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Opportunities and Challenges in the Emerging Field of Synthetic Biology

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Agenda Item: Welcome

MR. CICERONE: Good morning. My name is Ralph Cicerone and I am the president of the National Academy of Sciences and I want to welcome everyone this morning on behalf of all the organizations here who worked together, the National Academy of Sciences, the National Academy of Engineering, the Institute of Medicine and then what is called our operating arm, the National Research Council. This emerging field of synthetic biology I think represents what can happen when some powerful streams converge and the one I have in mind are rapid advances in fundamental biology along with tremendously expanded laboratory techniques and of course the demanding human condition not only in terms of health but also agriculture and management of environmental systems and so forth, and indeed the curiosity to understand and in some cases manipulate life.

Things so fundamental clearly are inherently international in the way that they are going to have to be explored perhaps adopted, monitored, optimized, in some cases controlled. We have a terrific group today in terms of its international representation and I think that is

absolutely essential because there are certainly policy issues that will have to be shared and perspectives and perceptions that will have to be understood across cultural and national boundaries.

The field is going to be very multidimensional and not being fundamentally a biologist myself I can only imagine, but I will claim one prediction. In 1984 I think around New Year's Day of 1985 I was living in Colorado and the Denver Post called up a few people, scientists to ask us what to look out for in the next 25 years that would be really transforming and I told them synthetic biology. I went on to tell them everything I knew in about 30 seconds but that sound byte was too long for them so they didn't print it. I don't have any proof but I saw some of these things coming and they are very exciting.

Before I introduce our keynote speaker this morning, Dr. Bement, I want to acknowledge and just point out how much cross disciplinary and different kinds of organizational support has been contributed to today's meeting come about in the first place. We have the support of the Sloan Foundation, the National Science Foundation, of course. We are very impressed that NSF is ahead of the

pack again and the biotechnology industry organization is well represented here today and was in the planning. Then of course the OECD and the Royal Society of London worked with our academies and our organizations here in creating this symposium. We are all looking forward to it frankly to see what comes out today and we hope that each one of you leaves with some new actions and new thoughts in mind.

It is my pleasure today and really a pleasure to introduce a friend. Maybe before introducing Dr. Bement I will say one more thing. In case any of you haven't read any of the morning newspapers it has been announced that Francis Collins will be nominated to be the director of the NIH and we don't know how long that is going to take, but the announcement has been made now at least according to the New York Times and Washington Post.

It is now my pleasure to introduce Dr. Arden Bement who is not only a personal friend but he is a great friend of the scientific and engineering and technical community in general. He was sworn in to be the 12th director I think of NSF in November of 2004. By leading NSF this is the only federal agency that funds research and education essentially in all fields of science and

engineering in the United States and he directs their budget, which is more than $6 billion annually.

He oversees also a robust international research program, for example, in polar region research and a number of international partnerships, which build and operate a number of research and experimental facilities around the world.

Before he was invited to serve and confirm to be the director of NSF, Dr. Bement directed the National Institutes of Standards and Technology in the Department of Commerce. Some of you can remember when that was called the National Bureau of Standards. Now it is NIST. He is originally a metallurgical engineer with a degree from the Colorado School of Minds and then a doctorate in a similar field from University of Michigan, metallurgical engineering.

He holds numerous honorary doctorates. He is a retired lieutenant colonel from the United States Army Corps of Engineers and he is a recipient of the Distinguished Service Medal of the United States Department of Defense. As I said first of all he is a friend of science, a supporter of science and very knowledge so we

look forward to whatever it is you are going to speak about this morning, Dr. Bement. Thank you.

Agenda Item: Keynote Address

DR. BEMENT: Thank you very much, Ralph. It was very kind remarks. Good morning everyone. This is quite a group and I hope those of you who are standing will see that there are some seats up front. Before we get too serious I want to share a lighthearted tale that describes the challenges involved in pursuing a different course and in bringing about change especially in the fields of science, engineering, and technology.

A synthetic biologist and a social scientist await death at the hands of an executioner. The executioner asks the social scientist if he has a final wish. Yes, he says, I have some new findings on the societal and ethical dimensions of synthetic biology and I want to present them to the scientific community before I die. The executioner then turns to the synthetic biologist and asks if she has a final wish. Yes, she said, just shoot me before I have to listen to that lecture.

I am certain that those of us gathered here today have no such sentiments about the broad issues that this

symposium will address. We know the contemporary research at the frontier is characterized by how it draws on and contributes to advances in many fields of science and engineering. We also know that research and discovery move forward within the context of society's larger goals and values.

Over the past several years reports and commentary on synthetic biology have proliferated. They raise important issues and catalog both the promise and the potential peril of this emerging field. As in most transformative fields we can already glimpse the promise that is to come. At the same time uncertainty about potential impacts gives us pause.

Many feel the sense of urgency and this tension between benefits and risks of emerging technologies. Balancing both is a difficult challenge even for quite simple choices. In the case of emerging technologies that are very complex we require sophisticated and subtle solutions. The very best we can devise.

This is an arena in which science and policy should work hand and glove but very often doesn't. The nexus between science and engineering and policy is not a

new subject, but more urgent today is technology penetrates every aspect of our lives. In the words of one technology scholar it is a challenge to understand how intelligent social decisions could be made in the face of great uncertainty, high complexity, and rampant disagreement. None of us want to be caught between a doomsday sila(?) and a utopian shiribdus(?).

You will hear from many experts in science engineering and policy over the course of this symposium that will shed some light on what we can do to facilitate sound decision making.

Supporting emerging areas of research is central to the business of the National Science Foundation. We call embryonic fields transformative because they hold great potential for advancing knowledge and providing benefits to society. The term transformative describes science and engineering endeavors that can revolutionize research thinking, create entirely new fields, disrupt accepted theories and perspectives, and destabilize markets.

Over the years that commitment has led NSF to encourage the fundamental and catalytic research underpinning and leading to advances in biotechnology,

computer and communications technologies and more recently nanotechnology and synthetic biology is subject of our discussions here today.

NSF also has a firm commitment to weave social science and environmental studies into research projects involving emergent technologies. Dr. Endy and Dr. Rabinow whom you will hear from shortly are both associated with SynBERC, the NSF supported Synthetic Biology Engineering Research Center. Studies of human practices were integrated into the center program right from the very start. The NSF Center for Nanotechnology in Society at Arizona State University helped pioneer this integrative approach several years ago. Indeed we have an extensive research program in the social, environmental, and safety aspects of nanotechnology.

Last year NSF funded two new centers for exploring the environmental implications of nano. NSF also supports fundamental research on decision making, risk, and uncertainty to gain insight into decision making processes, loss of mitigation models and risk perception. This work helps us to manage the risks in general governance associated with emerging technologies including synthetic

biology.

We often work jointly with mission agencies that have a regulatory responsibility when fundamental research will enhance the ability to carry out their missions. These activities in fundamental research also serve as catalyst for the education and training of the next generation of researchers as well as in the development of a science and technology workforce.

Transformative research today demands not only innovative concepts but also creative and fresh approaches to generating ideas. I will only mention the recent ideas factory sandpit on synthetic biology that NSF jointly sponsored with the UK research councils. The exercise produced truly visionary projects and a number of potential collaborations among UK and US researchers.

Innovative concepts are the sine qua non of scientific progress. We now recognize in addition that exploration, safety, security, environmental and social implications must be undertaken coincident with investigations to advance to science leading to the development of emerging technologies. This recognition is an important step in establishing science and technology

policy that is appropriate to the science and responsive to the values of our societies. But it is only a first step. The path is steep and we have some arduous climbing you have to undertake.

The pace of discovery and commercialization today is both swift and critical to global prosperity. We need totally new paths to develop a policy framework that is appropriate to the new realities of our technology intensive world. No one wants to forego the potential benefits and no one wants to ignore the potential perils of new technology.

Yogi Bear once said, a great scientific mind, the future ain’t what it used to be. Of course he also said I didn’t say most of the things I said. Certainly we can say today that science ain’t what it used to be and I would add it isn’t what it will become in the years ahead. Nonetheless there are some features that characterize the current context of science and engineering that have consequences for our discussions today.

The changing context of research requires some rethinking of our present path and some innovative responses. First, we now have a much deeper understanding

of complexity and particularly of complex systems. This gives us a deeper understanding of technology. Current policy discussion should reflect this contemporary reality. IPCC climate change assessment products are an example of how this can work from the science side. We need energetic efforts to ensure our emerging technologies are thoroughly understood in a holistic context.

This brings me to a second feature of contemporary science. Modeling and simulation provide powerful new tools for exploring consequences. Modeling and simulation not only provide improve methods for testing hypothesis and theories, they enhance our ability to anticipate future developments as we design public policy. In this way science can better inform the policy dialogue in ways that were literally impossible only decades ago. Again, climate science is a leading example. The construction of scenarios using not only physical variables but economic and social ones as well is a sophisticated approach to a very complex predicament.

A third feature of contemporary research involves the social sciences. Our understanding of human and social dimensions as well as the mechanisms of learning has

progressed rapidly in recent years. In fact with today's computer and communication tools there is every reason to believe that the social sciences are poised to accelerate progress in many research areas. Despite this ripeness funding and support has been woefully inadequate.

I have already mentioned the involvement of the social scientists and synthetic biology research, a path many governments are following. This is a vital point so I would like to elaborate. Just consider what the demand is for social scientists these days. Economists are asked to provide policy guidance and make forecast for national and global economies. When we ask what is wrong in today's schools we turn with frustration to studies in learning and cognition and we expect immediate answers. When disasters like Hurricane Katrina occur we expect disaster management plans to reflect sophisticated knowledge of human behavior. And we have only just begun to consider human responses to climate change. As we design policies for mitigation and adaptation, we need to know at the very least how people and the market will react to incentives and to education about energy alternatives. We need a very aggressive research agenda to answer all of these questions and many

more.

The agenda for synthetic biology will differ in details but the principle is the same. Technology is created and used by human beings and without a thorough understanding of humans of our institutions we have at best only a partial understanding of the technology.

With synthetic biology we have an opportunity to get this right from the outset but not without a firm commitment to integrate the social behavior, cognitive and economic sciences into our research agenda. Without this input it would be difficult indeed to adequately explore environment, health, safety, and security issues. Government funding agencies can help make this happen. Thanks to progress and many fields of science and engineering we now have the improved tools to inform decisions and policy but what more do we need.

Many years ago the British mathematician and biologist, Jacob Bronowski, wrote a slim book. He wrote several slim books and they are all very powerful. This one was entitled *Science and Human Values*. Among many wise observations he wrote tolerance among scientists cannot be based on indifference. It must be based on respect. The

same holds true for scientist, decision makers, and the public. At the very least tolerance means listening attentively to each other. Tolerance also means respecting the public's perception of an emerging technology even when we disagree. Tolerance does not mean displaying indifference to genuine concerns by getting ahead of the public on these issues.

Democratic ideals and values can be at risk in an increasingly technological society when we do not educate in fully engaged citizens and dialogue on critical issues. In this respect synthetic biology and other emerging technologies are now different than many other social issues.

The challenge today, however, is that our societies are infused with technologies that are once complex and ubiquitous. That makes a dialogue about science and technology much more difficult but also immensely much more important to get right. At a minimum we need a clear statement of the science. Although this seems obvious science that is accessible to policy makers and the broader public is in short supply. Communicating science is a very complex endeavor but one we must work to achieve.

We also need an analysis of possible policy options and a transparent decision. In the US President Obama not only embraces science-based policy but has made greater transparency and accountability an overarching goal as well.

Engaging citizens in genuine dialogue is the essential final ingredient, yet, one that presents enormous challenges. Just consider a recent public opinion survey on energy issues conducted by public agenda, a survey organization. The survey revealed that 51 percent of those surveyed could not name a renewable energy source. Thirty-nine percent could not name a fossil fuel. Clearly there is an urgent need for public education on these issues, yet, that is not what strikes as most significant about the survey. Despite a lack of knowledge about energy sources three-quarters of those surveyed believed that the US should move toward increased use of alternative energy even if oil prices go down. These strong attitudes are based on something other than knowledge but they are important to take seriously.

Crude as this snapshot may be it points to a pervasive and serious problem and one that lies at the

heart broader dialogue on emerging technologies. We need an informed public to arrive at informed decisions. It is a fundamental responsibility of everyone to promote and support science, technology, engineering, and mathematics education at all levels. Without this goal our decisions will be made exclusively rather than inclusively. We know that pursuing new knowledge and innovation is the best path toward economic prosperity and a solution to persistent societal problems from energy security to climate change and from poverty to disease.

I believe that synthetic biology can make substantial contributions to the quality of life and prosperity in the years ahead. Our ability to address the most pressing needs of our times depends upon our resolve to pursue a future shaped by scientific vision and leadership.

As for broader societal dimensions I turn to the famous 17th century Japanese swordsman, Miyamoto Musashi. To express this perspective he wants wrote, in strategy it is important to see distant things as if they were close and to take a distance view of close things. This advice applies to the intersection of science, technology, and

policy no less than it does in considering strategy. Although this perspective may sound first like a contradiction, the deeper reality is that we must see emerging technologies from without which is a citizen's standpoint and we must find a way to help citizens to see it from within as researchers do.

If policy aims to develop the world to which we aspire, science and technology creates the paths by which we realize those aspirations for all of the world citizens. That puts us all together in the same boat steering for the future with all its uncertainties and as promises. Thank you.

PARTICIPANT: Dr. Bement has graciously said that he would take a question or two from the audience so if you have any questions we have microphones on either side of the room and please come up. Thank you.

PARTICIPANT: I'm from Beijing, China. I just want to know how much you have funded for synthetic biology and since when and what is the percentages of your funding from NSF for the total amount?

DR. BEMENT: For synthetic biology?

PARTICIPANT: Yes.

DR. BEMENT: I would have to give a wild stab at that number. Does someone from NSF have a specific answer? I would guess that if you took all the dimensions of synthetic biology in the field of biology through the tree of life but especially at solar level and molecular level it is probably of the order of $100 million roughly, which is pretty significant.

PARTICIPANT: The problem of public understanding of science has been remarkably resistant to something that we have been able to make progress on for as long as we have been keeping statistics on science literacy. Another perspective might be that that’s just a system condition that we have to accept. Plus I thought the point that you made about the difference between particular knowledge about particular technologies and general sentiments about what society ought to do was a very important one that is often neglected. Could you just address how we might think differently about the problem of public science literacy given that we have been rending our hands about this for at least since the time of Sputnik with almost nothing to show for it in terms of actual statistical progress?

DR. BEMENT: I was in the UK just a short time

ago and (?) for the first time but one of the things that I found which was most impressive is the extent to which they have gone to the public through public hearings to raise these issues and get their thoughts and impacts, their attitudes toward the subject. There is not an emerging technology that exists today that doesn't have a balance of risks and benefits. It is always going to be a balancing act with the general public whether the promises outweigh the risks and that is something scientists shouldn't take together when they are very deeply involved in the science that there is this balance that has to be attended to.

The public hearings that have been held in the UK on this subject are very impressive. But you don't have to wait for federal agency to establish a public hearing. You can have every university in the country can certainly bring this subject up and tap public attitudes. That is what I would encourage.

MR. WINSTON: Robert Winston (?) College London. I was very grateful to hear your last comment about what we are trying to do in the UK. Do you not think that it is about time we stop talking about the public understanding of science? I think that is a misnomer. What the UK

experience shows very clearly that when we have dialogue with the public there is a hugely wide accord about a large mass of scientific mass. It's not merely a question of scientific literacy. It goes to our being able to listen as scientists to what the public are telling us.

DR. BEMENT: That is a very good point and I take your point and again in many of these subjects because of the complexity of the subject you are going to have a wide spectrum of opinions and findings by the scientific community itself. So developing a consensus of thought on some of the serious issues such as the anthropogenic impact of global warming is an ongoing process that is part of the scientific method. Of course as the job of skeptics and critics, which we all are, but nevertheless if there is uncertainty and if there is this wide divergence of use that too ought to be known to the public and we should fess up that we don't have all the answers.

MR. MAYNARD: Andrew Maynard, Woodrow Wilson Center. I was very gratified by your emphasis on citizen engagement and dialogue. But I was interested. I know the NSF have put a lot of resources into developing and understanding of how people respond to different scientific

issues and how you might engage with members of the public. Can you say something about the agency's experiences in actually bringing citizens into decision-making processes where science is concerned?

DR. BEMENT: We find that our tools are inadequate at the present time. One of the missing components is the database or databases that one can draw on in order to do scientific research and analysis. In our science and science innovation policy program we have now recognized that in very stark terms. We are now making investments to try and fill in that database that will inform how to inform policy makers and how to put science agencies as well as scientists on the side of being an honest broker.

MR. RABINOW: Paul Rabinow, Berkeley. I hope we will talk about this in a number times today, but I just want to put on the agenda that there is vast illiteracy and ignorance among the natural scientific community about many social, cultural, political, ethical interests as well as other specialties in the natural sciences. It is an overly self-laudatory to think the public is stupid but the scientists know what's going on. Being an anthropologist I

can assure you it is more complicated than that. I'm sure you agree. What happened with Sputnik forward was the American education system was changed and almost no one has any general education requirements anymore. One of the classic comments at a lab meeting in Jay Keasling's lab that I was talking to. Some I mentioned skepticism and someone said oh I took that course at Harvard. That was all you needed to know and he was more open than most.

I think this is a multi-channeled problem, which absolutely cannot be taken as if the problem is only on one side. I think it is more complicated than that.

DR. BEMENT: I agree with that point. I think also we have to clarify our questions to the public especially through surveys. I was taken by this public survey that in some cases you may have to explain what you mean by renewable when you talk about renewable fuels. In some cases you may have to clarify what you mean by fossil when you ask about fossil fuels. In the minds of some that is the fuel you feed fossils.

MR. RABINOW: But again if you were to do a survey of biochemists and ask them about anything of the history of ethics, I think you would find an even lower

percentage of knowledge answers.

DR. BEMENT: It has been brought to my attention and I should have recognized that just this past week from two or three different sources that the difficulty in bringing the social scientist to some of these problems is that many social scientists are not ready yet to engage in interdisciplinary research. They want to build the basic foundations of the field. That is where they want to focus their attention.

Secondly, our tenure process is inimical to interdisciplinary research. How do you judge a person's value based on integration and convergence and problem solving or application when it comes to tenure review? What value does the university play not the university but the community within the university? That is the limited partnership called faculty.

This is where I think we need some workshops in order to explore those issues because as I indicated every mission agency in Washington is very much in tune. They want more social science input into the problems that they are dealing with and they looked at the NSF because we have about the only funded program for social scientists in the

federal government.

It is more than just building the funding base. It is also building the community base that is interested in engaging and thank heavens you are an exception Paul.

MS. SILVER: I am Pam Silver. I am from Harvard and I did not teach the course on skepticism although I remain skeptical. First of all I want to say that I really admire the NSF for leading the way in funding in synthetic biology. With that said and this is again not a question that is going to have a short answer. Maybe it is one for discussion later. I am wondering what your thoughts are on the current mechanisms for giving out federal funds in the US and the level of frustration you might feel or not feel with the current peer review system and also refer to the Gina Kolata's front page piece in the New York Times, which admittedly only address cancer, but those problems run deeper than just cancer funding.

DR. BEMENT: You ask a very important question but one that is a little difficult to answer because the system of funding research from the federal government depends specifically on which agency you are referring to and which program within an agency in some respects you are

referring to. Throughout the world I think there is a growing recognition of the importance of competitive research or competitive proposals, competitive review, competitive and objective review and the value of the peer-review system and (?) review system. Now we have chased around the block for 50 years as a foundation looking for alternative ways of investing taxpayer's funding and being good stewards of taxpayer's funds. We have yet to find a better mechanism in general that will --

MS. SILVER: Well, I would like to maybe put on that the table for discussion later.

DR. BEMENT: Thank you.

PARTICIPANT: Please join me in thanking Dr. Bement.

Agenda Item: Session 1: Synthetic Biology Overview

MS. JASANOFF: Good morning. I am Sheila Jasanoff and it is an honor to be asked to introduce and moderate this first overview session. I was delighted first of all to see that the title of the conference as a whole is opportunities and challenges. We have heard about risks and benefits. I think it is important to shift the language

because risk and benefit are somewhat closed-minded concepts. They lend themselves immediately to economic and numerical analysis whereas opportunities and challenges suggest something much more open-ended. I think we have already broached the sense in which the discussion in this room has to be thought about as part of a much more open-ended kind of process.

In 1956 the English philosopher W.B. Gallie wrote an article on what he termed essentially contested concepts. He said these were concepts where people kind of agreed on how to judge whether something was good or bad but would disagree among themselves on whether particular instantiations of that thing were good or bad. He set democracy as an example, but he also used the analogy of sports. He wasn’t an American so he didn’t talk about baseball but if you want to understand the concept you can think about the Red Sox and the Yankees. There are committed fans who would go to the wall defending one team or the other. Obviously winning strategies cannot be the criterion by which the Red Sox fans decide what their loyalties are and yet most people would agree that by and large whether a team wins or not should be one of the

criteria by which you judge excellence.

In that sense I think that what we are talking about today in relation to the opportunities and challenges of synthetic biology suggests that we are talking about essentially contested concepts, things that are open-ended, things whose value lies in the fact that we continually debate them and not that we get them boxed up and find solutions and make decisions and move onward from there.

One of the sponsors of this meeting is the Royal Society and next year in 2010 they will be celebrating their 350th anniversary so I guess a little bit younger than Harvard University, but in competition. What should that 350th anniversary be about? Well, the Royal Society's foundation is associated with the enlightenment and one way to think about what this meeting is about and what the Royal Society's forthcoming anniversary will be about is that perhaps we are talking about a second enlightenment. The first enlightenment took science away from superstition and made it necessary for all of us who live in the modern era to acknowledge that scientific foundation, scientific skepticism and scientific reason are utterly indispensable parts of our lives.

The second enlightenment I think has to do with putting science back into society in meaningful ways. That is where we get into the essential contestations because we start talking not about things that are measurable and pinned downable in any sense but about things that are ongoing and whose very meaning changes.

I think that the kinds of themes that have already been broached and that you hear broached more eloquently and pointedly in the two forthcoming talks will be about considerations like imagination, who gets to imagine the future with science and technology? About meaning, what are the institutions with which we assign meaning? To innovation, how do we welcome particular innovations into our lives or decide that other ones are not desirable and also questions of responsibility. If we are changing the playing field, if we are creating new objects, new ways of going about doing things then who is responsible for the consequences whether they are good consequences but need to be distributed or bad consequences that need to be prevented.

If you go back and look at the historical record of Asilomar, which stands the 1975 meeting as one of the

milestones and thinking about a new emerging technology namely recombinant DNA technology, genetic engineering you will find that people actually didn't think that the release of genetically modified organisms into the environment was something to worry about. It was put into the class of prohibited experiments at that time but within two years people were doing just exactly that. Imaginations are limited and I think we will be hearing from our two next speakers ways in which we might be a little more in charge of the process by which imaginative futures enter our lives.

You couldn't have two better speakers than the two we have. The biographies are listed in the papers that you have in your folders. I will just very quickly introduce them in order.

Drew Endy is assistant professor in the Department of Bioengineering at Stanford University. It is rather sad for me to say Stanford because until a very few months ago he was down the river even though I may see him more at Stanford than at MIT. Drew has emerged as one of the most eloquent scientific voices talking about the meaning of synthetic biology revolution.

Following him will be Paul Rabinow who has already introduced himself from the sidelines. He is the director of Human Practice as the Synthetic Biology Engineering Research Center at Berkeley. Paul's work has been long identified with meaning making at the biological sciences.

Without further ado Drew.

MR. ENDY: It is always surprising to me how hard certain things are to get done and it makes me very grateful for the process and venue we have today to continue to work together on stuff.

I am going to give an overview on synthetic biology and be pretty direct at the end. The overview though is meant to represent and reflect on the great diversity of the field as it has come together over a period of time.

Without apology let me get started. What and why is synthetic biology? It turns out I was able to find a paper with this as a section title and in reading the paper four different areas were brought to light: natural science, synthetic science, re-writers, and engineers. I thought looking back at this text there was something

missing, humanity. Whatever that means and we will have to figure it out.

Let me talk about these four or five areas quickly, the nature of synthetic biology. We inherit in molecular and cellular biology a tradition of over 70 years basically having to do with taking things apart and that has worked pretty well. When you take something apart, a car or a cell you develop some sort of understanding, an operational understanding perhaps of that artifact. For example, in the 1950s Esther Lederberg and Margaret Lieb and others began to notice that bacteria could be infected by viruses when in fact the bacteria can do different things. Sometimes the bacteria will be destroyed by the virus. Sometimes the virus will go dormant and propagate as a silent messenger within the cell.

This has been taken apart for the better part of half a century. You can read books on things like this, the genetic switches that control sulfate outcomes. If you read these books the high water marks of much of molecular and cellular biology, they are amazing. They are very good descriptions of the componentry within these natural living systems. I first experienced this as a student and looking

back on the books it turns out I missed some of the important sentences. For example, in describing how a cell might decide to be destroyed or not by a virus we find in this wonderful book the genetic switch. We don't know. We do not have a complete understanding of these matters, but we can construct a plausible scenario. In other words we can tell you a story for how these things might work together. We are familiar with stories from Kipling and other folks. What we know about the stories is that they can be very satisfying but they don't lead to an operational understanding that would instruct you how you might change things necessarily.

It turns out that thus one of the most exciting things for the science of synthetic biology is to take a constructive approach so that we better understand nature not only taking things apart but also putting them back together and seeing what happens. You get to a different type of understanding as a result. The work shown here now a decade old represents Michael Elowitz taking the componentry from viruses and bacteria and what have you reorganizing the proteins that regulate the reading out of genes and in this case making a very permanent clock or

oscillator that causes a cell to blink. If you follow the movie very quickly you will see the cells all blink differently. There is a lot of variation. What this really leads to is first a demonstration of some degree of sufficiency of understanding for how proteins work inside cells and DNA is read out but then very immediately dramatic attention placed on where does this apparently spontaneous variation come from and a whole line of research over the last 10 years has picked up to follow this.

The synthesis of synthetic biology. Let me move to this tradition quickly. There was idea a long while ago that mice might come from dirty rags sitting in a corner sort of spontaneous generation. That is a neat idea. It wasn’t shown to be true in that case. Wouldn’t it be neat if you could take base chemicals, raw chemicals and somehow have them self assemble into a reproducing system? Synthetic chemistry applied more and more to the world of life perhaps making a new type of artificial life and I am showing here very early but sophisticated work to make artificial organelles and vesicles that might lead to reproducing systems.

Along these lines unbelievable work coming from Steven Benner, a synthetic chemist in Florida, who looked at the structure of DNA which when it was put forward in the 1950s made it evident to many how this might work as a mechanism for heredity but then started asking pretty interesting questions like why does DNA have a negative charge along the backbone? That one seemed to be a bummer if you are trying to get two things to come together. Opposites attract not likes attract. It turns out you can answer these questions and begin to develop a much richer understanding of the chemistry of life by simply changing it. His laboratory over a period of time working with colleagues in Switzerland was able to replace the phosphates with dimethylene sulfones basically making a neutral backbone to the DNA without these negative charges. As it turns out the resulting molecule does not work as DNA. It collapses upon itself because the negative charges are needed to repel. It doesn’t allow the basis to be presented cleanly for interaction and it doesn’t provide a scaffold by which if there is a mutation you still have effectively the same architecture of the molecule. All of a sudden simply by recomposing if you will the very base

molecules of life we understand them much more.

This leads to outstanding conclusions such as if you were looking for life on another planet you might expect to see a polyanite. It may not be nucleic acids, as we know it, but something that would present this sort of geometry.

Liberation of synthetic biology. This is a new idea. It may not be any good. For what's worth here you go. The living world that we know exists via this process of direct descent and replication with error. If you are familiar with poetry the poem from Thomas Hardy about the family face going from generation from generation. Leaping over oblivion is the one to look at. This is an amazing process but from an engineer's perspective it is an unbelievable constraint and limitation on system market texture. All living things have to be able to reproduce. They have to be able to tolerate or buffer or accept mutations and keep going. You can thus conclude naively and I mean it naively that evolution isn't really cool as much as we might like to celebrate Darwin this year and last, but it is a tyrant that gives us mutation without representation. That's not just a catchy phrase in the

context of synthetic biology because you can take technologies like sequencing of DNA, go from material to information, do some engineering or scientific redesign at the information layer, recompile back down to an object, and off it goes. All of a sudden now we have an alternative path forward in time to the propagation of living systems no longer constrained by material replication and direct descent.

To put this in context if you were to take an electrical circuit that had been developed via an evolutionary process this is the type of architecture humans can find. This is an evolved electrical circuit. It is not designed by human being. You might ask yourself, what does it do? How does it work? Why does it look this way? The answer is we don’t know to first approximation. It takes the square root of an input voltage and what an interesting design.

When I show this to electrical engineering colleagues at MIT, they to a first degree refuse to consider this system because it hasn’t been designed to be easy for them to understand. They say really intelligent design would have documentation that would help me think

about how to explain this to you.

What if all of biology is like that? What if we have these evolved systems that internally are often times spaghetti code? Could we reorganize, refactor the architecture of genetic systems making engineered surrogates that are easier to understand? It turns out that there is the hint of this becoming possible and becoming possible to much greater scale.

Then lastly looking back five years there is this idea of engineering and synthetic biology. Imagine being a teenager today inheriting a first generation of biotechs and ser combinant DNA and asking well geez I have a nanotechnology that actually works. I don’t need a national nanotech initiative. I don’t need to worry about gray goo. I have green goo that has already taken over the planet and I can sort of imagine programming this stuff with genetic material and oh it’s the stuff of life, which means our entire civilization depends upon it. That is pretty exciting and it turns out that a lot of people are working on this. Here is a paper that came across the transom yesterday where people have figured out how to program very nice band filters and bacteria thus they automatically

control their growth and differentiate spelling out hello, hi there.

Thus we now have in the US and elsewhere new schools of engineering getting starting including biological engineering departments which basically include the following remit teach students how to design and build living organisms that work, debug natural and write new genetic programs that behave as expected.

Lastly, for this part the humanity of synthetic biology. A lot of people are curious about biology appropriately so because it is who we are. It is what we are. Here is a recent photograph from the New York Times. For a different generation experience with other types of media I can find entire generations of folks in the US who are more familiar not with the New York Times but with South Park and the ideas of polygluteal monkeys and then obviously our hopes and fantasies around making sustainable ecosystems both on this planet and elsewhere.

More practically we can find as we work with colleagues across disciplines a lot of lessons from how technologies develop, impact the environment, and shape our own human environment. Here is a study on the impact of

Chicago across the North American continent over a period of time. Thus it leads to questions I don't know the answer to but we can at least pose and consider. How will we change ourselves with the next generations of biotechnology and our environments? Should we do it? Can we develop new schools of science and engineering? Could we think about how to integrate things without as much isolation and decoupling from the natural world? Could we invent or understand new modes of humanity involving better representation and access to technologies along with responsibility for our actions? I don't know.

To zoom out then synthetic biology might be described as learning and playing by making things. It might also include helping and enabling by building a scientific and engineering agenda brought together with all of humanity.

Of course it becomes much more interesting to consider the consequences and opportunities or challenges if you will when we recognize that we are talking about a part of the natural world, the living part which relatively speaking we have not yet engaged full scale engineering and science on. Can we make this easy to engineer? Can we

enable humanity? Could we enable all constructive biotech not at some arbitrary point at the end of the century but as soon as possible and thus better understand nature?

How does this map into the big challenges of the day so to speak? If you artificially bend our civilization into different areas of work and open up one of those here in chemicals you might find things like this, a report of the US Department of Energy circa 2004. We would like to make over a 100 chemicals, key feedstocks that our civilization builds other things on from renewable sources, stuff related to industry, transportation, textiles and so on. We don’t have the capacity right now to deliver on this sort of promise to be frank and I will come back to why that might be true.

If you open up another one here a lesson from a colleague at Cambridge University in the UK say food and agriculture, you could note how long it took us to go from the precursor to corn as we know it today to what we depend on. You could recognize that a very small number of crop species give us most of our calories and proteins, but then when you look at the natural plant world there are tens of thousands of things we might consider. How important does

it become to develop agility and scalability in terms of accessing this given a world that may be going through significant changes with respect to climate and environment?

Then of course you have the fantasies of the architects and others, the dreamers who might be imagining very more advanced world of biotech where you can take a gigantic programmable gourd and have it automatically differentiate into a four bedroom, two bath.

Where are we today? Let me give an example from a friend and colleague Jay Keasling at Berkeley. He had the insight to recognize the horror that’s malaria across much of the world and that he could do something about it using biotechnology. What his team was able to do was spend about $25 million in a research and development process to take genes from plants and elsewhere, put them into E. coli and yeast and via of order of 10-step metabolic engineering process produce a chemical called artemisinin for treating malaria instead of producing this chemical by extracting it from a bark of a tree. That took of order 150-person years, experts, postdocs doing the genetic engineering work and it represents not so much synthetic biology but the high water

mark of metabolic engineering as it is practiced today.

Each project practically speaking requires a Hercules. Meanwhile we have resistance to artemisinin in developing, which means we probably need to do this project again and again and again. Even if you didn’t want a 120 chemicals made to have a sustainable white and green chemistry just for therapeutics we are just needing to scale. Twenty-five million dollars for each project requires a lot of resources. It requires an incredible fundraiser, leader, scientist, engineer, project manager. All those skills are rare. Having them in one person is just improbable so we are not going to do very many projects like this.

Meanwhile human civilization has gotten much better at manipulating the natural world and so it becomes very exciting in the context of synthetic biology to think about how we might go from found objects like these rocks to standardized objects that come from quarries that let us make more improbable artifacts to synthetic rocks that let us make viaducts such as this one from France and compile cities like Hong Kong in decades as opposed to generations. It lets us go from computers circa 1952 helping to design

nuclear weapons to artifacts produced in garages and elsewhere to personal computers found in pockets all over.

When you go buy your mobile phone you typically think about the applications that it can help you with. I can make a phone call. I can check my email. I can send text messages with photographs on them. You don’t think about the tools that led to the transitions that happened over very dramatically short periods of time.

In the case of computing over the last 70 years you could think about investments and tools like this, languages and grammars for programming computers. JAVA, the programming language was not found growing on a tree. Somebody actually had to pay for that and develop it. Fabrication of silicone wafers represents decades of investment both public and private. Industries related to electronic design automation, computed design practically didn’t exist in the 1970s.

How about biotech then? Well here is the paper a lot of folks are familiar with circa 1973, Cohen and Boyer and recombinant production of a plasmid. This leads to the cloning of insulin, the founding of genentech and the birth of modern biotech. Twelve years later the early days of

Amgen we have the cloning erythropoietin and the production of that compound. If you are familiar with bike racing perhaps not a good thing. Then three years ago the production of artemisinin, the Jay Keasling project.

What is shown below is the method section of the papers. We could read them. Purification and use of EcoRI restriction endonuclease –- after converting BstEII site into BamHI with linkert -– it is very hard to read. The big change is that methods have moved to online supplements so the text isn't as good. The amplified product was cleaved with SpeI and HindIII and -– that is really weird. Over my entire life the workflow of genetic engineering has still apparently depended upon experts who have to know a whole bunch of esoteria and manually bash DNA just to produce the artifact to test out to see if it makes the products you want. Wow, how did that happen? Could we make new tools?

To wrap up very quickly I will give you an introduction to that. I am sure we will come back to it. From a policy and practical perspective one way to filter synthetic biology is to recognize that we use our opposable thumbs to do things and we make better opposable thumbs, recombinant DNA, PCR and sequencing to find the last

generation of biotech oftentimes. In synthetic biology we have advanced DNA synthesis techniques. We have abstraction for managing biocomplexity. We have standardization supporting reuse. These new categories of tools are probably at least as important. That's what's come over the last 30 years. For example, a metabolic engineering project might not require Hercules and millions of dollars but teenagers and five minutes who thus could compile an integrated genetic program like this controlling the odor of E. coli as a function of its growth state.

It turns out this is almost true already. It is not a five-minute project. It is a 10-week project, which means we still have a lot of room to improve.

As these tools come online and I won't highlight the tools but I will highlight here the humanity if you will, the number of people who are attracted to the next generation of biotechnology grows geometrically is distributed worldwide and is quite exciting and extraordinary.

Students, teenagers, high school students, college students can design and build genetic engineered machines of their own choosing that leads to many

questions. Here I will wrap up. Should teenagers practice genetic engineering? Not so much as a specific question but one meant to recognize and evoke issues of safety as we go from one generation to the next in genetic engineering.

Should military force include biotechnology? We have lived through the past century where we saw offensive biological weapons programs relatively widely deployed. What happens if this were to happen again? Will biohackers exist? Yes, they probably already do. Will they be good or bad? That depends. Do you choose to acknowledge them or not? Should these components be freely shared or patented or both? Who owns it? Should the public support this research or will private investment take care of it? Should genetic engineers sign their work? Is there a profession here or is it a bunch of scientists so to speak? How much can we make with biology? I would love to get Steve Chew to answer this question. It is not clear to me the manufacturing capacity of the living world and are we going to be in limits or surplus scenarios in which case land use, politics, and other things are going to affected.

I will end with the following pointer. This is not a consensus document but a colleague Ed Lazowska and I

attempted to draft some things that might be workable now. If you are interested in it you can see arguments for why we might choose to invest in DNA synthesis technology, open libraries of parts, legal framework supporting biotech, and integrated strategies for biosecurity reflecting not only what is happening at nation states but at the levels of individuals. Thank you again for the venue and future conversations.

MR. RABINOW: I am attempted to repeat director Bement's joke and sit down but I won't. Being an anthropologist I am not used to PowerPoint. You will see a few PowerPoints in a second. Two or three quick comments and then I will start my talk. As many of you know in California we are in a deep fiscal crisis. The governator as he is affectionately called is in the process of basically destroying a hundred years in the University of California rather than tax automobiles. Had he not rescinded the automobile license fee there would be no fiscal crisis in California. I think this raises the question that is going to circulate around the political economy of what we are doing in a country with immense resources and how are they being used and distributed

including California they are being using extremely poorly. It is a big crisis point.

Second, Pam(?) skepticism in Greek means inquiry. So probably we are all skeptical. Third, I think the core problem at one level is the crisis of pedagogy in the American universities. I went to a science high school in Stuyvesant, New York, a public high school. I have always enjoyed and liked science. I realized in my honors math class at age 16 I was the only one who had not invented a geometry or an algebra. I decided I probably wasn't going to be a mathematician at that point. Then I went to the University of Chicago, which believed you could learn anything and you should. I placed out of all the sciences and decided to do something difficult and went into anthropology and in France I am a philosopher.

There is a lot of reform that is necessary and I see few signs of it although actually in the NSF I have seen much more interesting and awareness of this than in certainly the deans and provosts at my distinguished university.

Human practices. Where is the venue? Let me point out for a start that we are working with a terrific web

designer who works at the exploratorium in San Francisco, Adrian Van Allen, and obviously the exploratorium is one of the central places in the world where this discussion of how and in what ways a technical scientific knowledge can be used and presented and encouraging people to participate in its use. Adrian is working on two websites, the SynBERC website and then this Ars Synthetica which is associated with SynBERC and which we are going to attempt to do a good deal of the presentation on various levels of technical interest of what synthetic biology, what the debates and problems are and we think we are off to a good start, but give us another few months and again thanks to NSF for funding a lot of this.

Off we go. Today in the wake of the various genome-sequencing projects of the 1990s the life sciences are being redesigned and recast with an eye to productive forms to experimentation and organization. Although varied alternatives and postgenomics are being explored it is our central working hypothesis that the life sciences once again are unsure of their objects, the best venues in which to work on these objects, and the broader ethical framing of their undertakings.

If today there is a broad consensus that the genome sequences were not the key to life but only “the end of the beginning” of biology as Sydney Brenner put it then it falls logically at least that the LC programs that were constructed within the political and scientific consensus about the significance of the genome sequencing projects while continuing to provide useful safeguards and its venues for conducing public conversations are themselves limited in their scope by their original mandate to operate downstream and outside of the sequencing efforts.

Agreeing with Brenner that there is a compelling need for scientists to rethink the understanding of the gene we argue in a parallel fashion that there is an equally if not more compelling need to rethink the ethical framing and metric of LC and associated programs, i.e., social consequences.

The need for rethinking what is meant by social consequences is actually more compelling because while it is standard practice at least in principle and biology that outdated concepts and experimental techniques will sooner or later be replaced. There is absolutely no guarantee whatsoever that a parallel process exists in the human

sciences.

It follows logically although many pragmatic obstacles remain in place before it becomes a reality that contemporary postgenomic research programs can no longer be constituted as they were in the recent past. In some the new arts and technologies and synthesis in biology call for the invention of new arts and technologies of both analysis and synthesis in the human sciences.

Synthetic biology exemplifies an important reassemblage of the life sciences underway today. Its emphasis on instrumental goods, its shift of attention away from the molecule and the gene, its primary objects of interest, its attempt to render biologies and engineering discipline, its goal of establishing new collaborative venues for scientific research as Drew and others have alluded to.

Moreover, the conditions and problems under which prior venues such as Asilomar and LC were considered, were constructed have changed. As such there can be no simply appeal to prior models or modes of operation. In the briefest of terms and we can talk about this and Sheila has much to say about this about this as well. Globalization

has changed the rules of the game. Capitalism is reshaping the infrastructure of scientific research at a global scale. The Internet has provided unequal access to materials and scientific knowledge. The political landscape provides a dramatically different ecology of security. All of these yield a dynamic set of emergent interconnections in which older distinctions such as technology, science, nature, culture, and ethics, politics can no longer provide a sufficient framing.

This is a detailed chart, which we worked out recently from Asilomar to the present which I am not going to talk about in my remaining seven minutes but I am happy to discuss this with you in more detail if you are interested. This is a simpler version of it, which goes down to various -– there have been a lot that has happened aside from Asilomar and LC particularly in the United States. It would be very interesting to compare this to both England on the one hand and other European and nonEuropean countries on the other. But again there is not enough time to do this in any detail although I will make this available on the Ars Synthetica website and I am happy to discuss this with you in more detail.

The three issues that I want to discuss briefly today is the concentration of what kind of venue should the human practices for synthetic biology and perhaps nanotechnology operate within. The question of a venue is not composed usually in those terms but I think it is extremely important.

What is the function of the venue? In my opinion today the function of the venue for synthetic biology, nanotechnology, and the rest is reconstruction. What is reconstruction? Here I turned to I actually think one of the most amazing thinkers in science and technology studies, John Dewey. His essays in experimental logic in 1896 and 1912 I think presages almost all of the advances in the 20th century that have followed it. It has a distinction, however, of being extremely clear and without any jargon.

Dewey says reconstruction, this is from reconstruction and philosophy, reconstruction can be nothing less than the work of developing, of forming, of producing in the literal sense of the word the intellectual instrumentalities which will progressively direct inquiry, skepticism, into the deeply and inclusively human,

humanity. That is to say moral facts of the present scene and situation. Whatever venues we are going to do they have to be more than technical and they have to provide a rather different framing for what the whole enterprise of perhaps a second or third or fourth enlightenment might be about.

It may seem like that’s a banality so let me just – it might seem that the function of reconstruction was a banality or self evidence. Here is a list of the other venues which are on the longer chart what they can see as their basic function as being starting with Iraq, audit, audit, advisory functions and then as we move into the President’s commissions and eventually into LC the questions were – since ethical considerations were outside and downstream of the technical and scientific implications, the functions of these venues were diagnosis in implications in a series of them. As we come closer to the present the function becomes monitoring and possibly intervening and then under the guidance of the Sloan Foundation and NSABB many of you worked on. Formal guidelines for instance in terms of regulating synthesis distribution. Again we can talk about that in more detail if I had more time.

Then the metric of what these venues should be guided by. We think that we are proposing in any case that the metric of a new venue in human practices for the emergent biosciences and related other sciences should be flourishing. This time I will remember to put the quote up. Flourishing is a translation of a classical Greek term, eudaemonia, and as such a range of other possible words could be used: thriving, the good life, happiness, fulfillment, felicity, abundance and the like. Above all, eudaemonia should not be confused with technical optimization as we hold that our capacities are not already known and that we do not understand flourishing to be uncontrolled growth, as we agree with Leon Kass in that, or the undirected maximization of existing capacities for their own sake. The question of what constitutes a good life today, and the contribution of the biosciences to that form of life must be vigilantly posed and reposed.

Again then this might seem like it was somewhat obvious but going through these other venues in the past actually the metric that was guiding their construction and their operation and their principles was quite different. Starting in the Asilomar in the early days the metric was

autonomy. How can the biosciences maintain their autonomy with the least government regulation possible? It shifted slightly later than to questions of values and responsibility in the LC projects, for example. There is a vast philosophic and anthropological critique of values and responsibility. We can talk about that in more detail if we had more time.

Then under Leon Kass and the president's commission the metric became the truly human that which could not be violated. Then in more recent days as many of you in this room know the metric shifted to security and security and responsibility.

None of these per se are illegitimate are uninteresting or unimportant but we think that they are actually not sufficient given the globalized context that we are talking about and given the potential capacities for synthetic biology and other new biological practices and disciplines to provide a comprehensive metric for where we should be going.

Finally in this series capacities. There is a technical distinction we make between metrics and parameters which if you look on the website we spell out in

some detail. We think that the parameters that should be paid attention to in a venue guided by a metric of flourishing are capacities. Again, a very quick definition of capacities from my friend Michel Foucault. How can the growth of capacities be disconnected from the intensification of power relations? This is what he calls the paradox of modernity. Probably the wrong words but nonetheless probably the right problem space. I think Drew pointed at this. That is to say we are unquestionably at a moment in which the capacities of the biological science and perhaps the human sciences and perhaps some of the other industrial organizations of the world are exponentially growing and will continue to grow more and more in the years to come.

However, back to the idea of flourishing, how can this growth of capacities be disconnected from massive exploitation and domination and in some way lead to something not only contributes but is constituted of the general good?

Again, this might seem like common sense that this would be a goal that might be shared by other venues but in fact looking carefully at the series of venues that

I just showed you very briefly in the beginning the parameters that guided them under their different metrics were protection, safety, social consequences, implications, protection, security, and reassurance. None of those are capacity building within an understanding of power and ethics.

We have much to learn from previous venues but I think we also have much to change from previous venues. I think the challenge in a radically new context, which is to say not that everything is new, but just that the context and the framing and the challenges are different is before us. Obviously there are many people in this room who are thinking and working on this and extremely grateful to the National Science Foundation for being so farsighted to include unusual anthropology philosopher skeptics like myself and we need more of this kind of thinking, more of this kind of practice, and let’s get to work.

Agenda Item: Questions and Answers

MS. JASANOFF: Thank you Drew and Paul for opening up the two words, opportunity and challenge so elegantly. We have about 20 minutes for questions. There are microphones on the two sides. May I ask that you

introduce yourself very briefly name and affiliation and if there is a specific person you want to target your question to feel free to do that and make sure that these are questions are brief and not separate lectures? The mikes are open and I invite you to come. Let me start on that side.

PARTICIPANT: -- working party on nanotechnology of OECD. My question is for Drew Endy and for you Sheila Jasanoff and related to concepts and their grammar and languages. The problem about languages and grammar is that it can be addressed by the scientific people but it is needed for the dialogue and public engagements. One of the things we are faced within the OECD working party on nanotechnology is the limit. We elected to organization of knowledge in the field of converting technologies (?) synthetic biology being an application of that. My question is related to this language and grammar concept, which has been raised. –- seemed interesting for international corporation, scientific corporation to be and achieved in the for(?) around those two concepts. Thank you.

MR. ENDY: The word language and grammar bring so much to bear on the world of synthetic biology both at the

technical and scientific level thinking about how to think about biology. If you could construct a piece of DNA as we can today of order 10 million base pairs long, what the heck do you want to say? Just within the research community itself there is a tremendous challenge to invent languages and grammars for describing the living world. I just want to use your question as an excuse to acknowledge that challenge. The challenge of communicating across factions, parties, and peoples including diverse publics about what is going on came up in the opening remarks and is a tricky one. I had a very enjoyable conversation with Paul Berg last Thursday out at Stanford and he surprised me by making the suggestion or wondering out loud perhaps we could do away with the word genetic in talking about genetic engineering so far as I could figure. That was sufficiently different from how I had viewed any possibilities that we wondered a lot about that.

In my limited experience when I talk to folks about what I am doing outside of a laboratory setting I often observe as soon as I mention the letters DNA there is a weird glazing in the eye of many of the folks I am talking with. It is surprising to me that it is not more

exciting and engaging. This weirdness of opposite expected responses and whether or not that it linked to language I am sure it is leads me with a bunch of puzzles.

In very limited experience what I have found to be useful is going to entirely differently forms of communication. Felice Frankel and others, for example, have done a tremendous job exploring how image and meaning are related and how you can use visual objects to communicate and represent things in forms that are tremendously more accessible or just different.

MS. JASANOFF: I will just add one thing since you explicitly asked about this that the problem of language is not only between the scientists and the public but also that natural languages are different and the same concepts do not mean there is sort of a hegemony of English in the sciences but there is not the same hegemony of English in fields like law or ethics. I think there is a great deal more need for comparative understanding of even terms like risk as they are played out in different places. I hope that your participation through OECD includes that comparative dimension.

MS. PAUWELS: Eleonore Pauwels from the Woodrow

Wilson Center. The session opens with thought provoking reflections on imagination and reinvention. I will ask the panelists to use their imagination. My question is the following. What effect do you envision synthetic biology will have on the social technical systems that other human relationship? So new ways of understanding new entities and may be new ways of understanding old ones. How could we start an inclusive discussion with society about a so complex topic using imagination collective learning?

MS. JASANOFF: Paul, do you want to take that?

PARTICIPANT: (Not near microphone)

MS. JASANOFF: Are you both happy with that? Okay.

PARTICIPANT: I have a (?) question. Should be abandon the (?) bad technology and adapt synthetic biology? That would be simpler and definitely covers what we recognize as bad technology.

MS. JASANOFF: Maybe I will take one more on this side and one more on that side and then come back to you.

MR. MILLETT: Piers Millet, Biological Weapons Convention Implementation Support Unit. I am very happy that Asilomar has been mentioned so much this morning. I

was a little bit disappointed that Drew didn't use his fantastic photographs from Asilomar because my question comes down to how do we get back to the point where magazines like Rolling Stone are interested in these sorts of issues and the access that sort of interest from popular culture can give to framing the issues like synthetic biology.

MR. OYE: Ken Oye from MIT, Engineering Systems and Political Science and SynBERC. The two speakers did a great job of laying out two sets of issues. I am going to push a little bit to bring them together. If we look at Drew at the end of his talk, he raised a number of impending disputes and fights. How do we set protocols and standards? How should we evaluate safety and security? What kinds of activities should take place? What kinds of intellectual property and commons, provisions should be made?

Then Paul raised a challenge. He noted that we can't turn simply to the past for framing and at the same time we recognize that there are antecedents for pieces of the agenda that Drew raised and that we have a problem with contending bodies of expertise and a need for ways of doing

the public deliberation on the tough set of issues that Drew laid out. So a simple question to the panelists and to Sheila, what advice would you offer to us on how to set up or structure public deliberation under conditions of uncertainty, controversy and claims of expertise?

MS. JASANOFF: You can select which ones you want to answer.

MR. RABINOW: Obviously these are huge. I think the vocabulary and concept questions are important. One of the first things that I insisted on before accepting to work in SynBERC was that what the NSF wanted was ethic and social consequences and I said I don't actually like that and coin the term human practices, why? Pretty much everyone would agree that a concept like RNA on the go is evaluation and change and what have you. The concept of society is a 19th century concept. It is the foundations of the 19th century social sciences. It is completely meaningless in my view in the 21st century and therefore yet having tried 150 times to get people to stop using society or at least ask them what they mean by it and that there is a vast literature in my friend Nicholas Rosen, London, myself, and many others questioning what the function of

that concept is. Step one might well be that this mutual learning entails mutual learning and that just as I can't talk about the ether in discussions of physics, people better stop talking about society in discussions at least in a nonreflective way. These are where the inner quality of power relations come in at least in this audience and some other audiences. Of course as Drew indicated people hear DNA and go blank but if you said the destruction of society many people would just nod.

That is part of what needs to go on. There are more than the two cultures. There are vast divides of resources, power, inequality, knowledge, and the rest and so having an LC model where there is a little bit of humanitarianism thrown in after the fact is really not the way to go.

I will give one last example in that. We had a conference call at SynBERC a while back and someone said is synthetic biology good or bad for humanity? I said I couldn't answer that question. What do you mean by humanity? They said everyone knows what humanity is. It happened to be a day or two after the Pope and the Vatican had issued a new statement on what humanity was. Well,

obviously I don't agree with the Pope's definition of humanity and this is a rather old debate and with some new contributions. Again, this is a plea particularly also as Sheila is pointing out in a global transnational, multicultural context that much more attention by all concerned to the exciting changes in biology and 15 years ago who knew what interference RNA was. Fifteen years ago or fifteen years from hence I hope no one will use society anymore.

MR. ENDY: I can try and get out three things quickly in response to the four questions. Directly I would not be in favor of replacing biotechnology with synthetic biology. As it pained to me to spend time on I think there is a tremendous scientific contribution from the field of synthetic biology which stands separate from technology and engineering and that's great. I submit for your consideration words like biologics, drawing from electronics, or biological technology expanding the word biotech.

As a second thought it strikes me that we have been starting to see our societies whatever that might be develop a third perspective on the living world. The first

perspective is that the natural living world exists and it does not change. It is static. A second perspective is that the natural living world exists. It changes over time, be an evolutionary process. A third emerging perspective is that the natural living world exists. That's great but by the way we are starting to make our own version of it and we need to figure out how to take responsibility for that.

MR. RABINOW: One of the core definitions of society is a business association so I would certainly agree that that's appropriate to biotechnology and synthetic biology but that's a restricted sense.

MR. ENDY: Thank you, Paul. There is this interesting to me it seems this third new perspective on the living world means that there is at least two new conversations that we need to have. You can imagine the conversations, which take place in this country between the pre and postevolutionary perspectives. Now we have a post synthesis perspective emerging. That means we have to have two additional conversations, the post synthesis, pre-evolutionary, post-evolutionary, post synthesis. Figuring out how to popularize that and get that into rolling stone I don't know.

Advice on structure of venues and conversations I think actually you brought forward a very powerful and important point. We shouldn't expect to bundle many of these issues up and be done with them in one or six months. But given the complexity of the situations and giving the ongoing and continued change in the tools we should expect to have constructive dialogues that sustain themselves for decades probably that allow people to return to the issues and change their minds as things progress.

MS. JASANOFF: Just a very small footnote to Ken since he directly addressed me. First of all I am a lawyer by training and I feel nervous when people want to read words out of the language and I am not quite sure what we do if we got rid of genetics and society in the same breath. Lawyers take more pleasure in reconstrueing words to suit new factual contexts and that is also related to Drew's last point about institutions. I guess Dr. Bement has now left the room but if NSF were to fund a few centers that are really dedicated to the social, political, ethical, and legal studies of science and technology without tying them to particular developments of science and technology, that might be a way to begin in the

academic context or that one would have that kind of training and those kinds of development not as a tail following the dog of the latest best thing in the sciences. That is one thought.

Let me collect a few questions again starting there.

MR. RETTBERG: I am Randy Rettberg at MIT. I am also the director of iGEM. I am also an engineer. I am not a scientist rather intentionally. I am an engineer. I am not an ethicist or an anthropologist. I like to build things. I really enjoy it. I want to have a fun, exciting adventurous life. I don't want to have a cautious life that is carefully audited, examined, reviewed, measured, and all of that.

I think that many people in the rest of society enjoy Red Sox games and when the Yankees play the Red Sox they have even more fun. It is hard to see what is the human measure, the human need to do that but it is very powerful.

I remember when I was in high school. I remember sitting in classrooms and listening to reports on the space program. I remember everybody being excited about the space

program. I remember sitting around in somebody's apartment the night we landed on the moon. This was something that engaged the interest and enthusiasm of people all over. We have a similar thing. We have all shared with the Internet and the growth of electronics and computers.

My question is can synthetic biology be something that is fun, exciting, good, and adventurous that the world can enjoy developing rather than worry about constantly?

MS. JASANOFF: Paul, did I interpret body language to mean you want to say something immediately.

MR. MCCRAY: I will try to keep my questions short. Bob McCray with George Washington University. If today we tried to write the Declaration of Independence we probably wouldn't hand it off to university science faculty and yet Thomas Jefferson when he wrote it was both a political scientist and a scientist. Likewise when J. Robert Oppenheimer worked on the atom bomb, he didn't run around a whole town hold meetings to see whether or not this was a good thing. What I am getting at here is the question of how do you ensure public access and public influence and make sure that you create structures that enable that?

The second part is in a globalized system like we have here with science with wide open frontiers, how do you homogenize for want of a better term, how do you homogenize the differences that exist among the different states in reaching what you would call ethical boundaries?

MS. JASANOFF: Let me take two more and then go back to the panel.

MR. HANSEN: I am J.D. Hansen at the International Center for Technology Assessment. One of the things we are quite concerned about is how you have public involved in these conversations and how we keep from having things sold by height. At one point in my life I worked for United Methodist Church and that helped me understand a lot about ethical language buried in religious language. What constantly strikes me about the conversation about new technologies is how similar so much of it is to tocolyptic(?) literature where the promise of the new technology is no child would die before just a few days. Every person will live a hundred years. That the new technology will really bring in the new age. My question is how do we have technology funded in a way that doesn’t just tap into this is the new messiah that we need to do this? I

have never heard one of the conversations artemisinin talk about how the congo has had the worst war since World War II and that is a large reason for the spread of malaria in this large area. That is a social issue that requires a different engagement.

MS. JASANOFF: Let me take one more on this side.

MR. BEDAU: I am Mark Bedau from Reed College and the Initiative for Scientific Social Responsibility in Denmark. I have a question for Paul Rabinow. The framework that you outlined with the conceptualization of venues and metrics and frames seem very general and seem like it would apply to lots of different large issues that confront society not specifically and especially synthetic biology. My question is there something special about synthetic biology that particularly needs or calls for or requires this new way of approaching LC studies?

MR. RABINOW: Hi Mark. Mark just stated at a book on the ethics of protocells, which I have an essay in, but more interesting essays and a great topic. Two things. The framework is somewhat general for sure and I think that synthetic biology is not absolutely unique and in some of the issues with nano are similar and I have students

working with people at ASU, et cetera. That being said I think what is quite unique about synthetic biology as opposed to nano is really what Drew was outlining for us. This is a construction process which Randy was saying as well which has a good chance of succeeding which is already showing that it can do certain kinds of things, but it is quite distinctive in its shift to, again, I won't repeat Drew's talk. Nanos and technology that applies in a thousand different places without any great unification to it. Synthetic biology is emerging in a fashion such that to the degree that it succeeds and that is unpredictable where it will succeed and how it will succeed. A particular venue from the start would be appropriate it seems to me because of all the construction and production and design questions. I think design is something that would link everything in SynBERC together if we could make that work.

Let me say quickly one other thing. I will give my little spiel and we have heard society again twice. The public is also a meaningless concept. It is an 18th century idea. We could talk about that. There has been vast literature on what publicity means, h(?) and all that. It's generally worn itself out because today it means nothing.

It's the very least plural.

In the UK, which has the most audit society organizations with the various genome centers, genome and society centers. They of course wanted public representation, but of course there is no public so they had to invent one. As Marilyn Strathern and many others in Britain have shown if you want to represent the public you have to identify representatives that there is no amorphous green goo called the public. There are interest groups, there are patient groups, there are lobbies, and there are specific and politic organizations and the rest. That is very good. Why call that the public? That is obfuscating rather than enabling. Then you get into a more technical discussion of who should be represented and how. Then you are more sociological and political. Then you might be by hand waving about the public.

Then finally I complete agree with the question of the Congo, the war in the Congo among others, but the Congo is the most atrocious and genocidal and destructive war, which is barely covered in the press, and of course it has massive ecological, environmental and human consequences, which propagates all kinds of diseases.

Again, one would need to think of a design in which some of this was more integrated from the start.

MS. JASANOFF: Drew, would you like to add something?

MR. ENDY: It is really challenging to figure out how to develop resources without claiming that you are solving a tremendously important problem. One of the challenges in biotechnology in particularly is the humanity of the imaginable solutions of the technology overdrive in many cases the investments. That for example if you are working on an artemisinin production problem not only do you not consider the congo, you also do not leave behind any legacy engineering infrastructure such that the next time you have to do a biosynthesis project of this form it's not $25 million but maybe $2.5 million. That is biotech to a large degree. Meanwhile we find a funding infrastructure where if you can provide a very simple story for how what you are doing is going to save somebody or benefit a large number of people it becomes qualitatively easier to get money.

Let me acknowledge that from limited experience I am sure I am overstating certain things and being naïve in

other ways but for what it is worth. There is a very tremendous challenge within the heart and soul of synthetic biology having to do with figuring out how you advocate for and justify investments and tools independent of any one specific application of those tools. Still working on that.

In terms of public access to the technologies we very naively and the process by which they are developed lacking alternatives started making all sorts of things open as much as possible and having a lot of fun with it. That has been tremendous. I have now encountered some surprises. For example, over the last 12 to 18 months the emergence of a do it yourself biology community which I am not a part of in part because it may not be a community but also because all of a sudden I have found myself institutional somehow and thus not of myself or yourself whatever that might be. So better work on figuring out how to do that would be tremendous.

MS. JASANOFF: I know there are still some questions but with this large a group I am reluctant to cut any further into our scheduled coffee break. So with apologies to – are you waiting to ask a question?

PARTICIPANT: I am very happy to see your

confidence, acquire professional confidence or scientific confidence appreciated. What I am concerned is what happened to GMO would also happen to synthetic biology. It would be (?) rejected or refused by some of the public or in some of the countries. What should we do when we talk about a sense before it is too late?

MR. ENDY: We can talk about it. To be specific almost every year somebody makes a very good argument that the field of synthetic biology should be renamed. At this synthetic biology 2.01 conference in Berkeley a proposal was semi-jokingly put forward to rename it shiny happy biology. Perhaps that would make it more acceptable. The counter arguments, which continue to hold today, are that there are things to have fun with. There things to worry about and it would be disingenuous if not dangerous to disallow fun but also to ignore things that need to be discussed. To the extent that the word triggers a little bit of a response more broadly might help to ensure that we have sustainable conversations.

MR. RABINOW: I think we also need to explore what the GMO controversy was, how it began, and then how it has changed and where it has changed, which is not the same

as you know everywhere. It is particularly acute in Europe but much less out here where abortion and stem cells is much more acute here and much less acute in Europe and in China I don't know. I would be very interested to hear more about that.

Just final provocative comment. This is a challenge for enlightenment thought of promoting the worth and value of science because there is tremendous fear of science and that is not just the enlightenment view that superstition and ignorance reign which they do, Michael Jackson, Sarah Palin and the rest, but there is a lot of work to be done on that so that for instance in the UK and in Europe or Germany tremendous resistance the GMOs and whatever on the one hand. On the other hand, the new cuisine which is embraced by the elite in all of these countries and coming from Berkeley I know what it is. When Alice Waters grows X varieties of arugula in the Sierras, that says unnatural genetically modified organisms that has ever existed in the universe. But since it is not done scientifically it is acceptable.

There is a very strange paradox that people eat arugula grown in the Sierra Mountains, foothills of the

Sierra Mountains, because no one knows what's going on with those genomes. But if you do know what's going on with the genomes or begin to know what's going on with the genomes then people are afraid.

This is profoundly troubling to me as someone who is extremely pro enlightenment and pro science but I think the diagnosis of that type of problem is something we all need to spend more time paying attention to.

MS. JASANOFF: That is a sufficiently provocative note to end on. Would you please join me in thanking the panel and the questioners?

(Break)

Agenda Item: Session 2: Public Policy – Government Perspectives and Approaches

MR. WILSDON: Welcome back ladies and gentlemen. I think we will make a start. My name is James Wilsdon from the Royal Society in London. I am going to be moderating this second panel session. Just a couple of process points before we kick off. I have been asked to remind participants and speakers as this is an open meeting there may be journalists present. I am not quite sure if we are supposed to encouraged or perturbed by that fact.

Secondly, we have been asked just to clarify the outputs of the meeting. Through the joint efforts of the organizing team, the National Academies, the Royal Society, the OECD, just to let you know that there will be a transcript of the entire meeting that the National Academies will be pulling together and putting on their website. We are the Royal Society and OECD will be producing a summary document, which we are trying to still more of the essence of the discussion over these two days. Those will all be available as soon as we can make them so after the meeting.

Our second session is looking now at government perspectives and approaches. We have already touched this morning on globalization and its implications for where synthetic biology research takes place and also how we govern and regulate it. Sheila Jasanoff reminded us in the last session we need a richer comparative understanding of the national cultures of innovation in this area in order to recognize both the differences as well as the opportunities for collaboration and eventual harmonization.

Arden Bement gave us an excellent overview of the context verse in bioresearch here in the US. We are now

going to hear two perspectives from the UK and then from China.

Our first speaker is Professor Adrian Smith. Adrian is the director general of Science and Research in the UK's Department for Business Innovation and Skills, which covers all public science and research investment. Prior to taking up that role last year he was principal of Queen Mary in the University of London. He is a fellow of the Royal Society and a past president of the Royal Statistical Society.

After Adrian we are then going to hear from Huanming Yang who is the founder and director of the Beijing Genomics Institute, well known for his contribution as part of the Chinese team feeding into the human genome project. BGI is now the third largest sensor for genomics research in the world with campuses in Zhijiang, Hangzhou, Shanghai, Wuhan, and Tibet and is involved in a number of large international collaborative projects. We are very pleased to have them both here. I am not going to hand over to Adrian Smith.

MS. SMITH: Thank you for that. Good morning everybody. We had a fabulous session earlier on the very

big picture challenges and opportunities scientifically and the implications of that science. What I am going to talk about now brings that slightly more down to earth from the perspective of a government funder. In my job I look after the strategy and the spend of all the money in the UK that goes through our research councils and goes into our universities for research and currently that is about $9 billion a year.

To understand the UK we have two broad ideas. One is that the government has a legitimate role in setting overall funding strategy for science and research. Once it has made those overall big picture strategic decisions and the funding has gone to the agency there is a line drawn and essentially the government and ministers have no role in detailed decision making about that expenditure, about the particular programs and the particular people and the particular centers to whom it goes.

In addition to the money that comes out of the ministry goes to the research councils and to the universities we also aid and abet various national partners, the Royal Academy for Science, the Royal Academy for Engineering, and in the UK we have other partners in

the funding business including very powerful medical charities like the Wellcome Trust. We have to try and join together in a synergistic way overall strategy and that of course would include how do we think systematically now and what should be our strategies in relation to synthetic biology. I won't comment on the nature of synthetic biology. We had a fabulous presentation on that a little earlier.

How much does one spend on synthetic biology? The numbers I am quoting here are of course totally misleading because there are vast tracks of basic science and biology and chemistry, which are intimately connected with synthetic biology and also work that is going on in engineering. What I am going to quote you now is money that we have released with the specific words synthetic biology somehow to do with it. That currently is totally about $15 million at the moment.

Three main research councils that are involved in this business. We have a research council for biotechnology and biological sciences, engineering and physical sciences and medicine. They are clearly at the forefront of pushing the science.

Can I keep going back to the big issue of the last session and was also raised in the keynote speech at the beginning? We have taken on board right from the very beginning that the funding of the science and the thinking about the implications of the science has to proceed in parallel. We have two other research councils, the Economic and Social Research Council and the Arts and Humanities Research Council and we are also interested in funding them in parallel along the lines of the kind of integration of the science and the thinking about the implications of the science that we heard about earlier.

First just let me say something about the actual science. In bringing together colleagues from communities in various parts of the engineering spectrum of the biological spectrum we have I think an initial task to actually get the right people talking together and using the right kind of language. We are systematically funding a number of networks covering eight of the leading scientific and engineering institutions to deliberately foster that kind of multidisciplinary conversations and the creation of a language where those communities can get together in addition to exploring the toolkits and the technological

challenges.

There is too much detail on this slide but just to give some kind of flavor. The networks are covering a wide range of stuff that you heard talked about earlier. The putting together of the modules, the toolkits, looking specifically at areas of plant biology and linking that to industry and we didn't hear too much about the industrial commercial stuff later but part of our strategy all the way along the line we are trying to look out for and integrate possibilities of industrial involvements. Clearly in the agricultural setting that is highly relevant. A lot of stuff on engineering design and the modularization and just a few other topic headings of that kind that I won't dwell on. But bringing in modelers, bringing in the mathematical community and linking if you look at the second bullet there linking right from the very beginning the ethical issues.

Forming networks, getting people from the engineering, the biological, and the social science communities talking right from the beginning about all the issues that we have heard of.

In addition to spreading the money out in the

networks and trying to encourage those multidisciplinary conversations we have also funded a center at Imperial College in London. The center within the Imperial College is Institute of Systems and Synthetic Biology and at the same time linking that funding to another London institution, a social science institution, London School of Economics, which has a center for research and policy on the social aspects of the life sciences and biomedicine. We are trying to build in right from the very beginning the two kind of themes, the two strands that people talked about in the last session. The aim of the center is really to stand back and identify the big challenges both within synthetic biology then to look at how we establish the relevant research clusters, which will typically involve multiple university institutions, and to link that through to the social aspects of everything that we are doing. And in addition to engage as we go along the industrial and business community with the issues and the opportunities to also have some kind of systematic view of what are the implications of all this with things like intellectual property entering new domains here and collaborative possibilities with industry. Over something like a five-

year time horizon we want to use these centers to actually systematize what we are trying to do overall in the UK.

The international dimension I think seems to everybody immensely important in this particular space. The first talk this morning just referred in passing what we did our engineering physical sciences research council together with NSF had in April of this year a so-called sandpit, the image is that of little children scrambling around and playing and seeing what they can make and find which seems entirely appropriate. That was incredibly popular. A lot of people wanted to come and it acted in a tremendous way to stimulate and identify mutually viewed promising areas of synthetic biology and to look for ways of funding new collaborations and the first instance between the US and the UK. We have agreed in principle through the funding agencies to follow this up and actually do some systematic funding. On the UK/US front that is what we have done so far.

The UK of course is deeply part of Europe and so looking across the spectrum in terms of European activities in very broad brush terms one of the big funding streams in Europe of the framework programs, the research and

technological development, and conglomerates of universities and business from several different countries within Europe perhaps with other partners as well apply for funds there and the sort of level of funds we are talking about are kind of $50 billion over the period of the framework. Within that there is a program called NEST, New and Emerging Science and Technology. That has taken some particular interest in synthetic biology and funded a number of projects.

We have an enterprise and I think somebody is here from that enterprise, TESSY, Towards a European Strategy for Synthetic Biology trying to work out a roadmap for Europe. Then we have other entities, which are looking at commercial aspects and looking at educational infrastructure needs. There is a lot going on in that European space.

In terms of policy issues how in the UK are we trying to grope our way towards a coherent set of policies and attitudes. I am thinking carefully the press being in the room. It can often be the case at least in the UK that an initiative which is launched from government is already suspicious in some sense and so within the UK it is often

most constructive to use arm's length entities like the National Academies, the Royal Society, and the Royal Academy of Engineering, and the research councils which are arm's length from government to actually drive the conversations and start the dialogues. That is what we have been doing in this recent major project paper from the Royal Academy of Engineering in the UK, for example, looking at a vision for the future of synthetic biology and all the time each of these entities are enjoying and encouraging and in a sense has to look at the societal and ethical implications as we go along.

On the ethical side in Europe there is actually a group, which has been charged in addition to look at issues around the ethics of synthetic biology.

We do not have an all singing, all dancing UK policy and strategy. I think we may all be in the same position that we are groping our way towards what does all this mean and sorting out the opportunities and the implications in much the same way as the debate started just a little while ago before coffee. However it turns out there are certain things that we know we want to do and have to do. For example, something again I don't think was

mentioned very explicitly so far the skills. What are the sets of skills, training, education that are needed to create that next generation who are going to contribute in this interface space between engineering and biology?

How do we improve those skills? How do we strengthen overall capability whatever that might mean? It might mean infrastructure. It might mean more bodies. What is the best way of driving forward innovation? Should there be a diversion of funds into some large pot called synthetic biology and people now play in that space or is that premature and we should let people play in their own spaces and define them and then a little further along the line work out what actually it is that synthetic biology means. Certainly within the UK context in parallel with the scientific development and the ethics and the societal aspects the commercialization. What does all that mean? How is that going to work? How are we going to encourage it? How are we going to get the right kind of balance between if you like the science and the commercialization?

Then there is the issue of regulatory frameworks. Just to say what we are starting from the entities we have in the UK with responsibilities that you might broadly say

are in the area of synthetic biology. We have a government department for environmental, food and rural affairs and of course we have a health and safety entity. Within the health and safety executive there is a particular entity called the Scientific Advisory Committee on Genetically Modified Organisms. Synthetic biology obviously goes much wider than that but there are armies of lawyers and others I think looking at our current legislation and regulation trying to see if there are things that aren't actually covered when we did the genetically modified organisms, regulating frameworks that are emerging and do we need new regulations. So far it doesn't seem to be a view that we need any immediate massive new legislation.

Let me go back to skills, which is just a word. It means education training in any broad sense that you want. WE are encouraging a number of leading universities to actually systematically look at what it would mean to create master's degrees and PhD programs with a label synthetic biology. That just lists a few of the things that are going on. In particular it is interesting that the structure that Imperial College is building in and around this has attracted wider interest in Europe as a possible

model for a master's degree that would be recognized across Europe.

I feel very guilty at the title of this slide of course because as we know there is no such as the public and society at least. I now know that. But I would find it rather difficult to write a slide and give a discourse that wasn't 30 pages long without some kind of shorthand. You can construe the word public in whatever way you want that makes sense in connection with this slide. Clearly there is a dialogue with somebody out there or some people out there. Yes, you can dialogue as well. Well if you are going to go the whole hog let's deconstruct business, innovation, and skill. Let's be grown up and say you know what I mean.

A recent document I draw your attention to the Royal Academy of Engineering was the first I think that has gone out on what we might construe as a public dialogue. We have various kinds of surveys going on to try and understand in some inclusive ways public perceptions and reactions and we have had bad experiences in the UK and Europe as was mentioned earlier with the whole GM saga. There are strenuous efforts made to try and understand the deconstruct, the history of that, and how not to go there

again. That is not to say we know the answers but we at least know what the problems were and we are trying to understand better how to conduct the dialogues in the future.

Even worse than the word public I run a unit called the science and society unit and the point of this is a recognition within the research and the science base in the UK and I think we embedded this quite early on the piece in the UK particularly following the GM stuff that you cannot look strategically at the development of the science base without linking it all the time to the social science and humanities insights into the implications in all the processes. We have an actual unit, which is trying to think through all these issues in particular things about communication, about dialogue, engagement, confidence, whatever, and we have a number of working groups we have set up with heavyweight external folk in the UK, many of whom are drawn from the humanities and social science background. We have a group, for example, on science and trust which is doing a major kind of study as to what does that mean. We have a group on science in the media because a lot of public understanding is mediated

through media opinion forums.

We have a strong central recognition of the social science, humanities and the implication aspects and we are trying through these various mechanisms to get that level of engagement.

In terms of a national strategy here are the four things still on the table that we are trying to work through and if any of you have answers please send them to me on a postcard. What should be the role of government in stimulating activity and driving innovation, a particular role of government and government funding?

Another question, within the framework of investing in science innovation particularly within the UK obviously any major changes of direction or emphasis have to be tensioned against the implications of other spends whether it be climate change or whatever. How do we come to a view of that kind of prioritization?

What responsibility should government take, government and its agencies take for the policy issues in and around security, ethics and public dialogue and who are the other players? Who else has those responsibilities?

Finally, what is the positioning if you are a

national funder in terms of what you take on and try and drive perhaps the national advantage or commercial advantage at a national level versus things that we should be doing and cooperating on at the international level?

Those are the things we are pondering. Thank you for your attention.

MR. WILSDON: Adrian, thank you for that very clear and helpful overview and particularly those questions at the end, which I hope we will come back to in discussion. We won't, however, take questions now but we will move straight on to our second speaker Dr. Yuanming Yang who will tell us about the same context in China.

MR. YANG: I am very happy to be here. I think you would agree with me that it is a privilege to be a scientist because we have friends all over the world. That is the first reason for me to thank the organizers to give me this opportunity to -– friends even though there is so many and to make many more new friends in another community.

Perhaps I am not the right person to talk about the common (?) only here as the chief scientist of Omics Project including genomics (?) biology. I would (?) not so

much in the policy making in China in natural sciences, but I am also co-vice chairman of EAGLES, European Actions on Global Life Sciences with the slogan to raise the banners of science in the community. It is part of the Common and the (?) organizations.

It is true that one of the reasons to thank the organizer is to discuss such an important new issue with you all. I want to say we are talking about something with the aim, which is so ambitious as big as to put a man on the moon and we are doing something to change definition of biology. From life is what we want to know, to life is what we make it. That is my personal and general understanding of synthetic biology. We are talking about a new branch on science, which would change the whole world and change the future of man. I think many of you will be familiar with this term or this title, Biology and the Future of Man.

I do think that synthetic biology is one of the biggest breakthroughs in life sciences. We all know that global civilization, social progress, and scientific development all depend on technological breakthroughs like synthetic biology. I am quite confident that in this sense will have significant impacts on our life and on our world,

on our environment and on the whole globe. I would like to congratulate on our colleagues for their success and achievements in the field of synthetic biology. For those in the United States like him we all know, and then for those found in another way also in the States and especially for this report which I am so deeply impressed. It is embarrassing for me to give the talk. This time China almost has not done anything, again a latecomer, as did before in many other fields. For preparing this report I have searched for synthetic biology in the public database of all Chinese governmental funding agencies and just how funds so few projects already funded by the common (?). The first one in my institute beginning October 2006, was funded EC(?) thanks to the help from Victor Hayes(?). He is also here. Thank you for giving the opportunity to be involved.

Then I also searched for all publications related to synthetic biology by Chinese in China. Only 14 articles five groups in Beijing, in Shanghai, in Tianjin, Chendgu, as well as in Taipei. But trust me in a few years you will see the situation will be totally changed.

Please don’t say that China has benefited us too

much from international collaboration in the past decades. In return now China is contributing a lot at least in my field, genomics, for the biggest project in this field, the Genomic Project. Beijing Genomics Institute, BGI, were contributed at least of 20 percent. All the data will be freely available in return for the help from you all.

If we say that in the past BGI would have been regarded as a showcase for genomics – we are now called conventional sequencers. We have done something on the rice, on silkworm, other genomes. Now the situation has been totally changed. We are regarded as the third biggest center in sequencing concerning its capacity and the contribution. Now you can see we have stably maintained our approach 315 megabases per week or 50 gb per day. I am afraid there would be almost the biggest producer of sequencing data.

In past we have all the computers. Now we have expanded our capacity of about informatics of computing significantly. We also have developed many(?) for the second generation sequencers for assembling and for (?) sequencing and for (?) and the metagenomics. We have de novo reassembled the first Asian genome sequences and found

that the difference between Asians and Europeans are much bigger than we expected it before.

We also have been also under the umbrella of international collaboration, the whole genome (?) sequencing. We have just finished the de novo sequencing of the giant panda and the cucumber genomes. Also as part of international collaboration we have sequenced more than 200 meta-samples of human (?) tracks and we also begin to sequence all the samples, or as many as we can credit of pathogenic sequences, bacterias, and others like (?) including both pathogenic and the non-pathogenic strains.

We have just initiated the one plant(?) genomes in collaboration with our colleagues in Canada. I am sure which would contribute a lot to the designing of synthesis of the genome which all of as we know discovery and elucidation of more metabolic pathways signal transmitting(?) pathways and the gene expression migration networks fundamental to synthetic biology. The example has already been heard about us that this one topanoids(?) is a big contribution by Chinese for treatment of malaria, but now this can be produced in (?) skill by our colleagues by means of synthetic biology. As another example the

synthetic biology would change a lot over the biotech(?).

As genomicist I would look at a synthetic biology in another point of view that synthetic biology is a natural reasonable development of further extension of genomics. Now we are reading genome sequences and in synthetic biology we are going to write genome sequences. I was surprised myself by this. The program of life was written four billion years ago. It’s time for us humans beings now to rewrite the program. Many people would be shocked by this claim and don’t know in one decade whether synthetic biology would be accepted by the majority or not.

What I am concerned is any breakthrough in science would have another problem. Remember we all acknowledge, especially as scientists, that science has brought us all good things, but if we look at all the troubles, especially the recent global economic crisis then we cannot deny that science at the least is partially to blame. This is an imbalance world. I do think the communication and collaboration and a mutual friendship, mutual understanding, and a mutual trust among us from various countries would be much more important than ever before. It would be at least equally important as during

the period of a Cold War.

I would say synthetic biology should not create more differences or more troubles or to make the differences already there in favor. In a sense, (?) I would hope that to turn an institute or a country's project from international collaborative project, I would like here again to call for more developing countries to join. Actually what I said when we had the first meeting on the International Cancer Genome Consortium. What can we do? Everything can be done by one or few countries especially by USA and the UK. Everything will be done better through international collaboration. At least we can have better communication and exchange of ideas and second we might possible have better coordination of (?) and the resource worldwide. There would never be too much resource in a single country.

The third if we can coordinate data release or data sharing policies, if we can reach consensus on patenting and other intellectual property right issues and then the things would be done better.

Finally, we are facing the challenges from the public, especially from the bioethics community, from the

bio-safety, from the bio-security and bioethical issues. If we have a sort of coordination or consortium definitely we would have better responses for those challenges.

For me I would like as we already have done for the Human Genome Project, human haplomap(?) project, and Human Cancer Genome Project. We might also have a Chinese synthetic biology consortium to coordinate the effort and resource in China to contribute for the international community of a synthetic biology.

As a scientist in a developing country like China I fully understand the importance of bioethical discussions and self-responsibility or self-governance inside the scientific community. As I claimed in 1984 when I came(?) to China I told my colleagues what we bring back should not only be the advanced technology but also the internationally acknowledged ethical principles which is equally important and seriously regarded in China. As a scientist who is involved in these issues I said several times I would be extremely ashamed as a scientist that what we have discussed at this meeting could really take place. It is a meeting on biological and policy and weapon(?) conventions. I think you all would not misunderstand me. I

am not going to tell you that the synthetic biology would be misused on the people, but I would like to tell myself the risk is there. Perhaps you have not been told of those kind of stories and those meetings. Some of our colleagues are doing something that would be very, very difficult to be accepted by most of us.

It reminds me of a book, which allows so much. It was published here. Probably many of you would have been involved writing this book. It is titled Biology and the Future of Man. The Chinese version was just published at the end of that riot(?) in China and would like to follow the title Synthetic Biology and the Future of Man. Chapter 20 of that book was really excellent. What the summary of the whole book that talked about the nature of the human being and talked about the great (?) now we say challenges especially the opportunities. I loved it.

I would like to quote from it. Human being, the creation of nature, has transcended her. From a product of circumstances, he has risen to responsibility. At last, he is man. May he behave so. Nothing could be done by scientists in China without international collaboration. It would also be the case of synthetic biology. I would like

to quote again a Chinese proverb to thank organizer, to thank you all for your attention. When you drink the sweet water from the well, please don't forget who helped dig it. Thank you very much.

Agenda Item: Questions and Answers

MR. WILSDON: Huanming, thank you very much for that encouraging presentation. I hope we will be able to touch now in the discussion on this balance between competition and collaboration in SynBio. We have 15 minutes or just a few more minutes than that for questions. As before if you could introduce yourselves and keep your remarks down to a minimum to allow for proper response.

MR. WINSTON: Robert Winston, Imperial College, London. Just a comment and then a question to Adrian Smith if I may. It is wonderful to hear great words of how we are going to collaborate but it is a little unfortunate that we can't even begin to agree about the issue of carbon and energy usage with the various countries in the world at the moment. That seems to be a very serious issue that we need to just remember when we are talking about collaboration.

The other thing I really want to ask particularly Adrian is a question about the government and the economy.

It is that recently we have heard more and more rhetoric from our government in Britain but also governments I think in Europe that science would improve economic potential to the extent that now of course science has seemed to be more and more an economic drive. Does he see any risks in that particularly as people in the public may feel somewhat disenfranchised from being able to take a proper part in how science is being used in the future?

MR. SMITH: In terms of issues of general and international collaboration I don't have any particular words of wisdom. It is depressing and makes one slightly pessimistic the difficulties that have been add over climate change and curing rates of carbon release, et cetera. I think we just have to keep plugging away at it. If I may say so the US is a major player in this field and as I read it all the signals from the US in recent times should give us greater grounds for optimism than perhaps recently.

In terms of sciences and economic driver this is a very interesting and double-edged weapon. In the UK the investment in science over the last 10 years that has been such that if you look more broadly you could say that has

been a golden age and the rhetoric in and around the importance of science has been enormously encouraging. Part of the rationale for politicians to line up behind that and to believe it have been the studies that have linked scientific innovation with greater productivity and growth.

On the one hand is has been good for investment in science that rightly or wrongly it is believed that science is an economic driver. The danger is that that rhetoric then turns in on itself and you begin to be selective about the science you found thinking that you know the bits that are going to be the economic drivers. It is the job for all grown ups to keep arguing and presenting the evidential database which demonstrates over and over again the time lags of the impact of science, the serendipity and to do case studies where some of the major effects, 30 billion pound monoclonal antibody business around the world came from scientific serendipity not from focus research programs and it is the job of people like myself to keep conducting that dialogue with government ministers.

MR. YANG: I just have a brief comment on these two issues. First when we talk about international

collaboration I think for me I would rather pay more attention to the personal understanding, personal trust because any official going to collaborate your projects would be based on the personality and the friendship of the people who are doing this, the scientists.

Then the second. Now I am afraid just as far as I know in the developing or relatively poorer countries the people would expect too much from sense and forgetting the importance of political system and democracy or something else. But in the developed or relatively richer countries people or the public would have a trend against the sense. Perhaps they think sense has already done too much good. Now sense would do more harm than good. We need a balance. Thank you.

MR. WILSDON: I will take one from this side.

MR. IMPERIALE: Michael Imperiale, University of Michigan. I also have a question for Adrian Smith. In your efforts to engage the public in a dialogue, have you also involved the media so journalists and those sorts of folks?

MR. SMITH: That is a very simple one to answer. Yes. I think the media fundamentally important quality not only of scientific journalism but the editorial opinion

forming aspect of the media certainly in the UK. There are substantial number of very influential opinion formers who are quite key. We are trying to do two things. One is to get more scientific education into schools of journalism but also to cultivate and make friends with and not see as constant enemy the opinion formers in the meeting.

MR. HENNEY: It is a question also for Adrian. Adriano Henney. I am now an independent consultant formerly in pharmaceutical industry. I was completely support the idea of the engagement of the social sciences and the ethicist in driving for these discussions as you develop where you go. I think what was missing for me in your presentation is an understanding of where the impact is going to come in terms of benefiting society and the economic impact in terms of the question really is how are you going about engaging industry as a partner in ensuring that the academic output has its right focus in order to generate that impact. Are you doing the same sort of thing? I think it is nice that you brought up monoclonal story because of course it may have been serendipity but it was hugely missed opportunity in the UK when it was not picked up at a time and recognized and I think that if you have

that opportunity and that engagement it might have been.

MR. SMITH: The broad question is in my part of the world the dialogue with industry that we do a great deal of and a lot more than we did two or three years ago. We regularly meet with major scientific industrial players. We meet with the confederation with British industry. We have joint working parties. We are bringing in people from that sector to sit on these major bodies, which are trying to look at issues like science and trust. I think we are trying to do an awful lot which is another way of saying I totally accept and recognize that these are major players that we have to deal with.

In terms of communicating societal benefit there was a bit on the slide that I didn’t point to. We have a campaign, which is very much aimed actually just segmenting the market, which is another way of admitting that the public is a very beast. If you segment the market into how you get the attention of young children about the importance of science, we actually have a media campaign running which is called Science, So What? The answer to the so what can be in terms of sport. It can be in terms of health and these are full of images and follow up tracks

and follow up web connections where you try and sow the seeds of the question and then you answer it with a huge range of benefits, which are closely related to the person who is responding to the question Science, So What. I am not saying we know exactly how to do all this but we are trying a lot of novel techniques to get at that kind of communication.

MR. KITNEY: I am Richard Kitney from Imperial College, London. I am the co-director of the Center of Synthetic Biology. Adrian mentioned that we have a strategy in terms of synthetic biology, which I developed with Paul Fremont, my colleague. The key point of our strategy at Imperial is to marry both research and education. We see this as being incredibly important. (?) chairman of the Raleigh Covenant of Engineering Reports we also built that into our report. We have our program of our (?) and PhD program working at Imperial but we are also now working with colleagues that Gina probably in France to develop a European wide masters program. My question actually for both speakers but initially for Adrian is to really ask you whether you are in agreement that what you need in this area is a joint approach as sort of a two-pronged attack on

this problem. One is to develop the research in terms let's say major universities but in parallel with that also to develop the education program to build up the man power to tackle this problem.

MR. SMITH: Easy one to answer. I totally agree. I think we have not systematically addressed that in the past and we are planning to have a major national review of more generally than synthetic biology but addressing the question of the need for national strategy for postgraduate education.

MR. YANG: I know many discussions related to culture are not. We are not just talking about the press media about adaptation. The press media is very important for us to make friends with the editor, with the journalists. I think we cannot avoid communication with them. For something I really cannot understand is the fate of GM in UK as well as the human embryonic stem cell. The latter stem cell is so popular in UK by the public and GM is still now is rejected. What's the difference? Then it related to genomics especially for the human genome research. I have told that the public in different ways many times the risk is much bigger than embryonic cells and

then GM. But I still got the support at the least in China from the public. We have to think of something and then do something before it is too late and don't simply blame the press and media and blame the ignorance of the public.

The second concerning the education.. In China we don't have any education directly related to synthetic biology but we did a lot for genomics or for other fields of life sciences. I myself wrote the preface of the most popular textbook for middle school children and also dialogue with press and media to answer many questions related to genomics also as the first part of the textbook of so-called natural sciences. I think it would be obligation for us as scientists for directly talk with the press and media and the kids. That is what I want to say, thank you.

MR. WILSDON: We have about six questions and five minutes left. I am going to suggest that we just take the six questions and then come back to the panel for a final remark. We will start here.

MS. GAISSER: Sibylle Gaisser, Fraunhofer Institute Systems and Innovation Research in Germany. As Adrian mentioned we developed a European roadmap for the

development of synthetic biology in Europe, which addresses the different dimensions in which how you could stimulate the biology. I would like to know whether you have a similar approach in China. This would be very helpful in order to match activities in Europe and in China and stimulate collaboration.

MS. JASANOFF: Sheila Jasanoff from Kennedy School of Government at Harvard. I have a quick question for Adrian Smith and a more general one for both of you. The quick question is was there public consultation of dialogue over the decision that synthetic biology needed no different regulation from GM in general.

The more general question is you talked a lot about communication dialogue, understanding, and so on and so forth. Do you think either scientists or policymakers need any special skills in order to engage in those activities and if so whose responsibility do you think it is to provide those skills?

MR. PANDIAN: Sithian Pandian from Department of Health in Canada. I am the policy manager for emerging sciences. The policy on synthetic biology as has been nanotechnology for some time. Internationally is that we

have existing regulations sufficient to deal with the products that are coming into the market. I have a slightly difficult situation in taking that position. I believe this is because the regulatory community has come to the conclusion that we are unable to define how to describe the new materials that are coming to us whether it is nano material or products developed out of synthetic biology. Going back to the situation 15 years or 20 years ago with biotechnology we were reasonably clear about the nature of genetic engineering, the science was pretty clear to us, and therefore we could describe the boundaries of genetic engineering and therefore we could tell the industry this is what we are going to regulate from now on. New regulations and acts came up. We are unable to do that now because we do not know how to describe the boundaries of this. This done what happened in Asilomar conference in 1973 the community of scientists is unable to bring out a self-regulating boundary to these new products. We cannot afford to postpone the change of new definition of these new materials and new technologies in order to define a process for revelation of these new products. We cannot deal with it with the current revelation. It is going to go

out of our hands pretty soon.

MR. YANG: I just missed it. What country are you from?

MR. PANDIAN: Canada.

MR. WILSDON: We have three more and then we will come back to the panel.

MR. OYE: Kenneth from MIT. Both panelists have spoken with real passion on the need for partnership in terms of collaboration on development of the technologies internationally and on sharing of the fruits of the technologies. If we to climate change talks right now we see big fights both in the public sessions and in the private sessions over sharing, specifically over intellectual property rights. If we look ahead a little bit one can anticipate fights over security, with security base regulations limiting the diffusion of skills, crafts, and education. To the panelists in the near term and in the long term to what extent do you believe that intellectual property rights, conventions, and their invocation and/or security regulations here pose threats to the kind of sharing and partnership that you envisage.

PARTICIPANT: -- we got divided them into two

parts.

MR. WILSDON: We will just take these two and then we will come back.

MR. MAYNARD: Andrew Maynard, Woodrow Wilson Center. From a policy perspective do you think that having an emphasis on synthetic biology is ultimately going to enable progress however you define progress or do you think it could ultimately create barriers in and of itself which are harder to overcome and thus inhibit progress?

MR. RABINOW: Paul Rabinow, Berkeley. I taught a course once on AIDS and the midterm question was comparing AIDS to another epidemic. The epidemic you compared it to tell you a lot about how you approach AIDS. I would say the same thing here. We have heard about GMOs now eight or nine times. What about mad cow disease?

MR. WILSDON: There’s far more there than you can answer in a minute. Adrian and Huanming have a go and we will do the rest over lunch.

MR. YANG: Just briefly on several questions. The first concern is whether China has a roadmap in synthetic biology to match those in UK and USA. I would say no. That is really my failure. I have tried to convince the Chinese

authorities to fund a synthetic biology until now that humans are very limited or poor and I strongly proposed the 50-year vision by CASS(?). Now there is a short paragraph about the synthetic biology. I am still working together with my colleagues, especially in Shanghai will work catch up.

The second, I am so interested in your question in Canada concerning the regulation. That is really very sad. Now the rule by scientists in any policy making regulation is less smaller and the smaller. I really have to tell you at least in China as far as I know also in many other countries so-called how to say emerging country, developing country -- now it is very difficult for the policymakers just to take again GMO as an example. For China itself they would agree with the USA. They need a GMO, GM food, and GM crops to feed such a huge population. Then also under the strong pressure perhaps just because of the big surplus of the trading between USA and China. China has to import a lot of GM food. Just last year 30 million tons of GM soybeans, half from South America, and half from North America.

Then China still cannot make the position that a

GM food, mainly GM rice, legal in China. That is how -- do you say -- under the pressure from the EU countries. So you see is this a scientific issue. That is exactly what I am concerned of the future of synthetic biology. Further we will have nowhere to speak out our opinions.

Then concerning the international partnership especially the industry and the companies is really a challenge to me. For human genome project under the following (?) you know I have been one of the advocates for free sharing. I do think the upstream knowledge concerning genome just because it is so important for all of us must be freely shared. Otherwise if we -– China is not so bad. If we (?) these basic knowledge and then the framework would be fixed. The other people who are coming earlier to this field would always wonder.

Then how to balance –- then I am serious to criticism by my colleagues that our (?) our country resource. You know this. Why do you publish so much? Is it for nothing? They also need something, need some from the companies and money right. That is the first challenge I cannot answer. For the synthetic biology it is even more difficult. What I still hope we can separate two fields,

something which should be shared freely. Something could be patented individually.

Then the second concerning what we should publish, what not. It immediately reminds me of the pathogen genomes. I don't know in the future someday I myself would be a criminal because we have published so many pathogens, SAS(?) and then avian and the swine, it is so easy to leave the chemical is synthesized or genome as more as a virus. But what would it be a better choice if we did not publish it. I think no way. We have run all the risk. We have to be confident until this moment science has done much more good than harm. That's all.

MR. WILSDON: Adrian, final word.

MR. SMITH: We are desperately running out of time so no disrespect to the questions but I will be very brief. The public dialogue on regulation and is what we've got in the UK satisfactory. I think this is a moving feast and I think there hasn't been any formal public consultation but I think that is because some of us feel we haven't and I think it was alluded to by another question. That we are actually struggling a bit to understand whether we do understand the boundaries of what we are asking and

how it relates to previous things. I think that is definitely ongoing business where we don't know the answers.

In terms of conducting public dialogue does the scientific community have the skills? Absolutely not. There is a big need to think out of the box and one of the things we are trying to do is get fabulous advertising and PR executives into the game.

In terms of the sensitivity, the fights in and around security and intellectual property and the difficulty of getting at government level joined up thinking. I don't have a magic answer to that. I think those are very real issues where there are national interests that won't go away over night. Should we raise the banner of synthetic biology in a very strident way? Does that help progress or hinder it? I actually don't know. I think the jury is out there. My own instinct is to let a lot more happen bottom up and not this moment to create some gigantic top-down part of money labels in synthetic biology. I want to see it emerge from the bottom up.

Mad cows and the rest. Why does stem work and GM

not. In turns into something else, doesn't it? Stem is to do with doctors curing people and saving lives. Tick in the box. GM could have been to do with feeding the millions and savings lives. It got into another box, which was irresponsible industrial greed so we went wrong. So one could learn what happened. It doesn't necessarily mean I think we know to avoid it in the future but I think we know a lot about the tracks that went down in the past.

MR. WILSDON: Great. We are going to pause for lunch. Please try and be back promptly at one for the next session on tools and techniques. But before we go just join me in thanking again our two speakers, Adrian Smith and Huanming Yang.

(Break)

Agenda Item: Session 3: Roundtable Discussions on Innovation in Synthetic Biology

Agenda Item: Tools and Techniques – Enabling Innovation

MS. AJO-FRANKLIN: -- enabling innovation. This afternoon we are going to hear from two great speakers, Christina Smolke of Stanford University, an assistant professor in the bioengineering department, who is one of

the bright starts I think in the field of synthetic biology and has really motivated us in the much beautiful work that she has done in RNA regulation and synthetic devices.

Secondly, we are going to hear from Cord Staehler who is president and CEO of the febit and is an industrial who heads this company for making genomic DNA or genomics to go ahead and really move the field of synthetic biology forward.

I apologize for being tongue-tied a little bit today. My four-month-old daughter did not sleep last night. I am running low on sleep.

However, before we get to them I would like just a quick opportunity since I have the opportunity to ahead and promote what I think where we are in terms the tools and techniques of synthetic biology and where we need to go.

I think without question one of the things that synthetic biology has really developed is the ability to create regulatory networks in which we can control the timing, the amount, and why gene products are made.

The other thing that I think we have really accomplished our tools to create new synthetic ecosystems

by enabling intercellular communication.

What are the techniques that have allowed us to get there? I think as Drew pointed out actually these efforts to create these systems have been somewhat Herculean and the reason for this is that in some ways our techniques are as Drew pointed out 30 years. Particularly in the design sense we basically have a couple major paradigms of design in which we first start with an initial design that mainly comes from our intuition we assemble the DNA and then we test this. Then we frequently find our design system did not work as we would have liked. Perhaps it shows some function. We can either do two things. We can go through the cycle again by mutating the system and then either using selective pressure or just iteratively trying to rationally redesign our system towards a better function.

The other technique that we very heavily rely on is physical assembly of DNA. Cord will talk more about this, but the basic idea is that we are getting better at taking small fragments of DNA and assembling them into larger segments that allow us to actually encode all of these functions that we like.

As synthetic biologists where do we want to go next? The major promises of synthetic biology are to go ahead and tackle challenges in energy, environment, and health. We actually need to start creating more protein tools that can actually function as energy transducers that can function in human and mammalian cells and that can actually work in the extremes of environment.

Another challenge that we really face is the idea of as we build complexity one of the major challenges is how do we actually integrate different modules from different systems. Trying to interface the different modules becomes a major challenge so we are looking at new tools such as creating orthogonal machineries and orthogonal spaces to decrease that complexity.

We are also thinking about can we actually instead of using modules that are heavily based on gene transcription and translation, can we actually do more in terms of protein regulation by engineering in more allosteric regulation?

Lastly, what are the technical hurdles that are preventing us from getting where we need to go in terms of synthetic biology? The major thing that I think we all face

in synthetic biology is being able to go from a conceptual design to a sequence that will fully implement that design in the first try. Mostly as I showed before we have to go through an iterative cycle. Are there tools and sort of computation that will allow us with more frequency go ahead and go from a single design to a single sequence.

Or alternatively we are essentially engineering with incomplete is there a way of actually making many different variations of a single design and actually getting just by this variation being able to get to our desired function much more quickly.

With that I would like to go ahead and turn over the podium to Christina.

MS. SMOLKE: I am going to discuss with you today the application and development of technologies and tools that are being developed to be able to program genetic systems and in particular the approaches that are being taken in the synthetic biology community.

One of the long-term and ultimate goals of what people are doing in synthetic biology is to ultimately be able to engineer systems. Where other engineering disciplines where we have been interested in products of

different types of complex systems that have been engineered showing an example here often times we think about them when we build these systems, different types of functions that we want them to be able to demonstrate. Often times we ask these systems to perform different functions in environments that are not controlled and environments that we can't necessarily predict all of the inputs that they are going to receive and what we will want them to respond to. In doing this then we think a lot of times about the different types of functions that we want to build into these systems. We want the system to be able to respond to its environment and so for that we need to be able to develop sensors. Sensors should need different types of inputs: chemicals, biomolecules, light, and temperature.

We also want the system to be able to affect responses on its environment and to perform different functions. For this we think about functions of actuation or the outputs of the system. There are many different types of outputs that we want a system to exhibit, things like reporting, delivery, motility, phenotype, self-organization, and then finally connecting our inputs and

outputs, our different types of circuitry. Again there we have a wide variety of different functions but things like single processing, remote control, memory, communication, and automated response.

In synthetic biology when we think about engineering biological systems the functions that we want to be able to engineer into that system are quite similar and we can describe them with similar if not identical names. We want to think about sensing and biological systems. We want to think about actuation and biological systems and also how to build the circuitry that connects the two. The approaches and the way of sort of describing the systems can be quite similar although the approaches to design and how these functions are going to be encoded will be different.

In synthetic biology we often have a flow from developing foundational technologies and also frameworks that will support the design and development of these functions and their integration and ultimately then being able to implement these different types of functions into engineered biological systems.

In foundational technology and engineering

framework development we have capabilities like synthesis and fabrication, which you will be hearing about in the second talk in this session. We also have the development of engineering frameworks and things like standardization and composition that allow us to build systems much more rapidly and that perform much more reliably.

Finally there are a wide variety of different applications for which biotechnology has implications for and in particular areas of the environment in health and medicine have gained a lot of attention.

In addition to this linear flow there is actually a feedback flow between these different activities and in particular it is very important that the work that we do in the application area feeds back into tools and technologies that we are developing. It is important both that there is a link and a flow between the tools that we are developing to support applications and biological systems both so that we can build systems faster and more reliably and with less cost, but it’s also important then in doing that that we take what we have learned from that implementation and optimize and develop more effective tools.

Just to give examples of different types of tools

that have been developed and are being developed in the synthetic biology community we have a set of tools that are around fabrication. You will hear about this more in the second talk I am sure, but there have been different approaches that have taken. To just highlight a two here on the slide, one in which researchers took genomes from two different microorganisms and then cut and pasted them together to form one genome. There are also more standard techniques where people chemically synthesize long pieces of DNA or actually shorter pieces of DNA from scratch and then go through systematic assembly strategies to assemble them into larger pieces of DNA and coding entire genomes of microorganisms at this stage.

In addition to those sorts of foundational technologies we also have tools in the area of people developing model circuits. Some examples were given in the introduction. I am highlighting here two examples that were very exciting for the community. The first example on the top we have a model circuit that was put into bacteria to allow bacteria to respond to light. The researchers use this model circuit in order to develop a type of bacterial photography system where they would lay out a film of

bacteria on a plate and then shine a certain light mask on it and it was able to reflect back to them that picture. Really what they were doing there is linking an input of light to an output that researchers could visualize.

The second example Drew Endy in his talk earlier today actually gave a more recent example of a bandpass filter that came out. This is an earlier example of a bandpass filter that was published in bacteria as well. What is interesting I think about these two examples is even more recently the research groups that have developed this bacterial photography system actually took these two model circuits and combined them to build an edge detection circuit.

What you will note here is that we refer to these as model circuits because the outputs are things that we can visualize and they are not yet linked to a real application. There are many examples of these types of model circuits within the synthetic biology community.

On the right hand side we have the applications and we have heard a lot about different types of applications today. The ones that have been the most well developed in the community are biosynthesis applications. I

think you have seen this picture on the right a couple times previously. This is because this is actually a very well developed example in the field of basically taking different types of enzymes from different organisms combining them in a microorganism and being able to produce a valuable product in this case a drug to treat malaria.

You know have other types of biosynthesis applications that industries are looking at as well. We have chemical commodities like 1,3 propanediol and you also have a lot of effort being directed towards alternative energy sources including biofuels and the engineering of microorganisms and algae for that.

What you note in this and in the field of synthetic biology thus far is that there is a gap between the tools that we see being developed by the different academic research communities and the applications and how they are approached in the field.

One question is why does this gap exist and how can we more effectively bridge it? I think was mentioned in the first session today the title of this conference and symposium is really challenges and opportunities. I am listing the challenges that I see that result in that gap

and they also really present with us for us opportunities of how we can most effectively bridge that gap.

The first one that I would say is that bridging that gap actually represents a significant challenge one that is not often appreciated. From the point of initial development of a tool the refinement and optimization of that tool for applications represents a significant challenge and therefore significant investment of time and money. In addition the culture of biological research traditionally rewards novelty and does not equally celebrate engineering contributions. Engineering contributions often times can be thought of being able to reduce something to practice so that other people can take it and use it and that’s often times not getting you the cover of science or nature, which is what would be celebrated more widely in the community.

We have the challenge of being able to try to change models and perspectives for how biological applications should be approached. By this I mean we are building upon many years of research in genetic engineering and biotechnology and so there are sometimes ingrained ideas about how biotechnology should be approached. For

instance, I have talked to people who have told me and feel quite strongly that a biosynthesis application is not feasible if it has more than three conversion steps with artemisinin project had over 10.

I have also heard from people out in industry that their computed applications are not feasible if they are anything beyond approaching base therapeutic or small molecule base therapeutic. So being able to then envision different types of genetic therapies become something that is not viewed as feasible by some people on the field. We have to work on being able to change perspectives.

In addition applications are generally narrowly directed to the end product and not towards developing a technology base to broadly support many different products. When you are a company you have milestones that you need to reach. Your end product will be the product that you are distributing and making money off of and so you don’t often times have the leeway and the funds to sort of think about integrating new tools and technologies, which will take more time, or even leaving tools behind for other researchers and other companies to use to support their applications.

Finally, this is all sort of leading up to the idea that technology and tool development requires an upfront investment of time and effort. After upfront investment of time and effort, it can often pay off in terms of the speed through which you can develop systems but it does require that you make that effort upfront.

Now I am going to go into a case study and do so fairly quickly and just highlight different points from my own laboratory and the tool development that we have been doing. My own laboratory has been thinking quite a bit about tools that enable information processing and control in biological systems. Our approach to this I am going to highlight different aspects of our approach to this. Again, to emphasize the approaches that is taken in design and synthetic biology. Here you see a schematic of what we might think of as an information processing and control molecule. It has basic functions of sensing, control, and computation. If we think about not one particular application that we want to apply this to but very broadly about many different applications, we can list very broadly a wide variety of different types of inputs that we might want to detect on the left hand side and also a wide

variety of different types of mechanisms through which we would want to actuate control.

What is important to note here in approaching this problem an approach we might take that might be unconventional is to not to think about developing one particular molecule for one application that will do an information processing and control function but think more broadly about how we can enable very broadly the design of these types of molecules. This requires us then to integrate different types of engineering design properties and think about how you build scalability into a system, how you can make systems portable across different organisms. If you are working in a microorganism or a mammalian cell how you get that to work and things like compose ability and reliability.

To highlight the approach I am giving again a very specific example of different types of information processing and control devices that we develop in my lab. We could think of them as input/output tools and again to start with the basic premise we have a device. We will call this a device that we want to develop. It is an assessing actuation device as you see there. We are going to break

the design into something that would be more achievable so that instead of saying we want to design many different types of devices what we want to do is actually break the design, decouple the design and more simpler design challenges. In this case what we are going to do is take a device and break it down into simpler functional parts. Now the problem becomes how do you generate and specific sensors and actuators. That becomes the design challenge there and not how do you design different types of integrated sensing actuation systems. The hope would be then that this would be a simpler design challenge to solve.

In order to support that you need to develop frameworks and basically general design principles that will allow you to take these different parts and integrate them through standard methods to build a more complicated device and this is something that other engineering disciplines have sort of developed and the question is how do you do this in biology. Ultimately then you would take this and integrate into an engineered system and finally supporting all of this are different foundational technologies.

We heard earlier today about the importance of computational design tools that would allow you to take different types of devices you build and circuits and integrate them into systems. Finally here we have foundational technologies that basically support this flow between devices and parts and in particular how do you generate and populate these types of refined biological libraries, which we will see later today.

Just to give you an example of this in my own laboratory. We have worked on building these types of input/output tools out of RNA. It is a very similar molecule to DNA. The details of it aren't that important. But what you see here is a basic schematic of the framework where we are defining refine sensors, actuators, and transmitters and we are defining basic rules for assembling them. We have shown that we can do this and in the example that I am showing here we have shown that we can basically take these parts and mix and match them to form different types of gates or functions inside cells. What you see here is an example of us building a buffer gate and an inverter gate. You see the response properties of them over on the right hand side where a buffer gate is basically going to

give you a high output as your input goes high so the X-axis here is input. This is output. An inverter gate will give you the opposite function. The important thing to note here is that we achieve this by simply modulating that transmitter function. So again we don't have to redesign the device every time. We only have to change different parts of it.

The second thing that is again important for this to be applicable to many different types of applications is modularity in the framework so that we can swap out different parts and tailor it to different applications. Shown here is the example of modulator and a sensor where we can take that same platform, swap out just the sensor component that you see there and now get two different devices, one that responds to one pure alkaloid small molecule and one that responds to an antibiotic tetracycline. Again, keeping the framework and design the same, only replacing the parts that we integrate into it.

Another thing that would make these types of frameworks very valuable and important is that they are extensible. What that means here is that you can take those very simple functions that I showed you and actually extend

them by just putting together more parts to build higher order devices. Shown here on the top is an example of an AND gate by coupling multiple sensors and actuators using the same architecture but changing the specific types of transmitters that we use. We can build a NOR gate.

Finally, and again I just want to highlight the challenges here. We want to look how we can actually take these types of tools and implement them into applications. We have heard a lot about biosynthesis. I want to talk about a different example, which will be cellular therapeutics. In this example we are looking at being able to engineer the immune system as a way to treat different diseases and in this particular case different types of cancers. Normally our natural T cells would function by having receptor binding events to an infected dendritic cell. That T cell would then do two things. It would release cytolytic proteins, which would allow it in a very localized way, which would allow it to kill the disease cell. It also releases different proteins that tell it to amplify so that it amplifies the response as it detects its target cell.

There has been a lot of effort and interest in

being to able to engineer different types of immune cell function. In this example we are looking at T cell function where we are doing two things. We are engineering receptive proteins to allow a T cell to recognize a disease cell that it would not normally recognize. In addition what we need to do to solve this problem is to build in a type of synthetic control system around that proliferation amplification response as it does not normally exist in ex vivo engineered cells.

What we have done basically is take the tools that we developed and that I showed you previously for information processing and control and now translating it to a very different application of cellular therapeutics. In this case for the design the thing that you need to understand is that there are two states, a state where the clinician is not administering the drug to the patient and a state where the clinician is administering the drug. Our device will be able to detect the drug molecule and when it does it implements the circuit that tells that T cell to activate and proliferate and therefore in the presence of drug you get a population of your engineered T cells that will activate and proliferate when you want the therapy to

go away, you remove the drug molecule.

The important part about this application and the thing I just want to highlight and bring home is that by building a device framework in which we have these properties of modularity and programmability and tune ability we are able to take a prototype device that we developed in a microorganism with a reporter gene and move it to this type of application. We are very quickly able to implement our higher order, sort of tuning strategies, and move it into an animal system where you see here now with our device and the presence of our drug molecule. We are seeing about a 13-fold difference in growth rate inside of the animal model. Again, this idea of investing in device design allows you then to move very quickly into the optimization, translation to very specific types of applications.

What are the challenges to this field and the challenges to tool development? Again, I am going to highlight this with the particular applications that I am talking about here, but it is more general than just the particular input/output tool development design. The challenges that exist are really down here in these

enabling technologies that support this flow from parts, devices, to systems. In particular I just want to highlight two challenges, which I think are prevalent across other types of tool developments. The first one is having computer-aided design tools that support the design and programming of these types of devices and implementation into systems. In particular for the type of devices that I have demonstrated here what we really need in the field is the ability to start with the primary sequence of this biological polymer, be able to predict structure, which is then linked to sort of quantitative function of the device in the circuit, and ultimately you can link that to system response. This is an area of synthetic biology that needs a lot. It is sort of a challenge both from scientific knowledge but also then in the development of these types of computational design tools.

The second challenge is really one of addressing scalability and in this case, but I think it is true in other tool development; the challenge exists around the libraries of the parts that make up the devices. Being able to have very large library of refined parts that you can plug and play into the device platforms that you build. You

can imagine there are many different applications and for this you would like to have libraries of many different classes of molecules, metabolites for those of us doing biosynthesis to readily optimize energy usage and flow through different pathways, disease biomarkers for those of us working in therapeutics, and finally exogenous chemicals for those of us working in agricultural biotechnology and other types of applications. These refined sensor libraries should feed into standard platforms as you see here and ultimately then what that will allow you to do is feed into a broad subset of different applications: noninvasive diagnostics, bioprocessing, agricultural biotechnology, and intelligent therapeutics. Again, all of this feeding into a wide range of applications and if you do it in a way where you have engineered the devices, the idea is that you have reduced it to practice so other people can take it and use it for their applications of interest and again the challenges are being able to populate these libraries, which really comes down to scientific and technological challenges. A lot of engineering optimization and development is needed in the selection and characterization strategies.

Now I want to take a step back and just briefly summarize the points that I hope you take away from this talk. The first again is that there is a gap that exists between technology and tool development and applications and it is really important for the field that we bridge this gap.

Invention and implementation of engineering design principles is critical to effective tool development. In order to have tools that other people can use and make a broad difference in a variety of applications. The engineering aspect of that becomes very important.

It is also important that we invest time and effort. Thinking about strategies and mindsets that support the implementation of foundational technologies and tools that we foster those types of changes and perspective in thinking within the community.

Finally, I think what is important is that we realize that technology and tool development takes time and it actually takes a lot of resources. We need funding in place that will support this at scales and time frames appropriate for the challenges that we are trying to

address. Thank you.

MR. STAEHLER: I guess we are switching computers here. I can already see it back there so it should be up here. I wanted to speak here today. I think I am one of the rare industry people giving a presentation here today. I will quickly walk you through the big picture from our perspective, our vision then to innovation we bring to the field of synthetic biology, and then lastly what we mean with sustainability because I think it is a key element and we have heard a lot of what went wrong with these genetically modified organisms, but I think it is also a good starting point we can take from a legal perspective on how to handle synthetic biology field.

Just briefly about febit. We are so-called genomic tool provider company. We are mainly backed by Diet Hopp. He is the founder of the software giant SAP. I think quite a lot of the people who became famous in the software industry are now also in the synthetic biology field. We are financed by one of them. The other new investor and strategic partner we got on board last year is In-Q-Tel. That is the investment arm of the broader intelligence community they say. In our precise case it is the CIA who

funds that work to use our technology for the good piece of it, the biosecurity piece, to make sure that we first have the high tech in place and to secure interests and then see how to handle risks which come with it. I think we have a very strong innovation track record and we are located in Boston and in Heidelberg.

The question, which drives us at febit I think, is a very broad and very prominent question and some of you might know where it comes from. It is scientific literature from a very special perspective and it is from a guy called Douglas Noel Adams, short DNA, and he wrote this famous book about the Hitchhiker’s Guide to the Galaxy. We already hear today it is just 40 years after mankind landed on the moon. I think, yes, it is time for another thing here and we have to reach out into the universe. I do believe the more I am involved in genetics in the last 15 years that having a harder and harder time to think that this complex system just happened by accident and then it causes years of actions over a few billions years. But I think we all have to discover a lot on that and we might have to discover on earth and in universe. When he wrote this nice novel here the stories that build a super computer and that

super computer gets asked this famous question about the universe and all the rest. Then the super computer finally after computing and computing has the answer and has this big party and the yelling and now really the answer comes and everybody is waiting for it and it is 42. People keep on yelling a little bit and then the first one asks, stops, and what does that tells us. The computer says I don't know. I forgot the precise question but I have a solution to it. Just build another super computer and we are back what is calculated and then we have to provide a question and then we can use it to provide answer. Then the story goes on and I will entertain another time.

I think the answer is right. I don't know if the answer when you thought about it. If you think about 42 as a 4 and a 2, I think he is absolutely right. It is the four letters of the genetic code, a super powerful system living in all of us. The next evolution we did we invented the two-digital thing which brings it into a position that we can control massive amounts of data understand systems. The interface between the two things is that where genomic tools come into play on.

We heard a lot especially here from China this

morning about what is going on the analysis side and that is all the efforts. It started with the human genome product. It took us a few billion dollars. It took us I think 13 years until we discovered one person. Now you can buy service for $50,000. It is still expensive but we are getting there. That is all about analysis, understanding complex genetic systems. The human as the most complex from the four letters to the two letters of the digital code, but it is also that synthetic biology is the other way around. Now we get more and more of digital understanding of the genetic code. How can we best use it in the other direction? That is really where we build the device around it and that is the tool.

It is just an industry format for doing so and when you talk about it from the industry perspective from an engineering perspective you would rather call it a read and write device then you would call it synthesis and analysis. That’s the language of science. We heard a lot today already about language, about French and English and German and all the others and then all the scientific talks. I can tell you it is very hard to have science person with an engineer to develop systems like that. If

you look into technologies inside there is not much what you can study which you don't have it in a team like that.

I also want to entertain the biological system and I think there are a lot of people in the room who know that much better than I because I am an engineer by training is the biological system we are made of. Imagine you all sitting here and all of you are 70 trillion cells, just that number, and all of the cells have the complete genetic code in them and they all interact. There are a lot of interesting things we learned from sequencing these days, for example, 90 percent of these cells are nonhuman. They only have 10 percent of your body volume because they are just about one hundredth of the size of a human cell, but you are mainly a huge genetic mixture while sitting here. By sequencing we now can even tell that you have a different population of all of these little things on your one hand than on the other one. I don't even want to imagine where that comes from. It is all well orchestrated.

It all works well together and we are also celebrating Darwin these days. I would argue there is a lot of thinking if you think about is Darwin true for us sitting here because it is not the strongest cell surviving

at least in me and efforts at least not for more than 80 years. I think when the strong cells survives and doesn't live together peacefully there is all the tools and techniques we have inside ourselves then we will have a cancer and you have an issue and if we can imagine to get there for decades. I would argue if 70 trillion cells live together peacefully and always maneuver on any conflicts this is not a Darwinistic principle inside a human being.

Now a good question is a group of human being is we all work like Darwin describes it. But take the big number again we are only six billion human beings. Each of us made of 70 trillion cells. That is 10,000 times more. There is another very exciting number I think about. If you backwards calculate you easily come up with that all the cells we all started from. We all started with one single cell. If you all put them together it's just a few grams. In essence means the genetic and the protein variation of human mankind can easily sit on my hand. If we alluded to genetic differences in there I could form a chocolate you can hardly see. We can shoot that into the universe to spread a genetic code. I think it is at least much more effective than have long place and gold.

There is another fundamental principle when we come to synthetic biology to the benefits of it but also where the risk comes into play. That is this super powerful system that our cells are in an environment of a little bit water and energy, self-sustainable, and a system unfolds. When you all started at a day of birth you were a single cell with a complete genetic code. That genetic code is now easily accessible to what we do technically. Once it is unfolded and you are sitting here there is no where that you can get anywhere near in the next hundred years I would say to the genetic complexity of your 7 trillion cells working together while only 10,000 result from this process, 10 trillion. The other 60 trillion start to populate you after birth. That is a super powerful tool and if we can get access to the starting point of cell systems and interconnect it, the digital world in the genetic world, then you can really get a new generation of tools. That is what’s going to make it disruptive.

But it is the concern everybody has. I think it wasn’t correct to have a concern about genetically mode of organisms but the concerns in place are the ones which might occur now and be reasonable because if you engineer a

system like that and it is in the mode of a cell system which is sustainable, all it needs is water and energy. But from there on you can't bring it back. That is the point you have to take care of and that's a fundamental difference to other things. We have to be careful from the starting point because you might not get the chance to correct something.

That is principle what our technology does. It produces a lot of this genetic code, tons of it, and that is one piece of the equation you have to solve to get to send by applications. The other piece of it is the massive production is just dirty. It's just like dirty oil so to say. You want very clean one, very precise one. What we simply did we applied next generation sequencing what they call it. We heard that in picking to have roughly 40 if I counted it right of the systems sitting there. What we do is we take our synthetic DNA, feed it to the sequencer, and get huge variety on there, but all the data points are decoded so transferred in to digital so we have a hundred percent quality control on millions of parts.

Then this is already staged but then we simply use a picking robot and kind of take the little parts we

sequenced and separate them again and then use them as building blocks. Just to give you an understanding by the numbers this primitive first set up, just one machine gives you roughly 20 megabases of sequenced fully quality checked DNA. That is about maybe a third of the work production of last year. Just to give you an understanding that is really just like it was described for computers the starting point to have a function and availability. It brings us to the breaking point. There is this accomplished job but it shows on the top, technology on the low, biology how complex is different elements. Maybe we want to highlight here on the right side is the human genome which sits in every cell of us which has 3.2 gigabases of total code. You don’t have to change all of that to change the functionality and other organisms have bigger ones or smaller ones listed on here. Viruses are rather small, bacteria. Up there is technology so what has been achieved and there are people here so people – completely assembled on the level of bacteria and assembling on the level of viruses is pretty much standard at the moment.

A single system of ours as we have just put it together brings roughly 15 gig a year at the moment. So you

are really coming to the scale of completely programming any type of complex cell. You are still missing a lot of the information understanding as we just learned how they evolve once we reprogram it but at the point now that we can so. That changes the game.

I think we heard a lot about the potential applications there and it is the steps moving forward to explore a lot of them and there is activity going on in all of these fields. I think the positive aspects of it are obvious.

To come to the challenges this is one of it as I said exponential growth and once released it makes its way if it is functional. That is why we need we think guidance to that and we really have to handle that with care in thinking about what we are doing so we will never release the wrong system and let it go. That is the critical point. The power and the complete difference to a computer system sits in this copying but it is also the thing which we have to control because that makes the big difference also on the risk side.

What we do is febit involved in two activities. One is called International Association for Synthetic

Biology where we bundle a group of people who are interested to and get these guidance set up before the complete industry takes off. It is a group in Europe. We are trying to enlarge that. We have an agenda. The most important piece is this code of conduct to start with. We are working intensively on that as really saying what rules and frames can we allow to move forward with programming complete genomes.

We are also working on getting a broader base. In spring there was a similar group formed here in the United States called the Synthetic Biology Industry Agency, different perspective and another co-director of that is Mark Waxman. He is giving a talk tomorrow so we try to bring these things together and there are other groups in Europe as well in Asia who are interested to work on that. We hope to form a very good international setup because the task and the issues are international and that is the thing we work on at a moment.

One thing down here is we are intensely also working on is just control. A lot of these elements have what effect. So virulent meaning viruses although DNA elements which go into a cell and redirect its

functionality. That is the most easiest and most obvious way to change something not completely replace the genetic program but inference in the right way as just simply the starting point because the complexity is low enough to handle it to look at. But it can only be a starting point.

That will be about it. It is an exciting industry. I think it is still in its infancy. It is more like the early days of Intel, for example, where nobody could really envision where to go and they put their last bet I think on doing computer processors because that was the one application that had a few customers for and we know what developed from that. On the other side I would say the complexity of biological system is so high and this massive amount of information, which is run in our organism. When 70 trillion cells can live together, work together, form a big something, it will take us a long time at least in our lifetime that we get a real glimpse of how it works that at least will be what I await. If you are interested to support that effort especially from industry in our academic perspective, you are happy to join or visit our website. Thank you very much.

Agenda Item: Questions and Answers

MS. AJO-FRANKLIN: Questions?

PARTICIPANT: A question to both speakers. I thought that the talks were marvelous and they also fit together very well. Christina emphasized the development of tools as critical to the development of the field noting that there was a little incentives mismatch between the culture and providing the tools.

There is also a material incentives mismatch because if it is infrastructure and comments that you are providing there is a potential free riding issue.

The question that I raise is to both of you. If you look to the role of firms, collectives cutting across firms and government for developing the tools that Christina rightly points to us is critical to the development of the field, what mixtures of initiatives and support from those sources do you see as critical to tools development?

MS. SMOLKE: I try to emphasize the link between tools and applications and I think it is important that there is a link and that there is a flow. I think Drew Endy and other people; speakers earlier today also mentioned the danger of linking too closely to an application early on. I

think that also needs to be recognized. Because again when you are in the very early stages of tool development if you push too much towards one application very early on in that tool development you are going to be narrowing the focus of that tool development and I think the narrowing the broader applicability of any tool that you might build.

It's not exactly I'm sure your question, but let me just first preface that I think that balance needs to be very carefully weighed. I think it also needs to be recognized then the current funding climate what I think many of us find is that it is very hard to actually get funding for research in academic environments without linking to an application. It is very hard to put in a proposal that is strictly tool development without describing at least and make a convincing case for how this is going to change the world and link to some application in order for it to be reviewed positively and to get funded. I think that is a challenge that many academics face and I hear a lot of complaints about for those people who are actually very interested in tools is that they often times feel they have to focus the tool development too narrowly in the beginning and it's not supported.

I would say from the funding agencies there needs to be I think a greater appreciation of this. I think one of Pam's comments early on is part of the challenge is that it is linked to a peer review process and so there also needs to be a change in the culture of those of us in academia who are doing the peer review so that we are actually supporting and positively trying to grow a community for which there is tool development.

I think that is actually very critically important that aspect. Do you want to add anything on top of that from an industry point of view?

MR. STAEHLER: I would agree completely on your view. I think from an industry perspective it is also funding but we are raising capital and we are making revenues out of we pay things like that. I think the environment we are in at the moment is not easy to fund something like this initiative here and this work in the right way. If you are purely doing it for profit basis you are pretty challenged pretty quick because you want to make the best revenue and failure with these product is not doing that. We are not doing the business as fast as we can to make the best revenue. We are trying to make it

sustainable and for that you have a very limited group of people you can do that with. In our case it's Diet Hopp and he is just an entrepreneur himself, a visionary, and he learned himself when he was at IBM that a lot of things which seemed to be -– and new and he couldn't convince IBM to follow and so he formed SAP with his colleagues and made a new success story. He is a person who really gives everything he made was that kind of life story back to the people. So he is the right person to finance this type of high tech but also manage it in the right way. I would say these kinds of resources are rather limited and we need more of that.

MS. SMOLKE: I will just maybe add and say from the point of view of industry and leaders in industry and policymakers. I think researchers and community members in the synthetic biology community are categorizing these discussions, but I think we also need to think about the model under which we do biotechnology right now because a model under which we operate is very IP heavy where you don't have tools that are shared across different companies and different industries and that has been traditionally frowned upon or something that is just very opposite of the

current model. I think we need to have discussions about how we can change the model. Maybe there are discussions around how you make tools freely available and the applications that come out of that are where you develop IP around it. I'm not saying that is the correct model, but I think those discussions also need to happen and people from the different parties as you said industry, policymakers, et cetera need to be involved in those discussions.

PARTICIPANT: I have two questions very fast. One is for Christina or for both of you. I think we all agree that this a field that is engaging a lot of young people yet you spoke of a potentially ambiguous and stifling reward system in form of the publication system. I wondered if you had any thoughts going forward that you could briefly share with us.

My second question is for Cord. You talked a lot about size, but you didn't talk a lot about price and so I wondered if you could comment on where you see the future because again thinking as a young student who wants to make a genome. When are they going to be able to afford to do that without asking their advisor first?

MS. SMOLKE: The question around especially

younger researchers in this field and the reward system that is set up around it I think that is a challenge. I have encountered that challenge myself. I think what would help is having leadership within departments being aware of this difference between science and engineering and developing a culture that actually rewards engineering for those of us that are in engineering departments. I think that that would help so that there are expectations and they can internally set up reward systems that match that.

I think it is interesting that PNAS has a journal but National Academy of Engineering does not have its own journal. Maybe that is something that they want to consider as a way to celebrate engineering advances within the community. I think we are seeing more journals come up that celebrate technology and engineering but it is a question of recognition in the field and that is given from others in the community.

I think leadership within engineering communities particularly biological engineering has to really work on and figure out how engineering can be a celebrated component of those departments in addition to the scientific advances. I think as well the leadership across

different nations needs to think about that as well.

MR. STAEHLER: Maybe a brief comment also on the publication piece. We see on the industry side it is much harder to get things published when I had a much easier time when it was on the academic side. And as any system it is again about networks. As my prominent boss of what's – easy to get good stuff and good papers as biotech company without that directly and not being academic, I would say double the content not even in half the paper. I would say is a reality of our system.

Coming for cost I think it is just underway to be industrialized. I showed you the amount of what was the market last year for -– biology and we are talking there probably of a business of I don't know a few 10 million for the really raw material. We can reproduce in a few days and you are talking about I don't know a maximum of a few thousand dollars. This is disruptive. It will completely change the price bases and the hindering piece will more be how we can apply this amount of genetic information into useful and controlled experiments. That is more coming I think to the software piece mentioned already how you will engineer these things, how you let the cells grow, and how

you have the whole thing under control and well understood and so you don't end up with the wrong result. I think that ought to pace maker's price. Sooner or later it is a question of how fast you can commercialize it but to what it is today implode. So reprogramming a genome would just be extended in a few years I would guess you do in a computer.

Technically it is there. You can do that if we want to. End of the week you have a synthetic genome. It is a reality. Making it commercially available and make it in a way available we all want it, taking all the consequences into account. If you give me the order in our lab we have dozens of these machines sitting. The work production of genetic DNA or things like that this is just minutes on average for us to reproduce that. I think what man can synthesize in DNA you can reproduce in hours to days in our lab. Anything out there, any pathogenic sequence I can turn it into reality over night and I can give you millions of mutants. So anything you ever thought about that piece of reprogramming over viruses is there. It is nothing to do it. Besides you have to take care how you handle that and how you allow that.

A lab -– we have standards for where you allow to work this biological material. There are a few labs only allowed for example to work with this type of virus, an S4 standard. You find a few of them, maybe a dozen in the world to where you break out. An S3 already is super high standards where you have four levels of security until you get in there and you have this nice little d(?) and all that. The sequence information in these genes is on the Internet and it is everywhere. So every one of you can download the sequence of the worst stuff we know onto your computer right now and it will take you seconds. We blast it against these sequences. They are spread all over. You can’t bring them back. Digital sequence information in zeroes and ones about all that we know about pathogens is out there. It is already shared. Nobody is really aware that these technologies can turn that into a genetic code, H, E, C, and T over night. Then we have to see what happens if the biological self-copying system gets in contact with that. That is the piece we have to take care of. The technical piece is there. Is that understandable? That is where we need guidance on how to do that.

MS. AJO-FRANKLIN: We are going to have time for

one more question and then I think we have to move on.

MR. ENDY: Drew Endy from Stanford and BioBricks Foundation cord for you. I want to unpack a little bit of Pam's question. In your talk you talked about the exponential decrease and cost of sequencing going from a bacterial genome read out in 1995 to a human draft in 2001 to the 50,000-dollar street price of a human genome sequence today. If we look last year in the world of synthesis we saw an assembly of a bacterial genome. Would you expect then that six years in the future we will be able to assemble a human set of chromosomes and if not why not? I wonder what your perspective is in terms of capitalization of some of the process engineering requirements around construction of genetic material with all respect to the sequence screening and other issues. If I think about the collapse if you will of sequencing pricing, a lot of that was driven by the demand from the human genome projects and from the economies that took shape where there became known markets around next generation sequencers. Do you see all of that happening naturally for synthesis and assembly of genetic material or is it something completely different that is playing out in

your view?

MR. STAEHLER: I would comment on the commercial piece. It could just work like that. If you would direct your efforts to that it was arranging the machine as it is it could probably capture a complete human genome in a day or two and reproduce it on a daily basis.

MR. ENDY: You have to do the assembly and everything else.

MR. STAEHLER: That is the critical piece of it. It is the amount of data you get and the problem of it that you get pure quality. So the whole assembly piece of it and the process is the quality piece. You can see a lot of the stuff works but what you get as I said is a dirty source what you get with this new technology so you have to clean them. Then when you have elements you keep on building them together and you get the same problem again. You get mistakes. There are errors in there.

The troubling piece is that if you just go for something that is destroying something negative that is good enough. If you have many mutations if you build yourself a huge library of viruses then the mutations can be in favor of you just if you are applying to a biological

system. If you want to have one discreet function you want to make sure that you get a hundred percent pure sequence of what you want and you want to make sure that you understand that or if you don't understand it that you apply to –- system in a secure environment. I would say in these relation standards it now for the tools. You get perfect parts to have a controlled process to make it to something, which is really what you want that will be a few more years I would guess to work on. Does that answer it? Maybe we could elaborate on it.

MS. AJO-FRANKLIN: I think we have time now just to thank our two speakers.

Agenda Item: Eco-Innovation

MR. GREENWOOD: Good afternoon. My name is Jim Greenwood and I am the president and CEO of BIO, the Biotechnology Industry Organization. I just walked in and the absence of somebody telling me to do I guess I will just take over. Let me ask our panelists to come forward if they haven't all. It appears that we have two of four. If the panelists would prefer to not have a stiff neck they may remain in the front row and observe the screens.

Good afternoon. Let me thank the academy for

putting on this conference especially thank Anne-Marie Mazza for her role in organizing it. SynBio has become a hot buzzword that has generated understandable attention recently. Synthetic biology may seem radically new to some but BIO and our members see this field as a natural progression in what we have been doing all along. Human beings have always sought to select genes beneficial to our survival and prosperity from our early history involving the breeding of domestic livestocks and crops and using yeast to make bread and beer. We seek to harness nature's genetic diversity in ways that improve upon what nature provides.

Today biotechnology gives us new tools to select for genes that add beneficial traits and allow us to engineer better medicines, more abundant food, renewable biofuels or other useful products.

Synthetic biology is yet another tool at our disposable to accomplish these goals. I believe that synthetic biology is an evolution of this process not a revolution in our technology. We are now beginning to build custom genes from the ground up. This is a logical extension of gene shuffling, metabolic engineering, and

other technologies already in use.

As with all new technological developments there are new questions raised for society. BIO and our members are very much engaged in developing these technologies and also in making sure that we have proper ethical framework for their utilization. BIO's board of directors has a standing committee on bioethics and its charge is to stay up to speed on technological developments and to discuss ethical issues that may need to be addressed as we move forward. That is why we are proud to be a sponsor of this conference and I am pleased to be here today to moderate this panel on eco innovation.

We call industrial and environmental biotechnology the third wave of biotech innovation following the first two waves in healthcare and agriculture. At BIO our industrial and environmental section has a very active synthetic biology working group. Kinkead Reiling, one of our speakers today, is chair of that group.

I also want to mention that BIO is hosting two upcoming conferences dedicated to industrial biotech. The week after next we will convene the world congress on

industrial biotechnology in Montreal, Canada. I guess it's not too late to register for that, right? It's commercial. In November we will host the Pacific Rim Summit on industrial biotechnology for those of you willing to brave the weather in Honolulu.

Some of the most daunting challenges we will face this century relate to energy and our environment. How will we reduce our reliance on petroleum? How will we reduce greenhouse gas emissions? How can we improve our manufacturing processes to make them generate less hazardous waste? How can we do this so that people in the developing world can do it as well? These are some of the questions I hope our panelists can help us address this afternoon.

Let me briefly introduce our panelists. The first standing to my right is Dr. Sven Panke. Did I say that right? He is an associate professor of Bioprocess Engineering at ETH in Switzerland. Professor Panke's researcher interests revolve around high throughput screening, biocatalyst design, and separation integrated bioprocessing.

We will also hear from Dr. Victor De Lorenzo. He

is the research professor with the Spanish National Research Council. There he heads the laboratory of environmental molecular microbiology at the National Center for Biotechnology.

Dr. Kinkead Reiling is co-founder and senior vice president of Corporate Development at Amyris. Dr. Reiling brings his experience linking protein structures to biocatalyst development to his work at Amyrus.

Dr. Vitor Martins Dos Santos and his degrees in food and bioprocess engineering and environmental bioprocess engineering. He heads the Synthetic and Systems Biology Research Group at the Helmholtz Center for Infection Research in Germany. There he runs several systems in synthetic biology projects focused on the understanding and exploitation of microbial behavior for industrial and medical applications.

Each of our panelists will give a presentation of about 10 to 15 minutes and I will bring down the hammer when it gets beyond that. Following that we will have a panel discussion including questions from the audience and we will begin with Dr. Panke.

MR. PANKE: Thank you very much for the kind

introduction and thanks also for the invitation to come here and present some of the ideas we have on synthetic biology in chemistry. So opposed to what Christina did earlier today taking one particular example of a tool and that can be used broadly and elaborating on how it can be used broadly. I will take a discipline and try to find out what synthetic biology can do in such a discipline.

Let me make a couple of statements at the beginning kind of a disclaimer so that the points I am trying to raise get down the right way. I would argue that in my view synthetic biology is a set of technologies to do biotechnology much more efficiently than before. I would argue that biotechnology is such as a broader term is crucial for future sustainable chemical industry and I would argue that synthetic biology is may be a little in contrast to what my moderator just announced is the way to advance to accelerate this transition.

My first point will be about biotechnology, chemical industry, and sustainability. Just to give us all the same picture those in particular those of you who are not necessarily familiar with the role of biotechnology in the chemical industry. Let me briefly point out how this

usually works. We have a couple of complex renewable feedstocks, wood chips, whatever you can have – wet to dry biomarks. This is usually in one or the other way to be in a chemical processing step reduced to the feedstocks that we actually work with, glucose, glycerol, whatever you want. Then from these feedstocks we produced with bacteria, with fungal strains to produce enzymes, to produce with strains, molecules. These molecules typically can be classified in one of these four sectors below here from the compounds with a relatively low annual volume in terms of a couple of tons or a couple of hundred tons per year, pharmaceuticals, -- to special chemicals of chemicals, polymers, polymers themselves, materials and then you make application if you want biofuels.

As I pointed out volume, annual volume goes in this direction up. The current impact of biotechnology –- goes a different way. I would argue that here in this area the impact at the moment is lowest and it increases into this direction and increases into this direction. I guess the argument for this direction here is –- given the current political situation. The reasons why biotechnology has a large impact here in this area is simply because here

we have a couple of very complex molecules that have never been really able to manufacture in a different way and biotechnology here has traditionally a very important role.

The general outlook on biotechnology in a chemical industry is pretty clear. Everybody predicts it is set to grow. People disagree on the rate of growth, 5 percent for fermentation products per year. It was a famous study by McKinsey that predicted that 10 percent of all chemicals would be made by biotechnology in 2010. This has received an update, of which I am not quite familiar, but still the rates are very impressive, but as I said they differ. The general tendencies are clear. It is going up. The reasons for this are also pretty clear. We have to look at changing raw material base while oil declines. We are interested in novel products. We are interested in an environmentally sustainable production and we are interested in attractive price and cost. All these things can be provided by biotechnology.

You have seen this slide before. I just bring it up again in order to convince you that this is basically reasonably thought through strategy. It’s not that biotechnology just frozen in a product every once in a

while. There are people who have thought very long and very carefully about real and relatively complete product tree starting from biomass and then going into all of the different types of chemicals that you need in order to fuel our current chemical industry. It is a strategy that I think is reasonably well developed to serve as a basis for future chemical industry.

One important driver, this is the session of eco-innovation, has to be the question for sustainability. Is biotech and chemical industry is a sustainable option? I looked at a relatively old report from the OECD from 2001 on the application of biotechnology to industrial sustainability and came up with a couple of points that they were mentioned there as hallmarks of their idea of sustainability, obviously energy use being one: energy resources, energy amount, energy efficiency. That is biotechnology make a big impact there. I would say a careful yes not all new products and all new processes score very good on this level but some do.

Raw materials. I think this is no brainer obviously being based on a renewables. This is a very clear yes. Waste production, amount of waste, type of waste,

biodegradability, et cetera. Basically biotech produces products, biomass and water or uses water. Again, a clear yes for sustainability. Products and by-products are recyclability, stability, biodegradability, et cetera. It is a yes but not as clear a yes as before simply for the reasons that the products -– if we make the same products as before the sustainability doesn't change much, but on the other hand people think about bioplastics for a long time and so on. The point is that some of the products will be I guess much more sustainable than the ones we have before, but others won't.

The number of process itself, the number of processing steps, streamlining, time reduction, et cetera. There are some very interesting examples of why biotechnology is an excellent option. If you think about for example Vitamin B2 production where I guess a 12-step chemical process has been substituted by a 1-step fermentation. This is a very prominent example.

In the end safety, again, in my view a big yes because bioprocesses tend to run at room temperature, pH 7 and under no particular pressure so inherently I guess I would argue safer than much of what we have in the current

chemical industry.

People have very carefully looked at cases to support these arguments here and I won't go through the details. People looked at 21 industrial cases where they compared chemical and biotechnological processing schemes and just a couple of numbers, energy 70 percent down, raw materials 65 percent down and chlorinated solvents and reagents, waste to air, waste to water, et cetera. It is always the same story. The case is very convincing.

Here is one of the classics, production of amoxicillin (?) antibiotic. Again, I am not going to roll through all the details. Just look at this particular number here. Kilograms waste per kilogram product goes down from 50 in 1970s to something in the area of 2 to 5 today.

Sustainability but it is not the only driver. If you look at the case of propanediol again something that we have heard before, a product commercialized by Dupont as part of a new polymer that they market Sorona. This is their chemical structure of this one. This is propanediol. This is the part that is made by biotechnology. If you look here at the life cycle analysis for this particular product then it turns out that the energy that you have to invest

in order to produce a kilogram of propanediol goes down by 35 percent but if you look at the overall energy balance of making this polymer, it turns out that the energy balance is pretty much the same as before. Here clearly it is the novel product that was the driver to biotech and not sustainability. Sustainability is an important point. It's not the only point. There are also many other very strong arguments to do biotech and chemistry. As a summary of this part here I would say yes biotechnology would have a very strong influence on the structure to products and the environmental footprint of the chemical industry.

I take this as a fact and then go on and try to find out why synthetic biology could be important and in particular why we need something new if synthetic biology is that new because we have already something that is metabolic engineering. Much of the things that I just introduced are about making strains, making microbes to find those strains, performing certain functions better than they used to do. People used to do this with metabolic engineering so what's all the fuss.

I would argue that metabolic engineering as it is today reflects very much one central problem of dealing

with biological systems and that is complexity. Let me briefly use these two cartoons to introduce this. This is a metabolic map of the basic metabolism in basically every living cell and to all the dots you see here are chemicals and all the lines in between are reactions that are catalyzed by enzymes. What you see is you don’t see only one strain root going through the system here but you see all sorts of connections that are highly interconnected metabolic network.

If you now switch to perspective and look at the all the enzymes and all the lines here and in this here what we call a protein interaction map. You see between all the dots, which are the proteins now. You see all these lines, which represent presumed interactions. I guess it is easily perceivable that once you throw in another dot somewhere here in the center of this interaction map it is very difficult to predict what type of effect this particular new dot in the entire system will have just as it might not be quite easy to predict if you just put another intermediate here the dot into this system what kind of effect it will have on rerouting the various chemicals, the various intermediates here in the system.

Let me try to make this point once more. Let's assume we want to make something like this here. It is a pharmaceutical. It is market by Sanofi-aventis called (?). Let's assume we want to make these five monomers of this particular pentamer. What you could easily imagine is you start from glucose. It's very cheap. You put together a couple of enzymes of which you know that you can from glucose to this particular monomer and this couple of steps. You assemble all the relevant enzymes and then you end up with this particular molecule. That is obvious what you would like to have, straightforward and simple, but what you actually find is that you do not have five independent roads to these particular monomers, but you have all sorts of interconnections between the molecules that can deviate your intermediates into other pathways.

In addition to that you have traffic lights along the streets that simply tell you not today because this is red. For some reason that this is not quite obvious at the beginning. The accumulation of this particular intermediate here slows down this direction and accelerates this direction and creates all sorts of imbalances but in the end make the pathway collapse. Collapse in a sense that one

intermediate accumulates to an extent that it toxic to the cell or collapses in a sense that one intermediate that is important for the cell to function is drained away into your artificial pathway and the cell again can no longer function.

As a result I would argue that the traditional metabolic engineering experiences a set of problems. In particular in dealing with complexity in the availability of system wide tools for cells and pathway engineering and tools to address or to give the right dimension of complexity to your answer to this problem, and in the availability of pathways and enzymes for quick pathway assembly in your favorite host because as we heard before if you a chance to assemble a hundred thousand base pairs of DNA, you need to have a hundred thousand base pairs worth of information and that’s not exactly easy to come by. It is out there in the literature. You can look for it. It takes a better part of a year but it is not available in the system that is available to rapid engineering and solar engineering.

In other words I would argue metabolic engineering is at the heart still more a discovery science

than a true engineering discipline. I guess we might disagree about the various degrees of trueness of this particular statement but I would argue that in essence this goes in the right direction.

The problem here is that this leads to a disproportionally large number of failed projects, reinforcement of the chemical mindset. Chemistry is better, more reliable, quicker, cheaper, and so on. I worked in a chemical company. I experienced this mindset myself. A lack in chemical talent suitably trained in biochemical opportunities and a severe delay in delivering of the biotechnology promise.

How can synthetic biology interfere? I would argue that the problem with complexity is addressed by synthetic biology in the concept of chassis strains. When I say chassis strains I mean strains that we provide as a basic material to the metabolic engineering world, for example, ideas such as minimal strains, chassis strains that can provide parallel metabolism, alternative chemistries and so on. So all techniques that allow us to evade the problem of interconnectivity of complexity and biological systems. I would argue that DNA synthesis or DNA

foundries, large scale synthetic labs, and computer added design will help us in the large scale engineering of cells and pathways and gene registries, gene circuits, and computer added design will help us in the assembly of pathways for novel products.

Just to give you one idea of how I mean this I talked about reduced genomes. The argument would be that if you reduce this huge network for such a small network and also the chance for interference and unexpected implications is hopefully a lot smaller. I would argue that the future metabolic engineering or the assembly of novel pathways with a synthetic biology approach looks like this. At some point we are interested in a particular product, X or Y. We know that we can start from glucose or the metabolites you like. In between you need a couple of enzymes to select your pathway. It will be computational pathway design. Making use of available databases, making use of directed evolution, rational design, screening in all possibilities. It will be DNA synthesis to assemble genes for the pathways. There will be DNA synthesis and circuits to provide the proper stoichiometry of the pathway. This pathway will then be plucked into a cell but

not your standard E. coli cell as we do today but a chassis strain that will be able to run this particular pathway in an orthogonal fashion without any extensive interaction with the remaining metabolism and the stools here are minimal strains or alternative metabolisms.

I would argue as summary that the successful implementation of synthetic biology for the chemical industry would make the development much more predictable and faster. So robustness of development would be the key word here that we would be allowed to do much more complex production pathways that would disallow us to do novel products. The example here is artemisinin, which we heard about already. I would say it is a true option for to convert metabolic engineering in a true engineering science and I would argue that in order to have biotechnology play its role in chemistry we need synthetic biology in order to make this paradigm shift.

The current bottlenecks I would argue are research in chassis strains. These ideas are research ideas. They are not really fully developed. The other bottleneck is high quality registries, access to the material, and the currently compartmentalized IP structures

if we want to put together a system and has to get every part from somebody else. This is going to be very difficult exercise. Thank you for much and questions will be later.

MR. DE LORENZO: My name is Victor De Lorenzo our chairman mentioned before. I have been for a long time in the business of designing bacteria for environment cell by irradiation. That means going to laboratory, tried to combine these of different origins and put them back into environment with expectation that these new bacteria will be able to exert some degree of environmental catalysis and therefore get rid of some pollution out there.

I am going to discuss with you some of our experiences and I hope that some of them will be useful for taking in the new stage of synthetic batch or synthetic microbes for environment determination as well.

Let me give you some historical perspective. The gentleman that you see there is called Ajoy Chakrabarty and as you see as early in his year ’72 he came up with this idea of using genetics in one way or the other to produce bacteria with superior catalytic activities for getting rid of toxic compounds. He is very happy because after a 10-year fight he was able to get a patent out of the Supreme

Court of the United States in which he could patent a living organism. As you see in the flask in front of him this bacteria were able to the great petroleum or some petroleum components. I would qualify this time in the mid-70s or late ‘70s or early ‘80s of the big moment and expectation for the use of genetic engineering in environmental obligations.

So what can genetic engineering do for the environment? Well, many things can be entertained. I will just mention four of them. The easiest of all is mobilization. So many bacteria, many microbes have been engineered in different ways to have them an increased ability to absorb metal, for instance. Detection -- there are many biosensors out there that have use for different application that have been very successful also in terms of engineering.

They have transformations as Sven just mentioned some of them. In other cases the transformations can be applied to get rid of toxic chemicals in origin, so that means that when one industry has a waste that industry doesn’t know what to do with it, it is possible to set up some catalytic set up for getting rid of it or converting

it either in a (?) or in CO2 water. And here comes the big problem. In situ by degradation or bioremediation(?). The popular idea is that you go to a field, you take bacteria, its spread there and then magically the contamination goes. While this could eb the most ideal scenario, but we know now that for the time being that doesn't work at all. That has been a complete failure of the whole early ideas that were around in the mid-80s on the possibility of using genetic engineering for these purposes.

What went wrong? There are many reasons why it went wrong but this slide summarizes most of them. This slide was made by someone in Oklahoma called Joseph Freda(?) and by the time that people started to realize that perhaps genetic engineering for bacteria to put in the environment was not as easy as one would have liked to have. Basically what happens and this has an air of truth behind it is that bacteria that you do in the laboratory that you construct in a laboratory are not doing robust enough to work in the very harsh conditions that you have in the environment. It is paradoxical that many people are concerned about having bacteria spreading and eating everything. Well, it is just the contract, that they are so

weak that you are unable to deliver them having them working properly.

What can be done? From the very beginning obviously engineering, first as a metaphor and in the last few years as a real technology, has been brought in to metabolic engineering including the part of the metabolic engineering that has to do with bio-remediatiion. And if from an engineer point of view you have a repository of parts, promoters, regulators, genes, and all the rest of it or you have to just go there and perhaps will help of some computational simulation platform you can just make your choice of these and do something like that. You put together the genes, the connectors, the promoters, and then maybe you try to engineer some regulation. In that transformation regulation is not a big deal but still you can put some feedback loop or whatever and in principle it should work fine.

We have all these tools. We may think that we are doing very well but in fact we are not doing very well at all. Why are you not doing very well? Here come some of the topics that have been brought out before in some of the previous presentations.

Number one is that like it or not biological companies, biological elements, biological parts as they are in nature are systematically context dependent. That is nothing that is not very good for engineering. The other thing that was mentioned by you before is that like or not biological objects are always subject to Darwinian evolution, again, something not very nice for engineering. The other thing is that proteins, promoters, and the rest of it are not just floating in there. They are submerged in a soup of thousands of metabolites that may interact with the proteins or other components in many different ways. The other thing and this is something that engineers hate is that their combinations create emergent properties. I will just quote one of your syntheses, Drew, from Internet. Engineers hate complexity. I hate emergent properties. I like simplicity. I don’t want the plane I take tomorrow to have some emergent properties while it is flying or believe in something that you don’t like.

The situation you find out you have is something like this. It’s not something who have reaction A and B and C. What we have is a collection of problems, challenges or nightmares as you want to call them. You want to transfer A

into zed for whatever reason, for transformation, for bio-remediation, all types of things can go wrong. You may have a problem of bioavailability, toxicity, misrouting, diffusion, you name it. This is the type of scenarios that I think we really want to have an impact to have to be ours that this is the real problem that will have to face.

On the basis of these experiences that I just summarized, I want to spend the rest of my talk like declaring seven propositions. I may not get to the end of the seven and the chairman will cut me off but I could argue that there are some relations to come from the previous experience that we and others had on the history of the construction of the environment that I am sure we can capitalize for the upcoming production of synthetic microbes for environmental obligations as well. That means we should capitalize on some of the failures. You can learn many things from the failures as well.

Proposition number one. I will get up to seven if possible. I would argue and I would state and really discuss that. Standards are feasible for a limited number of simple biological objects and functions but not yet for those for which we still ignore fundamental facts. This is

something that is one of the accomplishments of the previous story of recommending DNA for environmental obligations. The consequence of that is that perhaps we should start by standardizing the very tools that we use for putting together different functions and this is something that I have seen that other speakers agree with me.

One of the first things that you can perhaps standardize is plasmids. Believe it or not the plasmid formatting nomenclature and a cloning procedures is completely chaotic. Every laboratory uses a different set of plasmids, different sites, different antibiotics. It is complete chaos. We and others are engaged the last few years in trying to put some order and propose to the community what we call Standard European Vector Architecture, in which we take care of really assembling a collection of replications(?) and cargos that can vary to different extents and made that compatible also with transposon vectors. Let me make a little comment on transposons and use that for environmental obligations where you want to put things into environment. You should never use plasmids because plasmids create all types of

problems in bacteria you put in the scenarios without selective pressure. This is one of the ways to go. The last transcription I will return later.

Proposition number two is that you really cannot escape Darwinian evolution. Instead of trying to avoid it and trying to combat it, my proposition is that we should make an alliance with evolution, with Darwinian evolution. I want to be always subject to evolution. Why should we make an alliance with it rather than trying to suppress it or to ignore it?

I will give you another example. If you want to implant a new activity in a pre-existing network, a transcription network, or whatever then the new implant has to find its way in the pre-existing niche of protein-protein direction for instance. There are only two possibilities. One of them is to make the system orthogonal and this out of interesting ideas in that respect. You have heard some of them. And the other, why not, is to try to evolve that part or that new implant in the new biological systems to just to evolve spontaneously the right connectivity to make the system stable and (?).

I will tell you one example of how forward

engineering hasn't worked very well whereas evolution has worked very well in this context. For a long time different people have been trying to look for transcription regulators responsive to 2,4-dinitrotoluene and this is because the descriptor of explosives and the components of (?) regulator able to respond to this compound you may have the basis to develop by a sensor for a wide area of ecplosives, for instance. Numerous attempts to this forward fashion have failed. However, if you start with a protein, a transcription regulator, that natural response to toluene, and you set up a genetic system and let the system evolve and give some advantage to those protein variance that little by little develop the ability to respond to 2,4-dinitrotoluene then you are able to isolate mutants of this protein that indeed and are able to respond to 2,4-dinitrotoluene. We have recently elected this new protein that we develop in the laboratory for making a biosensor strain that when you are spreading soil indeed is able to detect 2,4-dinitrotoluene in soil. If you want the details you can get the reference there.

This is where you see that evolution may provide a solution to your question that perhaps for an engineering

point of view may not be so much at hand.

Proposition number three. Functions that we still miss in our engineered systems are to be found in environmental DNA. I would like to propose a connection between synthetic biology and metagenomics. Obviously I am not the first to make this connection, but in this context I think it is important that sometimes some of the programs that we have in biologic engineering of misrouting of toxicity and strength may have a solution. If we are able to retrieve from the environment that very activity that will solve our problem even if up front we are not sure of what activity that is going to be.

Again, I show you an example. In any microbial community you have a bunch of different bacteria. You can start the DNA. You have a controlled fraction, an uncontrolled fraction, and then there you have pool of genes, such a pool of functions. Many of them are known. Many of them are unknown. But in principle you have such a wealth of biological activities that in my opinion this will be the big fishpond where one has to go to fish activities that will solve our problems.

Again, I will give you an example. One way to

retrieve activities from the environment is to set up genetic trap that you can do with tools or the concepts of synthetic biology to make sure that when the activity manifests itself then you can select the strains that can grow in a selective medium. This is one of the traps that have developed, others have developed traps, but basically set a trasncription regulator that will detect the production of a compound that will appear only in the right activity has been captured in (?) laboratory. For instance in this process we have been able to capture a new genes for biodesulphurization of the dibenzothiophene -- that is one of the golden areas of a (?) biotechnology. So by doing that and setting that trap in which the capturing of DNA in (?) activity was able to tell us exactly the activity that we were after.

Proposition number four. I think it is very important that taking for granted that this is a new thing collected to students and to enthusiasm and to Internet and all these graphic interfaces and everything. Let’s not forget that there is a history behind and that we can capitalize tremendously from what you may call a transgenerational cooperation or intergenerational

cooperation. That means we think on engineered systems or new systems let’s make sure that we can still use the information that has been produced by our other friends and why not. I will give you again one example.

Transcription. I am very concerned with transcription. With transcriptional you need some with transcriptional standards because I am convinced and everyone knows that that you want to make a serious engineering of genetic circuits you have to take into account what this promoter strength, how much is transcription, in terms of real units and all the rest of it.

There is this thing that we still don’t know enough about transcription to really set up very strong standards on that. There is this issue of metabolic coupling of transcription activity that is still very complicated to tackle, but it is still the same way that in circuits you have current and you have (?) waiver in genetic circuits. There is a big need to have a real good description of transcription units and (?) standards. For instance you go to literature and then you find different reporters and you discover that there are many 5,000 papers

in which different people throughout the years have used (?) reporter of promoter activity. Why should we ignore that there is this work there and why should not capitalize on the work that has been made by other people?

In connection to that again essentially the) finding (?) commission and other agencies we are organizing a meeting in Mallorca in October where we are trying to convince some of you to join us where we will discuss inter alia, this precise problem on how to set up transcriptional standards. We will bring people from all generation of transcriptional experts together with people coming from the synthetic biology field.

Let me just rush the last two thesis. We can now think big because for the first time we can entertain scenarios for engineering global biocatalysis interventions. Why not? So if you look at the history of environmental biocatalysis you are starting with (?) areas expanding and then we can really think on terms of producing in the future artificial cells with the idea of executing some type of artificial and global catalysis. I have to rush through this. I’m sure you can go into the details. We can really think on expanding tremendously the

area of fabrication of bacteria or microbes for environmental obligations.

Finally and let me tell you this is the corollary of thesis or propositions one to five. I leave you with intrigue of what will be the other two. I would argue that we have to bring engineering into biology and this is what system biology is about but also please let’s bring biology into engineering and do not ignore biology if we are going to be successful in the universe of this wonderful field of application. Thank you.

MR. REILING: Hello and thank you for the invitation. I also have to say I am humbled and excited to be speaking at the National Academies. This is a real treat. When I received the invitation I also received a daunting list of questions in a 15-minute time limit. I decided to try and maybe just look at one or two and what synthetic biology means to Amyris. I was also reminded when Drew asked me earlier were we a synthetic biology company and I thought about that a little bit and said we are a company that wants to be profitable whose one of its favorite children is synthetic biology. I will talk a little bit about how we are trying kind of integrate

synthetic biology in to make our processes better, cheaper, and faster.

I had to especially based on earlier talk a bit about the Artemisinin Project, which was the first project that Amyris worked on and has talked quite a bit about as an example of synthetic biology. While I would definitely not disagree with that statement I would also say it is a great example of integrating synthetic biology in with chemistry to be better, cheaper, and faster. What I mean by that is that what was actually done with synthetic biology was to get from glucose to artemisinin acid which is a intermediate found in the plant and has actually thought to interior to the plant with the photo reaction to be turned through chemistry but in a biological system and in a final product. We actually combined the synthetic biology with traditional chemistry and there are quite a few hard working chemists who at times feel left out when they talk about the Artemisinin Project being just synthetic biology. It is very important to integrate the new microbe with traditional chemistry, low-cost chemistry and also with a lot of good just basic fermentation knowledge.

The project was a five-year project which we

finished our part back in December and the goal of course is to save a lot of lives through a more stable and cheaper supply and the project has been partnered off along with the title on the slide partnered off to Sanofi-aventis and they will be doing the final scale-up. So at the end it reminds it we're not actually trying to sell synthetic biology. We are trying to sell as a cheap product that synthetic biology can contribute.

The next area that Amyris has moved into is in biofuels, which is CleanTech but biofuels specifically, which is kind of an interesting mash up of high-tech money, biotech R&D and the constraints of the energy markets. I will comment a little bit on how we think synthetic biology is allowing us to deal with the challenges, which are that you are trying to enter into a novel business eco system and again trying to be better, faster, and cheaper.

What Amyris is a company based around this better, cheaper, and faster into fuels industry. We have part of the company that actually takes themselves fuels and a part of the company that develops new processes. Both of those benefit from what we can do with synthetic biology. From the marketing side actually some of the

synthetic biology allows us to identify something that was found in an apple peel, bring it into a lab, and then eventually sell it as diesel. It is important to say that at the end of the day a switch is useful tool, but it is actually what it allows you to do with that. So it is the idea to pull a molecule from nature and take it to a safe environment and make it. That is how it affects our marketing and sales group which is selling ethanol today but hopefully will sell renewable diesel in the next two years.

Then we have about 150 employees that are working on development of that diesel. That is again an integrated approach of what can biology with synthetic biology be cheaply and then how do you follow that with chemistries. How do you coax a sale into making something very cheaply that can be then transferred on?

I have this slide just to kind of talk a bit about where we fit in that chain and making biofuels. There are a lot of synthetic biology approaches that fall outside of the box that Jen and Brett can speak quite a bit about in terms of synthetic biology. There is work that is being done on the front end with the crops. We don’t focus on

that area but a lot of great work for synthetic biology. Cellulosic deconstruction with enzymes. This is another area where the better, cheaper, faster synthetic biology comes in. There we focused on is how you convert a sugar that you have today. We have actually looked at cane and sweet sorghum cheaply into a fuel. That has really been the focus. This fuel again is molecule you find in an apple peel that you can now make in fermenter at very large scale.

Actually the part of just putting the genes in I don’t think is what synthetic biology is really excelling at because for many years one could put the gene in and make a little bit of a product. What has really been the revolution and for us and what we focused on is the need to go from gene end in many years to fitting in with the development timeline you actually need to get the market for something like biofuels. So taking something that might have been a 15-year project and turning it into a 2 to 3-year project.

This is what in terms of our development site what we have really focused on for synthetic biology. A couple parts. One taking kind of the initial simple

prospect of putting in a set of genes, optimizing production, and turning that into a very fast cycle time process with high fidelity. First thing that we have developed is computer-aided design systems. This is a system called thumper for a variety of odds reasons that we use for design. This allows scientists in a web-based fashion to pick out the genes they want, assemble them through standard interconnections, and put them into a microbe.

Hands-free fabrication. When bringing together engineers and biologists, biologists are very good at understanding the kind of feel of a biological system and making predictions on how to work. Unfortunately they are not really good with high fidelity putting that system together. We have an engineering group that will actually with very high fidelity and thus a low failure rate and lower cost assembles that together. We call it kind of a hands-free assembly.

Then a high throughput screening and metabolic-profiling test. This has been a challenge that we have looked at and a lot of other companies have. An important thing is that synthetic biology deals with something on a

very small scale, but we are going to buy biofuels that are produced at the 200,000-liter scale. You have to have something that allows a genetic network to somehow be translated to a lower cost for gasoline or diesel. A lot of time has been spent in taking a predictive sense from this is if we change this in a gene network. How does that affect the price and that goes through standardized screening and testing in both fermentation and kind of microscreening tests. At the end of the day the goal is to build and test and learn and build again much more quickly with simple synthetic biology systems. Then as the tools coming out of what I call the bleeding edge of development being switches and others come along we can actually apply those new tricks and systems to a set up that allows a read out that you know means to a lower cost product at the end of the day.

At the end of the day what we started off doing primarily looking at the tools of synthetic biology, it was focusing on how we integrate that into a scale-up setting and how do we get the low-cost end product from a innovative front-end microbe that is really allowed that we need to look at when we transition from fun to hopefully

profitable at some point in the future.

I tried to keep my comments brief. It looks like I succeeded. This is a picture of where we are in Emeryville. Please come out and visit.

MR. DOS SANTOS: In the next 15 minutes I will focus essentially on the description of applications in the food field. I will not go so much into the detail on what are the specific technicalities behind these examples. I want to give a little bit of an overview. Synthetic biology is less known. I would like to give an outline of some of the possibilities in this field.

First of all I would like to have a disclaimer. Food in synthetic biology is not about square tomatoes or many other crazy things that you can imagine. It is also not about magic food or ingredients are disclaimer. This is perhaps one of the things that have been terrorizing most people for the last 20 years when you think about GMOs or genetic modified plants and all the rest of it. Synthetic biology in food is not about all this.

In reality I would agree with the statements made early today that synthetic biology is more about to make incremental or perhaps quantum increases in processes or

idea of concepts that they have long ago. Genetic engineering as such reality. There is no engineering behind the so-called genetic engineering some 30 years ago that wasn't an analogy. It is like calling fashion calling fashion engineering because you cut and paste. Just because of the fancy name. In reality synthetic biology now and the bringing the engineering paradigm to biology help us to realize the potential that was not possible to achieve before not that we are really that far yet but the perspectives and the basis are there. We have seen today a number of descriptions and pinpointing the various points, where are the technical challenges, what are perspectives and potentials?

I would like to now rush a little bit through a number of obligations within the fields where synthetic biology could bring benefits. While indeed it is not about magic, it is not about square tomatoes, it is about trying to help us and promote health and nutrition. That is the reason you play around with – you have synthetic biology of engineering of food products or food-related products related to health.

How will we do this? As I was saying up to a

large extent just by bringing the ethos, methodologies, expertise within the various areas related to synthetic biology as today several speakers have presented already. Essentially you follow the same kind of ethos as in while biotechnology just as Sven Panke presented and environment that Victor De Lorenzo just said. Energy, health that will be coming tomorrow. Essentially the ethos and the conceptual methods are essentially the sign. You look at particular products. You try to have rational framework for forward engineering, specific problems in the food industries.

Now some of the applications in the food so essentially I will divide them into four broad categories. You can think of more but just for the sake of the examples today. You could think more of the general field of metabolites, health products, and processing aids that is helping on the manufacturing process of foods and food derivatives.

You have the broad field of probiotics, microbial communities in probiotics or say yogurts for example. You have the more let’s say probably perceived distribution of plants and plant-derived products and feedstocks and the

downstream processing of food waste.

If you look at the first class you look metabolites, health compounds, and processing aids. You see already a rather diverse array of possible compounds. You have the so-called nutraceuticals. Glyco nutrients, all kinds of different nutrients that people use to enhance foods to raise the value of particular foods. You have metabolites and enzymes. These are all kinds of compounds that become more and more important as societies age, become wealthier, become perhaps fatter, so people start to take more attention to food ingredients and nutrients. This is clearly an emerging market.

I have food preservatives. We probably if you are not familiar with the food industries but there is a lot of technology behind it. There is a lot of protection. There is a lot of metabolic engineering so to speak as Sven Panke was mentioning before. Food preservatives, for example, one of the things that people consider important as well.

We have obligations in the fields of flavors and fragrances. If you drink these sweet drinks and refreshments and all the rest of it, there are always flavors. There are always fragrances into it and there is a

lot of research behind it, very large research behind it. This is essentially related to production of metabolites and chemicals, very much in the way that Sven Panke was mentioning before for find chemicals in the pharmaceutical industries.

You can think of biosensors like Victor De Lorenzo mentioned for environmental complications that you could imagine. Biosensors as well for the flavor industry where as instead of having people with very good noses going in an smelling the different types of wines or different types of products. You would have very good systems where you could have many compounds being automatically detected, for example, by an artificial nose. These are technological improvements that you may not realize. In fact most of the foods related industry and research you don’t really realize that is out there. You just see the final products. There is a lot more happening between it. This is where so to speak the advancements are where. This is also where the money is.

If you look at the nutraceuticals and again I break down some of these topics so that you can see already this is a very broad area. You have the vitamins and

supplements who are technically enough for nutraceuticals but unless they put them in these terms of fortification of ingredients and nutrients.

You have all kinds of compounds claim to have beneficial effects to health say resveratrol or antioxidants. You would have soluble dietary fiber products like nutrients. You have sulforaphane. You have flavonoids, isoflavonoids, and all these kinds of compounds that have claimed to have a particular effect.

Here I do not claim that all those compounds do have a positive effect. This is a different research. I go here from the technological point of view. If there is a certain kind of class of compound that is beneficial and is important to produce for particular purpose and the food industries that is where synthetic biology could help.

One small example you have the food preservative, Nisin, that people use for example in cheese industries and the many other compounds to make sure the food items that you produce they reach you at a good shape and they are not degraded beforehand and this is one of such compounds is produced by a natural fermentation by Lactobacillus plantarum and this is a picture of Lactobacillus plantarum

that you have seen in yogurt essentially and they produce these particular molecule. This is a peptide that has an activity against a wide variety of undesirable food-borne pathogens and uses salts commercially.

Now this is done usually this is a structure of the molecule. The reason I showed a structure is not for you to all decorate how we look like but essentially to show that there is a certain pattern as a complex molecule as most chemical molecules are and there are modules are. In this kind of compounds there are many such compounds and synthetic biology provides an opportunity looking at the modularity of designing these compounds and producing these compounds in much more efficient way instead of just fermenting these compounds then extracting as you do with dartemisin(?). That is how this progression used to be done. They would be extracted from plants. People would accumulate them and it was a very expensive procedure. This is what you can do and what you try to do in many of these food components is that instead of just having relatively low efficiency fermentations you try to design them from scratch. You try to design them from a forward engineering perspective and try to have it much more efficiently. You

can increase this for orders of magnitude. This is not just for these particular compound but it is for the whole family of lantibiotics, so-called lantibiotics, which often have the problem of low productivities in natural fermentations. This often is one of the critical cost factors in production of certain compounds.

This is the kind of other compounds. This is not exactly on the food side but what you see here the different colors represent different modules so to speak and the beauty of synthetic biology one of the aims is indeed to use this modularity that you have natural modularity so that you can assemble and producing many different combinations of novel products. If you extract the product that exists you are stuck with it. It is good you did a lot of research perhaps. You found out a particular product that is good such as Nisin and then you are stuck with it. If you look at to enlarge your range of products you need to have ways of generating diversity. That is what people do in pharmaceutical industry. That is what we try to do in food industries as well by relying on these tools and methods of synthetic biology and looking at modularity, singularization(?) and so forth.

This is the only sort to speak technical slide I will show here. In fact where you have your molecules that you want to scale up, you want to stitch together as if you were so to speak (?) with them. Then you would translate this biochemical molecule and the genetic make up into some kind of softer design program, then you test in a very specific way, for example, using microflow(?) than you have bacterial chassis that Sven Panke has mentioned before where you have a very good theoretical and mathematical and experimental framework studying how these interactions among the various components in the complex network. You have to look at interplay between the circuits that you plug in and the chassis as Sven has mentioned for the pharmaceutical products.

As I mentioned the other example is on the biosensors as I was mentioning. That is one of the needs. People are expensive and of course you would still require people to have very good noses but still there is a whole deal of research that you would like to have done let’s say semi-automatically and ideally you would have an artificial nose with thousands of different microsensors. Each microsensor would be based on particular bacteria or enzyme

systems that would detect one specific compound that would allow concentrations. You can imagine this is a Holy Grail in some industries and it is something that synthetic biology could contribute strongly towards to and eventually you would design this kind of systems exactly how it would design for the sensors that Victor described before.

Going on to probiotics and nutrigenomics. People have seen that a growing number of health problems, going from inflammatory bowel diseases to obesity or even autism have been linked to disruptions of human-associated microflora and a host. This has been getting increasing importance. People have been realizing this. That is why people are let’s say increasing their attention on the use of probiotics and then there are ways of interfering and influencing the microflora in yogurt so that you will be able to balance. Some of the balances for example are related to obesity or some of these inflammatory bowel diseases. Essentially probiotics as I said are just supplements. Often of life organisms that most known ones are perhaps yogurts and yakut(?) for example. It is one of them. At least it is popular in Europe.

This is how it works. This is not for you to know

all these but it represents the epithelial cells. You got in here you have your natural bacteria that you have in yogurt see and how they interfere and how they interact to the immune system. They will essentially go through a number of signaling pathways. They are important in the way of human response. It creates tolerance to particular compounds. This is let’s say a relatively complex process, but it is how it exemplifies how these interactions exist between organisms in the probiotic compositions and hosts so the idea is that you start to understand these components and you try to engineer these components in communities, for instance, so that you are able to influence your communities that will have a positive influence in your gut.

Some of the further claims are what to exemplify to relationship between microbiotics and the guts and some of the other claims all of them have references. I can’t say if they are true or not but these are the claims. They are probiotics or interventions that may lead to managing lactose intolerance, prevention of colon cancer or contribution towards it and a whole list of different possibilities.

Providing that these claims are true for other compounds that's the idea of course that you have to have ways of influencing your gut and your microflora to achieve these desired effects. The idea is in fact is to have a forward engineering approach that combines systems and synthetic biology systems in terms of understanding the system. You need to understand what is going in the gut here and then you do all kinds of analysis as today our speakers today in the morning. All the sequencing and analysis of all the microflora as one of the speakers says 90 percent of the cells in our body are actually not ours. They are from these other organisms there and you try to engineer these both from the computational point of view and excremental to achieve right compositions.

An example out there in literature where people, for example, design artificial components by having two different strains being dependent on each other by needing these particular amino acids and one needing these amino acids so they need to work together. By working together and carrying out complimentary functions they are more robust to our expectations and they are able to influence more effectively your system.

I won't go through this but okay I had only touched upon two of the major classes. Then you have of course the plant arriving to your foods and feedstocks. You have the nutrient-enriched plants, plant cellular reprogramming, and production of microbial from starch, waste materials. There is a whole field of it. I just wanted to list them here. There are of course the other possibility of not just using plants but in fact looking at food waste materials to produce compounds that are of interest, for example, as carbon sources for say the biodiesel or biogasoline production. You still need a C source. You can use food waste processing which is very large. You can use this more efficiently. Synthetic biology can help us on that as well. You close your cycle without wasting.

To sum up I didn't hear approach, the technical challenges. I mostly gave the potential or the errors of applications in foods, synthetic biology in foods. The technical challenges are pretty much the same technical challenges by specifics the technical challenge in the pharmaceutical industries that the various speakers today spoke about, standardization, having proper methods of

being able to construct circuits(?), for being able to intervene and being able to have proper computational techniques.

The aging population and increasing life expectancy fuels the growing the demand for this kind of products for health related products and interventions. This is clearly offers a clear market possibility as well. We do believe synthetic biology will play a pivotal role in here. And again as with any other technological activity synthetic biology applied to the food field or any of the fuel discussed to you today has to be of course embedded in a societal context in terms of all the implications and IP ethical aspects and security, biosecurity, biosafety, and so forth. These are aspects that will be discussed I believe tomorrow and today. Thank you.

Agenda Item: Questions and Answers

MR. GREENWOOD: Thank you our presenters. We really did pretty well on time. We are only about 5 minutes early. That will give us 30 minutes for Q&A. I am going to start off with a question just to get things going. If you have a question please go to the mike and I will recognize you soon thereafter.

The first question I would like to pose and I would like one answer from each of the panelists maybe starting from my left and working down and that is five years from now what is the application of synthetic biology that will have the most profound impact on society on the public? What is the practical application that will have the most effect on the quality of life for people for humans on the planet?

MR. PANKE: I would say some relatively low volume biofuel or biofuel additive.

MR. DE LORENZO: In terms of environmental bioremediation I think we will be able to construct bacteria to get rid of pollutants that have never been able to tackle success -- dioxin another very bad pollutant.

MR. REILING: I would modify the first answer, which is biofuels but to say that we can make a lot more biofuels today. There are just certain challenges with existing ones so it would be biofuels that work with our existing cars and infrastructure. You won’t even notice the difference.

MR. DOS SANTOS: I actually don’t think that in five years we will have any clearer applications to be

honest but I do think we will have good applications in making invisible compounds such as the compounds – in the industry that are important that reduce costs and complexity very much, but I am not sure we will have really clear application that you can say well this synthetic biology will save the world. I would like to be a bit careful on that.

MR.GREENWOOD: We will return here five years from now and see who is smart.

MS. MADILL: I have a couple of questions that are directed to all the panelists. I am Gilian Madill from Friends of the Earth, one of the genetic technology's campaign for Friends of the Earth US. A couple of questions. First I know that in all your presentations you mentioned that a lot of the inputs that you need to do the synthetic biology ventures that also are absolutely fascinating and exciting are required feedstocks and a lot of the feedstocks that you are focusing on were corn and sugar cane. I know that existing production methods for corn and sugar cane are pretty unsustainable. Viewing that as a green technology an alternative doesn't make sense to me because the amount of feedstocks you are going to need

to make such a large scale of that biofuel. I mean the existing large scale mono cultures don't work. As an aside from that question if we are going to try and do a green venture why are we making another form of fossil fuel? Isn't the idea to transition away from that?

Then the other question is the idea of control. A lot of these especially the second presenter talked about how this was supposed to be released into the environment to help biosensor to help clean things up, but we are talking about microorganisms that have the unique ability to mutate very quickly and amplify over time. The idea that we could even implement some kind of feedback loop that would prevent them from spreading or changing or interacting with other microorganisms or other higher-level organisms seems -– I don't understand how that works.

MR. GREENWOOD: Who would like to take a crack at any or all of those three questions? Probably we don't need each of you to answer all three of them.

PARTICIPANT: I can try one and two. As far as feedstock inputs. There is a lot of debate exactly how much you can scale the two crops you mentioned debate is corn and sugar cane. I would argue there is data that say we

have headroom in both of those. But what I would say to actually allow us to grow to where we ideally be all bio-derived or nonfossil fuels what we need to have is a discussion around sustainable agriculture and I think once you approach it from that side that it's all about how do have enough biomass to have either electricity or fuels or whatever else we need. As long as you approach it from sustainable agriculture then I think you are going to be fine.

From the point of view of why do we want fossil fuels. We just want to get rid of the fossil part of the fuel. We actually like the fuel itself. It works fine. It's just where we are getting it now. There is about a trillion to two trillion dollars invested in the infrastructure in the US for fuels depending on how you count it. Ideally we just keep using that and just have a different liquid fuel that runs through it.

MR. DE LORENZO: In connection to your second question. The issue of environment release of bacteria – there is vast literature on different tricks for releasing bacteria with some degree of containment and this is not from the times of synthetic biology but it is much earlier

and like 10 years ago and for nearly 10 years there has been vast amounts of money spent in products in connection to your question. I think at the moment the – solution to that is clear. You have other tricks like making a conditional (?) system to have the bacteria (?) for some compound that runs out in the environment. You have a whole collection of things to tackle that. However, I would insist that a proud moment is not what you say. It is just the opposite. How to make bacteria to resist and to be robust enough in the environment to do their job without being out competed by the members of habitat community.

PARTICIPANT: I would argue that there is no reason to assume that you need to go through corn or other forms of directly food-related compounds to fuel any sustainable chemical industry. You can do it as well on agricultural waste products. You can start with cellulose in order to get to glucose as well. In addition to complexity and microbial strains and fungal strains you product but the principle you can as well start from agricultural base products in order to make your products.

PARTICIPANT: I would add a note and that is that biotech crop technology is continuously expanding the yield

per acre even if you are still using for instance the starch from corn. We are expanding the yield per acre, which compensates for again some of the fuel versus food on – arguments.

PARTICIPANT: I was very interested that you asked the panel to predict what would be the situation in five year's time. Lord Kelvin, pretty famous individual in science, predicted five years before Orville Wright flew the first aircraft. You can take it from me heavier than air flight is impossible. More recently in London we have the directors of the Wellcome Trust suggest that the sequencing of the genome is more important than the event of the wheel but so far it hasn't actually benefited a large number of people. In my own field stem cell biology we have made all sorts of promises to the public but they have not actually materialized at least in embryonic stem cells, which is where I work. I wonder if we don't feel given that we are talking about public engagement we need to be extremely cautious about the predictions that we make about synthetic biology and I wonder if your panel would like to comment on that having heard what they have just said.

PARTICIPANT: I would argue that predictions are extremely cautious. I am a hundred percent sure the colleague from Amyris if he was able to tell about all the secrets that he is not able to talk about he would agree with me and would be reasonable 80 to 90 percent chance that it's actually true. I think the predictions were reasonably cautious.

MR. GREENWOOD: I think an interesting phenomenon in all of this is that companies seeking to raise funds have a tendency to speak in growing terms about the magnitude and the shortness of time to which how quickly we will accomplish some of these things and that sometimes does create an effect of over promising. Do you have a question over there?

MS. KING: I am Suzanne King from People Science and Policy, which is a science policy consultancy based in London. I was also the lead researcher on the public dialogue on synthetic biology sponsored by the Royal Academy of Engineering that Adrian Smith mentioned. I was interested in Victor De Lorenzo's presentation because the work we did actually combined a nationally represented survey of a thousand people with 16 people who came to two

three-hour meetings. People who came to the meetings were quite enthusiastic about synthetic biology and its potential with the exception of bio-remediation. I was quite interested in your presentation and the caveats that you put on that. But I was interested if you could briefly say what your proposition six and seven were because I think as you closed it down I very briefly saw that proposition was something to do with social and ethical something or others. I am interested to hear just quickly what your other two were.

MR. DE LORENZO: Well thank you. Number six was that when racing ethical societal security issues we should again learn from the past. I could argue that in the type of programs that we are debating, the connection to these areas are identical. I cannot see really very big difference to the ones that happen in both sides of the Atlantic 20 years ago in connection to recommending (?) technology. Obviously Asilomar have you mentioned but after Asilomar many things happened and I really cannot see. I was in the middle of this debate 15 years ago. I really cannot see anything really new in connection to that. The argument that I wanted to make is that any time there is a

new technology and the example I was going to -– the interaction of anesthetics in the middle of the 19th century. It had tremendous societal debate on the science, the security, the safety, the intellectual property, are we playing God, that sort of thing. These debates have been already there. We have to read what has been debated and concluded by that time and perhaps we will save time on discussion at the present time.

MS. KING: That is interesting because when we did the presentation of the findings of that report Professor George Gaskell from the London School of Economics said the same issues are coming up across a lot of technologies.

MR. GREENWOOD: It begs the question as to whether the industry should take the lead in trying to establish regulatory regimes so that all of this take place within an agreed to framework as opposed to having the same kind of public concerns raised with the GMOs cause an irrational response by policymakers. I don’t know if anyone wants to comment on whether you think that the industry ought to take the lead or whether we need more time to ascertain exactly what kind of regulatory framework we

need.

PARTICIPANT: I would agree that the industry should be engaged in figuring out what the framework is. Of course we will need external groups to help enforce it but we should be engaging at least providing the data so that the right decisions can be made.

PARTICIPANT: I am actually resisting the temptation to follow up on Robert's question, which I think was a very personal one, but I had a technical question that I wanted to pose. I think it might be a very naïve one. I am a physicist, which means I tend to be extremely naïve. There has been quite a lot of talk in this session and the previous session about some of the challenges that still have to be faced to make synthetic biology and yet there seems to be an implicit assumption that bringing an engineering sensibility to biology is ultimately going to lead to something successful. Yet I wonder whether somewhere in this process if we are going to be successful we are going to have to change our ideas of what effective engineering is. Just one very simple I think probably a simplistic example. If you look at how biology works as opposed to how large-scale engineering works there is this

issue of redundancy. If you are designing something systematically to make it work generally you try to make it robust by making it resistant to failure whereas in biology you tend to have systems which fail fairly easily but there are so many backups that you tend not to notice that. I wonder whether we are going to have to go through a paradigm shift of how we think about engineering things in order to be successful in the biological world.

PARTICIPANT: You are not really shifting the idea of engineering. It is just you are modifying the idea of how you can apply additional engineering principles to the way you would do biotechnology today.

PARTICIPANT: But do you think that that's actually a very small shift? You don't think that there has to be a shift in thinking or shift in conceptualization to make that work in the new environment.

PARTICIPANT: I do stand by my comment that I think that if synthetic biology is truly successful it is going to pretty much of a paradigm shift because we have to deal with issues that are in a way at the heart of life, complexity emerging properties, which we need to deal with. I don't think that it is going to be a very easy ride. It's

also not that we have to solve every problem tomorrow. The biotechnology industry has left ever since it began with the problem evolution and it's not problem today to go to antibiotics company you want to visit and then see that there is a producible regime in place, how you can make reliably whatever it is 80 grams per liter of pen G per permutation and they do it once a week every week in the year in six-rack fermenters and so on. Even though the rest of evolution people have developed strategies to deal with this and at least to come up with an industrial relevant set of stabilities and strains. We don't have to succeed in everything tomorrow.

MR. DE LORENZO: I understand that material scientists are growingly excited about what they call soft new materials, some of them inspiring biological origins. I wonder with the time they will be a type of self-engineering and would you bring into engineering biological concepts as well as the other way around.

PARTICIPANT: One comment I would make is that I think biology traditionally was an observational science and categorizing. I think engineering is more of what I would call precise approximation and prediction. I think it

is merging those two. It is not really I would say changing engineering. It is just bringing a slightly different way of looking at things in biology.

MR. GREENWOOD: Did you have a question, sir, on the right?

MR. MUKUNDA: Gautam Mukunda, MIT and SynBERC. On the topic of prediction I am reminded that the head of the royal (?) when asked to comment on the invention of the telephone before parliament said that he thought it would be useful for the Americans but not so much in Great Britain because and I quote, “We have plenty of office boys.” I do think the office boys kind of makes it art. In thinking about this question when I was thinking about the particular applications that you guys were highlighting, what struck me was the fact that all of them were essentially examples of doing something that we already do a little bit better or maybe even a lot better.

When I think about the history of technology and theories of technological innovation particularly from the business world what it seems to me is that there are two learnings from those that we can apply to that. One is that that sort of application the new technologies often have

less of an impact than we think they do. Well, largely because the legacy technology is advanced over the same span of time, sometimes in unanticipated ways. But that the new technologies have a real impact in two sets of things that weren't talked about and may be can't be talked about, right. The creation of an entirely new applications. Applications that were unanticipated because they were simply outside the purview of the people you would go to ask to make the predictions, the heads of big companies, things like that. Or the diffusion of what was extremely expensive and high-cost applications to the broader public. You can come up with lots of examples of any those. One easy one would be GPS, which had much larger impact than anybody thought because it allowed something that was very difficult to do, calculating your position and just made it cheap and easy. This is somewhat different approach.

I wonder if we could think – if I could ask you to push a little bit more with your predictions and your models of future of SynBio and think a little bit about that way of applications and that way of techniques and how you can structure the field in research agenda for the field that would allow those sorts of benefits to be

captured beyond the sort of immediate first wave commercial ones that we talked about today.

PARTICIPANT: The question was very precise five years and that is why I try to be very modest in my prediction. I think if we take the idea of standardization of parts, of engineering strategies, how to assemble these parts in context insensitive backgrounds if we take this really further for 10 or 15 years successfully further then it is a little bit like you mentioned. It is very difficult to predict where the innovation will be because by then we will have hopefully established a platform technology that allows many more people than today to think about relatively incremental ideas and incremental improvements, but many people think about incremental improvements. Many very exciting things might happen. Just ask people started to quote one of the examples of Randy as people started with big computer machines in the 1960s or ‘70s and now everybody has a computer on the desktop and nobody could predict the Internet in 1970. If you ask me for the real killer application 20 years from now I don’t know.

PARTICIPANT: I don’t think that is doable. I don’t think anyone can make that prediction. What I would

ask is how would you think about structuring the field in a way to make unanticipated applications like that, the ones that come out of left field more likely and more achievable?

PARTICIPANT: I think the crucial thing was set by Christina early this morning that technology platforms are really crucial and it should be possible to pursue research in these areas because these are tools that you need in order to spread the potential impact of synthetic biology further and further. I think that would be an extremely important point of the agenda. The other thing is I do think we have a problem with IP because if I want to make complex systems I have to worry about everything part. It is going to get me nowhere.

PARTICIPANT: I would like to add a little bit on that. One of the points that Christina Smolke brought up today that in reality this is the process of doing the research that we need to overcome all the challenges that were presented today because today presented many challenges, but actually we presented potentials and possible applications. In reality all the work will be done on trying to overcome the many technical issues there.

Overcoming these technical issues per se will help generate innovation because you will have to draw on different disciplines. You will have to overcome problems of course that you would not anticipate and by not necessarily all those pursuing let's say the objective of having the application right away you would give room to play around in fact. So having space also financial space to play around within boundaries of course is I think an important aspect that will help in fostering new directions and potentially new inventions in the future that nobody can predict as you say.

MR. DE LORENZO: No anticipated applications are the result in many cases of freethinking without limitations of intellectual property and the rest of it. I think we need to maintain in synthetic biology realm a degree of freethinking reservation for people to really imagine whatever is scenario. I think with all the limitations that is a wonderful one. To allow and encourage people to come out with trace areas(?) and maybe some of them at the end will result in very interesting applications.

PARTICIPANT: I want to comment on what Jim said

earlier the idea of what I think this conference and others is doing is getting out in front of regulation and framing it because you can do a lot of innovation and kind of bounded hope but if you are trying to innovate in an area of fear of what the consequences could be you are actually going to not get the unintended positive benefits. It is building a regulatory framework that allows innovation.

MR. GREENWOOD: I am sorry if my question about five years to short appeared. It is just that I grew up watching the Jetsons and I was sure we would all have personal flying saucers by now. Did you have a question, sir?

MR. WAXMAN: Mark Waxman from Foley and Lardner. I wanted to pick up on the last point and a topic that you opened today and we will get more into tomorrow, which is this topic of regulation. There was a whole panoply of things that were put on the board ranging from let’s invent in the lab to let’s go sell over the market pharmaceuticals and then a comment that we ought to have a regulatory scheme which presumably would govern everything from working in the lab to construction to distribution, sales, marketing, and the like. I am intrigued by the comment the

industry ought to go get in front of regulation which I support but I am curious from the panel just exactly what it is and who it is you think ought to be regulated as we sit here today that we actually want to get in front of. I understand biosecurity. Let's put that aside because that raises its own problems. Let's talk about the commercial aspects that you just raised and say okay what do you think we ought to regulate and who ought to do it?

PARTICIPANT: What I would say is actually I think all of the pieces are regulated today so the discussion is do we need to adjust the regulations because of new technologies. There are established groups that look at an engineered microbe, how is that regulated in the environment when you scale it up? For instance we are going through registering our microbes so that we can use them in production. We registered our fuels already so we can go on production. It's not as much that it is an unregulated environment and we better get some regulation. It's we need an ongoing dialogue to make sure that the regulation does what we need which is allow innovation and prevent problems from occurring.

MR. WAXMAN: When you say registration I

understand, but when you say so that it creates a dialogue and it regulates that suggests there is some sort of restriction or some sort empowering certification that would allow you to continue to participate. Are you talking about either one of those things or are we happy with the Department of Agriculture, the Department of Energy in terms of what we see right now?

PARTICIPANT: For instance all the work that we do in our labs is currently regulated and we can discuss what happens and if we need additional regulation that should be part of the discussion. I think we are fine but let’s have a discussion. When we go to scale there is an agency that we will go to and discuss what we have done and how we think it interacts with the environment. We will actually have data that we bring and present. What I would rather have is a discussion around whether or not that is sufficient to protect the public versus just a fear of something bad happening. There is regulation. The discussion should be around is it appropriate. I think it is but we should have the discussion.

PARTICIPANT: A slightly more European perspective on that. The idea of novel regulatory rules

required happens to a much smaller extent in Europe and this might have something to do with the fact that the original network of regulations that is in place is somehow stricter or closer network of regulations in place. This has a good side and a bad side. The good side for me is as a scientist is that I move in a set of regulations that still allow me a lot of liberty to do whatever I need or whatever I want to do, but on the other hand there is also clear framework that I can present to the public saying that we are doing new things here and we feel we do exciting things but as a clear set of regulations that defines the room in which I can move. For my point of view I have only very few discussions of this type in Europe because simply the framework is in place and it is pretty clear how things are going. All the discussions about regulations that I see a lot in the US are simply not that important at this point for synthetic biology in Europe.

MS. NELSON: Janet Nelson, Parsons Corporation. We had a nice discussion about the potential applications of synthetic biology and some speculation and I would like to draw back to the point that Christina Smolke made about bridging the gaps between the tools that are being

developed and how these applications can become commercial realizations and economical. We have just some discussion about the regulatory issues but I would also like to ask if there are pieces missing in bridging this gap from the development of these tools from the bench top to pilot scale or commercial scale realities. Are there things in our infrastructure that are missing partnerships, collaborative efforts? Do we need a new paradigm to make these a reality?

PARTICIPANT: Are you asking research agendas?

MS. NELSON: From an industrial perspective. From a commercialization perspective.

MR. DE LORENZO: My real profession at this institution is very different in America, the US, and perhaps in nation countries. The connection between academia and industry is more fluent than the situation we have in Europe and perhaps the solution is to tackle the point you mentioned cannot be analyzed and they require case-by-case reflections and actions.

MR. PANKE: Something that I would -– what has been said before is if you believe in the small, medium enterprise model to be the actual driver of commercial

innovation then I would argue that IP or compartmentalization of IP is a problem. In particular if you are not with a big company where you simply can do a freedom to operate analysis on the order of a couple of hundred thousand dollars or euros. But if you are just a university group that has a cool idea or wants to go ahead with this then IP remains a problem. I think it is a problem in driving innovation.

MR. GREENWOOD: Final question.

PARTICIPANT: The question actually cuts across the fact that we have a whole bunch of disaggregated and compartmentalized areas. We have talked a little bit on IP. We have regulations that are set forth and promulgating by a whole bunch of agencies. It is certainly not an unregulated field, but how these pieces come together regulation and IP may be a little problematic. If you look for example at the relationship between firms, regulatories, and academics on ascertaining safety. In the area of GM seed we have had companies asserting claims to control intellectual property that have forestalled or prevented testing of the seeds by academics, which then creates a situation where regulators are in a sense denied

access to a source of information that might be useful over the long term. This is Syngenta, Pioneer and some others. The question here is that if we step back and look at the combination of a patchwork of regulations, differences in intellectual property, US and Europe on fundamental research exemption, as people who are living in companies and in the academy, what combination of intellectual property conventions on fundamental research to attack on uncertainty and regulation makes sense to you?

PARTICIPANT: You tell me. You are the expert. I don’t know. From European perspective I have an idea that I am fenced in by dozens of different authorities, offices, and so on. It is pretty clear whom I talk to of which step of the innovation chain. As I am an academic, as I am an entrepreneur or whatever to me it is pretty clear which way I go. I don’t have this experience of all sorts of authorities coming down on me.

PARTICIPANT: It’s not that bad in the US right either. It is simply regulated. But I am talking here about responses to the uncertainty associated with emerging applications and the potential use of IP to limit private studies that could better evaluate or assess risk in those

areas of uncertainty.

Obvious a very good question. Thank you all. Our time is up. Thank you to our panelists for their excellent presentations.

(Break)

Agenda Item: Health and Medicine

MR. KITNEY: Good afternoon everyone. I am Richard Kitney. I from Imperial College London as I think I was saying earlier. I am the moderator for this session on health and medicine, the final session for this afternoon. I'm not really going to say a lot by way of introduction to this session except to say that I will make two points. The first point I will make is that there has been quite a lot of discussion this afternoon about the complexities of synthetic biology and as somebody who works in this field because I am as I was saying earlier the co-director of the Center of Synthetic Biology at Imperial College. Nobody ever told me that this was going to be easy so I think that is something to bear in mind when you look at some of the developments and things like transistors. We are still 50 or 60 years to get to the point where we are at now if you project that far out in terms of synthetic biology I am

sure I believe there are going to be some major applications, major industrial developments, et cetera.

Why now is the question I am often asked. For me the reason is because we have now reached the point in terms of sequencing the human genome and sequencing in general plus the power of computers, the Internet in such a way you have the confluence of the two fields, biology on the one hand and engineering and physics on the other, which has made this new field of synthetic biology really possible.

I have spent quite a lot of my research life working on biomedical applications of various kinds and so when I started working in synthetic biology, for me it was an extension, really exciting extension of a lot of the work that my colleagues around the world have done in the past in terms of different applications. For example, in physiological applications now beginning to apply the same kind of engineering theory, physics theory, signal processing, systems theory, et cetera to looking down at the areas related to synthetic biology.

It is particularly pleasant for me actually to moderating this session on biomedical applications. As was

said in the last session it is already quite difficult to predict what are the applications indeed in this area. If we wanted to project (?) I believe it is pretty hard to set any kind of timescale but I think we will see major advances in biosensors coming out of this field. I would also probably predict that we might see major advances in terms of vaccines, third-generation vaccines being influenced by synthetic biology and indeed optimization of drug developments, which Adriano is going to talk about.

That really takes me there forward to brief introductions to the three speakers all of whom I know well. The first is Adriano Henney who is sitting at the front here. Adriano has a PhD in medicine so he is from the UK. He has worked for many years in research and until very recently I won’t go through the whole biographical sketches of these people. He has until recently been a senior member of AstraZeneca in the UK and is now an independent consultant.

The second of our speakers is Frank Notka who is a very senior scientist at Geneart in Germany. Some of you who have come Europe as I do Geneart are really exciting in a company that we actually work directly with. I think it

is a great pleasure for me to have Frank here to present the industrial perspective from the point of view of Geneart in terms of synthetic biology.

Finally, we have Roman Jerala who is the head of the biotechnology department at the National Institute of Chemistry in Slovenia. I think one of the things that takes us about Roman's work is that he like me is one of the leaders of the iGEM teams. I am a leader with my colleague Paul Fremont. But iGEM has been an incredibly stimulating way of getting into synthetic biology. I would actually say that Randy Rettberg and Drew Endy and the other people who are involved in and who has really started iGEM really started something, which has now turned into a major field.

Without further ado I am going to ask Adriano to give the first of these presentations.

MR. HENNEY: Thanks Dick and thanks very much to the organizers for inviting me to this very interesting meeting. Just to pick up on what Dick said about not saying it was very easy. It is quite interesting. It is now 40 years since man first put their foot on the moon and I think it was '61 or '62 that President Kennedy actually said that they decided to put that program together not

because it was going to be easy but precisely because it was going to be very hard and it was going to stretch human endeavor and really test our ability to see where we could go. I think that there are many analogies here, which are being made about man on the moon project for synthetic biology. The same analogies have been made for systems biology, which is really where I come from. But there are huge parallels and overlaps and I think it would be an injustice and perhaps a huge mistake to ignore these two parallel and sister communities. I think it is important for us to remember that.

The focus is health and medicine here. I am going to give you a view from the pharmaceutical sector specifically big companies, major issues, and that is where I am going to come from.

It is very difficult actually to talk about synthetic biology in that context simply because as far as I am aware major pharmaceutical companies are not indulging in synthetic biology to any great extent. To look at where these things could have an impact I have gone to the report that Dick chaired at the Royal Academy of Engineering where there are 5, 10, and 25-year horizons that are reported.

Now taking from those the key elements that may have an impact on pharmaceutical industry and elements of medicines.

The first is around improving and reproducing natural therapies. Artemisinin is an example of that. The opportunities for scaling up and improving processes, which is going to have an impact on reducing the bottom line and therefore improving the margins that the companies have to face at the moment is always going to be important. There is a lot of focus on that and processes and proving processes.

Biosensors are a very interesting point. I think as we go into looking at more exotic, more challenging, more difficult therapies in complex disease, one of the difficulties is that we don’t really understand them terribly well and we don’t have much quantitative dynamic data and the ability to collect that quantitative dynamic data noninvasively or minimally invasive ways is a challenge and I suspect that synthetic biology may have a part to play there.

Optimization of biopharmaceutical production that is therapeutic antibodies and the like obviously is

something that has already been mentioned.

Really the big one is around personalized therapy. I don't particularly like that word but it is used a lot. I prefer to think in terms of patient segmentation. That is to be able to identify effectively those groups which have a far better chance of responding to your complex therapies compared with those who are less likely to do so and the ability to use markers and approaches, which confidently can segment your patient groups will be an important advance in the way that we go forward with pharmaceuticals in general. It will also help us to reduce the concomitant toxicity that is presented with all of these therapies to patients.

That is a list of push. If you want to think about we as academics, we as scientists can see quite logically where this is going to go and why industry should be interested in and you are actually pushing it towards industry. Actually the truth of the matter is you have to have a suck. You have to have industry there, which is wanting to take this on board if they are going to receive it.

The way I want to look at this is actually to

look at the demand that could potentially be there, where that is going to come from in the near future, and perhaps that will help to shape and to put into context the kind of proposals that the synthetic and the systems biology communities could put to industry more persuasively in order to work together, which I think is an important point.

Starting with the valedictory article by Jean-Pierre Garnier as he left GlaxoSmithKline he pointed out and you can see it in the little red box there that from December 2000 to February 2008 the top 15 companies in the industry lost approximately 850 billion US dollars in terms of shareholder value, and the price of their shares fell from 32 times their earnings to an average of 13. That is quite an impact.

That wasn’t really big news because there were other articles that were predicting four or five years earlier that this was going to be the case. This is one such in Nature Biotechnology by Lee Hood and Roger Perlmutter where they presently suggested that 18 billion of revenue would be lost by 2008. But more importantly I think that they actually focus on the point that the

current processes and approaches to generating pharmaceuticals was not going to be sustainable for the future. It needed to change in some kind of way and they were proposing systems approaches in this paper.

Why is this? If you look at the way we have built up the pharmaceutical industry is becoming credibly reductionist. Post genome everything is focused on single entities. Everything is focused on isolated proteins, cell lines, engineered cell lines, exquisitely tailored chemicals taken completely out of physiological context and then trying to translate that data back to humans by increasingly using associative models which may or may not have any relationship to the pure human physiology at the end. You are making tenuous connections, fusing screens, and building up from a very reductionist space.

I think the consequence of that of course is you can’t predict how your compound is going to respond in an aged individual who is already taking five or six other drugs and has comorbidities beyond the one that you are trying to treat. This is a dynamic complex series of network interactions where the networks in pathology have shifted from normal into pathology and you need to treat a

network to drag it back to normality. That is impossible to understand in an isolated protein and chemical basis.

We need then to move from where we are now to have a step change in science where we move from this sort of guess and pray mentality that we have been having with these screens and hoping that we are going to hit pay dirt by running many more compounds and playing the numbers game. When we adopt a predict and test strategy and in that sense modeling and simulation is key to being able to generate high hypotheses which are testable and which then help you to focus your way forward. This is the systems biology approach that I am talking about.

A comment was made earlier that we started as an observational science. Actually physiology started very much as an organ function and metabolism science that was descriptive and identifying cellular components. With the advent of molecular biology we became reductionist. Being able to focus on those things where they were missing in the descriptions in the early physiology. Now we have come full circle. We have a stack of data, huge amount of data and information, but we can’t put it together in the networks and understand how they interact to generate the

emergent properties of the physiological points that you are looking at. For me systems biology is the basis for generating 21st century modern physiology with a toolbox that they would have loved to have back in the 19th century and earlier.

If we look at synthetic biology then in terms of drug discovering development, I think what we have seen so far is that the current success is in the area essentially of metabolic engineering around artemisinin and greatly lauded, fantastic success story. But it is in a particular side of therapeutics which if you look at it compared with the sorts of drugs that we are trying to develop for cancer or cardiovascular disease or metabolism or whatever is much more straightforward in development terms than it is to target metabolic dysfunction or cancer networks in humans because essentially you are trying to kill off the invading organism.

If you are extending to complex target physiology, human physiology as targets compared with an invading organism or a microbiological then you need to have an understanding of how that system is going to respond to the therapy and the way that it is operating to

generate the pathology in the first place. We need to understand those interventions if we are able then to design those drugs appropriately because you still have the same problems that we have with current therapies. Synthetic biology will face that as soon as it starts thinking cancer, as soon as it starts thinking infection. Synthetic and systems biology are very tightly linked in the context of human biology and medicine.

The hurdles and challenges that we have in industry, building evidence of potential utility we have to be able to have credible and reproducible evidence. We have to be able to talk the same language. That is the cartoon up there. There is a natural resistance and a skepticism in industry simply because we had our fingers burnt post genome with huge promises and under delivery.

The skills point that was made earlier today. Absolutely in terms of industry we need to have these skills in place.

Key developments in synthetic and systems biology will largely be driven out of academia. We absolutely have to find ways of bringing academic and industry together but at the same time be able to demonstrate applicability of

the academic learning in an industrial and commercially relevant context. That I think is where the drive will come. That is where the suck will come. That is what happened with the genome. You needed new DNA machines. You needed technology development. As soon as you got the suck there then the innovation and inventiveness will come on around the outside.

We have significant economic and regulatory constraints in industry right now. The question is how do we actually work this at a time when the appetite for doing blue-sky stuff with industry is going to be reduced simply because it is not delivering quickly to the bottom line. There are opportunities there. There are mechanisms as I have mentioned.

As far as going back to Lee Hood and Perlmutter's paper is concerned, they actually put this forward at the time in 2004 and asked the question, who will lead the extraordinary change process, the step change in science, the seed change in thinking an approach to where we go? Unfortunately the jury is still out on that.

We picked this up last year to workshop when we published a commentary in Nature in October, which

suggested some ways of actually bringing the different communities and stakeholders together to actually drive this forward from a systems biology perspective but it is equally relevant in synthetic biology, perhaps even more so because you have a tangible deliverable whereas systems biology is more about doing things in a different way.

I picked this up also quite recently in an EMBO reports on the science and society topic, which is basically again asking who is going to take up the gauntlet to make this happen in a coordinated focused way.

Concluding points. There is no alternative to adopting systems approaches if we are going to face and tackle complex disease. We have to gather the right kind of evidence. We have to show success and it is imperative to demonstrate impact. This is relevant both for synthetic and systems biology.

There is a lot of effort going on. I suspect there is quite a lot of funding. There certainly is for systems biology. Perhaps it is so the case with synthetic biology but the question is better coordination to generate impact.

Are we ignoring potential benefits of the human

simply because we are failing to find the mechanisms to get industry on board and demonstrate that impact.

Finally and my concluding perhaps slightly tongue in cheek in suggesting that we get rid of all of these terms. I think we are doing ourselves no favors. Somebody said this earlier today. My suggestion would be that perhaps systems biology is nothing more than 21st century physiology and synthetic biology is nothing more than modern bioengineering. Thank you very much indeed.

MR. KITNEY: Thank you, Adriano. Our next speaker is Frank Notka who is from Geneart.

MR. NOTKA: Good afternoon everybody. Today I am going to talk about the opportunities that gene synthesis offers for synthetic biology. I am actually focusing on one example from the biomedical sector and probably the only more technical presentation. The title is vaccine development in the context of synthetic biology principles. The principle I am referring is this construction cycle that can also be seen as a process workflow for the development of novel systems that is also used for synthetic biology.

The cyclists actually based on knowledge and from

this knowledge we have different steps regarding specification, the science circuits, specifications, the design, modeling, implementation, and the final step was testing.

What I want to show you is that this construction cycle can also be applied for modern vaccine development. The objective of this project that we are realized during the last years was to develop an HIV vaccine based on HIV genes that would be positive to use as a genetic vaccine. That is the requirement for this objective was that the genes that we included in our vectors really had to express very nicely. That was actually the first challenge because HIV genes are not very well expressed in human cells if they are isolated from their background.

I guess I will skip all these technical details. The main message is that actually this failure of expression could be attributed to this acting with repressor sequence within the whole genome that promoted a reproduction of the RNA and only if you apply or if you supply some viral(?) factors this rapid degradation can be rescued.

The point is that once we exchanged the codons

that were used by the HIV with codons used more frequently in human genes we could circumvent this whole process, this whole regulation and we really got nice expression of our antigen.

Coming to the specifications this was of course also challenged because up until now we are working on HIV vaccine development for more than 15 years and there is no really success story up to date. In this process we use then integrative vaccine strategy where we looked at different aspects. The first one was really to identify the prevalent virus strain in the area where we wanted to test and also later apply this vaccine and at the same time we were asking what kind of numerous points do we actually want to induce and at that time it was actually acknowledged that for effective HIV vaccine we need really to induce a broad numerous(?) points.

Now from these different aspects we were able to define the targets that we would like to include in our vaccine as listed here and in a second step we had also to decide which delivery system we would use and from the many options including proteins or peptides, DNA, viral or bacterial vectors. We have chosen naked DNA and viral

vectors for the development.

With specification's attempt we did a rational antigen design with a strong focus on function safety and frequency. So starting from the isolate, the C virus that identified as the prevalence strain we wanted to include as much as possible from the genetic sequence in order to include as many as possible functions that is neurological relevant epitopes in our antigen. For safety reasons part of the proteins were split and sometimes scrabbled and the active sides were removed from this whole construct and some additional modifications were introduced to enhance the efficacy of the production and also for secretion of the antigen.

Now look at conventional modeling. It was some modeling for let's say expression characteristics. We developed an algorithm that usually optimized a given gene for specific host and in this optimization process we take different parameters into account like adaptation of the codon usage or GC content. We avoid negative elements like sequence repeat, RNA secondary structures or functionally motives like splice sites. Then the sliding window approach. All these different parameters go up in parallel

and overlapping windows where they are sequentially moved forward.

The application in our course is a two-step process where you use gene synthesis of course and a second step the vector production. In contrast to what Cord Staehler had presented in the previous session we do a rather old-fashioned gene synthesis at GENEART. This is also a multidisciplinary process where we have a T-based(?) design. We have chemically synthesized oligonucleotides nucleotides and we have genetic engineering for gene synthesis and assembly.

From the different delivery systems that we have categorized in actually two categories. That is DNA plain plasmid DNA or vaccinia-derived viral vectors. We have chosen the DNA and the New York vaccinia Ankara viral system to proceed to the clinical trial. For the development of a vaccine the ultimate test is of course a clinical study and here just a short overview of the risk site of the phase one cumulative study where we compared to immunization regiments. One part of the volunteers received vaccinia virus only. This is represented in the white bars and the other 20 volunteers received a prime boost regiment

where we used our synthetic DNA expression construct and the vaccine virus. Overall we got a very good response. As you can see here from the different bars the prime boost was superior to the vaccinia alone regiment and not only in the overall number of responders but also in terms of their ability which can be seen as a success in inducing memory immune cells.

Actually what I have shown is that the vaccine our candidate vaccine was developed along this construction cycle. Someone might argue that what I have just shown you is preliminary DNA genetic protein engineering whatever. Since we are talking about opportunities and innovation I think that gene optimization and gene synthesis can greatly attribute to at least the highlighted steps of the cycle. For example if you look at design then the gene optimization provides very much to standardization just by making use of the high flexibility that is provided by codon choice and by sequence modification.

We did a comparative study where we analyzed 50 genes for expression in human cells. We compared wild type and optimized sequences and from this we got a couple of implications. One is that optimization and gene synthesis

is really reliable, that is to say not all of the wild type genes were expressed in cells whereas all the tests that optimized genes for all of these genes we could detect protein in the cells.

The second implication is just availability. It was just not possible to get all the wild type sequences from commercial and other sources, others in gene synthesis. The last one is efficacy. In this comparative study we have seen that the majority of genes perform much better in the optimized version where the wild type version. I can stop here.

MR. JERALA: Thank you very much particularly for the organizers for inviting me to present our results and how my view on the role of synthetic biology in medicine. Basically what I would like to show that basically I think that there are four different types of applications in synthetic biology in meds and mainly as alternative means of drug production as we have heard today several times, (?) then biosensors and then engineering for human cells which would be more applied in the form of gene therapy and then new therapies that haven’t been used before. In my presentation I will at the end of the day show you two

examples of our applications.

The first one is in the area of engineering the synthetic cell signaling pathways particularly that will be an example to the device mutation insensitive device to detect viruses and trigger antiviral activity. Then the second example to use the designed vaccines we heard today about the potential of vaccines in synthetic biology. In our example I will show you how we made the components of bacteria that otherwise invade the immune system again visible immune response.

I am sure you are all aware with the problem of HIV and AIDS. Life cycle of virus has been extensively started and inhibitors of lots of the stages in viral replication have been designed. But the main problem is the high rate of mutation. As Victor said before there is a Darwinian evolution but in the case of HIV virus it works against us. Almost every fifth individual in USA carries the strain of virus that is resistant to one or another type of drugs. That is why we have to use the combination therapy, which makes the virus difficult to become resistant against several that way(?). It is about the idea of using the principles of synthetic biology, how to devise

a system that will divide this problem of mutations. We came to the conclusion that the only way would be to couple the response to the viral function rather than specific viral protein.

Virus can develop mutation resistance against drugs that target certain proteins but they need certain functions and we have tested this principle in two cases in two viral functions. One is cell attachment and the second is specific viral protease. What is important about this principle that that’s the general principle that can be applied to also gain other viruses that have a certain specific function that we can attach to.

The second important feature is that this type of response is versatile so we can see later in schematic presentation. We can attach to it any type of desired antiviral defense.

The first function that I mentioned is the very step in viral replication, the attachment of virus to cells. It binds to the two-cell receptors CD4 and CCR5 and forms heterodimer. That is exactly the step which we could detect namely the formation of heterodimer. Formation of heterodimer could be detected by reconstitution of split

proteins. You can take protein with defined fold and cut it in to the two segments and then only when the binding partners to both segments associate then you get reconstitution of all of this function. It is even better if split protein is an enzyme because you get amplification of the function so you do not detect only one signal from one virus, but an amplified signal.

The principle idea is following so we will have engineered two cellular receptors by the addition of two segments of the specific protease. When the virus binds to cell it triggers formation of heterodimer. The protease that is attached to those partners constitutes and this protease can then cleave the transcription factor that is anchored to the cell membrane. So in this case we can select any type of orthogonal transcription factor that does not activate any of the normal eukaryotic cell proteins. In our case we selected the T7 RNA polymerase which is well known particularly for the working duct here but does not transcribe any of the proteins in human genome so when the protease is activated the transcription factor locates into the nucleus and then it can select any type of program be it either the caspase to kill the infected cells

to prevent further spread of infection or to producing interferon to prime other neighboring cells against the virus or to activate top or back or any other similar type of function.

We have also of course shown the proof of the principle. In this case we coupled a green fluorescent(?) protein as a reporter and you can see in the normal cells which harbor this antiviral device you get no activation but in the cells which have been exposed to the viral gp120 or pseudovirus you get activation showing that the system detects binding of the virus.

The second viral function is the specific HIV, a specific protease that cleaves certain specific sequence and we can use basically very similar approach. The only difference that anchors the transcription factor to the membrane contains the specific site for HIV protease which is cleaved and then again the antiviral program is activated which have been also shown to work in infected cells so those are the cells without the protease and cells which have the HIV specific protease.

The second part that I want to describe is the vaccines. Helicobacter pylori is gram negative bacteria

that colonizes human stomach and duodenum. In the audience I guess probably I could estimate probably 50 people harbor these bacteria and probably in 20 percent of the people have some symptoms like gastritis or (?) the small but nevertheless important fraction of people develop gastric cancer which is one of the most lehtal types of cancer. This infection can be treated but probably the effective vaccine would be the best treatment perhaps even to advocate the bacteria.

The problem is how to develop a good vaccine. The bacteria have coexisted with humans for more than a hundred thousand years and it adapted to humans by avoiding the recognition by the new systems through several different mechanisms. One of the mechanisms is that this is flagellating bacteria containing flagellin, which are composed of the protein flagellin also in E. coli or salmonella. They have the flagellin. The difference is that the flagellin from E. coli or salmonella activates the innate immunity so binding to the toll-like receptor 5, which then activate the innate immunity response leading to the maturation of adaptive immune system as well but not the flagellin from Helicobacter pylori.

While our approach was to engineer the flagellin by making the chimeric version of flagellin. we know that the (?) segment of flagellin from E. coli is responsible for (?) activation of TLR5 and the central segment is mostly important(?) for the activation of adapting new system. The solution was to make the chimeric protein composed of the segment from E. coli and the segment from Helicobacter pylori, which is now able to activate the innate immune system but also has the antigens for the adaptive immune system.

We have additionally proved this vaccine by adding some other antigens like important virulence factor, ursb(?) or in another application several composed artificial antidotes from several important virulence factors so that’s to use the model of principle of synthetic biology to devise perhaps you could say high tech vaccine. We have tested several implementations so the vaccine either as a normal protein vaccine DNA vaccine or is engineered bacteria which might be used perhaps for the all applications so indicates a protein vaccine have isolated protein shown that it does. Chimeric protein does activate the TLR5, teh flagellin from salmonella.

In the case of DNA vaccine we have used the similar approach as shown in the previous presentation. In this case we introduce the DNA into the epithelium cells, which then produces the flagellin, which then activates the antigen presenting cells, which lead to the maturation of the new system and to response again. We have shown that the principle works in cells but we have done also the first established in mice. We have shown mice strongest points after three weeks and also that synthetic vaccine indeed recognizes the living bacteria.

To summarize I think the combination of our understanding of the basic principles of immunology that has really tremendously advanced in the last decade and the powerful tools of synthetic biology really opens very exciting therapeutic potentials. I have shown two examples. One is the antiviral genetic device based on the viral function that avoids mutations. The second designed vaccines that the same principle can again be used against other bacteria or perhaps even against the cancer and other diseases.

But of course the synthetic biology medicine has many other potential applications like the development of

engineering of defined cell types. Christina showed a very nice example –- and then so on.

In the end let me just mention of course have to acknowledge the people who did the experimental work so all those results can be made by the undergraduate students that participated in the iGEM competition and Randy will speak more about it tomorrow. I just have to say that that's really an excellent way to introduce young people into the synthetic biology but to also beyond that I think it is really a sort of an excellent testing ground to try really some very new radical ideas and I would like to thank you for your attention.

Agenda Item: Questions and Answers

MR. KITNEY: Three very interesting talks. I wonder if we can open the discussion now. Starting off on the left over here. Could you identify yourself please?

MR. MILLETT: Piers Millett with Biological Weapons Convention Implementation Support Unit. Absolutely nothing to do with weapons. Given the potential of exactly the sort of things you are talking about to have real medical benefits. I noticed these are also diseases that perhaps disproportionately affect the developing world,

which is also highly important. How do you think we can create frameworks where developing countries directly benefit in developing synthetic biology? Do you think it is possible? How can we bring partners in from developing countries to create a great sense of ownership around the world?

MR. HENNEY: There are such partnerships already in place. There are not for profit organizations such as the Medicines for Malaria Venture. One World Health I think is the other one. There are various ones, which are joint ventures that bring academics and industrial partners together to create that. I was actually just reading the annual report from the Medicines for Malaria Venture yesterday. They do exist for the benefit of third world. I think that is quite a neat way of looking at it if you think about the imperatives for large pharmaceutical companies. The opportunity to exemplify new approaches and areas where as far as they are concerned that it is not necessarily something that would be high on their agenda because of the return on the investment. It would be necessary to be successful. I think that’s quite a pragmatic way of road testing ways forward and I think

increasingly there may be opportunities to think about that at the same time benefit areas which are underserved in that way.

MR. JERALA: That is also some potential to develop some vaccines that might really be quite cheap. For example, more defined bacteria that could perhaps – I'm not saying that it works as of now but perhaps to bacteria the vaccines that are stable that can be transported and that can be perhaps used orally. I think that is also quite important.

MR. NOTKA: I just would like to add there is a lot of sponsoring opportunities in the EC. So especially in the sixth and the seventh framework. They have a lot of projects that are really related to poverty related diseases. There is also a lot of international and transEurope, Africa for example, process going on.

MR. KITNEY: Let's take the next question over here.

MR. MUKUNDA: Gautam Mukunda from MIT. I once interviewed the CEO of a large pharmaceutical company who commented on the intelligent drug design experience, the last attempt at doing this better. He had wasted more than

a billion dollars and he would have been better off putting all the money in cash and putting it in a pile and lighting it on fire because at least that would have been entertaining in terms of the results that he got from drug development, which was his first reason for really objecting to new attempts to this.

The second and I thought more striking one apart from I have been burn reaction was that he felt that many of these approaches were more likely to target much smaller populations, patients than the big pharmaceutical companies had made their bread and butter on. He felt and I thought this seemed reasonable that to target populations of that size would require significant maybe even wholesale revisions on the regulatory structure surrounding pharmaceutical introduction. That running clinical trials powered to deal with the small numbers or the expenses involved and potential profitability would be, his phrase was nightmarish.

I wonder if you want to comment a little bit about the potential regulatory changes that we need to think about in terms of how we structure drug approvals, how we pay for clinical trials that would allow us to take

advantage of the new techniques that you are talking about.

PARTICIPANT: I have a similar question to that. I have a follow up question. Maybe they could answer both.

MR. HENNEY: It is a great question. I think that there are two aspects. Firstly let me just put my – I wasn't involved in development. I was at the early end of drug discovery and my experience in development is limited. Certainly the FDA through that critical path initiative is looking very hard at different ways of changing the paradigm of drug discovery to address some of those things. Undoubtedly the point about small patient groups and being powered statistically to be able to get a result is an important one, but I think what we are looking at here is why I was thinking less of personalization but more of segmentation. If you look a study on arthritis with normal therapy, if you can produce a series of biomarkers that can improve your prediction of response from 40 percent to 60 or 70 percent then in terms of the efficacy and the target population is increased significantly. The return on your investment is that much better. You can negotiate or at least the authorities will negotiate different pricing structures based on success of the therapeutic because they

know that you can actually segment the population. There is evidence that that's already happened with one company voluntarily doing that in the United Kingdom. I don't know when that interview took place but it is certainly a view that has to change.

The technologies that we have are increasingly going towards segmentation for all of the benefits that I have mentioned and to stick you head in the sand and say that is not going to happen I think is going to be a mistake.

PARTICIPANT: You are probably referring to HIV I guess or what types of disease was that vaccine because there are lots of examples where high-tech vaccines have been quite useful. For example influenza I think synthetic biology now really allows us to – literally in weeks or months you can have a new effective vaccine available.

PARTICIPANT: I wasn't thinking of vaccines which I know almost nothing about. The problem with the hypothetical arthritis example that you are talking about is right now without the biomarkers that drug will probably still score efficacy and I can sell it to 100 percent of arthritis sufferers. If I can only sell it to 40 percent,

yes, the efficacy is better and my cost to develop might be lower but I have also cut my potential market by more than half and it seems to me the economics once again cut against –

PARTICIPANT: I think it is an interesting point. The issue is that within all of our population that you are targeting you will still only get a small percentage that will respond. Those that don't respond probably will have side effects, which are not particularly pleasant, and those are consequences that you need to take into account. The ethics of it is if you know that you can segment and you can reduce the suffering to people who are going to respond, can you continue? The answer to that is no. The corollary is also that if you are able to segment and you know what those markers are and you are able to market alongside it the diagnostic then you have actually got a completely different investment stream and revenue stream rather. I think that those are things that need to be thought of in the context of development going forward.

PARTICIPANT: Can I just add one thing though? The COX inhibitors are exactly what you are talking about. If they had segmented the population they wouldn't have run

into the problems. I just have to say that.

PARTICIPANT: We talked about the market side. The regulatory side has a different problem with personalized medicine. Regulators across the world are moving on to life cycle approach rather than a snapshot approach. With a personalized target in medicine how do you evaluate a post market surveillance system? Right now post market surveillance depends on the signals that they receive and analysis of the signals, which are almost always statistical. If you are targeting one individual on a very limited population, how are we going to regulate this medicine post market?

PARTICIPANT: I can’t answer that because I don’t have any experience in that area.

PARTICIPANT: This is a problem. The personalized medicine approach. As a regulator I don’t know. How will I gather pharmacal vigilance?

PARTICIPANT: I wish I could help you. I honestly don’t know. I don’t have any experience in that area so I can’t offer any insight. It is a good question and I think it is one that needs to be tabled.

PARTICIPANT: Should I be approaching every

medicine individually and then withdraw it from the market –-

PARTICIPANT: All I can do is repeat. I can't –-

PARTICIPANT: Does the industry have thinking about it?

PARTICIPANT: I repeat again. I was not involved in development and I was not involved in regulatory processes so I can't answer your question. I have absolutely no idea but I am sure it is being looked like.

MR. KITNEY: Do either of the other speakers want to comment? While other people are thinking can I just say I was at a meeting at the Wellcome Trust two weeks ago where actually a major American pharmaceutical company presented. I won't name them. They were saying that unless systems biology and I know primarily talking about synthetic but they are really in my opinion two sides of the same coin. These techniques in relation to systems biology and I think you were saying also synthetic biology really brought in a major way and so the pharmaceutical industry. Their view was that certainly their company might implode. Would you like to comment on that?

MR. HENNEY: I had a telephone conversation with

an extremely senior European pharmaceutical executive two weeks ago where the comment that was made was that he is deeply concerned about the state of the pharmaceutical industry and its current processes. I think that there is no doubt that we do have to have that paradigm shift that change of where we go. Turning the handle faster, playing the numbers' game isn't going to solve the solution because we still don't address the physiology.

Will pharmaceutical companies implode? Who knows? They are not actually learning the lesson that was put at the door of the computer industry in the '70s and '80s. The challenge is if new technologies that the way that IBM and people just ignored that and eventually came in late. The music industry and all the rest of it have had to change their business models. GM producing cars and Chrysler producing cars that are not really the sorts of cars you want. I think you have to be able to change. I think unfortunately the pharmaceutical industry is late to change.

There are opportunities I think with (?) initiative in Europe. If that comes together properly and that comes together looking at true innovation then I think

there is an opportunity to provide the evidence that is necessary to persuade industry to adopt these changes, but it has to be reduced to practice to coin an engineering term and sufficiently robust and consistent for it to be part of a regulated process for the production of medicines for humans.

MR. KITNEY: Question over here.

PARTICIPANT: Thank you. I'm with the OECD. In the two previous sessions the speakers have identified some of the needs either for their industry or for research. They mentioned the development of registries, libraries, the standardization of parts as being something that is important in order for researchers and probably industry also to have access to the components that is going to make synthetic biology as powerful as people hope it is going to be. None of you have mentioned that. Is there a reason for that? Are components and parts something that are important also in pharma and medicine?

I am having another thought which I am sort of at the same time trailing off. One of the reasons we have been interested in this issue at the OECD is in fact we are very much interested in the whole set of issues around access to

data information, knowledge sharing. One of the areas in which we have seen an evolution and some new thinking in the pharma sector have been in compound libraries and access to compound libraries. There has been slow but certain movement towards more sharing of access to compound libraries. One of the areas that we have been thinking about is there a parallel between that and the way that one might create and share and access registries or libraries or whatever it is that is coming up in synthetic biology? If anybody has some comments on whether or not those are parallel situations and whether or not in the pharma sector libraries and registries of synthetic biology parts is important, I would be interested to hear that.

PARTICIPANT: Maybe I could just say first that the reason why we talk about parts, devices, and systems all being standard simply comes out of the engineering approach to how you design and develop devices and systems. That is the way it is done in engineering. Now, that may or may not be right in terms of synthetic biology but that is how it is done in engineering. If you look at any jumbo jets or any car or any of those devices that we use in our everyday lives the common approach to all of those devices

and systems is in terms of engineering is to produce standard systems from standard devices from standard parts. That is really the basis of this approach if you like synthetic biology. It may not be correct but it is the approach.

PARTICIPANT: I can't speak for synthetic biology but I can certainly talk about precisely this. It was one of the topics that came out of the workshop that we had, the commentary for which was in Nature last October. The consensus was undoubtedly that they needed to be some sort of standardization, for example, of the modeling approach. I think that is necessary if it is going to be reduced to practice and be robust. There needs to be standardization in terms of the languages of the computer systems that are being used for modeling and simulation and the databases that need to be put together. There needs to be consistency so that you know that what you are looking at in lab A is the same as what it is in lab B.

Similarly it is going to be for assays. There was huge free aura about assays and things like that simply because people would say well you know why do you need to standardize that? Why should we register our assays? Well,

actually if you go into any biochemical laboratory in a hospital all of the enzyme assays are standardized. They are tested and they are subjected to routine robustness testing all the time. I think that if you are going into regulated environments, if you are going to be operating that kind of system then it is unavoidable that you have to have some form of standardization and a process of verification and checking. It applies to systems and synthetic biology and that is why I say that there are from technologies and the tools there are huge overlaps that we must come together as a community to actually put that in place.

MR. KITNEY: That very nicely takes us up to quarter past five, which is the time scheduled for the end of the session. There are two things because I have an announcement to make. First of all I just wanted to thank all the speakers. They were very interesting. The housekeeping announcements are that there is an hour on the program. There is now a reception immediately after this session, but the reception is actually in the third floor atrium not the second floor atrium. The organizers of the meeting have asked me to say if you could possibly walk up

the stairs that would useful. Hopefully I will see everyone up in the third floor atrium not the second floor. Thank you.