acid synthesis were optimized in the most promising was 22 grams per liter of isobutanol being produced.

This is a screen shot from a LS9 website. I wanted to highlight the fact that they really do talk about themselves as being a synthetic biology company, being able to take advantage as one has already referred to of all the extensive information that's come to us from genome sequencing projects but increasingly the tools and technologies that we're developing and being able to take advantage of that had have to do with synthesis and construction of biology. They are focusing on fuels, but also on biochemicals.

This is an example I mentioned before in terms of energy but not being fuels. This is a paper from April of this year from a lab at MIT where again because of the multiple definitions of synthetic biology we may or may not think of this as synthetic biology. But it just describes briefly what was done here. The Belcher lab at MIT used M-13PHAGE as biotemplating devices. They were able to use them and the PHAGE interact with inorganic often metals and able to form these higher order structures. This is a case of biological inspiration and biology as a template for making these nanostructures.

We could certainly think about how to expand that towards now having the power of synthetic biology and constructive biology to be able to redesign these phages so the structures are complex. And the particular application was to be able to put together a light-driven hydrogen splitting structure that would allow you to have effectively

photosynthesis. And they had the idea you could use this for energy storage and capture the hydrogen from the splitting of water and that hydrogen can be stored and used at a later time. Whereas in traditional solar energy you have available when the sun is out and don't have it available when the sun is not out.

This is work from my own lab in collaboration. In the chemical space what we were looking at is being able to make a pathway for a compound acid where we don't actually have a natural metabolic pathway for this compound. This is different from the work I presented previously on the branch of alcohols where we weren't starting from a pathway and trying to reconstruct. We started here's a compound we want to make, how do we think about doing that? The particular innovation in this case was to be able to use these novel synthetic scaffolds.

And Dr. Bassler mentioned the wonderful spatial organization that happens with a naturally occurring system. This was a synthetic device designed to introduce this spatial organization into a microbial cell. And the result was to have increased productivity for the compounds we were interested in. And I want to refer to biological computing or a lot of the analogies to programmability. The first of which was a program about 10 years that described the repress later. And also from Jim's group, the first was from Princeton and Mike Elowitz now at Cal Tech, the synthetic gene metabolic oscillator which was called the metabolator, which is often a fluorescent protein.

This is oscillations in levels of a specific metabolite. Now going from again microbial systems into mammalian cells and this was referred to by Dr. Bassler and is now looking at these oscillators and genetic clocks taking advantage of intercellular communication. And this is often discussed and sometimes derided as toy applications and you're just making cells blink. What is that good for? From my own perspective from making these that make high quantities of synthetic chemicals, we're interested in these because we know that timing of gene expression is important for some systems that we're looking at. So we can look at oscillators that have been designed even with clean production proteins and think about how do we extend those into practical applications of systems where we're using them either in therapeutic purposes in order to have time expression of genes, for

example, in development, talking about stem cell biology or even in like a large bioreactor talking about chemicals.

The last sort of screen set I have is the paper that again was sort of the impetus for this particular discussion from the Venter group which you have already heard about. And I just — my comment I wanted to make sure is all the things I have talked about so far, you may be thinking what does that have to do with synthetic genomics and the ability to completely synthesize the bacterial genome, what I would say is: this is about trying to bridge this technological divide. What we currently have is the capacity to do very extensive reengineering of genomes from existing cells, taking out lots of genes. Putting in lots of genes. Beyond that, where the challenges often arise or how do you precisely control them, temporally, spatially, all these other issues about natural biology, they are complex and very confusing for us.

What you have here is now this very clear synthetic capability. And where I see this bridging is that as we get better and better at understanding how to do the kinds of engineering we're doing, then it really is about the differences in scale that Dr. Bassler referred to this morning, that we can think about now going from making these manipulations at the level of an existing genome towards designing them de novo and starting from scratch with a genome that works the way we want it to work. The final comments is: there are, of course, lots of challenges. Biology is complex as we have heard over and over again. I'll add it's often context dependent. We do have the stream of having interchangeable interoperable parts. I'll say from personal experience, you move them from one cell to the other, they don't work the same way. And that's exciting. It's a challenge. It's something that we have to become better at understanding.

The synthesis capabilities, as you've already heard, far exceed the design capabilities and that's a technological gap that does, in some way, point at what our future ambitions are but indicate what our current limitations are.

The potential benefits I think are enormous. I indicated a few of these, but, you know, we can think about this in any way where we think about biology being important. At the same time, the risks are real. Because there is this information gap between what we really un-

derstand about biology and what our capabilities are, it's impossible for us to really predict what's going to happen in every single experiment. And so I do think it's very worthwhile to think about being as careful as possible as we do this to minimize those risks.

And, two seconds over, I'll stop.

[AUDIENCE LAUGHTER]

Q & A

Jim Wagner:

Very impressive. Thank you very much for that list, and also ending with a challenge that we have ahead.

Keeping with the format we used before, I have asked the commissioners to get their thoughts together.

But I'll return the favor, Amy, if you would like to offer the first question.

Amy Gutmann:

Thank you very much. And thank you all.

Let me begin with a question to Craig, if I may. The potential power of synthetic biology creates hopes, and it creates fears. And we're all too well aware now of the fears. But I want to begin with the hopes as well. So you mentioned the one-day production of a vaccine for flu, for example.

So here's my question to you: What is the single hope that we should most believe in from synthetic biology moving forward?

And it would only be incumbent on me to ask you the same question with regard to fear: What is the single fear that we should take most seriously?

J. Craig Venter:

Well, they both give me wide latitude, so I appreciate that. I think.

Amy Gutmann:

Don't make it too wide.

J. Craig Venter:

On the hope side, obviously, what our own team and others are trying to do as well, we need new tools to make new medicines a lot faster — particularly, vaccines. It took quite a while with H1N1 to get a proper response, in part because the rate of building and deciding on seed stocks and in part because we're using 100-year-old technology with chicken eggs to produce vaccines. Both need to change, and quickly.

But with rapid sequencing and all these changes in reading the genetic code, and now the ability to quickly write the genetic code, it's now hours instead of weeks and months to make new seed stocks. The potential applications because we can design cells with hundreds to thousands of energetic variation, diseases like HIV that they were chatting about with that change their genetic code very quickly. The rhino virus, we don't have a vaccine against the common cold because the virus evolves rapidly. Designing things with the same rate of evolution or covering the spectrum of energetic variations gives us whole new ways to approach vaccines that never existed before.

On the environmental side, I think it's clear we need to do something different in the environment as we go from 6.5 to 9 to 10 billion people. We can't keep doing what we're doing.

So attempts, all these different attempts, they all need to be successful in creating new sources of fuel and energy and food, or humanity will be irreversibly damaged and altered. So we are a society dependent on science now for our future. Biology is a key part of that future science. Synthetic biology, synthetic genomes are key I hope components of altering that future.

On the fear side, obviously, the worst scenario is what happened in computing because we're talking about software. People make computer viruses that cause a lot of economic damage. Well, we don't want the same mentality going into making new animal or plant viruses — whether inadvertently or purposely. And some of that can

be readily prevented by some pretty straightforward regulations.

But obviously, nobody who develops new technology wants to see that ever produce harm to others. We just would like to see just the benefits. I think the molecular biology community has a pretty good track record for the last several decades because of the guidelines and rules that we have all been working under.

Nita Farahany:

So I also want to direct this question to Dr. Venter. I heard both in your views and in the literature people have talked about the publication in Science as “proof of concept.” And I wanted to understand exactly what it is that it is proving. In part, as I understand it, the cell wall of the bacteria was used in the first generation and it’s a natural organism that has been synthesized. I’d like to understand what it is that it proves and how significant that proof of concept is.

And, second, building on that, looking forward, I understand that you may be working on algae and other multi-cellular organisms where the genetic information is in the nucleus of the cell rather than a single strand. How far away from that are we? Is that the proof of concept that will propel this field forward?

J. Craig Venter:

What’s been possible in molecular biology is what several people have described this morning: changing one or a few genes in the cell by inserting the genes in plasmids. Although some evolve by taking up chromosomes, for example, color has two chromosomes from two very clearly different origins so they probably happen through these kind of processes.

But never before have we molecular biologists been able to take an entire bacterial chromosome, an entire chromosome of anything other than a small virus and transplant into a cell of one type and convert that cell into another. Then you add to that, starting with the digital code in the computer making the entire chromosome from scratch means now we have the means to start with that digital code and make dramatic changes. While we had built upon the base of an existing organism, we made changes to it and inserted the names of 46 authors, several quotations. It’s the first genome with a first web-

site and web address. These may seem like trivial changes but identify it as a synthetically made chromosome something we think is critical for this field. And we activated that and completely transformed that one cell into a new cell.

It was not trivial. One base pair being wrong set us back three months. One error out of a million base pairs did not enable this to happen. So it's now, because it's a proof of concept, we do know how to do it. And now we can make much more extensive modifications.

So we're building a robot to do combinatorial synthesis instead of making one chromosome over 10 years, our goal is to make 1 million or so a day by randomly sorting genes or selecting very specific ones, selecting living cells that you can't get. It's not a species that existed. It's very closely similar to a pre-existing cell, but it grows substantially faster because of the 14 genes we eliminated.

Nita Farahany:

... and on the multi-cellular front?

J. Craig Venter:

There are a lot of eukaryotes, a lot of algae are in that category. Moving nuclei around has been done 50 years or more. Changing the DNA in the nuclei and replacing the DNA we don't think will be a huge challenge. It's probably easier to replace all the chromosomes and eukaryote yeast by replacing them one at a time with synthetic DNA.

Jim Wagner:

Thank you.

Nelson Michael:

Dr. Venter, do you think it's fair to say that, you know, in the very elegant transformation experiment, that really that's how I read your paper first on that day, I saw it as, you know, probably the world's most elegant bacterial transformation that had been done to date.

I think I may be trying to clarify what Nita was driving at: you need, today, to collaborate with existing life in order to make that transformation experiment work. And while it's true that after several replica-

tions, all components, not just the proteins of that cell, were obviously derived from what you had produced in silico and printed out, it did require collaboration with existing life that had been derived by natural selection ...

J. Craig Venter:

Absolutely. So we're starting, as I said, with the 3.5 billion years of evolution. We used that starting system to read the new genetic code and start making all the new proteins. As I said earlier, I think it's an interesting scientific question how few of those components we can get away with. As I said, perhaps just a ribosome, some polymerase, TRNAs, a few lipids. So, you know, when people evoke that you start with existing life, it takes us back to vitalism, that people try and amazingly, the New York Times has tried to reinvoke vitalism. Most scientists view it as having disappeared 8 years ago as a concept and certainly with DNA being the material coding for everything, there's nothing vital in the cell other than the ability to read that new software. So we are clearly software-driven machines. That software is DNA.

Christine Grady:

First, thank you all very much for your comments.

I would like to ask Dr. Venter: This is an important scientific step, but as you described what you have been working on for many years, you also described a process of thinking about the ethical issues right from the very beginning. So I am wondering if you could say, from your perspective, what has changed now ethically, if anything.

And, building on Dr. Atkinson's question earlier, where you think — I think you mentioned we need an intelligent ethical-legal framework — what are we lacking in that regard? What do you think we can do to help in that regard?

I'd love to hear others' opinions on that as well.

J. Craig Venter:

I think it's a very critical question. It's not clear that anything has changed so dramatically as what some people describe as minor changes in biology with minor but significant changes in the ethical

and legal framework, primarily because the way we control who has, for example, A-list agents and has been controlling who has access to these agents.

Now, if all you need is the genetic code in the computer, it totally changes who has access and how you get access to them. If students can order anything from a DNA synthesis company and there's no tracking of what they order, some could try and make ebola virus which is only 8 genes or at least the DNA. The DNA is not infective but I'm sure if Homeland Security started detecting an ebola virus DNA, they'd probably get upset.

Those would be the kind of hacking things that we don't want to occur. I think those can be pretty much eliminated by requiring companies to screen against A-list agents and requiring bona fide institutions to be doing this work versus being done in somebody's garage.

I think creating new life forms — I think what we did is as much a philosophical step as a scientific-technical one — because it now opens the window for literally merging the digital world with the biology world, and because anything that's totally open-ended, we think there's some guidelines that are needed.

I think it's sensible to start in that framework, so that we don't get the negative consequences or the unintended ones from lack of paying proper attention.

Jim Wagner:

George, you have written on this as well. Would you weigh in, please?

George Church:

Yeah, I'm not sure whether this is an ethical or policy issue. But many of the previous discussions, the conclusions have been we should have more discussion. And I think that we are actually in a place that we can do more than that, which is to focus on licensing and surveillance.

And I don't know whether that's a new — whether that's ethics at all, much less a new one.

What's happened since 1999 is this exponential curve has gotten steeper. And I think that's something you can't ignore. So I would say that it's time to go beyond having more discussions.

Dan Sulmasy:

Following actually on that, it seems to me we have heard a lot both from the previous panel and from the three of you about the widespread availability of various codes, the "ability to do it in your garage." But that seems to me to refer to the obtaining of the sequences and perhaps the synthesizing of those, and that generates worries for people.

But the question I have is, how big a step is it — and you have alluded to this, I think, Dr. Venter — from having the sequence to actually getting it to work in a biological system? And is that gap big enough that we shouldn't be as fearful as we are of the possibility of this being misused because we could in fact have regulation or safeguards at that step that would be very helpful?

True or false.

J. Craig Venter:

That wasn't a yes-no question. I'm sorry.

Amy Gutmann:

You have a 50% chance of getting it right.

[AUDIENCE LAUGHTER]

J. Craig Venter:

Then I'll say false.

I think with each new cellular system, and by the way, the micro plasmas don't have a membrane which made it simple to get the DNA across. What we are trying to do with synthetic algae right now is maybe using a plasma membrane to transform things. We're at the earliest stages. We need to see how extendible these tools are.

Getting DNA past cell walls may be very tough, but there are other ways to get around things. The two areas go in parallel. One is the

design and the synthesis and the other is booting it up. The biggest worry was we were going to have this really nice macro molecule, the largest one of a defined structure ever made, and we couldn't activate it in the cell. We were there for a long time because of one single error in the genetic code.

So, I think it's going to have to be optimized for each individual biological system. It's totally different getting DNA into plants than it is to bacteria and totally different with cell walls, without cell walls. What I think is that this is going to be a rapid expanding area of research and probably difficult to regulate. I think the guidelines that get set up for approving projects at the institutional level with broader guidelines at the funding level — and even though our work was not federally funded because my institution is a major federal grant recipient, we have to follow the Federal rules regardless of whether it's funding that particular research.

So, I think the way molecular biology has been practiced, particularly in this country, has been I think a wonderful example of how to proceed, but expanding the repertoire and expanding some of the ways we monitor things.

Kristala Prather:

Yeah. I may be misinterpreting the question, but so the information is free. You go to the database and get as much sequence as you want. It is cheaper, but still not trivial to actually pay for synthesis.

So my lab does not yet, as a matter of practice, pay for synthesis of everything. We still do a tremendous amount of PCR. I just had a meeting with a student a couple of days ago and said, "Okay, you can get these things synthesized and it's going to cost about \$3,000 but you can't get the 12 other variants of it synthesized that you want because, now, we would be talking about \$36,000."

So as far as access, some of it is thinking to the future in terms of if we go — certainly we're not at \$10 a base as George showed but we're under \$1 per base but not at a dime per base, at the level of small amounts of orders. So you can do negotiations with some companies to get things on the order of 10 cents to 25 cents a base if you want a lot of sequence.

So because of that, I think again I may be misunderstanding your question. But I think there are different answers in terms of whether or not you're talking about institutional access versus non-institutional access, skilled labor versus unskilled labor.

In terms of access, because of the cost, I still think that a lot of the — “fear” was the word used earlier — the things that may evoke fear and apprehension are still beyond the cost of most non-institutional players.

And then because we're really talking about difficult biology and one base pair mistake setting you back three months, there's still a big difference between what you can do as a skilled practitioner versus an unskilled practitioner.

Dan Sulmasy:

Just to follow up, I appreciate hearing that it's a little more difficult than just doing it “in your garage” to get the sequencing done. But I was talking about the next step and whether people can do that “in their garages” — of getting that to replicate inside a cell and how difficult that is and what material is needed there and whether that's an important place in which regulatory safeguards could be placed to make sure this doesn't get into the wrong hands.

Kristala Prather:

So, at the simplest level, and if you read some of the blogs and the popular press, everybody wants to make things glow. You want fish that glow. And it's like, “Let's put fluorescent protein in anything you think about.” It is relatively inexpensive and on a skill level relatively easy to order a gene that would affectively be a plasmid that encodes for green fluorescence with a motor on one end and terminator on one end and transform a simple bacterium in your garage and say, “Hey, it glows!” It's very difficult to make your dog glow.

So again, we're still talking about a level of complexity there. And the one gene, being able to transfer one gene and getting that to work in a garage with a junior high school student, pretty close to trivial.

The types of things that the Venter lab did are not going to happen in

the garage with 14-year-olds.

[AUDIENCE LAUGHTER]

Raju Kucherlapati:

Thank you very much for your presentations. All three of you really talked about the need for some level of regulation. And I wonder if you could comment on whether all of these different things that fall under the definition of synthetic biology are already covered under existing regulations because certainly we have regulations of how to handle anthrax or ebola or other types of things.

Do you feel we need to have different and new types of regulations to deal with the issues of synthetic biology?

George Church:

We certainly have recombinant DNA regulations. Many of these depend on the person practicing and having federal grants or in some other way being a responsible citizen.

I think what we don't really have is surveillance that the regulations are being obeyed by all citizens, not just the standard members of society.

And I think we also don't really have many regulations about safety testing as we make things that either are intended or could accidentally get into the environment. I think as safety testing, we take for granted in many other engineering disciplines, there's relatively little of that in biology.

It probably doesn't require major overhauls but I think there are some gaps that we need to pay attention to.

J. Craig Venter:

There are really no limitations on what you can order from an oligonucleotide synthesis company. At the present time, they are not required to screen against any list of agents. Some are voluntarily doing it now.

And it's not just a U.S. problem. DNA synthesis is a global effort. If

you can't get what you want here, you can order it in Germany or you can order it in India or get things made in China.

You can buy DNA synthesizers off of eBay.

So maybe there are, as people said earlier, four companies that are probably 90% of the synthesis in the U.S., even though they are not all in the U.S., requiring them to screen against A-list agents, requiring them to have bona fide credentials of the ordering institution, I think are things that could go towards preventing the frivolous use.

There is a lot of home-brewed biology being done in kitchens. It's a new trend. I was pleased to see that Drew Endy stopped doing it and encouraging biohacking. You know, we want some reasonable restraints on that, without destroying this wonderful creativity that these kids are doing to come up with some new circuitry that could totally change what we work on.

But I don't think it's covered by any of the existing regulations.

Raju Kucherlapati:

Just as a follow-up, you know, in the kinds of experiments that you published, it is possible to be able to take 100 mers that nobody may be able to recognize and may come from a pathogenic organism and you could order a bunch from one company and a bunch from another company and be able to put together?

J. Craig Venter:

At the level of 100 mers or anything over probably an 18 mer or something, you could get a pretty good trend of what somebody was trying to do. The signatures are pretty clear-cut.

George Church:

Also, these companies are beginning to coordinate voluntarily. This is something that would be nice to be backed up with regulation. But they are voluntarily coordinating their efforts. So, if someone split their order over four companies, that in and of itself would be an alarming event, which combined with the sequences that could be recognized, I think you could put the story together. But it will be ongoing efforts to get around that.

Amy Gutmann:

How quickly will you put the story together realistically?

George Church:

Well, if it's entirely based on computational algorithms pretested — and I emphasize the importance of testing — you could put it together in hours — especially if you have got government agencies that are willing to act in hours.

Alex Garza:

I think you have gotten to the heart of a lot of my concerns. As you probably all know, there was a strain of anthrax that seems to be becoming a low hurdle to overcome in the ongoing biological processes.

I have heard a couple of different things. One is that this is still difficult to do, very difficult to do. But the second part is that it's getting easier. And so I think that Raju brought up an excellent point: there are regulations in place now for I think what we would consider traditional biology being able to reproduce organisms and select against agents that are on the biological toxins list.

However, we're talking more about the biobricks now which, quite frankly, are not part of the regulation. So what concerns — and I think you have expressed them here — concerns we have about this evolving technology and getting around the BSAT [Biological Select Agents and Toxins], the security measures that we would need to take to make sure that these would not happen, and what is the balance?

You have probably been privy to the discussions of the latest BSAT, in balancing scientific discovery versus security for the American people.

George Church:

I don't actually think that this is a trade-off between security and scientific discovery. I think if this is properly implemented, where most of the effort is in developing computer software and getting compliance at the company level and getting surveillance at the government level, the researchers in a certain sense shouldn't even see it. It should be transparent to them and they can get on with their work.

On the other hand, if you require them to sign a piece of paper every few minutes and every time they type something, you could interfere. I think that's unlikely that's where we would be going with this. I think some serious computational efforts are in order.

Barbara Atkinson:

I am interested in the money behind it all. It's a very expensive proposition now to come up with money for a new cell, as you did — over \$40 million — or for new products. And it is mostly funded now in small biotech companies and with venture capital kinds of money. Are there recommendations for being able to encourage the entrepreneurship, while not having so tight control on it that you can't get a payback to the amount of money you spend putting into a project and can't get that payback fairly quickly? Versus being able to also encourage entrepreneurs to work on projects.

I mean there's going to be huge profits in this, if it would work out the way it is looking like it might work out in biofuels or energy and so on. I just wondered if you had recommendations or thoughts on what the commission should recommend on those issues.

George Church:

Just my opinion is the current system is actually quite healthy. In contrast to the one that Rob Carlson described, most of my experience with dozens of companies is they can get the job done without spending a lot of money on lawyers. Very often you don't really even need the patents in the end. It's the know-how that's incredibly important.

I have very few examples of a patent getting in the way of academic research. And generally, not even in the getting in the way of start-ups as well. This is such a vibrant field that people are inventing so quickly, that they invent around or don't even concern themselves. I think it's actually quite healthy and going from small to large is happening quite quickly, too.

Craig mentioned Exxon and the case of LS9 and they have Procter & Gamble and Chevron. This is in theory a short number of years. I think in my opinion it's healthy.

J. Craig Venter:

In fact, if I can add briefly to it, it's healthy and critical.

I think if all these bets are right that everybody is placing to get proper ecological benefit and change the use and dependency on taking carbon out of the ground and burning it and putting it into the atmosphere, we need things to work economically. And I think there's a healthy investment climate in the U.S. despite the recent changes in the stock market. They have stepped in where the government hasn't. Most of the advancements in biotechnology have come with companies like Genentech. In our case, we would have been stuck back in 2003 with a small synthetic virus if we did not have independent money from starting Synthetic Genomics to fund this work at the not-for-profit institute.

Kristala Prather:

I would only add to that I think one — so I agree with what's been said. I think one of the impediments to progress, if you will, that can arise if all of the achievements are done individually, is one of the very big goals of synthetic biology is to have standardization and interoperability.

One of the ways the federal government can help with that is to promote in some tangible way an effort for the community to be able to organize on a regular basis around what those standards should be, so that you don't have innovation happening in isolation in a way that you have very great technologies evolving independently and to network those and interface those becomes very difficult.

As we dream about synthetic biologies — and you see the Lego kits all over the place as a good analogy — that works because you have standardization and you know you can get Legos from anywhere and they are going to work together.

That's an effort I think has been more difficult to get real support for. Because it's not ... It's fundamental. It's foundational. And it's enabling, but it doesn't, in-and-of-itself, get you biofuels, and it doesn't, in-and-of-itself, get you new vaccines. It facilitates all those things, and sometimes there is a gap between the foundational more engineering-oriented standardization work and the applications-oriented things which can be very interesting and attractive to investors.

John Arras:

I want to begin by thanking all of you three for excellent presentations. I have got a couple of concerns or questions for you.

One has to do with the fact this is all now accessible on the Internet and it's international. So if we're a commission set up to think about regulations here in the United States, I'm wondering what the context of our deliberations should be if these activities are really taking place all over the world. So, you know, I mean what sort of international collaboration has to take place for U.S. regulations to have any real effective bite? That's the first question.

J. Craig Venter:

I think it's a critical question because science is international. These tools are international. The Internet is international. And I think first and foremost, the U.S. can set a good positive example.

That didn't happen with stem cells in the recent past. And research expanded overseas at the expense of research in the U.S. I think we can do the opposite here if we do it intelligently. The same concerns that we have here have been expressed in the EU and basically every country I visited around the world.

So, I think if there's a positive example of how to deal with things — that would be a good start. But it has to be international ultimately to have any impact.

John Arras:

Thank you. A follow-up question about the role of industry: There has been some talk around the table about the movement from small to large, right? So, listening to all the panelists, you get that picture that we're currently living through an era, a kind of "Biological Woodstock" with people experimenting in their garages and so forth. But the movement will be, as it's been in the pharmaceutical industry and computer industry, from small to large. And so I'm wondering: what the implications of that might be with regard to access to the goods produced by this industry?

We have seen in the area of pharmaceuticals, a lot of public concern

about the patent system and the rules and regulations relating to access, particularly with regard to access to life-saving drugs for diseases like HIV, where it's perceived by many people that the patent system is working against access to life-saving medications.

So I'm wondering if we have anything to worry about that's analogous in this area. In other words, should we be worrying now about the synthetic bioanalogs of Microsoft and Pfizer limiting access to knowledge and limiting access to the goods that are produced?

J Craig Venter:

My answer is quite simple: No, I don't think there's any worry at all.

In fact, the worry is in the opposite direction. If we don't get the things that really work at a commercial level, this is an interesting academic field. Publishing a paper in a journal like my team did in *Science* is great for understanding the concepts. But converting it into reality where you can buy fuel at the gas pump made from carbon dioxide instead of from oil out of the ground will only work if that's done in an economically competitive environment.

LS9 and these companies, Synthetic Genomics, will only survive if they have economically competitive products. Unfortunately, most people aren't going to buy things just because they're better for the environment. So any new fuels, for example, have to be available and they have to be cheaper than existing fuels or at least cost competitive with them.

So we need economic driving forces to pull this stuff much more rapidly than is currently happening. I don't see any limitation of access. We need access pretty rapidly to CO₂-based fuels as an example.

Jim Wagner:

Before I go to Nita, I don't want a thought that was dropped, Kristalla, that you brought up and connected with something to George. There's the flip side of regulation. And that's stimulation.

Will one of the effective ways to ensure safety to be the sort of a way to be able to skate ahead of the puck, know where the puck was going? Were you suggesting, Dr. Prather ... ? — Maybe I should leave it

open.

The question that we had sort of posed in the prior panel to you was: What would be the very next thing to be funded? In view of being able to have a knowledge base and an ability both to advance the applications of the kinds you have all been talking about, but to have a deeper knowledge to help ensure that we can recognize as Dr. Church mentioned some of the potentially sinister applications of these things.

What would you fund next? Would it be your standardization?

Amy Gutmann:

You're not allowed to answer your own lab.

Jim Wagner:

Yeah, that's fair enough.

What's the second thing?

Kristala Prather:

It's a difficult question. So I think about, for example, the BIOFAB which Drew Endy is directing which has the ambitious goal of being a focal point where you can develop "parts" to use — a term in synthetic biology — discreet pieces of DNA in code for some biological function. And you can characterize them, understand them, see how they behave, and see things like composability — what happens with this thing and the other thing? And I think it's a very ambitious goal, and I think it's great. And they have got like \$2 million in two years. And so what happens when that's gone?

So I think that there's a need for an effort that is more ambitious in scope and much bigger in scope to say, okay, let's bring—that it does two things: One is that it can serve as a forum, if you will, for bringing different players together and brainstorming and saying, "Okay, here's what I'm doing; here's what you're doing; here's what this person is doing. How do we get those to interface in a way that we can actually set a standard moving forward so that as new technologies are developed, we know they are going to fit in very well?" And then how do we set priorities for ... For safety, yes.

And so I'll jump ahead to a thought. You know, I think one of the things that's been very nice about the SynBERC experience is that we have had all along discussions about the thrust called human practices that deals with biosafety and biosecurity and intellectual property. But that is a very, very small number of people. And what's becoming an increasingly populated academic field. If you look at the number of people associating themselves with synthetic biology, it's grown astronomically over the past few years. And so there are questions in terms of if you are focusing and if you take NSF's investment into SynBERC and take DOE into the joint bioenergy institute, you're talking about real money. We're not giving it back. It's not trivial but a very small number of people it's impacting.

I'd like to see efforts to bring the community together in a way that we can think about what the next steps are going forward and that we can be more progressive and proactive as opposed to reactive in saying, "Well, you did it wrong, so here's my other way to do better." We're in the midst of that now where it's a bunch of people going back and forth between "I did it this way; that way is all wrong. Here's why it's all wrong." And I'm not saying that won't eventually get us to where we're going. But if we want to be able to bridge this technological divide and say we have exciting technology and the potentials for the impact it can actually have on human existence are very real, we need to be able to move that forward more quickly.

Jim Wagner:

Thank you. Craig, did you have a comment?

J. Craig Venter:

The two questions I get more often, most often when I give lectures on this topic is: people are worried about bioterrorism and environmental release. And it depends where you are which one is first or second. And so George gave some wonderful examples of safety mechanisms that could be built in. It would be nice to have orders of magnitude more. We're trying to build in suicide genes to organisms. If we're going to have large algae plants made from genetically synthesized or modified organisms, they need to not be able to survive in the environment on their own.

Suicide genes, chemical dependencies, using artificial amino acids so they couldn't possibly grow in different environments, expanding the repertoire of what is safe and secure I think would be the most beneficial thing out of any government funding.

George Church:

I'll just quickly add — and I think coupling this question to the previous one of small versus large: Larger has safety advantages. It's only once we got to the large manufacturing of automobiles that we really started getting very high levels of safety. And furthermore, as the technology gets to a certain point, amateurs stop making it. So, you know, I made a computer when I was young. I wouldn't bother to make one today. The know-how starts to fade away at the grassroots level which is a mixed blessing. But from a safety standpoint, I think it's incredibly important.

Jim Wagner:

Certainly, since we're taking so much of a lead from engineering, it made me very proud of my heritage actually today. But one thing that has been demonstrated in so many physical systems is that it is far more effective to design in safety than it is to try to regulate in safety. That was the basis for those questions and very responsive. Thank you.

Nita, I think you're next. Anita is next?

Anita Allen:

Thank you. I really have appreciated all these remarks.

I wanted to ask Dr. Prather a very specific question about something that you said toward the end of your slides. You had a slide in which you made the intriguing point that our synthesis capabilities exceed our design capabilities. We know how, but not what. Could you elaborate?

The reason why I want you to elaborate is because I'm wondering that we know how but not what points to some limitations on the applications that may be forthcoming from this science.

Kristala Prather:

It absolutely does. Simply put, this is all back to comments that Bonnie Bassler made earlier that these are really complex systems that we're talking about. I don't yet know anyone in the field for whom their design works the first time they implement it. And the question is always — I describe when I am sort of giving my pitch to first-year graduate students, they say what we do is to pick molecules we want to build and then we have problems. And your thesis research is all about how do you solve those problems and what do you learn from solving those problems. And we often learn things we didn't expect to learn. Sometimes we run into problems and they go, "Yeah, we figured that was coming eventually."

There are two different aspects of it. One is that biology, even for very simple organisms, is still very complex. So being able to predictably know what's going to happen if you make even a single perturbation is difficult to do. That's one aspect of it.

The other part is the types of manipulation that we're talking about doing are, in and of themselves, somewhat different from what we see in nature. We are mimicking nature but we're trying to take natural components and stream them together in ways that haven't been done before. So there is, in some cases, a lack of fundamental knowledge of how that's going to behave.

So there's a need for experimentation, to actually have the observation that says, "Okay, this is what I observed when I did this particular configuration. Let me make four or five different variants and see those observations and then put it on a graph and see if it's just a random set of points or then if I can draw some conclusion that if I have these specific changes, here's the effect I'm going to get from that."

What the Venter lab group I think has shown that the capability, the capacity to go from sequence on a computer into something that is physical DNA, is there. But if you say to anybody, "Okay, you're free to write 500,000 base pairs, DNA, what would you do?" If most of us want something that functions, we are going to copy something that already exists because we just don't know how to make it all work together. And even the stuff that's working together, we don't know why it's working the way it's working.

Anita Allen:

How can we get better at knowing what — given our genius at knowing how, how do we get to the knowing what.

Kristala Prather:

There are two parts that also came through this morning. Some of it is more information about biology.

As an engineer, I have no desire to interfere with the biologist doing what he or she does on a day-to-day basis to uncover fundamental knowledge of biology. I applaud it and we steal as much of it as we can — with proper credit, of course, so we know where it comes from.

We need biology to have the freedom to continue and the investment in biology to learn this. At the same time, this was alluded to previously, because we have these synthetic capabilities, we have the possibility of doing kinds of experiments we didn't have before. And it's mostly at a pace and scale we couldn't access before. So we can use the tools of synthetic biology to help us actually understand fundamental biology, to have rewiring, if you will, of the cells and see if I make this perturbation what does the change in the input tell me about the change in the output. There are numerous mathematical algorithms that have been developed and more that are being developed to help fill in the black box between what you put in and the output that you can measure.

The other thing I think honestly that's a little more difficult, but it's about understanding. So there is, you know, sometimes a little bit of lack of respect of biologists for engineers and vice versa. Sometimes they think they don't care about making anything work and engineers say scientists don't care about how it works but just care about it working. So bridging that divide and having the understanding, especially for this field, where they really are very interdependent upon each other, moves that forward as well. If we start to have conversations and say, "Here are the tools and techniques and methodologies I'm developing, how does that help you in understanding fundamental biology?" And biologists are saying "Here are things that we have uncovered, parts we have called them. What can you do with those?" If we are able to have those conversations in a way that's respectful

and appreciative of each other's stream I think the whole field moves forward.

Jim Wagner:

I agree. Thank you. Genetic deconvolution.

Nita Farahany:

I want to focus on a couple of comments by Dr. Church and Dr. Prather about the role for government in regulation and promoting the development in this field.

In particular, I was hoping that Dr. Church, you could expand on what you mean by "surveillance." You mentioned a few times you think the government could play a role in surveillance. I'm not sure if you mean active or passive or what specifically you had in mind.

Dr. Prather, when you mentioned "standardization" and the government could play a role in standardization, I'm wondering what you are envisioning? Is it funding or setting up a large initiative like the Human Genome Project like a standardization project? If you could expand on that as well

George Church:

Yes. In terms of surveillance, I think one thing that was hard for the government to act until industry had shown what it was planning on doing. But at this point, I think they could tune into that and help it along and make it law and work internationally. I know that both Secretary Generals of the United Nations have been in favor of this.

So, it's a key time while there's still this bottleneck on synthesis. And not just to regulate, I'm sorry, to allow computer surveillance of orders of synthetic genes, but if you license the entire industry, then if someone wants to go around it, it's not just a matter of going to another shop or even going to an earlier step. They have to go around the entire system, obtaining the know-how to make the phosphoramidite chemicals all the way through to the know-how of getting DNA to work in a cell. I think that's a great opportunity. And I think it actually plays into what Kristala will say.

About a genome project scale, I think it is certainly appropriate in

this case. As a beneficiary of the human genome project, I saw just how great it was in terms of stimulating community and industry. So I think there is a huge opportunity there that will also result in greater responsibility.

Nita Farahany:

Thank you.

Kristala Prather:

I'll give a very simple answer. You said funding or project. I would say both, which is basically to set a priority and say we think this is really important and we're going to organize a project around that. And I don't know how you do projects without funding. I think they go together.

Jim Wagner:

Thank you. Are there questions from the audience? Yes, sir.

Terry Taylor:

Terry Taylor from the International Council for Life Sciences. My question is about the international environment, that being an excellent discussion about the fact that anything we might do in the United States has to be fitted into an international context if it's all to be in any way successful in regard to regulation or ethical conduct.

And I have two questions really. One for our excellent speakers, first-class presentations: you're at the leading edge of the development of a science, whether in academia and, of course, experienced in commercial industry. Where would you start in terms of the global environment? Is it best left to various networks which are academic, which are in commercial industry?

Dr. Venter mentioned the industry is already trying to do some of these things like the International Association for Synthetic Biology based in Germany attempting codes of conduct, and so on, some really quite successfully. Or should there be some central, more top-down approach? Is it a networking approach, multiple networks? Should we be doing something or encouraging the development of top-down and globally? That's question number one.

Second question really I suppose is for the commission, to what extent are you going to consult internationally on this subject in order to set whatever recommendations you might make in a global context? Thank you very much.

Amy Gutmann:

Let's begin with the second one, because I can answer that very quickly. We are going to consult internationally, not only are we going to, we have already begun to consult internationally. And we will have here as a presenter somebody, Markus Schmidt who represents an international voice in this. And we will continue to consult internationally. So I now push it back to our presenters to answer the substantive question which is an important one.

J Craig Venter:

I think the only way to start is in two ways, simultaneously. But it certainly has happened with molecular biology and international code of standards, that we all agree upon, such as simple things like labeling the DNA of synthetic organisms by watermarking them, as we tried to set the standard for trying to make sure no organisms are released to the environment unless they have these critical biological controls. We suggested early on no human pathogens but two out of the three first viruses were made were human pathogens, first with polio virus and the 1918 flu virus. But the 1918 flu virus was done in the right way and with the C.D.C. with extreme controls and was a critical experiment for understanding why the 1918 flu was so lethal because we couldn't tell from looking at the sequence.

I think it has to happen at the government and society levels as well in the key countries where the activities are going, starting with the EU, China, India and the U.S. would be great starting points.

Rob Carlson:

I can't help myself here. As tempted as I am to weigh in on licensing and regulation, I won't do that. I wanted to look at the small versus large conversation. That more than 50% of the jobs in this country are in small businesses, a little bit less than 50% of the payroll is in small businesses. And that's where a lot of our technology comes from.

There's already an example of small-scale distributed biological manufacturing being highly successful in this country: if you look at the size of breweries over the last 100 years, officially the number went to zero during prohibition, officially. After prohibition, brewing was dominated by very large-scale brewers around the world until 1980 roughly. And although a small number of very large brewers control most of the U.S. market, those number in the — you can count them on your one hand basically. There are 1500 craft brewers in the U.S. They supply about 5% of the volume but 9% of the revenue or take home 9% of the revenue. That is distributed biological manufacturing and it works just fine and they are covered by a regulatory regime to the extent that alcohol is still regulated in this country. That's all I wanted to throw into the discussion.

Jim Wagner:

Thanks, Rob.

Amy Gutmann:

I have a follow-up question, since this panel, we really wanted to focus on application. And here's the question. I'll try to make it as vivid as possible:

Next flu season, the most virulent flu begins. And there is real fear of how much it's going to spread and the lives lost and so on. Next flu season, could we have a one-day production through synthetic biology of a flu vaccine?

J Craig Venter:

Well, the seed stock for that vaccine could have been produced in probably about 12 hours. And because all the surveillance now with the rapid DNA sequencing, we can predict, we think, well in advance what the changes will be for next year's flu before WHO even makes the decision as to the vaccine stocks.

I think the biggest limitation going forward is how we actually produce the vaccine. Is it going to be in chicken eggs? Are we going to go to modern cellular systems? Or is the magnitude faster and under much better control? The second step is much better in producing the doses for the individuals. Well, Novartis and other companies are tooled up for it in part because of government funding, waiting

mostly for F.D.A. approval.

Amy Gutmann:

If I'm right, the answer is no, we're not yet ready to do it in a day.

J. Craig Venter:

No. Actually, I think we are ready. Depends on who the "we" is. If we're the F.D.A., we're not ready.

Amy Gutmann:

So, we're the public. We're the American public, and we want to know, next flu season, if there's some virulent flu strain, can synthetic biology come to the rescue? And I don't mean if it were in theory possible. But will it happen?

J Craig Venter:

It's very likely, as I said, the vaccine you get next year will be from synthetic genomic technologies.

Amy Gutmann:

So the answer is yes?

J Craig Venter:

The answer is definitely yes. NIH is funding us to make synthetic segments of every virus. It's easy just to put them together in a very rapid synthesis process to make any seed stock or any change we see for tracking new emerging infections.

Amy Gutmann:

Thank you for that.

Raju Kucherlapati:

There is a corollary to that. And the corollary to that question is: can it be done only by synthetic biology? Or are there other approaches that could equally effectively produce the kind of vaccine that you are talking about?

Amy Gutmann:

And what's the answer to that next flu season?

J Craig Venter:

The answer is yes, but nowhere near as fast.

Amy Gutmann:

And speed matters?

J. Craig Venter:

Speed definitely matters.

Amy Gutmann:

And nowhere near as cost effective?

J Craig Venter:

I mean the cost is a trivial part at that stage.

Amy Gutmann:

Great to know.

Kristala Prather:

I don't want to gloss over the manufacturing issues here because Dr. Venter made this point of if you are still making it in chicken eggs, it's not going to happen in a day. There's a difference between the tools of synthetic biology being able to give you what that starting material is. If we're stuck with chicken eggs, it's not going to happen. If you go to a chicken cell culture, it's going to be faster. If the DNA vaccine technology proves out and you can do it in microbes, you can do it in a day.

Amy Gutmann:

What do we need for that?

Kristala Prather:

That's not a synthetic biology problem. That's an immunology problem.

Jim Wagner:

The final question is yours, ma'am.

Nancy Jones:

Nancy Jones from NIH. So my question is: we have talked a lot about

external regulations for the government in this. As trainers of the future scientists and engineers in this, what are you all's obligations? What do you teach your engineers and scientists about what the ethical considerations are for moving this field forward?

J Craig Venter:

Well, at the Venter Institute in synthetic genomics we have internal IRB committees that any scientific experiments have to be approved in advance along guidelines published in the past by NIH. And also, just a commonsense approach. We wouldn't be testing new microbes to see if they survive in the environment. The micro-plasma that we made and changed was initially a goat pathogen. We have eliminated 14 genes that were originally associated with that pathogenicity but we're not going out to farms and testing to see whether it's still pathogenic.

There's a common sense level to all this work that I think most labs — it's a reason with millions of experiments in molecular biology, there's been no fundamental problems or accidents in part, the ethics of the scientists doing this and how they train scientists and the simple guidelines that are out there. I think they work very effectively.

George Church:

So I teach a course on responsible conduct of science, which is based on some of the NIH literature. In addition, in every other standard course that I teach, I inject some, both lectures and exercises, where they have to seriously understand it in order to do well in the course. I would say in addition, iGEM and SynBERC as part of our training includes what's called a human practices component where really they are judged in their competition as to how well they conquer that particular knowledge base as well. So I think there's certainly room for improvement, but there's some hope as well.

Kristala Prather:

I want to say thank you for the question, because I made a comment earlier to someone that I am here to learn myself. I didn't realize until recently — I don't have an NIH funding, therefore, my students aren't required to have any training in ethics. Because of our affiliation with SynBERC, they have exposure to it in a way that I think very few other students who are trained as engineers traditionally have.

There's a gap, I think, in terms of how we think about training the next generation of engineers to have a focus on what our responsibilities are beyond the science. So certainly, it's something to think about.

Jim Wagner:

Actually, I think we need to adjourn. We adjourn to reconvene at 1:45, I believe.

Please join me in thanking Drs. Prather, Church and Venter.

[AUDIENCE APPLAUSE]