UNITED STATES OF AMERICA
DEPARTMENT OF HEALTH AND HUMAN SERVICES

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NATIONAL SCIENCE ADVISORY BOARD FOR BIOSECURITY

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INAUGURAL MEETING

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FRIDAY, JULY 1, 2005

The Meeting convened in the Crystal Ballroom of the Hyatt Regency Bethesda, 7400 Wisconsin Avenue, Bethesda, Maryland, at 8:00 a.m., Dr. Dennis L. Kasper, M.D., Chair, presiding.

MEMBERS PRESENT:

DENNIS L. KASPER, M.D., Chair
ARTURO CASADEVALL, M.D., Ph.D., Member
MURRAY L. COHEN, Ph.D., M.P.H., C.I.H., Member
LYNN W. ENQUIST, Ph.D., Member
BARRY J. ERLICK, Ph.D., Member
DAVID R. FRANZ, DVM, Ph.D., Member
GENERAL JOHN A. GORDON (Ret.), Member
MICHAEL J. IMPERIALE, Ph.D., Member
PAUL S. KEIM. Ph.D., Member
STANLEY M. LEMON, M.D., Member
STUART B. LEVY, M.D., Member
JOHN R. LUMPKIN, M.D., M.P.H., Member
ADEL A.F. MAHMOUD, M.D., Ph.D., Member
MARK W. NANCE, J.D., Member
MICHAEL T. OSTERHOLM, Ph.D., M.P.H., Member
DAVID A. RELMAN, M.D., Member
JAMES A. ROTH, DVM, Ph.D., Member
HARVEY RUBIN, M.D., Ph.D., Member
ANDREW A. SORENSEN, Ph.D., Member
ANNE VIDAVER, Ph.D., Member
ADMIRAL WILLIAM O. STUDEMAN (Ret.), Member
DIANE W. WARA, M.D., Member

EX OFFICIO AGENCY REPRESENTATIVES:

NATALIA COMELLA, Ph.D., Department of State, for John Turner
BRENDA A. CUCCHERINI, Ph.D., M.P.H., Department of Veterans Affairs
DENNIS DIXON, Ph.D., NIH National Institute of Allergy and Infectious Diseases
MARYANNA HENKART, Ph.D., National Science Foundation, for Mary Clutter
PETER R. JUTRO, Ph.D. Environmental Protection Agency
RICK KEARNEY, US Geological Survey, for Sue Haseltine
LAWRENCE D. KERR, Ph.D., Executive Office Of the President
DALE E. KLEIN, Ph.D., P.E., Department of Defense
TERRY L. LOMAX, Ph.D., National Aeronautic and Space Administration
BORIS D. LUSHNIAK, M.D., M.P.H., Food and Drug Administration, Department of Health and Human Services
JANET K.A. NICHOLSON, Ph.D., Center for Disease Control and Prevention, Department of Health and Human Services
STUART L. NIGHTINGALE, M.D., Department of Health and Human Services
GERALD PARKER, Department of Homeland Security, for Elizabeth George
CAIRD E. REXROAD, JR., Ph.D., U.S. Department of Agriculture
SCOTT STEELE, Ph.D., Department of Justice
DAVID G. THOMASSEN, Ph.D., Department of Energy
VINCENT L. VILKER, Ph.D., Department of Commerce
RONALD A. WALTERS, Ph.D., Intelligence Community

ALSO PRESENT:

THOMAS HOLOHAN, M.D., NSABB Executive Director, NIH Office of Biotechnology Activities
AMY PATTERSON, M.D., Director, NIH Office of Biotechnology Activities

SPEAKERS AND PANELISTS:

RONALD M. ATLAS, Ph.D., Center for the Deterrence of Biowarfare and Bioterrorism, University of Louisville

GEORGE CHURCH, Ph.D., Professor of Genetics, Director of the Center for Computational Genetics, Harvard Medical School

SHANA DALE, ESQ., Chief of Staff and General Counsel, Office of Science and Technology Policy, White House

MALCOLM DANDO, Ph.D., Bradford University, U.K.

JOHN MULLIGAN, Ph.D., President and CEO, Blue Heron Biotechnology

BRIAN RAPPERT, Ph.D., University of Exeter, U.K.

PHILLIP A. SHARP, Ph.D., Institute Professor at the Center for Cancer Research, Massachusetts Institute of Technology

J. CRAIG VENTER, Ph.D., Founder and President, J.Craig Venter Institute

A-G-E-N-D-A

P-R-O-C-E-E-D-I-N-G-S

8:05 a.m.

CHAIRPERSON KASPER: Well, good morning. I want to briefly mention how strongly I feel that yesterday's session went very well. And I'm looking forward to the presentations and discussions that we have scheduled for today.

Once again, I would like to welcome the Board members, those in attendance in the audience, and those watching this on the webcast. So, let's get started.

One of the charges of the Board is to provide recommendations on the development of a Code of Conduct for scientists and laboratory workers that can be adopted by a professional organization and institution engaged in the performance of life science research.

In this next session we'll touch on issues related to the benefits of a code of conduct, as well as complexities in establishing such a code. We'll hear from three distinguished speakers, after which we'll have a general discussion and questions from the

Board.

So, our first speaker will be Dr. Philip A. Sharp. Dr. Sharp is currently an institute professor at the Center for Cancer Research at MIT. He's a member of the National Academy of Sciences and a recipient of the Nobel Prize in Physiology or Medicine.

Dr. Sharp will speak on the importance of guidelines and responsibilities in the life sciences.

DR. SHARP: Thank you. It's a pleasure to have the opportunity to speak here this morning before the National Science Advisory Board for Bio-Security.

I am impressed that you are engaged in this activity the afternoon, the Friday afternoon before the 4th of July weekend. I think about half of Washington was in the airport yesterday as I was coming through.

And the rest of them will probably in the airport today as I leave. I look forward to getting back to Boston to listening to the 1812 Overture and seeing the fireworks on the Espinot.

I've been asked to talk about Codes of

Conduct in life science. And there are many codes. And what I want to give you as a message is Codes of Conduct have been taken seriously.

It's part of our community. It's part of what we teach. It's part of what we do. The reason that these codes are so widely used and effective is that there are ethical and pragmatic reasons for them.

And, when viewed from the perspective of an active scientist, which is the perspective I'm talking from today, they are essential for our work. The many codes come from the activities of biomedical research and are taken -- have been developed as the biomedical research community has developed.

Let me try it the other way. The biomedical research community is a culture of responsibility. And I believe this science community, the biomedical research or life science community, is the one that's most involved in codes of conduct.

That probably comes from the fact that this community developed after World War II, mostly with the discovery of recombinant DNA and the expansion of life science after the war.

It also developed because it engages humans in part of the research activity as we have advanced life sciences and been involved in the medical aspects of translation of life sciences.

We have engaged in more and more regulation as a community vis-à-vis the use of humans and animals as subjects for experimentation or being involved in experimentation.

And then there was the second event or the other event that I will talk about today that also brought many Codes of Conduct and a formalism to it into the community.

And that was the discovery of recombinant DNA, the whole genetic engineering that occurred in the 70's, which I'll comment directly on. And that also brought Codes of Conduct into the community and brought us a formalism related to guidelines and RAC and other NIH activities.

This culture of responsibility is shared by both the scientists, institutes, and the Federal agencies, because we as a team in many cases have found it necessary to work together to implement these

Codes of Conduct and to translate our science and advance our science in research.

And, some of the shared facts, very pragmatic facts that have generated this Code of Conduct or culture of responsibility are listed here on this slide.

That's the continued advancement of biomedical research very much depends directly upon public support. If you think about it, the NIH is the major funder of discovery research and biomedical research in the country.

Its support by the public and by Congress, and by others, is essential for that research activity. That research activity underwrites the whole medical care system in this country, the pharmaceutical industry.

It underwrites healthcare delivery in our academic hospitals. It underwrites the knowledge base in which a physician interacts with a patient in any part of the country.

So we see as part of the biomedical community that we play a very fundamental part of the

country's development of health and health care delivery.

When you look at this public support, the private support in the country, the pharmaceutical and other activities that are privately funded also depend upon this structure of the interaction between NIH and scientists that is essential for the advancement of science in the country.

Now, continued development of biomedical research is critical for healthcare and security in the country. And every scientist who works in this field understands this today.

If you think about that the issue, 15 percent of the gross national product depends upon healthcare or involved in healthcare in some aspect in this country.

That number is growing to 20 percent of the gross national product. Underwriting that total part of the economy in the basic research is the NIH support and the activity of the biomedical research community.

Security in the country, both in the

context of the vibrant economy, the context of securing the health of soldiers, of bio-security, depends very much on this activity of the interaction between scientists and NIH.

And biomedical research must be done in a safe and transparent fashion with responsible use of human and animal subjects. This is an integral part.

And, when one begins to translate science into the involvement of humans as research subjects, then you become very involved in Codes of Conduct. And that has risen to promote Codes of Conduct to being widely taught and used in the country.

Now, in addition to those pragmatic facts, the scientific community, the biomedical research community has a culture of responsibility that is driven primarily from a set of values which are common of other scientists.

And I think these values need -- are important when you start thinking about Codes of Conduct and teaching Codes of Conduct. One of the most fundamental shared values among all scientists is the belief that new knowledge will ultimately lead to

a higher level of humanity, that as we understand the world about us, we will then elevate ourselves to a higher plane of understanding world and world about us.

So, whenever restrictions are placed upon the limitation of gaining new knowledge, of exploring new realms of biological space or chemical space, or other space, the scientific community is very unsure of accepting those types of limitations.

So, there is a commitment to advance society through the gaining of new knowledge and commitment of advancing healthcare. The scientific community as well is committed to education in terms of both transmitting and developing our science as well as educating people as to how to operate doing science in this community.

And then there's this validity of scientific data, an openness to expressions and exchange that are a fundamental part of being a scientist.

If you're involved in these very simple processes, a process that has been taught to students

since they were in the 8th grade of scientific experimentation, asking a question, getting an answer, asking a question, getting an answer.

A simple process as that has changed the world about us by creating all the things -- including the building we're standing in -- this technical scientific advances, is something that has to be dealt with in terms of open questioning, description and publication of details in how one does science, this process of forwarding science by question and debate.

So, these are values that are commonly shared. And, when those values are restricted, it's very complex for the scientific community to accept, particularly in the biomedical as other sciences.

And then, the last tradition of the field or value of the field is that this activity is international. We have over long periods of time benefited from learning from our international colleagues and as well sharing.

And, in fact, if you think about it, before World War II, every major scientist in the U.S. was trained in some part by some experiences in

Europe.

In fact, if you were a chemist, you'd travel to Europe in terms of being trained at some stage. And then, after World War II, that process is mostly come to the U.S.

So, these are shared values about restrictions in terms of -- or the culture of responsibility for biomedical research. I want to talk to one example of the development of Codes of Conduct.

And this was an example that arose through the development, as I mentioned before, of recombinant DNA. What I show here in the picture, just to give you some diversion from those line graphics, is a picture of Francis Crick and Jim Watson.

Watson was a -- as you well know -- in 1953, when the discovery of DNA, was a young American scientist from Chicago who had been interested in watching birds and then got his Ph.D. with Luria and went to travel through Europe to see if he could discover the structure of DNA because he believed it was a basis of genetic material.

Francis Crick, who just died a year or so ago, is one of the most brilliant people I have ever met, was a physicist who had been involved in World War II.

And this shows them in Cambridge. And it was in Cambridge where the discovery of DNA was made. And that set forth then the whole development of the molecular biology community and as well the recombinant DNA activities that I will speak about now.

Recombinant DNA was not the first set of guidelines that actually was developed by the life sciences community. IN fact, if you look at Codes of Conduct in life science, you have to go back to the Hippocratic Oath in terms of do no harm as a Code of Conduct for scientists who are involved in biomedical research.

Actually, human experimentation as a Code of Conduct came out of the Nuremberg trials in 1946 where use of humans in experimentations during that period led to issues.

And then the Codes of Conduct were further

developed through Helsinki declarations in '53 and '64, and then in this country by the Belmont report in 1979.

This was some of the first Codes of Conduct developed for the biomedical community. The recombinant DNA issue rose in the early 70's when a new technology was developed through basic science and in laboratories, really in many cases not so obviously related to biomedical research, the ability to seek one synthesis and recombine DNA.

This all developed in the early 70's about 20 years after the discovery of the structure of DNA and led to a whole new set of experiments that were possible that had not been possible before, experiments of the type of being able to take a gene from one organism and combine it with a gene of another organism and then ask in the process of experimentation what you could learn about the function and activity of the gene.

This led to a whole series of concerns that arose among the scientific community and then arose among the public about this new technology and

what it might mean for safety in doing research -- safety both to the people who are in the laboratory, but as well safety in terms of creating possible novel infectious and new agents.

In many cases the safety issues arose in the following. We were, by recombining DNA, violating boundaries of nature where boundaries of nature were genes from two organisms that had never mixed, end quote, were now being mixed by scientists.

And, could we create pathogens that would become highly infectious agents? And therefore, both inflict unanticipated harm, but as well discredit the whole biomedical research community and its public support.

And this led then to a lot of concerns that then in 1974 something happened that had not been before -- ever occurred before in the biomedical research community.

And that was a moratorium was called by leading scientific figures and the National Academy stating we should not do experiments in this area until we have met, discussed these issues and come to

some conclusion as to how as a community these issues should be addressed.

That led to an Asilomar Conference in '75. Note there is a six to nine month period here in which no experimentation was occurring which then was a very novel and interesting period in science in which possible experiments were not being done simply because there was this public concern in wanting to respond in a responsible way.

The 1975 Asilomar Conference then suggested or recommended that the NIH develop guidelines. Those guidelines were first issued in '76, again another year passed without a lot of advancement in this experimentation.

And then, in '76 with the NIH guidelines and the formalities of the RAC Committee and Institute Bio-safety Committees, research experimentation began.

I want you to note that in 1976 Genentech as a recombinant DNA company was first formed. Biogen was formed in 1978. It was in this period in which the whole genetic engineering recombinant DNA biotechnology community began to develop.

And biological science then grew from it. The guidelines in '76 were highly restrictive and then were again revised in '79 with the knowledge of what had transpired in the laboratory since '76, suggesting that the concerns were not as great as perhaps they were originally articulated.

And the guidelines were then reduced. As far as I'm aware, there has not been a single example of an infection from a laboratory over the last 30 years being due to a recombinant DNA organism having been created in a laboratory and then infecting either someone in the laboratory or someone in the public, creating a disease state.

Just to give you that arrow points to myself attending the Asilomar Conference. It was one of the most interesting experiences of my scientific life.

At this time I was about 30 years old and there wasn't anyone in the world more ambitious than I was in terms of this science. I was really excited about what this science could mean.

And this conference was a very interesting

life experience in terms of it moving forward. The guidelines have been viewed and have been very successful in terms of retaining the confidence of the public support for the National Institute of Health and the regulatory agents that work together and public support.

Why was it so successful? I think they were successful because they were led by the scientific community, including the funding agencies, working as a team to make these guidelines effective.

And, for them to be respected by everyone in the community, they were international at the onset. It was an international process, though there was some variation from country-to-country.

In essence, the same moratoriums, the same guidelines, the same rules for science were being developed in all these countries. The process from the Day 1 was public.

Compliance was almost universal. It was -- as far as I know, there were only two major, or as far as I know, noted violations of the guideline. One was more bureaucratic.

There was an announcement of a change in the rules and an experiment done before the rules were officially issued. And in another case there was what is apparently a violation, a knowing violation.

And the individual had funding withdrawn from the National Institute of Health and had other issues in terms of use of human subjects. What has made the guidelines so effective as a Code of Conduct is that built into the guidelines and anticipated in the administrative structure was a mechanism for change with the progress of science.

So, this process of being able to change the rules as we learn more is a very important part of why the guidelines have been so effective in terms of the community.

Now, we teach Codes of Conduct. In fact, over the last several years I, as a senior faculty member at MIT with Terry Orweaver, had been teaching Codes of Conduct as part of the process of educating graduate students and complying with some of the regulations of NIH in terms of support of graduate students.

The course that I will briefly summarize in the next two slides is the material we've taught in Codes of Conduct to all second year graduate students in the department of biology at MIT.

We teach these students Codes of Conduct from a departmental perspective because I thought we believe that senior faculty in the department would have the most rapport with these students.

There's also an MIT-wide course on similar topics for students that are in chemistry and engineering and other parts of the university. But, what I'll talk about is primarily our interactions in students teaching Codes of Conduct.

This is part lecture, part discussion. We start each of these sessions with some topics that will be covered in the session. And then we begin discussions.

And it goes on for four hours. And these are the sessions that we teach in responsible conduct and research. You note at the top is scientific misconduct, record keeping, reporting results, data selection.

This is how you view and must make decisions in terms of being an active scientist, reporting your experimental results, dealing with data, and retaining that data in case it needs to be surveyed.

Session two deals with mentoring, authorship, peer review and confidential information, parts of processes, again, that active scientists have to be comfortable with in making decisions.

Session three is intellectual property, patents, trade secrets and responsibility to the public. That latter issue is safety in terms of bio-recombinant DNA issues, guidelines and other issues.

And that perspective, in fact, a couple years ago or a year ago when Professor Jerry Fink at MIT was chairing in National Research Counsel Committee that suggested the establishment of this group, we invited Jerry to come over and talk to the graduate students about the process of bio-security and bio-agents.

And then Session four is the use of humans in biomedical experimentation where we talk about the

ethical uses of humans as research subjects, the compliance issues, what types of experiments have to be covered by that process.

And then session five is the use of animals in biomedical experimentation where we talk about the issue of philosophically using animals and as well the regulation issues of using animals.

So, these are sessions that two senior faculty members and every graduate student in the department participate in. And I have found teaching them really quite interesting.

Now, behind this interaction between students and faculty at MIT in terms of Codes of Conduct, are a number of institutional activities that are essential for our research programs and compliances with Federal regulations and NIH regulations in terms of activities at MIT.

You'll note at the top that these support activities and organization for biomedical research report into the MIT Office of Vice President for Research and Associate Provost Alice Gast who holds that position now.

Under that organization there is a committee on the use of humans as an experimental subject. The Institute Review Board and every grant and activity we have experimental activity that involves humans have to be reviewed either by a delegate authority from that board or by the Board.

There's a committee on animal use similar. There is the academic misconduct policy, which MIT is responsible for and needs to report to NIH about. That's the responsibility of this office.

There's an Office of Intellectual Property -- the issues of intellectual property in handling confidential information. The Office of Sponsored Research is engaged in or responsible for dealing with conflicts of interest.

The issue of whether in the context of grants and other activities investigators have economic conflicts of interest that would compromise their independence of judgment, that reports into the Office of Sponsored Programs, another Code of Conduct issue.

And then reporting academically to this

office, but independently to the Vice President of Operations at MIT, are the Environmental Program Offices.

Under that is the Committee for the Assessment of Biohazard, that's the Institute Bio-safety Committee Equivalent. Also in -- so that's where recombinant DNA guidelines are -- that's responsible for the implication at MIT.

There is the Select Agent Control that reports in the identification of agents who could be possibly used for known infectious pathogenic agents that could be used for infection or bioterrorism.

It is responsible for the retainment of those agents at MIT; it is the responsibility of that office, and then chemical and radiation lab safety.

So, what I've tried to do in these short moments is give you an overview of what motivates Codes of Conduct in the community. It is this responsibility to the public and the understanding that the activities in biomedical research underwrite an enormous part of the country's healthcare delivery process, some of the values.

I've tried to give you an overview of the experiences in terms of developing the recombinant DNA guidelines. And I've tried to give you a feeling for the implication of those types of Codes of Conduct on the ground in a research university with students at MIT. Thank you.

CHAIRPERSON KASPER: Well, thank you Dr. Sharp. I think there will probably be many questions. But we'll hold them until the other two speakers have their chance to speak.

Devising a successful Code of Conduct can really be a challenge. To discuss some of the challenges of recommending a new Code of Conduct we have two experts from institutions in the United Kingdom.

I'd like to introduce Dr. Brian Rappert, a Lecture in Sociology at the University of Exeter, and Dr. Malcolm Dando, Professor of International Security at the University of Bradford. Thank you.

DR. RAPPERT: Yes, many thanks for that, Chair. Malcolm has been gracious enough to allow me to give this presentation on my own. So, I should

start with a thanks to him.

Well, what we've been asked to do for this presentation is to examine some of the barriers to the uptake of Codes of Conduct in relationship to dual use issues to biological weapons.

And, our reflections are going to be based on a few different sources. One is an examination of various discussions over the last few years about Codes of Conduct that have been happening internationally, which I'll speak about.

Another is some of the recent experiences that we had at the meeting of experts for the Biological Weapons Convention just a couple weeks ago that was discussing Codes of Conduct for scientists.

And third are discussions that Malcolm and I have been having with life scientists in the U.K. about some of these issues about dual use. So, I said we were going to talk about some barriers.

So, it's going to have a sort of – in some sense, a sort of very negative feel to it. I think there are various challenges that need to be faced when talking about Codes of Conduct.

And I hope by examining some of these barriers, some of the difficulties, that I can help the Board in its deliberations. But it is going to speak of several changes.

A number of people began by talking about history. And I'll begin with my own sort of historical reflections. I think it's important to note that, not only as Philip said, there's a long tradition of discussions about Codes of Conduct for science and for medicine.

This discussion is also taking place in relation to biological weapons. So, just to give you a couple examples of that, something that came out of -- a paper that came out of the World Federation of Scientific Workers Conference was talking about the idea of Codes of Conduct in 1968, proposing that, in part, in relation to questions about biological weapons and debates that were happening at the time about various disarmament treaties.

And this was on the back of some plans that the International Council for Scientific Unions had at the time, ICSU, when they were themselves

talking about introducing some sort of identity card for scientists, which is a long way from where they are today.

Just to give you another example of that, it's not just if you like post-9/11, the New Scientist has been writing very sort of provocative editorials about issues of biological weapons.

So, this is just a short quote taken from one article that ends with the line that, unless some principles of conduct are established for men and women who manipulate the materials of nature, anarchy will develop and with anarchy disaster.

That was in 1968. And it's not just recently as well that prominent scientists have been writing codes for journals like *Science*. So, here's a code that was offered in 1977.

So, with that, I hope you can get a sense that this topic has been on the agenda for quite some time. And yet, despite that sort of attention, there hasn't really been a big uptake in relation to biological weapons vis-à-vis codes of conduct.

So, let me try to give you some for

contemporary examples of discussions about codes that have taken place in the post-9/11 context. And, by doing this, I want to give you a sense of the diversity of thinking that's been out there about codes and just give you a sort of illustration, maybe some of the frustrations that organizations have experienced trying to develop codes in this area.

If you just scan the sort of writings that have taken place about Codes of Conduct and dual use issues, you can see quite quickly that people are thinking about different kinds of codes for different audiences that are meant to have different purposes.

So, just to list these three here, the Working Group of the United Nations on Terrorism has advocated the development of Code of Conduct really thinking here about defense scientists and thinking about what restrictions there have to be about WMD related knowledge and expertise.

In Britain there has been quite a bit of discussion about Codes of Conduct because Britain has chaired this year's discussions under the Biological Weapons Convention that are talking about codes.

So, in 2003, one of the committees of Parliament advocated that establishing an ethical code is very similar to a sort of Hippocratic Oath, so this would be an idea of some sort of professional membership joining the scientific profession.

You know, you needed to take an oath as part of that. And, in 2001, George Bush called for a code that would provide a solid framework for bioscientists and one that would have universal recognition.

Now, from these initial statements there's been quite a bit of development in recent years. So, the Working Group of the United Nations on Terrorism gave a mandate to the International Center for Genetic Engineering and Biotechnology to develop this code that they were referring to.

Since then, however, the ICGEB has decided that it doesn't want to develop a code as such; it wants to develop principles that will inform other scientific organizations to develop their own codes.

In the U.K., I don't think there's much discussion about Hippocratic Oath kinds of codes

anymore. But there is a sense of wrapping up the biological weapons issues if you like within a wider discussion about professional responsibilities.

So that would be very much touching on some of the general remarks that Philip spoke to in his presentation, but not BW specific. And as well, just to the statement by President Bush about a code that has universal recognition, I think there has been, in the last few years, there's been a movement away from a sort of idea of a universal code, a sort of one size fits all code.

So, ideas are developing in this area. And there's plenty of them of what needs doing. And all this, I think, points to the importance of a very sort of simple question.

And that question is this, what is the problem to which these codes that we're talking about is a solution? NSABB has a very general remit in terms of the codes issue.

And that doesn't specify the purpose, the audience, or what type of code is necessary. These are questions that have to be discussed. I produced a

paper for the experts meeting of the biological weapons convention, which I distributed here and gave to the organizers.

I didn't see it in my folder. But that discussed various kinds of codes that could be developed in relation to these questions about dual use issues.

I've listed some of the possibilities here. That includes issues about awareness of dual use issues, questions about the revision of responsibility between individuals and collective organizations, such as professional societies.

It also speaks to the way in which I think a lot of the international agreements that we've talked about, the Biological Weapons Convention. These are really written for state parties.

They're not written for individuals. And a code could try to translate those sorts of international agreements that exist into something more specific for researchers.

And then there are questions about bio-safety and bio-security provisions. So, we've already

had some comments yesterday about whether codes were a good idea.

And some people seem to support the idea of establishing a code. Others seem more skeptical. I suppose my response to hearing those sorts of comments is what kind of code are you talking about and what's it supposed to be doing?

I just offer this typology up to just sort of provoke a sense of the range of types of codes that NSABB might think about developing. You could talk about aspirational codes, codes meant just to get people thinking about an issue.

The American Society of Microbiology has what I think is such an aspirational code in relationship to dual use issues. It calls on the researchers not to conduct or not to engage in activities contrary to the welfare of human kind.

It's not a code that is very detailed in relation to biological weapons issues. But it does try to get people to acknowledge that there is an issue to be dealt with.

And it serves various, if you like, sort

of organizational functions about highlighting the importance of dual use issues. That's a possibility.

I think those sort of aspirational codes more often than not are called codes of ethics, but I'm not going to be precious about these names that were offered.

Another type of code that the Board might think about is something much more educational, something meant to provide guidance to individual researchers to get them engaged in debates, and to foster their thinking in this area.

If I were to think of one code in relation to biological weapons issues that does that, I would point to the World Medical Association's Declaration of Geneva, which is not exactly a code itself.

But it does try to lay out some of these educational and advisory issues. One of the key recommendations that comes out of that declaration is that individuals' personal benign intent is not sufficient, that there needs to be a greater debate that just trying to lay out who are the good guys and who are the bad guys.

A code of conduct could be something that is much more about enforcing rules. We heard from Philip Campbell yesterday who was speaking about Nature and some of its code of practice in relation to what sort of materials authors have to submit along with their publications, or make available to other researchers.

Some people yesterday were talking about codes in relation to Select Agent regulations. I mean there, now you're starting to shade into legislation.

But there are these ranges of codes that might be developed. So, let me move on to some of the other barriers that we see in relation to dual use and biological weapons codes.

As has been said here many times, it's very important that anything that's done is international. And I agree with that. But there are barriers to developing a code in the life sciences that is not so universal, but widespread.

And I think that relates to -- in comparison to other professions -- a lack of a sort of key organization that would be able to take that on.

In chemistry there is the International Union of Pure and Applied Chemists which has taken a lead role in relation to the chemical weapons convention.

There is the WMA as far as medicine goes. But I don't think there is an equivalent umbrella organization in the life sciences. And that's going to make developing any international code very difficult.

The suggestion yesterday was put forth that maybe the National Academies internationally might be able to do this. I think it's worth reflecting on the process that they have been engaged with, the collective process over the last couple of years.

I think it's fair to say that pre-2004 you've had different national academies coming out with different policies in relation to codes. The national academies internationally differ in terms of their composition, in terms of their mandate, in terms of their relation to governments, what sort of advice they're supposed to supply.

The International Academy Panel was charged to, if you like, sort of produce a code of conduct which was originally going to be done with the ICGEB, who I mentioned earlier.

And I think through that process it became clear that, you know, there are different timeframes that national academies are working to. There are these different rationales.

There are different mandates. There are different relations to governments. And it does rather complicate devising a sort of single code that's going to be relevant for all organizations that all national academies could agree on.

So, what's happened is that the Inter-Academy Panel has done a bit like what the ICGEB did. It came out with some principles to inform codes that would be taken up by various individual national academies.

That is a useful act in itself. But it does speak to some of the difficulties, if you like, sort of trying to devise a sort of single code internationally in the way that that discussion has

been framed here so far.

There have been a lot of organizations that have thought about developing codes. The International Committee of the Red Cross has thought about codes.

And again, it's moved on from developing a code itself to thinking about principles that could inform other organizations to develop codes. The Biological Weapons Convention this year is having its discussions about Codes of Conduct.

I would be very surprised if out of that process there came an international proposal for a Code of Conduct. I think you're going to see lots of different Codes of Conduct.

And I would predict that the BWC is again going to come out with something like some principles that would inform other organizations to come out with codes.

So, the basic point here is that there isn't if you like, a sort of natural air in the life sciences that would take up some sort of universal or global code, as far as I can see.

I want to then try to, if you like, very sort of quickly summarize some of the discussions that have taken place internationally and nationally about Codes of Conduct to build on the point I just made about fragmentation.

I think in my experience, certainly in the experience of Malcolm and I, there's been a great reluctance in many governments to, if you like, come up with a Code of Conduct, to devise one, and to suggest that for life sciences community.

As we've heard from the discussions yesterday, it's been said that it's very important for the life sciences community to come up with codes, with ideas about regulation or what have you for itself.

But I think, married with that, there's been a -- despite some notable exceptions -- there's been a reluctance for the life sciences community to develop Codes of Conduct in relation to these issues about biological weapons and dual use research.

I think these last two points that have been raised, when you add those two together what you

get is where the current discussion about BW codes is, which is in a sort of continuing state of prelude, lots of discussions about building up to a code, not a lot of, if you like, initiative in terms of actually developing one and thinking about how it might be implemented.

So, certainly I would agree with the comments that were said yesterday about the importance of international codes or international criteria about dual use issues or what have you.

But I think the key issue is one of initiative. It's one of who is going to take up this challenge of devising codes. NSABB with its charter, with its ability to influence NIH funded research with a sort of geographical spread in the U.S. certainly has within its ability to come up with something that could provide a lead in terms of international discussions in this area.

Let's move on to another barrier, this question of what it's all supposed to mean. There was some discussion yesterday about, you know, getting a code that people would sign up to, that would in some

sense determine what constituted appropriate behavior.

I think a lot of the people that have looked into codes and practice, ethicists, social scientists and so on, have often come up with critical comments about whether or not a code is simply something that people sign up to that almost in some sense dictates behavior.

Often professional codes of conduct, particularly, I think, in the science area, are meant to be aspirational. They're often meant to be educational.

And with that, they are open up to forms of interpretation. If you take a classic example of that, you can go to the case of whistleblowers. A lot of the engineering codes, scientific codes, speak to the need to think about public interest, public good, and to speak out when individuals, engineers, scientists, see something that's questionable.

But, as well, many codes also speak to the importance of confidentiality and the importance of thinking about client relationships, which then cut across this idea of blowing the whistle.

And for individuals trying to think about well, what does a code tell me in relation to such a topic, they're often not very helpful. So, the question here is what is a code?

Or a key question to consider, the Board should consider is, what is a code going to say to current debates national and internationally about dual use issues?

So, if that's issues about transparency, if it's these questions about the dual use potential of research, if it's a question about some of the sort of mid-spectrum chemical biological incapacitants and their permissibility, if it's question about where are our global discussions going, about the prohibition of biological weapons, a key question to consider is whether or not the code that's going to be developed here is going to try to, if you like, resolve or further those discussions.

So, another way of sort of framing that is to ask whether a code that's going to be developed here is a way to state an agreement that's going to be developed over time, whether if it's like, if you

like, to defer disagreement, or is it to set the parameters for discussion?

I think you can see codes, the Center for Arms Control and Non-Proliferation, along with some other NGOs, have come out with a code that's trying to move toward something like stating agreement, coming to some accepted conventions about some of these issues of controversy.

But it may be that this board wants to take a sort of path to examine those issues and wants to set some sort of parameters for thinking about the discussion.

Either way, it's going to be a key question to address. Just to briefly speak about some seminars that Malcolm and I have been doing in the U.K., we've done about 25 seminars now with about 600 life science researchers in biology departments in the U.K.

And we did this really to promote a kind of conversation about some of these questions about dual use issues, to provoke people into engaging into some of the international discussions that are taking

place.

And, it would be very easy to sort of give a sort of glib summary of those seminars in terms of what has come out theme-wise. But I think it is fair to say that many of the researchers that we have spoken to just simply haven't engaged with the kinds of dual use issues that have been discussed yesterday.

The sort of debates that most people in this room would take for granted about, say, mousepox or polio virus, or what have you, knowledge of these sorts debates is not something we found to be very widespread at all in the U.K., nor was there widespread knowledge about the international conventions dealing with biological weapons.

And, I mean, the main point is that people just aren't engaged in the kinds of discussions that are happening in this room. So, if you want to think of another barrier, certainly our experience in the U.K. would suggest the barrier of what are you talking about?

Biological weapons and dual use is certainly going to be one of them that would be

experienced in the U.K. And anecdotal experience would suggest that this is the case in the U.S. as well.

On the basis of these seminars that Malcolm and I did, you know, we came up with, if you like, two very simplified types of scientists and just tried to say, okay, well which camp of the scientists that we spoke to are you in?

So, one of those ideal kind of types that we developed was this idea of a very sort of security conscious researcher knew about some of the issues about biological weapons, that thought it was a problem, was very at least willing to engage in some of these issues about pre-project review, pre-publication oversight and so on.

And, if you want to contrast that, if you like, with a sort of classic open science researcher who thought maybe some of these issues were a bit overblown in relation to biological weapons or biological terrorism, that the contribution of the advancement of life sciences to this problem was negligible, and that in many ways the pre-project

oversight mechanisms were ill-advised.

Certainly, if you want to compare those sorts of two ideal types, very sort of simple kind of analysis, most of the people we spoke to were overwhelmingly in this sort of classic open science category.

So, all this speaks to the point that was raised several times yesterday about the importance of awareness raising and education. I would certainly concur with those sentiments.

I think as well, though, this issue about raising awareness begs lots of questions. In some sense that's a very easy answer to give, the importance of education, raising awareness.

When Malcolm and I went around and spoke to researchers, we engaged them in this issue. And, having engaged them in this issue and raising their awareness of it, many of them were still very dismissive of the sorts of concerns that are being discussed here.

So, I think you have to go beyond this notion about just raising awareness and ask what is

that going to mean in practice. Is that a matter of challenging researchers' perspectives?

Is it a matter of just finding out what they're thinking? There are difficult issues that have to be addressed here that I think this consensus that quickly forms around the importance of raising awareness masks a lot of those much more difficult issues.

Okay. So, on to the last slide then. I have spoken to some of these sorts of initial barriers about, if you like, agreeing a Code of Conduct.

But all those initial points, if you like, are just part of the first phase about what codes mean in practice. Philip, in the previous presentation, spoke about the importance about thinking about codes as a kind of living document that changes, that becomes part of the research community that's taken forward through teaching or what have you.

There's all these sorts of issues about implementation, which are very important. In many ways, the conversation that's been had so far about codes internationally is very much in a kind of, still

a preliminary stage.

So, the key question to consider is this question about how codes will be taken forward. I think I put down here watch what the AMA is doing. As I mentioned at the start of my presentation, the World Medical Association has come out with a declaration of Washington, which spoke to some of these dual use biological weapons issues.

I'm not aware that that's really been taken up anywhere through the medical associations other than in the U.S. But, in the U.S. the AMA has come out these guidelines to prevent the malevolent use of biomedical research.

And what I think is very important about that work is that you have an organization, the AMA, which is very committed to thinking about Codes of Conduct in terms of the practice of medics.

It has a review process in place to think about what its various guidelines mean for the practice of medics and others. And it speaks to a lot of the dual issues considered here.

So, just to conclude, if you're interested

in more information about codes, particularly thawing out some of the international discussions which are actually quite numerous about Codes of Conduct, there is a website here for people to visit.

But I think there's going to be some key challenges to face in thinking about codes. And, just in conclusion, I would highlight this, the initial barrier I raised, which is "what is the problem to which codes are being offered to as a solution" and also "the importance of this question about awareness and education".

And I think that should be a topic of considerable discussion. Thank you.

CHAIRPERSON KASPER: Thank you Dr. Rappert. And I want to thank both you and Dr. Dando for making the trip here for this presentation. I'd like to now ask the people, Dr. Sharp, and Dr. Dando, and Ron Atlas, who is also here, to come up and have a panel discussion.

I'm sure that members of the Board and ex officios have questions which we'd like you to address. So, when you ask your question, perhaps it

would be best to at least initially define who you're asking the question of. We're open.

MEMBER SORENSEN: Yes, I thank you for the excellent presentations this morning. I'm very much distressed by what appears to be a lack of coherence among universities in this country -- I can't speak for the U.K. -- as to how we should collectively approach Codes of Conduct and stimulate discussions and disseminate information about them.

I'd like to ask a question of Phil. Phil, have you and/or your colleagues been approached by other universities asking to replicate or approximate the code that you developed in the Biology Department at MIT?

DR. SHARP: We -- if you look at NIH's guidelines for training graduate students now, those guidelines require an educational program that deals with the topics -- in many cases not all the topics, but most of the topics -- that I mentioned.

And, in the last, I'd say, five to ten years, a course of this type has been developed, I believe, at most universities. Sometimes it is

institutionalized university-wide.

Sometimes it is more departmental specific. The specific contents of this course are available. And I have sent them to several people who have asked about MIT's Codes of Conduct course, how we're dealing with it.

I, actually, having participated in the course for several years, found it a very useful thing to do for the students. I think students benefit by, you know, raising their awareness of these issues. And it's a good practice.

MEMBER SORENSEN: But, what I was particularly struck by was the fact that it was indeed institution-wide rather than peculiar to a department or two or three departments.

And the degree of organization and comprehensiveness was impressive. I wonder if other panelists have had experience in their respective institutions with doing this on a university-wide basis and getting consortia of universities to work together on these issues.

DR. SHARP: I'll only make a statement.

MIT is an engineering institution. And they engineer things.

MEMBER SORENSEN: Touché.

DR. KASPER: Dr. Sorensen.

DR. ENQUIST: They switched us.

DR. KASPER: Oh, sorry.

DR. ENQUIST: We both represent Scandinavia. Phil, this is a question more general. I mean, the ethical and practical conduct of science directed to students really is an NIH training grant mandate.

But I was wondering what's done at your institution to engage, for example, the senior faculty or perhaps what is done to educate incoming junior faculty about the very same issues that are there.

You mentioned that you and -- or we would do the job of teaching this course to graduate students. But, is there anything else that engages everybody doing research in your department?

DR. SHARP: The -- not specifically, but as an academic institution, you probably realize as well that, once you engage in training students in a

given class, that spreads through the whole department and then an ethos develops in the department from that experience, and a conversation that goes on in various laboratory settings.

So, there's no specific formal instruction offered to faculty at MIT. But you can create an environment just by creating the dialogue within the department.

CHAIRPERSON KASPER: Dr. Dando?

DR. DANDO: We wouldn't like to leave the impression that the U.K. is under-regulated in the kind of areas that Philip has been talking about. It's quite clear, in fact, that the U.K. life sciences is very heavily regulated and that they would know and have to know about things like regulation, animal experimentation and so on.

The point we were trying to make is that, despite that, despite their knowledge of animal welfare, bio-safety, all those kinds of issues, they were not aware of the kinds of issues that you have to grapple with, these issues concerned with the potential dual use of the life sciences.

And I think the same would apply in the U.S.

CHAIRPERSON KASPER: Dr. Cohen?

MEMBER COHEN: Thank you Dennis. My question I think is first going to be directed to Brian. But some of the other panelists may want to comment.

And the question's going to focus on your ideas of how we can bring clarity to this issue or at least shed light rather than more heat. I want to thank and congratulate both presenters this morning.

Phil, I think you did a very cogent job of taking a historical basis and leading to the clear need for codes. And Brian, your taxonomy also is very useful, a snapshot of the issues and some idea of what various people are already doing so we don't reinvent the wheel.

My question, my concern is that we are charged with developing a code of some type. How do we make sure, in your view, that we look through the right end of the binoculars and we don't get the problem smaller and farther away instead of closer up

and with greater clarity?

There are so many people doing things. There's so much talk, so much history already in the last four or five years. How would you guide us?

DR. RAPPERT: Well, I think I -- I mean, I would have two comments to that. One is the question of where is the guidance going? Spoke yesterday a lot -- about a lot of the difficulties associated with thinking about these questions about dual use.

And, I mean, there are certainly issues for this board to resolve for itself for its own satisfaction before any sort of a code is talked about elsewhere.

But, what I would say in relation to the code issue in not wanting to duplicate work elsewhere, what I would say would be to reiterate what I said in my presentation.

And that is that, you know, despite the interesting codes that's out there and despite if you go to the webpage, I mentioned you can scroll through page after page of discussions about codes in relation to biological weapons issues, despite that, I do see a

distinct lack of initiative in this area.

So, if you ask, you know, what is the thing that is required, I say the thing that is required is leadership. And if this panel thinks that -- if this board thinks that a code is a way to go, thinks that it has something it wants to say in particular about these dual use issues, then I say, you know, take it up here, provide that sort of leadership.

And I think you would see a lot of the current interesting codes, if you like, sort of coming behind that.

CHAIRPERSON KASPER: Dr. Franz?

MEMBER FRANZ: Yes, thank you. Brian and Malcolm, thank you for that. And I agree with regard to the point about the taxonomy. That's helpful to me.

I haven't really worked with codes that much myself. Your spectrum from sort of awareness codes to enforceable codes reminded me of areas I have worked in, and specifically in an international context.

I find that if I'm involved with a security council resolution or a treaty, or an agreement across a table issues often become contentious. Whereas, if I'm working with scientists on a common problem in public health or basic research or something, we build collaborations and barriers are brought down.

I'm just wondering -- and I haven't been involved in Geneva at all this year -- I'm wondering if you saw any of that across your spectrum of proposed codes.

If you're talking about awareness codes, was it easier to find consensus versus if you talk about regulatory or enforceable codes? Did that change sort of the feel in the room?

DR. DANDO: I think there are people more knowledgeable than me in the audience about what happened at Geneva this time. I think the atmosphere seemed to me to be much better than it had been on the previous two years.

It was good also in that the structure had changed so that there were many more presentations and

involvement from scientists and scientific organizations than is usual in the Geneva meetings.

But I came away with the feeling that there was a lot of information being put there. But it will take quite a lot of work between the experts meeting that's just taken place and December for the state parties meeting for that to be boiled down into something which is easily assimilated outside of the Geneva context.

DR. RAPPERT: Just to add to that, just directly to your point about was there a difference between the tenor of the discussion for different kinds of codes.

And I suppose my answer to that would be, you know, not from what I saw. Malcolm and I and a lot of the other sort of NGO participants aren't always allowed into the room to hear what's being said.

So, in some sense we have a limited perspective on that. But I think, you know, from the meeting there was certainly much more common ground than I had originally thought there would be.

There was agreement about the importance of various kinds of codes. And certainly one of my worries going in was that people would just simply be talking past each other.

You know, people would be saying your code is a good thing, your code is a bad thing, you know. But, without kind of getting to the nitty gritty about what they were talking about, that didn't happen.

So, I do see quite a bit of common basis internationally for these different types of codes. But, a point that, you know, should be made is that the BWC for this year doesn't have as its mandate to, if you like, negotiate a code.

They are there to form a common agreement about these issues. So, you know, the development of something is not going to come out of that forum this year.

CHAIRPERSON KASPER: Dr. Imperiale?

MEMBER IMPERIALE: I have a related question, which is, do you have a sense for which type of code tends to be the most effective?

DR. RAPPERT: Yes. I mean, the follow-up

question has to be effective at what? And so, you know, if you're talking about questions about education or, you know, are you talking about questions about, you know, the regulation of materials in labs, there is a great deal of, you know, current legislation in the U.K., in the U.S. in relation to some of those bio-safety, bio-security issues.

Certainly that is there. So, really, you know, are codes effective? Well, effective at what?

MEMBER IMPERIALE: I guess I mean effective in terms of compliance?

DR. RAPPERT: Again, I would say that you're talking about changing behavior, then you're talking about some sort of code of practice. You're talking about wanting to have mechanisms and enforcement.

I think if you look at the literature that comes out of engineering ethics, that comes out of business ethics, what it says is that, you know, if you don't have the teeth in place and you want to change behavior, you know, a Code of Conduct is just not the way to go about it.

If you want to engage in a discussion with the life sciences community or between the life sciences community and the security community about some of these issues then, you know, you'd be looking much more at something like some sort of Code of Conduct, which is tried to, you know, used as a resource to promote discussion and debate.

You know, organizations can quite usefully develop aspirational codes that at least raise within the organization the whole questions about biological weapons or dual use issues.

So, it's a horses for courses kind of an answer that I would give for that.

DR. SHARP: I want to just add one little question or comment on this. Having been at a university and talked a little bit about this issue, I think there has to be an increase in the awareness of these questions among the students and scientific community as part of what you're doing in a Code of Conduct.

I think you can also easily put in places where there's obvious issues, Select Agents as

questions and control of them. But, stimulating a dialogue that increases awareness, creating a community where you understand these things, will get you 99 percent of the benefit of any code.

And I think it's a very important part of what needs to be done.

CHAIRPERSON KASPER: Dr. Dixon?

DR. DIXON: Yes, I have a question building on that. And it's for Dr. Sharp. And, thank you very much for your thoughtful and instructive summary.

It gets us back to the culture of responsibility. So, when you listed the topics of coverage, you included human subjects and animal use.

Do you cover recombinant DNA at present as an existing regulation or existing guideline there to lead us? And, how do you anticipate covering dual use, Select Agents, and so forth?

DR. SHARP: In the topic of responsibility to the public, we talk about recombinant DNA and issues of that type. And I would anticipate that one would discuss in that context the issue of bio-

security, issues of being aware of whether there is dual -- of what dual use technology could possibly mean, and how to view it, and how to view it if somebody -- if they come across it in their professional life.

You're training students for, you know, decades of activities in private sector, public sector as well. And you want to give them a sort of fundamental grounding as well as specifics.

So, you would talk about it in that context.

CHAIRPERSON KASPER: A representative from the Department of State, please.

DR. COMELLA: Thank you, Mr. Chairman. I have, as you know, and it has been mentioned by several of the speakers here, the U.S. is working to increase understanding of dual use and is seeking to develop tools and strategies which will help promote this discussion.

As several of the speakers have mentioned, this year in the Biological Weapons Convention Experts Meeting, the discussion was on Codes of Conduct.

That was actually something that the U.S. suggested as a discussion and was actively an active participant in those sets of discussions. If you had to prioritize where we should go in terms of either enhancing or promoting understanding of dual use and also then sharing it with the international community, what would that be?

What would be the best staring point from all of your perspectives?

DR. SHARP: I'm not --

DR. ATLAS: I guess the real starting point is the dialogue, the dialogue you're having and the dialogue that went on at the BWC, and the dialogue that's going on internationally.

Just as your group is being asked to address the question of Codes of Conduct, the World Health Organization is similarly holding meetings with other groups.

The term among ethicists is ethics talk. What will come out of that will be raised awareness of the issues. That there's unlikely to be one prescription for a code, I think, is clear.

On the other hand, as the inter-academy panel has suggested, there may well be underlying principles which can be accepted globally, which will then allow one to move forward.

I think the word that's resonating already in this group that's appropriate is not Codes of Conduct as much as culture of responsibility. What does it mean?

I mean, I'm very much captured by that term. I'm also captured by Brian's question of what are you trying to accomplish. Margo Summerville, a bioethicist from Canada, and I stood on the railroad tracks and put out a code for people to question a few weeks back in *Science*.

We began with the premise that what we were trying to do was help prevent the life sciences from becoming the death sciences, that when we talk of dual use research and the potential for misuse and doing harm, that as we see the advance in technology we see real danger in there.

That's the awareness raising. Then what do you do to impact act to protect the science? We

find some very interesting interactions, both at the BWC conference and others.

One group is saying the only way this works is to have teeth. We really need it to be set in law. And we need to regulate the community. I'd argue that's not the case.

I'd argue we need this culture of responsibility where we agree and discuss what we collectively need to do to protect science. But again, it really is that fundamental conversation which will lead to the basis for awareness and protection.

DR. DANDO: Fundamentally it seems to me that the problem we're facing is how do we prevent the militarization of the whole of biology? How do we prevent this revolution in biology being applied in a major way to warfare and other hostile purposes?

And, at the moment, you can see from the history how this could happen through the initiation of a series of new events at state level programs. You can see how the simplification and spread of biotechnology must increase our concerns about

substate groups undertaking hostile acts with these kinds of technologies.

But, underlying all of that, I think the concern that the Fink committee was worrying about was the general advance in life sciences leading to inadvertently given assistance either to bio-terrorists or to state programs.

And so, it seems to me that the Code of Conduct discussion is part of what the International Committee of the Red Cross calls the web of prevention, that set of integrated policies that we would like to have in place to stop the militarization of biology.

And it's one small piece of that overall web that we're talking about here. And it's necessary for understand it's that piece that we're talking about and to understand how that piece fits in with all the other range of policies that we are trying to develop.

And we have to remember always that this regime, this prohibition regime we've got in regard to biological knowledge and materials being misused, this

prohibition regime is the weakest by far of the regimes we have for dealing with materials and methods that could be used for production of weapons of mass destruction.

CHAIRPERSON KASPER: Dr. Osterholm?

MEMBER OSTERHOLM: Let me turn the question a bit. I think we've been moving towards this area. But, in the end, our job if we're successful is that it will be a very uneventful next 20 or 30 years.

And that to me would be a goal. If we could have that, we would have been very successful, whether it was because of us or in spite of us. If it happens and we have no biologic event, that's a successful outcome.

Having said that, let me ask kind of a -- maybe a rhetorical but hopefully common sense question that I hope you have an answer that will turn me in my head.

But, when I look back at the issue of what it is that codes are for or all about in the history of human kind, you know, we didn't need a code or a

set of commandments or a canon or some higher calling to make a Mother Theresa a Mother Theresa.

That happened regardless. For the vast majority of us as scientists, you might argue that a code is a guideline or a road map to help us should we start to stray a bit, whether it's out of guilt or out of informed compliance or whatever we don't do something.

But then there is that group for which, in the history of human kind, it didn't matter if there was a code. We're willing to do something in spite of or because of.

And they were governments. They were groups, and they were individuals. And I guess the question I have is, how much are we going to put into this effort from the construct of what you have to argue is motherhood and apple pie?

And I guess you used to be able to say Chevrolet. I don't think you can say that anymore, about what is good and what is right and how much of it we have to acknowledge.

It doesn't matter what we do on a code,

there are going to be those parties who may be the tail who will wag the world, not the dog, in terms of what we do.

And therefore, we just have to acknowledge that and figure out how we're going to deal with that. And what I had hoped you could tell me, are there examples somewhere in whether it's warfare or human rights or other areas of science where there's some evidence that a code or some type of standard had an impact on rogue individuals, rogue groups, rogue countries?

I mean, I continue to come back to the BWC and look at the former Soviet Union program and realize the sham that that was for so many years, even at a government level.

Do we have any evidence that we had an impact? And I say that not -- I hope you tell me that we do because I want very much to find a way to embrace and work hard on this issue.

But also, I don't want to do just something that makes us all feel good. But, in the end, does it really get us that goal of the 20 to 30

year freedom from some kind of attack?

So, if you could enlighten me, I would walk away from this meeting feeling much, much better.

DR. DANDO: First of all, let's go back to the people who won't do any harm. That was the first group of people. And you've said they don't need a code because they're reasonable people. They're not going to maliciously --

MEMBER OSTERHOLM: I wouldn't say they don't need a code. I would merely just say that they're going to do it whether a code exists or not in the sense, I guess, they might exemplify the code and use that as an example for others.

DR. DANDO: So these are all the members of the life science community who took such a huge interest in the developments, the state parties working all the way through the 1990's to try to strengthen the Biological Weapons Convention.

And all of these good people were taking a great interest, watching what was going on, putting information in, working hard to try to achieve success.

Were they? They weren't. There was hardly any interest in the scientific community for a whole decade. So, one thing that a code might do, even if it's the code that just raises awareness, is to actually engage people in looking at this whole issue, and providing the expertise that only scientists can provide into doing something about this.

In regard to the people who you worry about and I worry about, who won't be restrained by a code, what we have to rely on then is the whole range of other aspects of the web of prevention within which the code fits.

But the code won't address those people. But other aspects of the code will. Sorry, other aspects of the web certainly will. And, if we have good intelligence about what they're doing, we may be able to deal with them in that way.

If we have a very good export control system in place, we can prevent them getting some of the materials and information that they require. If we've got a strong international legal system

effectively implemented in national legislation universally we're a good step forward.

If we've got solid biodefense, reasonable, sensible bio-defense, that makes it more difficult for them. And, if the international community is absolutely determined to sit on a substate group or state that goes down this path, then that will do a great deal to persuade them that it's not a good idea.

So it's the other aspects that fit for the other part of the problem. But that doesn't mean that the codes can't be a very useful aspect of that whole web.

DR. SHARP: I just want to make one additional comment on that. The successful outcome you describe, I think, is totally correct. And we want to -- certainly that's it, what we are seeking.

But, unless the biomedical community remains a very vibrant community, and are actually engaged in research that will be able to control and influence a bio-defense, then that rogue possibility is always, becomes a much more difficult thing to deal with.

So, you have the responsibility not only of the successful outcome of not having a bio-terrorism attack, but also the responsibility of maintaining the community so that, if that type of activity occurs, we are prepared for it, recognize it, and control it.

CHAIRPERSON KASPER: We have time for two more questions. Dr. Casadevall has been waiting. And then Dr. Rexroad. And then that will be all for this session.

MEMBER CASADEVALL: I think Dr. Osterholm is right. I think that there is a significant -- there's some proportion of the people out there who are not going to be checked by any codes.

They also are not going to be checked by any laws. However, there is a large -- the rest of the community can be greatly influenced by codes. And I will give you my own experience.

As a physician, I remember taking the Hippocratic Oath the day I graduated. And I face innumerable situations in clinical practice where there is no obvious right or wrong, nothing on the

book.

What do you do? And, a lot of discussions with my fellow physicians have always begun with the three words, do no harm. And that provides a mechanism by which you can begin to discuss it within the context of something that has a long history in humanity.

And I will point out that even the Hippocratic Oath has been amended over and over again. You don't even swear by Apollo Physician anymore. So, codes in fact have to be living documents that can be amended to deal with new problems as they arise.

But, as somebody who has been in the trenches and faced very difficult decisions, that sense of humanity, those three words, do no harm, has helped me tremendously.

CHAIRPERSON KASPER: Thank you. Dr. Rexroad?

DR. REXROAD: Yes, to Brian, it strikes me that out of all of this that a Code of Conduct is best when it's organic to the values of the community that's espousing that Code of Conduct.

I guess my question is, from your point of view, is there a community that exists or are there many communities that exist that we need to speak to?

And what is the likelihood of success of a Code of Conduct that comes out of a -- you know, life sciences is very broad. So, it comes out of a group such as this as opposed to perhaps the option of providing again, as others have chosen to do, principles so that more readily identifiable communities can provide their own Codes of Conduct.

DR. RAPPERT: Well, sort of on your first point, this is the difficulty. I mean, we're not talking about a life science community. We're talking about lots of different communities.

And, of course, relevant to this topic is not just the life sciences, but a lot of other professions. Engineering professions has been mentioned yesterday.

So, I mean, it is a thorny issue. There's no way of getting around it. And, as I said in my presentation, I can't see, you know, a single, if you like, organization, forum, what have you, that's stood

up and said, okay, we'll take this issue on, or that's, if you like, had the scope to cover the range of communities that need to be addressed.

So, in terms of your comment about, you know, what can NSABB do, well, NSABB can do what it has power to do. And I will just go back to the points I made that there needs to be that -- there needs to be development of codes.

There needs to be an implementation if this is seen as a serious topic and a way forward. And there is no perfect sort of solution to who is going to do that.

So, if you want to take it forward here, you should do that.

CHAIRPERSON KASPER: Dr. Dando, you have the last word.

DR. DANDO: Just to say that you may have some very good allies very close to you in the American Medical Association, and some of the thinking they have been doing in regard to codes for physician researchers, seems to me to get to some of the really interesting and awkward questions that you're going to

have to confront.

CHAIRPERSON KASPER: I'd like to thank our panel for very interesting and challenging discussion. And we're going to move on to the fourth session.

This is the session where we're going to discuss topics of international perspective pertaining to dual use research. And the scientific community is truly an international body.

NSABB is charged with recommending strategies for coordinated international oversight of dual use biologic research. Ms. Shana Dale is here to provide us with a brief overview of some of the recent international discussions on dual use dilemma in which she has participated over the last several months.

Ms. Dale is the Chief of Staff and General Counsel of the Office of Science and Technology Policy in the Executive Office of the President. Ms. Dale.

MS. DALE: Thank you for the opportunity to come and speak to you today. For today's discussion I plan to put the balance between science and security in a historical context leading up to today's developments.

In 1947 a report from the President's scientific research board emphasized the need to maintain an environment of free inquiry and that security regulations should not attempt to cover basic principles of fundamental knowledge.

Similar statements continued in 1949 in a report from the AAAS Committee on Civil Liberties for Scientists. The 1950's saw the House Un-American Activities Committee, the McCarthy era, and also the period known as duck-and-cover drills in schools.

In the 1980's the U.S. continued to be concerned about the Soviet threat. And fears included loss of militarily significant technology, loss of technological leadership and know-how, and loss of industrial competitiveness.

Universities were seen as targets and points of leakage of technology. In 1982 the Corson Panel of the National Academy of Sciences issued the report Scientific Communication and National Security, noting in particular that restricting international scientific communication would necessarily disrupt domestic scientific communication.

In 1984 OSTP convened a DOD working group to grapple with the issues flowing from the recent climate that seemed to inhibit the free flow of science.

And the group laid out principles to guide us toward a more open scientific environment, including the fourth bullet here, benefits of open publication far outweigh the risk.

In 1985 NSDD-189 was issued by Ronald Reagan. And it states "it's the policy of this Administration that, to the maximum extent possible, the products of fundamental research remain unrestricted" and that if there is a need for control, the mechanism for control is classification.

Each Federal Government agency is charged with determining whether classification is appropriate prior to the award and also periodically reviewing all research grants, contracts, or cooperative agreements for proper classification.

This leads us to the concerns today post-9/11. National Security Advisor Rice reaffirmed NSDD-189 in November of 2001 explicitly stating in her

letter, "the policy on the transfer of scientific, technical, and engineering information set forth in NSDD-189 shall remain in effect."

Dr. Marburger, the President's Science Advisor, has since reaffirmed NSDD-189 at the National Academy of Sciences and also in Congressional testimony.

The policy laid out in NSDD-189 is extremely important, especially in the context of post-9/11. As you know, dual use research refers to the potential of certain life sciences research to be used for both positive and negative purposes.

For those of us who straddle both the homeland and national security and science and technology communities, the goal is to enhance bio-security while minimizing undue impacts on the free flow of science.

Since 9/11 and the anthrax attacks upon the United States, many other countries have begun to examine the potential threats posed to their country by the use of biological weapons.

These discussions have all prompted the

discussion of where dual use life sciences research fits into the discussion of international bio-security efforts.

Several organizations have sponsored conferences and symposia to address the policy issues surrounding the continual advancements in dual use technology.

Just a few of those conferences are listed here. And many of their reports are available on their individual websites. These meetings have surfaced many of the same types of concerns and issues, the first being what is the threat to my country?

Although not overtly articulated at some of the international meetings I've been to, there appears to be a feeling at least with some of the countries that this is a U.S. problem and not necessarily a concern for them.

All meetings have concurred on some basic themes. The support and cooperation of the international science community was confirmed as being integral to the process of describing a path forward

towards international bio-security efforts.

Defining the risks associated with the dual use nature of bioscience was universally acknowledged as conceptually difficult and difficult to quantify.

The availability of known dangerous pathogens has always been evident. But, in the age of genomics, genetic engineering, and mass informatics resources, the risk profile has become much more difficult to define.

Restricting access to biological material and/or information is one solution. But this creates new challenges in the form of possible impediments to the future advancement of science.

That biotechnology per se does not present a risk was acknowledged. But, that it presents a new potential for misuse of bioscience is evident. Distinction was made between access of known harmful pathogens and access to other biological material, techniques, and information -- many of which emerged from biotechnology that have the potential to be used for harm.

The value of having broad representation from the key communities was clear, and discussions characterizing the multifaceted threat drawn from different perspectives around the international communities, including the threat to public health, to plant and to animal life, and hence agriculture, the food security, and also economic stability.

Discussions acknowledged that not only technical advances, but also societal and geopolitical changes have influenced how science is conducted.

The global reach of the scientific community transcends national boundaries. And wider availability has greatly diminished controls over the use of technology.

In reconciling an open research environment with the threat of misuse of bioscience research, a number of key concerns were identified, including the need to understand the real, as well as perceived threat to each nation and region.

The need to establish a common international understanding of key terminology was emphasized. Participants reported diverse

interpretations and uses of the terms of biosafety and biosecurity.

It has been noted that in some languages there is a single word that encompasses both concepts, for example, in French and Italian. Discussions also highlighted the need for increased awareness among researchers of both biosafety and biosecurity.

In the context of encouraging responsible stewardship, and fostering a security conscious culture among scientists, the need for increasing awareness raising is stressed.

Discussions raised the need for Codes of Conduct, for accreditation of facilities, and for registration of personnel. The need for a balanced approach was deemed essential in assuring public and political confidence that the risks were being correctly identified.

This series of slides details some of the international bio-security efforts underway. In September 2004, 55 participants were selected from government, academia, industry, public research organizations, scientific societies, and the

scientific publishing field.

They gathered in Frascati, Italy for three days to discuss the promotion of responsible stewardship in the biosciences. And, as you can see here, these are the four sessions that we attended.

To facilitate these types of actions, a small scale biannual working group could be organized by OECD International Futures Programme to gather key players in the different stakeholder communities.

The general mandate of this working group would be to identify and document common concerns in various stakeholder communities regarding the oversight of biosciences research at its different stages, develop a common vocabulary concerning the new security issues facing society, particularly in relation to bio-sciences research, to help broker and integrate the concerns of the constituent stakeholder communities, and to facilitate the development of codes of conduct and the mechanisms to ensure their operability, to facilitate the convergence of minimum standards for codes of conduct among the science communities and academia, government and industry, and

to help develop criteria and relevant processes to render codes and other oversight tools, particularly in the international context.

A first concrete step is the inventory of all efforts in OECD and non-OECD countries where governments, associations, or industry groups are discussing or formulating different approaches to bio-security.

This inventory needs to include policy as well as legal approaches. The overview should detail specific tools being used to address problems.

Ideally a small working group would be formed to review and to assess the inventory and to provide guidance on further work. In particular, the group could focus on measures that have been implemented, looking at what has worked and under what conditions.

These first efforts would provide the basis for a gap analysis of current bio-security efforts, particularly at the international level. On a second point, there is ample scope to facilitate further action at the international level in the area

of development of scientific codes of conduct.

While several codes are currently being developed at different levels within industry, at the scientific association level, at the level of the InterAcademy Panel, and even within some governments, these are being done independently and are in different timeframes addressing different constituencies.

This chart actually shows the website from OECD that is now up and running. It allows you to click on different areas of the world. And this is what pops up when you click on North America.

So, if you were further to click on a country, say Canada, you could see who is working on these particular issues, what conferences, symposia, and other events are upcoming, and what type of legislation has either been passed or is pending.

The InterAcademy Panel on International Issues, the InterAcademy Medical Panel, the International Council for Science and the National Academy of Sciences of the United States hosted the International Forum on Bio-Security in March 2005 in

Italy.

There seems to be a recurring theme at these conferences occurring in Italy. It was by invitation only. And the participants attended as individuals and not in their official capacity.

People came from Senegal, Mongolia, U.K., Brazil, Canada, Belgium, Australia, the U.S. and several other countries. The forum grew out of recommendations in the 2003 NRC report "Biotechnology Research in an Age of Terrorism," the so-called Fink Report.

Recommendation seven of the report called for harmonized international oversight. Specifically, the recommendation stated, "we recommend that the international policymaking and scientific communities create an international forum on biosecurity to develop and promote harmonized national, regional, and international measures that will provide a counter-part to the system we recommend for the United States."

I found the format of this particular meeting to be very productive as we broke into small

groups and conducted parallel sessions on three issues, the first being guidelines and principles for professional conduct, including codes of conduct, the second, dissemination and communication of research results, including publication, and the third, oversight of research, including formal regulation and self-governance.

As agreed upon in 2002, there have been a series of expert meetings that you've heard about in relation to the BWC, the last one occurring June 13th through 24th of this year.

These meetings have provided an opportunity for international experts on potential biological weapons-related activities to meet and raise awareness about the need for each country to take steps to enhance bio-security.

The meetings have also facilitated dialogue on emerging codes of conduct. Participation included many agencies from the U.S. government, from the U.S. NGO community, to many actually with us here, as well as government participants.

These were the countries that were

actually listed on the program. Many more countries participated, as did international NGOs and also university and pharmaceutical representatives.

The issues agreed to at this last meeting were, I should say, consensus issues, including the need to heighten awareness and attention to life sciences research and dual use applications; that codes are useful to educate and promote responsible behavior; that codes can facilitate compliance with the BWC; that countries are already developing their own codes through advisory or regulatory bodies; the need to involve the scientific community in developing and implementing codes; and the need to balance transparency with security.

Controversial issues discussed at the last meeting include the idea of obligatory codes of conduct for all scientists, including government researchers; mandatory and multi-tiered review of all dual use experiments, including international review committees; codes of conduct that would be applicable to industry; registration or licensing of scientists; and then universal codes versus national codes.

In conclusion, I'd like to say that progress is being made. OECD's website listing activities in many countries with regard to dual use research will be very useful, as will efforts to analyze the data collected in order to make judgments about gaps and successes.

The experts meeting of the BWC showed that there's been significant progress in raising awareness and sharing information on individual country's activities.

The need continues for more dialogue, awareness of the issues, and sharing of ideas on how individual countries are dealing with these issues. Obstacles remain.

Many countries believe that these activities are a waste of money, that it does not encompass a substantial threat, that many bio-agents are readily available in nature so why invest in security at facilities containing bio-agents?

Many countries have expressed resistance to a concept of code of conduct. And other countries expressed resistance to any type of oversight over

scientific publications.

The goal should be increasing awareness of the issues, encouragement of national or regional codes of conduct and approaches to review of scientific publications.

On a parting note, I would like to thank this Board. The work is incredibly important. These are difficult issues that you need to provide guidance on.

The time is now. And I hope that you share our urgency in getting the work done within the NSABB. Good luck. And we do thank you for your willingness to serve on this Board.

CHAIRPERSON KASPER: Thank you, Ms. Dale. If you want to stay there just a minute or two, there may be some questions. We have a few minutes if there are questions for you from the Board.

MEMBER GORDON: Shana, on the last conference you had in Italy, were there findings of that? Or is it published? Is the information available?

MS. DALE: I don't think we actually

published this because, you know, the people that came to the Como, Italy meeting were there in their personal capacity.

And it was not -- we were not there as official representatives. But I think for the people that went to this meeting, I know in particular people that are sitting in the audience today, I was in the first session.

And we have a couple people in the audience that were in the second and third session. And we'd be happy to detail some of the discussions that went on in the individual sessions.

CHAIRPERSON KASPER: Dr. Rubin?

MEMBER RUBIN: Ms. Dale, it seems like you have a daunting job being the Chief Counsel in the White House on these scientific issues. Not speaking for the entire scientific community, but it's very clear that there are a number of very divisive issues where some of the scientific community have one set of thoughts, you know, stem cells, Kyoto, global warming, nuclear ground penetrating devices, all sorts of quote unquote scientific issues that the scientific

community, some members of the scientific community, have very strong feelings about.

Yet, there seems to be some disconnect at the higher levels of government. And I wonder if you could just help us understand some of the processes that the White House uses to adjudicate some of these more contentious issues.

And, if we do make some recommendations as a Board representing some of the scientific community, how will that be processed?

MS. DALE: Well, I can tell you the way that we engage in the policymaking process in the White House is typically through policy coordinating committees, and particularly for OSTP, it's through our National Science and Technology Council.

That is a cabinet-level council that is chaired by the President. Historically we don't call meetings at that level. The President's science advisor actually manages the day-to-day operations of NSTC through the OSTP.

And we are broken out into four different committees, science, technology, environment, and also

homeland and national security. Within those committees we have various sub-committees that grapple with scientific issues that are cross-cutting throughout the entire federal government.

And that's the way in which we actually deal with issues of science and technology throughout the federal government that bubble up. A lot of the issues that you will be discussing also obviously touch upon the processes of the Homeland Security Council.

We are very closely linked with the Homeland Security Council, as well as the National Security Council, being completely involved in their policymaking processes.

So that's the way that it moves up through the system. Assistant Secretary level is usually at the PCC, rising up to the Deputies Committee level and then Principals Committee with the President.

For the President's Science Advisor, for issues that touch upon science and technology, he is usually at the meetings with the President. And that's his opportunity to provide factual information

on science and technology.

We try to shy away from getting into any other areas beyond just what is factually correct because we want to maintain our credibility, both within the White House, to be honest brokers, and also in the outside community.

For the work that you're doing, as I said, it's critically important and we are very interested to see the NSABB move out expeditiously because we have all been waiting for guidance from this august body on what we should be pursuing in terms of codes of conduct and what should be set up in terms of actually expanding RAC committee, et cetera.

So, we're very receptive to the work of this Board. And we're very excited that this is the first meeting, and very enthusiastic about the progress that you'll be able to make.

MEMBER LEMON: Yes, Shana, over the course of these international meetings, have you sensed any kinetic change in overseas beliefs and awareness of the dual use issue?

MS. DALE: I would say in the meetings

that I have attended I have felt a certain amount of frustration that we're not moving a little bit quicker than I would like to see.

And that's -- you know, how we like to move out quickly in the United States. In the meeting I attended in September 2004 and then the meeting that I attended in March 2005, there were individual countries that were very interested in these issues.

And they're moving forward. And they're doing their own work. There are other countries, as I expressed, that have reservations about what the real threat is. They have concerns that the United States is spending way too much money and that it has overblown the proportion of this problem.

I am heartened by the discussions that I've heard coming out of BWC. It sounds like they actually had a very good dialogue and are interested in tracking nascent efforts in terms of development of codes of conduct.

Obviously, I wasn't there. But that sounds like it was more promising.

CHAIRPERSON KASPER: Okay, thank you.

Thank you, Ms. Dale. We're going to take a 20 minute break. And when we return, our final session will begin, which will cover biosecurity issues surrounding chemical synthesis of bacterial and viral genomes.

(Whereupon, the above-entitled matter went off the record at 9:56 a.m. and went back on the record at 10:22 a.m.)

CHAIRPERSON KASPER: Before we start the session, I wanted to take the opportunity to introduce Dr. Anne Vidaver, who is Professor and Chair of the Department of Plant Pathology at the University of Nebraska.

She's joining us today as a member of the committee. Welcome, Dr. Vidaver. We're going now to begin the session on chemical synthesis of bacterial and viral genomes.

This is a rapidly and accelerated technology in the era of recombinant DNA and has applications that are enormous and really, because of those applications, it really has raised all the issues that this committee is facing.

These advances in the field, though, we

can't forget, have had tremendous benefit to life sciences, medicine, and industry and will continue to do so.

There is, however, a possibility that this technology could be used in the synthesis of pathogens or genes from pathogens, which are toxins, could be used for malevolent purposes.

We are pleased to have an outstanding panel of speakers to update us on what the state of the art of this field is. The first will be Dr. Craig Venter.

And he's going to speak on the state of gene synthesis technology. Dr. Venter is founder and President of the J. Craig Venter Institute and the J. Craig Venter Science Foundation and founder of the Institute for Genomic Research.

He's also a member of the National Academy of Sciences. Welcome Dr. Venter.

DR. VENTER: Thank you very much Mr. Chairman. I'm pleased to be asked to give an update on science. I'm going to talk about reading and writing the genetic code.

And I think one of the key messages is we wouldn't begin to be able to write it without all the information we're getting from reading it. It's only ten years ago this month when we published the first genome of a free living organization, that of *Haemophilus influenzae*.

And then we've seen a tremendous escalation in just a short period of ten years of literally hundreds of microbial genomes moving into plants, animals, insects, human, etcetera.

And this is growing exponentially as we go forward. As we look at the microbial world, which is probably our greatest group of species, we're characterizing these around the globe for each milliliter of sea water has about a million bacteria and over ten million viruses.

Some of you have heard about our expedition, the Sorcerer II expedition where we're taking samples every 200 miles around the globe and sequencing our initial data in the Saragosa Sea where we published over 1.3 million new genes last April and maybe even up to 40,000 microbial species.

And that's just bacteria. We haven't even dealt with the viral populations there yet. Soon the next installment will be up to the Galapagos. And I'll show you some of that data.

Reading the genetic code has changed quite dramatically. Ten years ago the first government funded genome project, the *E. coli* genome took over 13 years to do.

At TIGR with *Haemophilus* genome we reduced that to four months. We've now reduced that to about two hours. And that's still changing dramatically as we get new DNA sequencing technologies.

For example, we're using the four five four system, which as about 100 times its input over the existing applied biosystem genomes. My Blackberry is interfering.

So, this is just some of the data off of this, where from a single machine we can get up to 200 million base pairs per day. With 37-30's we have 100 of those.

And they do a lot of accumulation. Gordon and Betty Moore Foundation gave us a nine million

dollar grant this year to sequence 130 microbial genomes.

So, we've gone from one genome in 13 years to 130 genomes in one year as a side project to our main efforts of sequencing. These samples are from around the globe and follow a lot of the tracks that we're doing on the expedition.

We've also, with a grant from the Sloan Foundation, started the Air Genome Project where we're sequencing viruses and bacteria captured from the air off the top of a building in New York City, and also here in Washington.

We're treating these the same way. But I can tell you that in what you're breathing right now there's a lot of microorganisms. We don't think any of them are synthetic yet.

In our initial analysis up to the Galapagos we have in the order of 8.3 million new genes from some untold maybe over 100 thousand new bacterial species, and maybe ten times that in terms of viral genomes that we're just starting to look at.

We tried to get a comprehensive view of

the whole earth gene catalog and a look at about 29 million orfs, looking at the number of gene families.

There's between 40 and 50,000. But I think the most important message here is, if we take a new sample from the environment from soil or from the ocean, the number of new gene families is still growing at a linear rate.

There's no hint of saturation, confirming that we only know a small portion of biology particularly microbial biology. Synthetic genomics, the topic of what we're talking about here, at least in our view, is the design and construction of genomes from chemical components.

We're more copying biology right now than designing new biology. And this project originated, in fact, from the second genome that was sequenced, *Mycoplasma genitalium*.

The following speakers are far more expert on this topic of DNA synthesis than we are. We are consumers and not suppliers. But DNA synthesis has grown close to the same pace that the ability to read the genetic code has.

And the following speakers have been two of the leaders in making this grow quite substantially. It's a difference between making -- synthesizing all of the oligonucleotides and being able to assemble those in larger units that's changing quite dramatically.

This is *Mycoplasma genitalium*. That's the smallest genome of any free living organism, or at least when it grows by itself in culture. We've now since 1997 been trying to work out a minimal gene set.

This came from just simple questions in biology. *Haemophilus* had 1,800 genes. *Mycoplasma genitalium* had roughly 500. We ask the question, can a species survive with a smaller number of genes.

We spend a lot of time doing transposon mutagenesis insertions and knocking genes out. But they knock them out one at a time. It became clear as far back as '97 and '98 that probably the only way to really understand a minimal genome would be to synthesize one because we couldn't do cumulative gene knock-outs.

We got a very different set of answers

when we did batch-wise analysis, actually showing that cells probably with different genes knocked out can survive in populations.

When we clone them out as individual cells with a gene knocked out, we actually get a different answer of which genes are actually essential for life.

So, with all these conflicting answers, we decided the only way to do it is to actually go forward and build the genome. We've either sequenced or accumulated the genomes from 13 different Mycoplasmas and compared them.

And so, looking at how these different genomes overlap, we've come up with a core set of genes. There's roughly 173 genes common to all these species.

We're absolutely certain those will not sustain life. If we eliminate one intercellular parasite, it goes up to 220. Basically the expanded set is on the order of 310 genes.

Of these 36 are non-essential genes in terms of as single genes we're able to knock them out. But, what we don't know is whether something can

compensate for each gene function.

And also, the definition of essential is very circumstantial. For example, there are genes that code for transporters for glucose and fructose in this organism.

If you only have glucose in the media, knocking out the fructose transporter makes it look like a non-essential gene. If you have glucose and fructose there and you knock out the glucose transporter, it looks like it's non-essential.

If you just have glucose in there and you knock out the glucose transporter, you would conclude it was an essential gene. So we decided that all of biology at the gene level is contextual based on what we have in the environment.

So the genetic code alone is not sufficient to find any species or any genome. In view of how we would construct things, we decided we would build things the way I view they were built in nature in a cassette base fashion and that we'd put these cassettes together so we could bury them.

And the challenge actually became to even

make an accurate cassette early on. This is work with my colleagues Ham Smith and Clyde Hutchison who developed an error correction method that enabled us to rapidly synthesize a 5 kb or so cassette, which we tested with the phi X174 genome.

I have to say it was actually quite exciting just taking the synthetic DNA and injecting it into *E. coli* and all of a sudden watching *E. coli* from this DNA make viral particles.

This is a cartoon of the structure of phi X. This is clearly now the situation where the software builds its own hardware. And that has obviously a lot of implications.

If we can change the software operating systems and cells, I could design and build hardware. So, where are we as we switch from reading to writing?

This is the same information I gave before a senate testimony a couple weeks ago. It's actually clear to me that any sequence viral genome, including any Select Agent genomes, can be made today.

If we don't treat that as a scientific

fact we're making a grave error. I think it's important to keep in mind though that the DNA from a large number of species, such as Ebola and smallpox is not infective on its own.

And just having a genome won't buy anybody anything. The fear of new designer viruses is at least a decade away if it will ever come to pass because understanding the first principles of viral infectivity is such a long way away.

And it's been only through state sponsorship both in the U.S. and the former Soviet Union where there are massive programs to try and design and develop new agents.

So it's unlikely that this field will continue to develop. We're certain prokaryote genomes will be synthesizable within two years and possibly eukaryotic genomes within a decade.

We're building things in these cassette bases. But, how do you put all these fragments together? And we're building a system of homologous recombination based on *Deinococcus radiodurans*.

This is the organism that can take

millions of rads of radiation. Its chromosomes get blown apart and it stitches them back together in about 24 hours.

If you look at the top part of this, this is after 1.75 million rads of radiation. The bottom is 24 hours later and the chromosome is back together again.

Our genomes and our systems don't work that way. But there's a very large number of species completely resistant to radiation because they have this capability.

We're isolating all the components for this and trying to reconstitute this in vitro in a cell free system to use this for assembling genomes. We think this will yield a new field that we're calling combinatorial genomics whereby putting the various cassettes together we think thousands or millions of cassettes and genomes could potentially be made per day.

This would allow for selection by screening, basically whatever question you ask you could screen for, whether it's producing a specific

chemical or just cellular viability, what leads to life in a certain environmental condition or hydrogen production, etcetera.

Right now we're starting with genome transplantation. We're taking cell ghosts and plan to put our new synthetic chromosomes into those to see if the new operating system will support life.

And I said I expect that is within a couple of years. While some people like to take their imaginations in dangerous directions, we like to take ours in constructive routes.

And we think synthetic cells have the potential to transform the world's industries and do things such as CO_2 capture. When we looked at the third genome that we sequenced in history, it was *Methanococcus jannaschii*, which lives in almost boiling water temperatures.

It uses hydrogen as its energy source. It captures CO_2 from the environment. And that CO_2 is the source of its carbon. There's probably tens of thousands if not more organisms on our planet that have those types of capabilities.

We think we could either combine synthetic cells and mix cultures to produce things like biopolymers, sugars, proteins, or simply capturing fixed CO_2.

We have organisms that capture and live off of carbon monoxide in using the reducing power to split water, producing hydrogen and oxygen. So, there's a variety of things in terms of the environment and energy that we think have tremendous capabilities.

Ham Smith and I have a grant from the Department of Energy to try and modify photosynthesis to take the energy from sunlight and switch it directly into hydrogen production.

And we hope to have some progress over the next year or two in that area. We're also trying to modify cellulases and combine those with fermentation in modified and synthetic genomes that could have potential for the ethanol production.

Here's just some partial lists of potential benefits of the futures of synthetic genomics. Obviously just understanding the first

principles of biology are going to come from trying to synthesize cells.

I don't think we truly understood chemistry until we went from looking at structures to be able to build the chemical molecules. This is the next key phase in our understanding of biology.

We talk about energy production, health, vaccine production, new materials, etcetera. I think these species could potentially replace much of what we know as the petro-chemical industry, maybe major sources of food, hopefully a source of energy and certainly bioremediation.

And the question is how to proceed with this area. Back in 1998, before proceeding with any experiments other than the knock-out experiments we paid for out of our foundation, an ethical policy review at the University of Pennsylvania, trying to review whether it was reasonable for us to proceed with making the first synthetic species.

The results of that were published in *Science* in 1999 along with our first minimal genome paper. And I think it's up to the scientific

community to set good standards.

I hate to see them set by a federal regulatory agency. And I think the recent announcement we had of a policy group supported by the Sloan Foundation is a step for the scientific community to move in this direction.

We're trying to lead the way as we go forward by good stewardship in the laboratory. We're taking things to stages that we don't think are necessary or should be required.

But we have a B3 laboratory that we're building any genomes in. We don't think human pathogens or human genome modifications should be taking place at this stage.

Organisms, as with recombinant DNA technology, should be designed so they can't survive outside the laboratory. We know from every genome we've done how to engineer out pathogenesis and self-evolution mechanisms in these genomes.

I think this session, this committee is important in terms of open communication both with science and non-science communities. And I think we

have a tremendous opportunity for doing good.

I mention the Mildred Cho study in *Science* in 1999 and the ongoing study with the Homeland Security Program at the Center for Strategic and International Studies and the Synthetic Biology Group at MIT and Bob Friedman's policy program at our institute. Thank you very much.

CHAIRPERSON KASPER: Thank you, Dr. Venter. Next we're going to hear from another pioneer in genetic research. I'm pleased to introduce Dr. George Church.

Dr. Church is professor of Genetics at Harvard Medical School and Director of the Lipper Center for Computational Genetics. He'll speak about some risks and benefits of synthetic biology.

DR. CHURCH: Could I have the first slide, please? So, thank you. What I hope to present is a technological view, which is a small piece of the problem here, and also the social fabric that we've been talking about quite a bit where the rewards of synthetic biology might actually address partially the risk as well.

And I think to do this we need to consider sequencing synthesis in systems. And I've just a -- where I've been to get to here is in 1974 the code. This is not a conduct code, but the computer code meetings and edit code.

This molecule is spinning here and is the molecule responsible for decoding RNA into proteins. And then in '84 I have made acquaintance with the Department of Energy, which was a wonderful -- our paper on genomic sequencing and then an early genome project grant.

And then, some of these companies have been a very good experience that *H. pylori* was sequenced commercially at GDC, which later fused with part of Agencourt.

And those have been part of the team within NIH for sequencing human and subsequent genomes. It's an interesting exercise in commercial cooperation with the Government.

And then, more recently, synthetic biology, which is what I'll mainly talk about. And my group and many others have been at the kind of the

intersection of these three exponential technologies, which is computational, synthetic, and analytic.

And this is a logarithmic plot. And even so, you can see that the slope might be changing recently upward. And this is the reason that we worry about -- we call them destructive technologies for more reasons than one.

And, how does this play out in terms of risks? We can see above the line are examples where code of ethics may or may not have had a big impact, where the rogues that we were talking in the previous session will do this.

And how can we minimize this sort of risk? And then below it are the things that we discover or engineer in the laboratory, presumably following those codes of ethics, but are enabling.

And we need to deal with those as well. So I'm going to suggest some ways of dealing with that. Some of us, various representatives of the synthetic biology community, and I have conferred.

And then there's this link down at the bottom of this slide for a particular proposal for

monitoring synthetic oligonucleotides. And I think John Mulligan, who will be next, will talk about this some more.

But, in particular, we need to extend the very good recombinant DNA Select Agents as starts. We need to extend them so that we not only have codes of ethics, but we actually have surveillance and ideally automated surveillance.

That is to say if computers can monitor these things, it would be more comprehensive. It's just a piece of the puzzle. But I think it's a very important one.

Because, right now chemicals, instruments, and synthetical oligonucleotides, although they may seem to be getting cheaper and more prolific, there are indications that this could be something that is economically feasible to be more centralized and more suitable for surveillance.

And, if it becomes uneconomical to produce things any other way, this might be beneficial. Sort of educational and news emphasis we put is to some extent under our control.

In the lower right you see a news item from 1977 on a recipe literally for weaponizing botulism. So that's '77. And also you can see that the innocent competitions, if they're given a war-like attitude for the younger generations is certainly not what we're trying to encourage in synthetic biology where the stakes are higher.

And I think we've talked about code of ethics engineering societies, which doesn't necessarily affect the rogues, unless we have a way of providing funding for meetings where we can network with past trainees.

And this has been suggested to me by a number of people. And I think it's a really great way of extending that Code of Ethics to monitoring where people are going with their research.

Bio-weather map in the upper right, you can see this is literally a satellite image of monitoring one of our favorite organisms -- photosynthetic organisms for which we have DOE funding to study.

But we also, as with Craig, are interested

in developing technology to monitor airborne and medical fluids as broadly as the technology costs will allow.

So, we're heavily focused on bringing down the cost of analysis. And I just -- the previous slide was about licensing and monitoring a supply chain while synthetic oligonucleotides become fewer and fewer.

Manufacturers of instruments are actually going into the business. Some of them are actually leaving the business, like ADI, which was one of the first ones.

So, it's a good time for having low impact on research, but still high surveillance. I think that's a win-win situation. We would like to be able -- we are, our team is working on improving vaccines and bio-synthetic drugs.

I'll give you some examples in a moment. And this is going in an increasing level of difficulty as we go down this set of bullets. It is possible to imagine making cells resistant to those existing viruses via codon changes, getting back to that

genetic code.

And I'll give an example of that that's fairly near at hand for a specific case. So, safer biology via synthetic biology. Computational systems biology can be increasingly in vogue, especially if people writing grants and papers phrase their proposals and their success stories in terms that are machine readable, not just human readable.

I think that that's a profound change that will be occurring. And it will hopefully help some of the outcomes of this committee to model in the future.

Synthetic biology is increasingly capable of making custom sensors. For example, by protein design has gotten much better. Our colleagues Dave Baker and Homa Holinga and so forth and riboregulators also are fantastically straightforward to design from abdomers.

We have -- we would like to have higher fidelity gene replacement. And I'll give you some examples of technology we're developing in that direction.

Metabolic dependencies is something that's

used in recombinant DNA to build better vectors. And I think it will be even more valuable as we go into synthetic genomics.

And I'll show an example of that. And novel genetic codes or restriction methods can be and are being engineered into some of our cells. So here's some examples.

The top one, we're in the process of implementing, and the second one is more speculative. So the idea is to change the genetic code, first change the mere 313 UAG stop codons, which is a favorite for a variety of purposes for amber suppression.

And then that will allow us to delete the RF1 which competes with good tRNAs that you'd like to introduce for new amino acids, such as this one here that Peter Schultz and his colleagues at Ambrex Company used to modify human growth hormone, a 2 billion dollar market so that it has higher survival in the human.

But, in order to produce this in large quantities, it would be nice to get rid of the

competing release factor and stop codon. And then you can -- there are other plans down below where you can actually remove some of the codons or switch them, the important thing being that these have two positive uses.

One is for engineering proteins. And the other is for isolating genomes so that nothing can go -- no piece of DNA can come in or go out in a functional way.

So we want to be able to engineer these DNA and RNA elements. Artemesinin is an anti-malarial drug which Jay Keasling and colleagues think can be made more efficiently by biosynthesis in *E. coli* than harvesting from plants.

And there are many other examples like that. Many of our drugs do come from biological systems and could be optimized synthetically. And we'd like to be able to go in and change codons not -- that genome-wide is one example.

But you can also do it gene-by-gene as you bring codons -- move them between organisms. It's very important to adapt them for high levels. There's

uses for making mouse models which are closer to human for testing immune reactions and toxicity as might be of importance to this committee.

So, why change full genomes? We're not going to take this lightly. But the genetic code arguments that I've been making already and safety, we can make the genome for stable, less able to evolve as Craig mentioned, and enhance recombination, which allows us to help engineer better.

So, how do we do this? We can make up to ten megabase pairs of oligonucleotides on 1,000 dollar chip by a variety of methods here, which we've had wonderful interactions with most of these companies, and a variety of methods.

The idea is that you get an image onto a standard glass slide or microchip fabricated. Just like this projector is projecting onto the screen, you can project it onto a chip and make synthetic oligonucleotides.

You can have basically the equivalent of two *E. coli* genomes or 20 *Mycoplasma* genomes on 1,000 dollar chip. This is about 1,000 dollars cheaper than

any other way currently available.

There are three papers that Joe Jacobson's group and Paul Modrich's group has joined together with us and is improving the accuracy from sort of on chips.

The accuracy is about 1 percent. And you can get the sub-accuracies that are better than the accuracies of PCR, sort of error rates of one in 100,000.

We have not put every piece of this together in assembly pipeline yet from chips that I showed in the previous slide. But we have greatly improved by orders of magnitude the error rate, and we're going to keep doing that.

The assembly process dates back to Carrie Mullis' 1986 follow-up of this PCR paper and other projects in 1990 to 1995 for polymerase assembly. All we did was add a computer-aided design and some multi-flexing.

But the idea is to extend oligonucleotides to those chips on each other eventually extending in vitro up to sort of the 10 to 15 kb range, which we

published in *Nature*.

And then those you can trim back the ends and anneal them up to sort of 100 kb range, which is a relatively small piece of DNA to introduce into *E. coli*.

People put in more than 300 kilobases in the process of genome project. *E. coli* genome was five megabase pairs on the far right there. And the last steps, because it's hard to handle large DNA on the five megabase scale without it fragmenting, we do the last steps in vivo.

That's a largely automated process that Nick Reppas has gone through. But the idea is you start with one pool of about 117,000 oligonucleotides, which is half of a chip, and that goes into 480 pools, and then it drops down to 48 in vivo constructs, which drop down to one.

And there are three ways that we are pursuing putting these together. We're at fairly early technology development stages here. We can either put in those 48 constructs serially one at a time, which takes about a day per stage, or there's a

hierarchical method where we can put them in using two and then four and dropping it from 48 strains to 24 to 12, down to one.

And there's also a highly multi-plex possibility for both of those, which could be as little as one stage. Here's the data -- not data, just, you know, where we made a 14 kilobase construct of some 21 genes from *E. coli*.

And, in the process, we did them both in the original form and by codon re-mapping where they could express at higher levels by changing their codon uses.

So we're really quite enamored with all the things that you can do with codon re-mapping. And, when we -- we want to be able make these genomes safe for both by changing the codons but also by metabolic dependency.

Here's an example where we made a large variety of metabolic dependencies and then determined how they could cooperate with one another to rescue one another in detail, and how they would evolve.

And so, the whole idea of metabolic

dependency and then monitoring possible escapees and resistances if evolved, here's one where we evolved these strains from initial seven hour doubling time to two hour doubling time.

And with the yellow arrow is one of the points that we've been analyzing in great detail with a new sequencing method where we can evolve these strains that have escaped our selection or resistance.

And this new sequencing method is intended to be easily distributed using standard equipment, which is a standard microscope, albeit automated with computer readout, but these are standard equipment in many laboratories worldwide now.

And it's done entirely -- it can be done entirely in vitro so that it doesn't have the problems of in vivo cloning and so forth. And it's also capable of doing single molecule detection, which you'll see in a moment.

We have seen already a 30 fold improvement in cost; it's a greater improvement than that in speed. But the important thing here is cost not speed. And the accuracies are extremely high.

And there's 100,000 fold improvement that I think is fairly easy to imagine without any real changes in technology just using it more effectively in terms of how the camera is taking pictures, things like that.

So this is important because, not only do we use sequencing for the synthetic to determine what we did synthetically, if it evolved, how the strain evolved, and monitoring the environment for viruses and bacteria such as Craig has mentioned, this is just sort of an academic summary slide of how we've been sequencing that strain of *E. coli* that we engineered and that evolved, showing that we're discovering things that make sense biologically.

And we have a very high accuracy on the order of better than ten to the minus six. This is very important for many applications, for example sequencing humans.

And then the last slide is just that we can do this on single molecules. It's very sensitive. So you want to do environmental monitoring where you really want to get every molecule.

There are many possibilities here because the PCR is -- each molecule is basically in its own little PCR tube without competing with the other ones.

So there are no cross-overs and so on. We can do this on molecules as large as 150 megabase pairs where we're sampling various points along them.

So, just in summary, this is the slide I showed earlier. We have these options where we can do -- I would love to see us doing more bio-weather map.

Our citizens should be at least as interested in what biology is swirling around them as what low pressure fronts are swirling in. And I think that that could be done with both airborne and medical fluids for very low cost and low impact on researchers anyway, and even lower impact by surveying the bio-chain supply, for example, the synthetic oligonucleotides and the machines and chemicals that are required to do that.

You can get some idea of intent, if somebody tries to hide their synthetic research, then you have some indication of intent. Just code of ethics combined with surveillance can help reveal

those attempts to be surreptitious.

And I mentioned bio-synthetic drugs like Artimesinin. And the question of how many vaccines can an individual handle at one time I think is a very interesting immunological one.

And finally, is the sort of thing we're doing with codon changes in *E. coli* transferable to other species of agricultural significance where bio-terrorists could act or possibly to human stems cells in the more distant future?

But I think we can test out these ideas by making codon changes in *E. coli*. So, thank you.

CHAIRPERSON KASPER: Thanks, Dr. Church. The next speaker is Dr. John Mulligan, who is President and CEO of Blue Heron Biotechnology. He's going to share his perspective on the issue of potential misuse of synthetic genomics and how it impacts on the life sciences industry.

DR. MULLIGAN: Okay. Well, thanks for inviting me today. So, I wanted to make really three main points about the regulation of DNA synthesis.

And some of these I think have been

covered very clearly by earlier speakers. One is that DNA manipulations are at the heart of modern biology and that anything that impacts the ability to manipulate DNA impacts all of our R&D capacity.

Our view is that the current regulations that involve Select Agents and sequences of Select Agents need some improvement. And that's due to lack of clarity and specificity.

And the other main point that I wanted to make today is that I believe that good choices in regulation can enhance our ability to respond to new diseases by strengthening and maintaining our R&D capacity.

The other point is that I think that good regulation, regulatory choices in this country are likely to be followed by other countries. So, our company, Blue Heron Biotechnology, is a gene synthesis company.

What we do is give customers a website. They paste the DNA sequence into that website. We manufacture that sequence from phosphoramadytes, clone it, verify the sequence, and then ship that clone in a

few weeks back to the customer.

And today almost all of our customers are conventional biomedical researchers in pharmaceutical companies, biotechnology companies, universities and government labs.

And one of the key points is that they're using this technology to substitute for other standard techniques. And they're using it because it's faster and cheaper.

Access to gene synthesis technology improves the productivity of the R&D process. It saves researchers time and money. And the cost of doing this continues to decline in part due to technologies like the ones that George described.

And having complete control of the DNA sequence, being able to design a sequence and then have that created for you, any sequence you need can improve the experimental design and allow new experimental approaches, like the synthetic biology approaches.

And we believe that gene synthesis can help to speed the responses to new diseases. One of

the perspectives that I have in thinking about regulation of the technology -- by the way, I wanted to say I consider myself a traditional open source biologist.

But, I feel like one who is very interested in bio-warfare and knowledgeable about the dangerous potentials. I don't think there's necessarily a complete contrast between being interested in open standard bio-science approaches and ignorant of the potential dangers.

Why is the regulation of the technology important? Molecular biology and genetics are integral to life science research. And the techniques are ubiquitous regardless of discipline.

Billions of dollars are spent globally to obtain and modify DNA each year. There's close to a billion dollars spent on the reagents that are used directly to manipulate DNA, vectors, enzymes, cells.

The direct costs to NIH are probably in the billion dollar range. Each of that dollar of that billion dollars of reagents' spending, probably represents three to five dollars of fully loaded cost.

So there's a huge amount of effort spent acquiring and manipulating DNA. And tools that improve the speed of R&D could be critical to responses to new diseases.

So we see that increasing our ability and this dispersed ability to create the DNA molecules we need for research is important in responding to diseases.

I believe that serious infectious diseases, pandemics, are likely to arise from nature regardless of nefarious efforts, so that there is a threat from bio-terror but there's an equal, perhaps greater threat, from the evolution of new diseases in the next few decades.

So it's really important that, even if we stopped all biological R&D, we're still going to have dangerous new diseases arise in the next few decades.

The technology that we provide does have a direct impact on infectious disease research. Scientists need the DNA for pathogens to study their basic biology and develop new therapeutics.

Some, and perhaps most, pathogens --

certainly all viral pathogens, as Craig said -- are within the range of today's technology, and maybe not completely unaltered.

But they could be made. And we expect that one or more bacterial genomes will be synthesized within the next year or two. So, nefarious uses of the technology are certainly possible.

However, as I'm sure many other people have pointed out, direct isolation of the same pathogens is certainly an easier way to acquire them today. So, our company has been very focused on complying with the current Select Agent regulations.

As you know, government approval is required to possess or distribute certain pathogens and pathogen genes. What we do to comply with these regulations is to screen all the orders we receive against a database of genes from Select Agents.

And then we review every sequence that resembles a Select Agent gene. And then we do a detailed analysis of any genes that actually are identical to Select Agent genes, or very close, to determine if they're covered by the regulations.

So the current regulations, the Select Agent regulations, require some interpretation. Many genes from Select Agents are not dangerous and are not controlled.

Many genes from Select Agents resemble harmless genes. And many scientists use non-functional parts of these genes in their research, viral code proteins, fragments of toxins and things like that.

Just to give you some recent examples of the kinds of things that we see when we analyze these sequences, we had an order that had 100 percent identity with a part of a toxin protein.

It matches about 30 percent of that toxin protein. If it matched the whole protein, it would be covered by the Select Agent rules. So we looked at the literature and found the papers that suggested that this domain was very useful for vaccine development and was consistent with the group that ordered it and that that domain was not functional on its own.

So we decided to build that gene. We find

genes that are -- many of the sequences of Select Agent pathogens are bacteria. So, any common metabolic gene will come up as a positive.

And many of the Select Agent viruses are similar to non-Select Agent viruses. So, each of these examples required some input from a Ph.D. biologist to decide whether or not we should provide that gene.

So we believe that regulatory clarity in the area of Select Agent DNA sequences would be very helpful for our business and for the industry as a whole.

And the goal should be to restrain and monitor access to dangerous DNA fragments, but to retain our ability to carry out rapid biomedical research and other life science R&D.

So, one of the other points that I want to make is that no national regulatory scheme can block the arrival of the pathogens. A national scheme won't control activities in other countries.

And, even if you could regulate all the activities in the world, there's still going to be

natural pathogens arising in the next few years. We also believe that poorly conceived regulation could impede our ability to respond to the emergence of new pathogens, whether they're from natural or human causes.

So, I just wanted to give you our perspective on one small aspect of the whole regulatory theme, which is that, if you're going to regulate DNA sequences, those regulations should be expressed in terms of the sequence information.

You should define the sequences that are covered. And, as I said, the current Select Agent rules require some interpretation. And they should, of course, define the actions you would take if we see an order that matches those sequences.

So, one possibility would be, in addition to regulations that are focused on the control of specific organisms, would be regulation focused on specific sequences.

So, the Select Agent rules already cover specific sequences. And so what we propose is a list of what we call select DNA sequences, or DNA sequences

that could be used to build pathogens or enhance pathogenicity, and that these sequences would be defined in terms of a reference sequence and a percent identity so that you can actually tell whether or not the sequence you have violates the law.

And that, you know, in order to be able to have that reference sequence, I think you need an active maintenance of the reference database by an oversight panel and a set of organism specific experts that would be updated on a regular basis.

So, one possibility would be to have, for these select sequences, three classes of sequences, the classes that exist now, the specific genes from Select Agents that require a permit to produce them.

Another class might be a set of related genes or other pathogenicity genes where you would require reporting but not necessarily any other controls on their possession by scientists.

And then all other genes where we would not support a reporting requirement. And so, this would allow you control of the high threat sequences, tracking the sequences that could be incorporated into

new pathogens.

And so, for instance, today it's perfectly -- the Select Agent rules allow you to order a fragment of a toxin, for instance, from three different gene synthesis groups.

And it's not -- you're not really violating the rules until you assemble those together into a complete pathogen, a complete toxin. So, it would be useful to track fragments of those sequences and potentially related sequences, and no reporting requirement for most sequences.

In terms of operational considerations for this kind of regulation, we would support a positive requirement to check orders against the select sequence database for providers like our company.

The current rules make it illegal to provide certain sequences. But they do not require providers to check for those sequences. Clear procedures for identifying the organizations and individuals that are authorized to possess them is pretty much in place today, and then a centralized database to collate information on reportable

sequences.

And, as I said, it's currently possible to buy the parts of a virus from several different providers without violating any of the regulations until you assemble the completed virus.

So that's one idea on how to deal with some of the regulation. I wanted to make a couple of other points. And one is that gene synthesis is an international industry.

We have three main competitors today. One is in Germany, one is in United States, and one is in mainland China. Researchers that use this technology are located all over the world.

And gene synthesis companies exist all over the world. There are a dozen or more in the U.S., a similar number in Europe, and several in Asia.

And ad hoc and non-commercial genes synthesis occurs regularly in labs all over the world, there are tens of thousands of people who are capable in their own laboratories of carrying out gene synthesis.

And U.S. regulations can't block nefarious

access to this technology. But it can impact their ability to respond to new pathogens. Another point is that the choice of regulations can impact the development of the technology.

So, it's our view that our customers will not outsource gene synthesis if regulations require disclosure of all sequences of orders. So, the sequence data -- much of the sequence data is highly confidential.

And this regulation, regulations that require us to report every sequence order we got, would drive the demand for gene synthesis in a more dispersed technology.

So, the technology that we use is perfectly amenable to building a box the size of this podium that would allow you to assemble genes. And, if our customers decided that they didn't want to order from us, the alternate is to provide them with the capability to do it themselves.

And I think that regulations which push towards a dispersion of the technology will loosen the control rather than tighten it. So I think that rapid

effect of R&D is the solution.

Our response to new pathogens depends on decades of basic research and immediate application to today's best technologies. And I think that gene synthesis could play a role in very rapid responses to new pathogens.

I believe that regulations that significantly restrict access to the best technology would be counterproductive. They'll increase the risk of pathogens by limiting legitimate researchers.

And it won't significantly restrict access, nefarious access to technology. So, I think another really important point to think about in considering regulation is that scientists working for the good of society have a many thousand or million fold advantage in resources over the small non-governmental organizations that might use the technology in nefarious ways.

There's a huge advantage. The number of people who are the unscrupulous and willing to kill innocent bystanders for political end, I believe, is very small, relative to the vast number of people who

are going to use this technology in good ways.

So, balanced regulations that discourage nefarious projects without chilling the R&D enterprise will preserve this advantage. And I think it's critical to preserve that huge advantage of the good guys over the bad guys.

So I think we have an opportunity to make regulatory and policy decisions that will improve lives by reducing the danger of infectious disease by retaining this capacity.

So, in summary, gene synthesis and molecular biology are central to modern biological research. The technology for doing this is ubiquitous and international, so control within the U.S. is not possible.

I think the current regulations need some improvement and that poor regulatory choices today can significantly reduce our ability to respond to new pandemics, whether natural or man-made. So, that's all I have to say.

CHAIRPERSON KASPER: Thank you, Dr. Mulligan. If Dr. Venter and Dr. Church would mind

joining Dr. Mulligan on the podium we can open for general discussion and questions.

(Pause.)

CHAIRPERSON KASPER: Okay, questions from the panel or discussion points?

MEMBER RUBIN: This is a question for Dr. Church. And I see Dr. Endy is in the audience as well. This returns to an issue we talked about yesterday, and that's -- that gets back to where the boundaries of dual use start and stop.

And a lot of your work, George, and Drew's work, and other people in the community, had been working out algorithms and mathematical models. And the question that I have in terms of dual use is, where would it start in your mind?

So, a computer science company wouldn't give you the source code. You know, they would give you the disk at the end of the day or something. But, where do you see our group getting together to think about where dual use actually starts, especially as you go towards more mathemetizing biology and engineering biology.

Can you give us some parameters on that score?

DR. CHURCH: I think, you know, one of the speakers yesterday pointed out how there is -- you can weaponize just about anything. I think that the main way of determining intent that I can think of -- and I'm not necessarily looking at it from every possible way -- is if they try to hide it, then that's probably an indication that they're trying to weaponize it.

So, you need to make it very clear who is trying to hide it or not. The adding mathematics and engineering, I think, if it's done in the open, will tend to reveal just how safe we can make it.

And so, it will drive -- it will make the currently blurred distinction between the two uses sharper because, as you engineer, you can make it very, very hard to weaponize.

And those that do try to keep the blurring going on, will probably try to do it surreptitiously. And everything you can do to expose that would be a good thing.

CHAIRPERSON KASPER: Dr. Franz?

MEMBER FRANZ: This is a question for any of the panel. What are the sorts of international demographics of these capabilities in this technology area? And what are the trends in that regard? U.S., China, India --

DR. MULLIGAN: I believe that, you know, the large, the vast majority of the capacity is presently in the west, in North America and Europe, but that the trend is very rapid expansion in China, India, and throughout the rest of the world.

So, as I said, one of our main competitors today is in Shanghai.

CHAIRPERSON KASPER: Dr. Osterholm?

MEMBER OSTERHOLM: To follow-up on the earlier question to help guide us, you know, just before 9/11 we had a potential terrorist in Minnesota, as you know, who went to flight school there who alerted authorities to his potential intent on using an airplane when he told them he just wanted to learn to take off, he didn't care if he landed or not.

And that was an obvious use of a high technology device to do harm that alerted authorities

to something bad. On the other hand, you have the guy that today goes into the local car dealership down the road here and wants to buy a tire jack.

And you assume the poor guy in a suit just has a flat tire somewhere and doesn't have a tire jack or tire iron and he is buying it for his flat tire.

But really he's walking down the street to the local fast food place to bop them over the head and rob the cash register. You know, that one you could not have anticipated at that car dealership that that was the intent of using the tire jack.

Where in your worlds would you see us trying to focus on the obvious terrorist 747 don't care if I land it versus where, you know what, if we tried to screen this, we would obviously be largely screening someone who had no ill intent in mind?

And how should we start to focus on the technologies you're presenting to even say what might be yellow lights, let alone red lights, versus what are obvious green lights?

Because we're going to struggle with this part. I mean, what you've shown us this morning is

the future. And this is where we're going to struggle mightily, I think, in terms of what advice we give about where do we even consider something potentially that 747 versus that tire jack.

DR. VENTER: Well, let me take at least a stab at what I think you're trying to ask. But, I don't think anybody that would want to do something nefarious -- I can only guess on this -- would order something from Blue Heron or from George Church's company.

There's some guess, and maybe my colleagues here have a better guess. There's probably well over 50,000 DNA synthesizers out there in the world.

There's blueprints for making them on the internet. I looked a couple days ago. There are several for sale on Ebay for about 5,000 dollars. Tracking what happens in a few reputable businesses isn't going to tell you anything.

I think maybe tracking what we're doing, with airborne samples and water samples and kind of surveillance George suggested, maybe is a wise thing

to do.

The DNA sequence is probably our most telling piece of information that's been largely ignored by everything that's going on out there as we look for simplistic methods of PCR fragments or restriction digest fragments.

The sequence would tell us instantly whether it was an engineered – a piece of DNA. But I think if we're not concentrating almost 100 percent of the efforts on providing defensive countermeasures, we're missing the big picture here.

We should assume that any, as I said and Dr. Mulligan countered, that any viral agent can be produced today. We should just assume that's possible and make sure that we have good vaccines and new vaccine development procedures to work against anything, whether they're natural occurring or man made.

But I think surveillance of water and air systems is totally feasible today and is largely being ignored.

MEMBER OSTERHOLM: Could I just ask a

follow-up to make sure I get clarification? So, what you're saying then is there's really nothing to monitor, you believe, in the industrial process -- and I thought that's what you might say -- but rather potentially monitoring the first potential attempt to hit or the first leakage of whatever work is going on out there.

And that basically the real key issue for us is to always stay one step ahead of some on a defensive basis. Is that a fair assessment?

DR. VENTER: I would say that's a very accurate assessment. You know, what we're doing with the DNA sampling around the planet we think we could tell, as more data is added on, exactly what part of the world, perhaps even what port a ship's ballast water came from, what part of the world the dirt on somebody's shoe came from all from the bacteria and viral elements there.

You know, the codes that, as we modify things in synthetic biology, we're all altering those, there would be telltale signs. They would easily show up in any kind of monitoring system.

So, I think detection and defense is what I would choose if I had the choices.

DR. MULLIGAN: I agree with that perspective. I think the idea of trying to monitor sequences in the environment is a great idea. It's very difficult to work with DNA, particularly if you're trying to do it in a garage manner without releasing some at some point in the process.

I think another thing that I would like to see would be an effort to try to detect -- this is something that probably won't be buildable in the next decade, but something that we should be thinking about -- how do you recognize sequences that are newly designed pathogens?

Is there a way to analyze sequences to try to recognize something that's been created completely de novo? For the next decade or two, people are going to be working with existing pathogens.

But, in the long run it's certainly a potential.

MEMBER ERLICK: I was just going to ask the question related to the inevitable trade secret

issue with pharmaceutical companies and others. Do you denote any push back in terms of this overwhelming ability to interrogate systems?

And it might be that there are some quote unquote trade secrets that they would not want to let loose. And this gives you the ability to have rather quick recognition of what might be an early process leading to a patented element.

DR. MULLIGAN: Are you referring to the environmental capture of DNA as finding out people's secret sequences?

MEMBER ERLICK: That and the fundamental capability itself to just capture a particular product and be able to quickly interrogate it.

DR. MULLIGAN: Yeah, I'm sure that would worry people. I mean, the pharmaceutical company is probably more capable of keeping its sequences completely internal than your nefarious actor.

CHAIRPERSON KASPER: Dr. Relman?

MEMBER RELMAN: I too share some of the skepticism that I think has been expressed about the feasibility of control or regulation and much of this

in part because of the dissemination or ubiquity even today of some of the pieces of the technology, but also for a few additional reasons that have not been, I think, adequately explored.

And that is an imprecise or insufficient understanding of the meaning of sequences. If we could in fact recognize all of those sequences that contribute to or are necessary for virulence, we'd be in a wonderful place today.

And, of course, every issue, every journal seems to bring about another surprise and unintended consequence of knocking something out that had exactly the opposite result as well as the combinatorial issues that Craig alluded to in biology and the difference between necessary and sufficient.

But, I'm struck by something that John said, which I think is really interesting that, if in fact, you push it at some point in the process thinking that it's a critical choke point, you may in fact cause an unintended, disproportionate flourishing of some other part of the process to circumvent.

And I'm wondering whether you can identify

specific actions that we might want to most avoid for just that purpose.

DR. CHURCH: Certainly. I'd just like to push back a little bit on why it might not be so hard to have some impact by looking at oligonucleotide sequences.

Yes, there are a lot of them that are available on Ebay, etcetera. But the objective here is to find intent. So, if people are making -- if it turns out it's cheaper to make oligonucleotides in a few centralized facilities like John and his three competitors, and people insist on making it at higher cost in their basement, then that's indication of intent to do something, no matter what it is.

It answers your question, David, of whether this particular thing is a toxin or not. They obviously think it is because they're doing it at higher cost than is necessary.

And there's a trail that they'll leave behind, just like drug manufacturers leave behind a trail of chemicals they buy, the instruments they buy, transactions on Ebay.

All these things are monitorable if we choose to. And that I don't think would drive -- that wouldn't drive people away the way John described.

What will drive them away is if you publish the pharmaceutical company sequences. But, if you just have a black box that checks them for Select Agents and nobody knows what's in that black box except for select people, then that will drive only the people who have nefarious things underground.

And the pharmaceutical companies can be convinced that it is safe for them.

DR. MULLIGAN: If there was a way to -- you know, ideally I'd like to, from the point of being a business and doing this screening, I'd rather not know what the sequences were.

So, if there was a scheme, you could give me a black box that I could keep in my building and I could screen all the orders against. And it either said, make it or don't make it.

I'd be a happy man. But, most of my customers are not going to buy from me if I ship it off to somebody that they don't know and they're doing

analysis on it. So, they're just not going to.

DR. VENTER: Actually, I was wondering if I could ask David a question back. What do you think our knowledge of pathogens is thus far in the world if we're going to build these magical boxes?

MEMBER RELMAN: Yes, I mean, I think the answer is a bit iffy. And certainly it's fraught with major voids because, I think right now it would be very hard to have a sufficiently robust black box data set with which to screen.

So, for example, I think it might be hazardous to venture down this line that Select Agents are a demonstrable concern and a concrete set of concerns therefore their sequences or some subset of their sequences are those things we ought to monitor for.

Because, I think I and many people could come up with go around for most of the sequences within a Select Agent using similar sequences of like function from elsewhere.

DR. MULLIGAN: I mean, I'm sure you could do it. But you're not going to do it. And it would

be a whole lot easier -- there are many easier ways to get, and lower tech ways to get a pathogen if you want to do it than designing a new one that doesn't match known published sequences.

DR. CHURCH: Also, if people don't know what's in the black box that's being checked for Select Agents, they're not going to know what's a work around.

And they're just going to play it safe and do it in their basement, which won't be playing it safe because they'll be revealing the fact they're not taking the cheapest price available and the best quality available.

And that will be a very revealing -- they will self-define what they consider nefarious and hazardous. I agree with Craig's point that we're not going to be able to make a perfect Select Agent list.

But, if all the creative red team guys put into that black box their best guess, then the people that are actually trying to do bad things will have a sufficient doubt that they won't use the cheapest and the most accurate services.

CHAIRPERSON KASPER: Dr. Keim?

DR. MULLIGAN: I would disagree with the contention that people will always use the cheapest and most accurate sequence.

DR. CHURCH: They won't choose the worst.

MEMBER KEIM: Craig, I'd like to ask you, I was very impressed by the combinatorial genomics approach, especially when coupled with selection. It's easy to imagine that someone would want to develop an infectious disease model using this approach.

Can you imagine where you would cross a line for dual use in this type of an endeavor? And can you also imagine any type of line that you would say where there should be a moratorium on such experiments?

DR. VENTER: I think the line would be personally crossed when you, in an unregulated fashion, worked on an infectious agent, period.

MEMBER KEIM: So, you wouldn't allow any work on infectious agents in a combinatorial genomics?

DR. VENTER: Without regulatory review.

Meaningful research to understand pathogenicity, I think, is critical in developing new vaccines and going forward.

I think, as with the early stages of recombinant DNA research or early stages of gene therapy having a discussion and review of the approaches before they're approved for being undertaken is a useful exercise.

These are tools that are still in early stages of development and are somewhat forward looking. But things are changing very rapidly these days.

So I think we need to be forward looking. I think, unless people are directly in the area of developing vaccines and understanding pathogenicity for that purpose, I would be uncomfortable with somebody just randomly doing these experiments.

MEMBER KEIM: I guess that was exactly what I was thinking, that there's some type of shotgun approach using a strong selection in an animal model.

DR. VENTER: Selection is a very powerful tool. That's the problem. The easiest thing to do is

to select for infectivity.

MEMBER KEIM: So, along those lines, when would you -- I mean, how feasible is it also for something more insidious or dangerous to be constructed in this fashion than, you know, what we have already, which is already pretty bad?

In other words, what's the timeline for concern here where this approach is going to actually create something that is more dangerous than Marburg or something we have already?

DR. VENTER: I think only if it was a dedicated program to do that, which I can't imagine any reputable nation or government wanting to undertake.

But we've seen that in some of the testimony from the former Soviet Union of some of the programs that were there. And I think if somebody applied these to a known human pathogen, you could try and select for something with greater pathogenicity.

But those would be pretty complex, expensive experiments to undertake. Somebody would have to really want to do that.

DR. MULLIGAN: And, to make it work in people you'd probably have to test it in people, which would allow you to detect it with the environmental detection most likely.

CHAIRPERSON KASPER: Last question from Dr. Klein.

DR. KLEIN: I have a question for Dr. Venter. He had commented that we should assume that people can create these pathogens and we should have vaccines to respond.

As one who spends a lot of time and money on protecting our men and women in uniform, I have a time constant problem. It takes about eight years to get a vaccine licensed.

And so, the challenge that -- it seems like there's a disconnect in time, that it takes a quicker time to create some of these pathogens than it does to get a licensed vaccine through our system.

Any comments on how we can shorten that time constant?

DR. VENTER: I agree 100 percent with what you've said. And I'm on a committee, along with

others, for Deputy Secretary of Defense, looking at the year 2025 to deal with some of those issues.

I think that's one of the promises of these technologies, is -- and it was on, I think, all three of our slides that, you know, rapid vaccine production is a potential outcome of synthetic genomics.

But right now there's a totally different time constant. Any one of the three labs here could synthesize one of the smaller viruses in a week or two.

Getting good vaccines would take dedicated programs. But, you know, this is an area of research that some of our major pharmaceutical companies have shut down and laid off all of their antimicrobial teams because they can't make as much money off of treating infectious disease as they can chronic diseases.

So, we're going backwards in that fight right now. And that's, I think, something we need to change pretty radically.

CHAIRPERSON KASPER: So, thank you very

much. This will conclude our final speaker session for the morning. We'll now have a discussion about the next steps for the NSABB committee, after which we will again open the floor for public comments.

During this next steps session I would like to ask Dr. Paul Keim to join me in outlining the actions for NSABB. As we mentioned earlier, we will establish working groups to maintain the momentum on particular issues that NSABB is engaged.

These groups will be composed of board members, ex officios, and invited outside experts. The establishment of particular groups and their schedules will vary depending on the current mission of the Board.

Once delegated a task by the Board, these groups will research, deliberate, and provide information back to the Board. I want to emphasize that, only after the entire board reaches a conclusion, will any recommendations be issued -- the entire board not part of the Board.

I emphasize that again. So, initially we'll be forming working groups to focus on the topics

that we covered in this meeting, dual use research, communications, Codes of Conduct, international collaboration and then synthetic genomes.

We'll give an overview of the initial charge, focus, and task for these groups. I'll ask board members who would be interested in -- as we go through, who would be interested in serving on these groups.

And someone from the support group will note who has that interest. You can volunteer for more than one group. But I will reserve the prerogative to reassign people as we see a need in a specific area.

So, there will be some flexibility needed in developing these groups. I think one of the main charges for the groups will be to quickly define their goals.

And this will have to be in a timeline to achieve these goals. It seems that the charges are rather broad. And we'll need to really focus in and within each group on what we want to accomplish and the timeline to get there.

So, with that we can now -- I want to put that first slide. Okay, we only have a subset of the slides. Okay. So, the first committee will be that developing and defining the criteria for identifying dual use research.

And the next steps that we think need to be accomplished in that committee are to define criteria for identifying dual use research and research results and secondly to consider the flexibility needed in the criteria by assuming that potential for harm may evolve in this area.

So that's the major charge for that committee. Now I'm going to ask for a show of hands for board and ex officio members who will be interested in serving on that subcommittee. And who is recording?

(No verbal response.)

CHAIRPERSON KASPER: Tell me when you have the name, when you're all set…

MEMBER COHEN: Dennis, excuse me. Would it work if we just punched our buttons and they read the lights?

CHAIRPERSON KASPER: If that will help. I don't know if it will.

(Pause.)

CHAIRPERSON KASPER: Do we have those recorded?

(No verbal response.)

CHAIRPERSON KASPER: Do we have everyone? Okay, thank you.

(No verbal response.)

CHAIRPERSON KASPER: Okay. Dr. Casadevall can be added to that group as well. The next group will be a communications group to develop methods and technologies for communicating results.

The steps that this group will be involved with will be to advise on policies and practices for communicating findings and technologies from dual use research and to facilitate consistent application of well considered principles to decisions about communication of information with bio-security implications.

Can I see a show of hands of members who would be interested in the communications group?

DR. JAMBOU: All right, starting with Board members, Lynn Enquist, Andrew Sorensen, Stanley Lemon. Other board members? Okay, ex officios?

Scott Steele, Natalia Comella, Brenda Cuccherini, Terry Lomax, Stuart Nightingale, and Boris Lushniak, Gerald Parker. That's it.

CHAIRPERSON KASPER: Okay, thank you. The next committee -- subcommittee is the Codes of Conduct for the life sciences, the topic we heard about this morning.

The steps here will be to solicit support and recommendations from the scientific community for a code to address dual use research and to provide recommendations for a Code of Conduct that may be adopted by the life sciences to address dual use research concerns.

Show of hands please, the people who are interested in working in this area.

DR. JAMBOU: Board members, Murray Cohen, Mark Nance, Dianne Wara, John Lumpkin. Ex officios? Stuart Nightingale, Scott Steele, Natalia Comella, Lawrence Kerr, Caird Rexroad.

CHAIRPERSON KASPER: Okay, thank you. The next committee is the international collaboration committee. The charge for the international working group is to recommend strategies for fostering international collaboration in the development of appropriate bio-security policies.

The next steps here will be to gather information, develop outreach networks, promote exchange of information and develop strategies for engaging the international community.

Please, a show of hands of people interested in working in this area.

DR. JAMBOU: Board members, Barry Erlick, David Franz, Stuart Levy, Harvey Rubin, Stanley Lemon, Anne Vidaver, Murray Cohen, Andrew Sorensen, Lynn Enquist.

Ex officios, please. Terry Lomax, Lawrence Kerr, Peter Jutro, Natalia Comella, Stuart Nightingale, Dale Klein, Gerald Parker, that's it.

CHAIRPERSON KASPER: Thank you. The final working group will be on synthetic genomes. The next step here will be to evaluate the dual use bio-

security concerns involving advanced DNA synthesis technologies and to develop potential strategies working with the scientific and genomes services providers community to facilitate the development of best practices in this area. A show of hands please.

DR. JAMBOU: Board members, Paul Keim, Harvey Rubin, Michael Imperiale, General Gordon. Ex officios, please. Caird Rexroad -- I'm sorry, one more board member, David Relman.

All right, back to our ex officios, Caird Rexroad, Ronald Walters, Lawrence Kerr, Scott Steele, Vincent Vilker, David Thompson, NIH, NIAID, and Rick Kearney. That's it.

CHAIRPERSON KASPER: That's it. Okay. Well, thank you. That gives us a good start. The plan now is to open the floor for discussion. I ask that members wait to be recognized by the Chair before answering questions.

The list -- we have an updated list of people who have asked to speak. And the first is Ranjan Gupta from the AAAS, an NIH Science policy fellow.

MR. GUPTA: Thank you very much for the very interesting discussions for the last two days that I've been hearing. My comment is regarding the much discussed subject of instilling a sense of a culture of responsibility.

And, while I was listening I was thinking how would we go about -- you're on the wall. You know, I heard about undergraduate and graduate students, bringing them into the -- it's the same culture.

And I was thinking how do we accomplish this? And one idea I thought I wanted to share with you is perhaps it's hard for scientists, especially young scientists, to listen to a whole bunch of ethics and codes, because that's probably the most boring thing to them when they are just doing laboratory research.

But what if we started something like a reward system? Maybe there could certification. Like, in addition to getting your degree, you can also get a certification through some professional society or an international organization like UNESCO where,

okay, I have taken an online course and become certified for bio-security and taking responsible ethical conduct in scientific behavior.

If something like that could be instituted, I think that would be encouraging to young scientists, maybe something they can put on their resume and it would add value as long as that's also recognized by the people at the receiving end, that this is something they would take as worthwhile. Thank you.

CHAIRPERSON KASPER: Thank you for your suggestion. We will consider that. Are there any specific members of the Board who would like to comment on that?

(No verbal response.)

CHAIRPERSON KASPER: Okay, thank you. The next speaker will be Brian Hanley.

DR. HANLEY: There was a statement made this morning regarding designer organisms that they are ten years away. And I think everybody here is aware of the field of human genome therapy.

And I would point out that there's at

least one textbook --

DR. PATTERSON: Dr. Hanley, could you please speak into the mike? We're having difficulty hearing you. Thanks.

DR. HAHLEY: Sorry. Should I restart?

(No verbal response.)

DR. HANLEY: Okay. There's been a statement made here this morning to the effect that designer organisms are ten years away, and that's been accepted.

And everyone here is, I think, aware of the field of human genome therapy. And I would refer you to a book which is an undergraduate text, "Adeno Viral Vectors for Human Genome Therapy" which, among other things, discusses how to modify and what to modify in terms of attachment moieties to improve the attachment capability of adeno viruses, which would apply to other organisms.

It talks about the attachment sites on -- the receptor sites on membranes. It discusses how to bypass the immune system. It discusses the structure of the viral genes and where to insert novel genes to

maintain the effective pathogenicity of the organism.

It also discusses -- well, the basic point is designer organisms aren't -- they've been here for a while. And, with all of the information that's out there, it's basically a cookbook now for anybody who wants to do it as to, okay, so you stick something else in there and you've got something that's really nasty.

You know, the same book discusses how to recombine with animal viruses to produce new viruses which do not -- to which human beings do not yet have a natural immunity.

So you can use these kinds of techniques as a base for, you know, constructing a new pathogen. So, I just want to make sure that that point was really clear to a group like this.

And I'm a little -- I found it a little alarming that that kind of a statement would go unchallenged by, you know, a group that's got this kind of a chart.

CHAIRPERSON KASPER: Thank you for your comment. The next speaker is Alan Pearson, Center for

Arms Control and Non-Proliferation.

MR. PEARSON: Good morning. Thank you for the opportunity to address you today on behalf of the Center for Arms Control and Non-Proliferation and its scientist's working group on biological and chemical weapons, which has over 25 years of experience dealing with BW issues on the national and international level.

And we would be happy to provide you with our recommendations on a code of practice that were mentioned by one of the speakers earlier today. We've often heard in these last couple days that the concept of dual use has multiple meanings.

And at least three such meanings have been offered to you. First, it's research having both civilian and military applications broadly defined.

Second it is legitimate research, having the potential for misuse. But, what exactly is misuse? The answer to that question may be found in the third meaning, research that can support both permitted and prohibited activities under the BWC, the Biological Weapons Convention.

And the BWC prohibits the development, production, stockpiling, and acquisition of biological weapons, biological agents or toxins in types and quantities that have no justification for prophylactic, protective, or other peaceful purposes.

And it categorically prohibits work on weapons and delivery systems designed to use biological agents or toxins for hostile purposes or in armed conflict.

Of course, this raises additional questions. Can we draw clear lines between research and development or between basic research and applied research?

Most importantly, between those permitted and prohibited activities. Can guidelines and oversight mechanisms be developed by you or anyone that actually help keep research projects and programs from crossing, whether inadvertently or deliberately, the thin line between permitted and prohibited activities?

The importance of considering how intent is perceived was also raised yesterday. And a test

was offered today for determining intent. Of course, states act based on their perceptions.

And their actions may decrease or increase the dual use problem that we're facing. What then about governmental compartmentalization of certain activities?

Are assertions of benign intent enough to meet our responsibilities to maintaining national security? Or does this aspect of the dual use problem illustrate yet one more reason why transparency and oversight are critical?

In considering these questions you might look for examples of current dual use research. And I'll suggest four possibilities. First, research which aims to develop more stable forms of Botulinum toxin, recently funded by NIAID and of particular relevance today given the paper just published in PNAS.

Two, research which aims to identify new therapies based on the modulation of innate immune responses to infection. Three, research on biochemical and incapacitating agents like the

fentanyl derivative used in Moscow in 2002; an area of current interest to many, many governments, including our own.

Fourth, threat assessment research which explores the offensive potential of various agents, genetic and physical modifications, and delivery mechanisms.

Having given some examples, I'll note that, while we have often heard in the last couple days a great deal of concern about the dual use problem in the abstract, we often have great difficulty in pointing to more than a very few concrete individual examples and practice. Why?

Is the problem any one experiment in say the field of synthetic biology? Or is it the direction of the entire field? I am, by reminding you, that prior to the BWC, the development of biological weapons was internationally acceptable.

Today governments still set the boundaries of and provide the justification of acceptable conduct by those they fund and employ. And I suggest to you that these points are very much worth your serious

consideration. Thank you.

CHAIRPERSON KASPER: Thank you for your comments. The next speaker is Venkat Rao from CSC National Security Program in Alexandria, Virginia.

MR. RAO: Good morning. At the outset I'd like to thank the NSABB for taking the leading role in tackling what could be described as one of the most intractable challenges facing the life sciences and biomedical research and development programs.

From the philosophical to the practical -- not only the foundations of academic freedom and pursuit of biomedical research, but also the national security challenges of the United States and the rest of the world.

We at the Computer Sciences Corporation National Security Programs, work on the CBR and threat reduction counter-proliferation and biological arms control programs and bio-defense counter measures development.

Issues relating to bio-security addressed by the Board are critical to our current engagements with the Federal Government agencies. The panel

attempted to delineate biological warfare from bio-terrorists, nuclear security versus bio-security, bio-safety versus bio-security, security of research at the individual scientist level versus institutional controls, and human creativity versus censorship, either self imposed or from external forces.

What we have on hand is an assortment of partial solutions to a very complex problem. No matter how we interpret the effectiveness and vigor of the available solutions, there is no clear solution at this time.

With limited baseline level assessment of the existing conditions and available options, we aught to be prepared for modest improvements from the proposed partial solutions.

However, it's good to have a partial solution than no solutions. In my assessment, bio-safety, bio-assurance, and bio-security are the three legs of this challenge where individual scientists and laboratory workers role is key to the success at the institutional level.

As some panelist pointed out yesterday,

bio-safety guidance and current institutional approaches to bio-safety offer attested and verified framework to incorporate bio-security and bio-assurance process.

Just as the Food and Drug Administration's requirement for good manufacturing practices and laboratory practices exceed the bio-safety requirements, bio-security requirements must be tied within the existing bio-safety framework such that institutions need not have to meet multiple requirements but one set of internally consistent rules covering all aspects.

The different threat reduction agencies join surveillance installation vulnerability assessment offer a practical guidance for development of institution level controls of bio-security.

In my opinion, threat assessment and risk assessment are not the same. And risk benefit analysis and dual use are not the same. The Board must ensure that these fundamentals are clearly laid out as part of guidance development process.

If choke points at the publication level

are too late, as a panelist pointed out yesterday, and if one journal refuses to publish, authors will find alternate journals and other web-based publication media.

Choke points at the grant application review and award stage is more preferable if good guidelines are developed for a transparent review and decision making process.

Finally, I conclude stating that, as part of guidance development, the Board should consider a case study based investigation for a variety of potential threat scenarios involving academia, private sector, and the government-supported major programs that involve bio-security components.

This will allow participation of key stakeholder communities and contribution to the development of very necessary bio-security guidelines.

Once again, thank you for your excellent efforts.

CHAIRPERSON KASPER: Thank you. The next speaker is David Silberman from Stanford University.

MR. SILBERMAN: I'd like to add my thanks to the work that the Committee will be doing. I think it's critical and important. And my remarks today really is kind of for me a summation of what I have learned here and maybe one hole that I've seen that hasn't been addressed.

We focused in the last couple of days on education, creating a culture of responsibility, and particularly getting buy-in from our international colleagues.

The prime focus of our efforts has been directed at the roles of scientists and their host institutions. There are, however, other contributors that play roles in the creation of a workable scenario.

They are represented by the ex officio members of NSABB. These are the people who promulgate policies and regulations under which we all work.

And so, I'd like to offer this case study or hypothetical case study or example that touches on one aspect where the backside is also important as well as the scientific side.

And that has to do with the fundamental research exemption and the export control. Let's say that a post-doctoral fellow has finally been accepted by a laboratory in France after much delay through bureaucratic red tape, gets his or her work done, completes the post-doctoral fellowship, even publishes some papers with the senior author, and then is told gee, when you go back, before you can do any work in your home country, you need to get an export license so that you can do that.

Now, this kind of thing would be kind of unacceptable, I would think. We would say *mon dieux*. I mean, the French, you know how they are. But, now it's the reverse.

And there have been challenges to the fundamental research exemption that are troublesome. And so, I think one of which would be that if you accept one restriction on publication you kind of restricted all.

That can compromise the source of funding. But, I think if we are looking for international cooperation we have to look at our own policies as

well and maybe offer some modifications.

International cooperation is critical. We heard Dr. Sharp refer to Salvador Luria earlier this morning. He, along with Max Delbruck as most of you know, is kind of the father of the contemporary field of genetics.

And, as well, Luria served as mentor to Jim Watson. Yet, both Delbruck and Luria came from countries that were either fascist or where certain hostilities were about to arise.

In fact, I think Luria was even a communist. I don't know that that would have mattered. But, it's the climate of change that is troubling to me.

Where in the past we were more accepting, and now we're more restrictive. We're preventing people from coming in. I believe MIT rejected a one million dollar DOD grant because of some restrictions on foreign nationals.

The last thing that I have to comment on is what does one do with the research that cannot be published, something that could not have been foreseen

by an IBC or anyone else that's reviewing it?

That's one of those wonderful things in science that come up unexpectedly. It's great. But it really truly does have a potential negative affect.

So now it's out there. It could be something as simple as discovering how a protein unfolds. What does one do with that? Do you put it in a special journal, a restrictive website?

Do you assemble a quarterly meeting of people who are in this category so they can talk to one another? How is this information which is scientifically important shared?

I'm not quite sure. And so, within your charge, you're given -- you're charged with providing advice, guidelines, and leadership. And so, my hope is that you will do it for both the scientific and policy-setting communities. Thank you very much.

CHAIRPERSON KASPER: Thank you. The floor is open for a few comments from people who didn't sign up. If you would like to say something, now is the time.

Please identify yourself. And, if you

represent some university or agency or industry, please identify that.

MR. ENDY: Thank you. My name is Drew Endy. I'm a professor of biological engineering at MIT. I wanted to make some remarks on the final panel exploring the topic of synthetic genomics.

First, with regards to the idea that anybody building a gene in their basement or garage must be up to something no good, would simply ask you to consider why somebody might build a radio in their garage, why somebody might educate their children at home.

And the complexity of the reasons for taking such an approach are impressive. And I'm concerned at the idea that we might simply try and presume the regulation we should consider for synthetic genomics is so straightforward.

I'm extremely uncomfortable by the idea that we're going to think through how to regulate this technology absent a decent consideration of the facts on the ground with respect to the distribution of the technology and the agents and knowledge by which

people might do this and why they might do it.

That said, in general I think there are two things that the Board might be well suited to consider at the outset before we understand all of the facts on the ground.

The first is, with respect to the question regarding when does dual use start, especially with respect to biological engineering and synthetic biology, it starts -- I believe -- in the mind of the designer or the individual.

And so, this gets back to the remarks from Dr. Sharp regarding -- and others -- regarding a culture of responsibility. I think one of the most important things that I'd ask the Board to consider is how we foster constructive culture within the development of next generation biological technologies.

The second point not too early to consider is how to foster a transition with respect to our strategy by which we address current and future biological risks.

At present it seems like we are developing

a strategy whereby we are concerned about specific threats, we develop defenses that are fixed defenses specific to those threats on some time scale, whether it's emerging infectious diseases, as Dr. Mulligan so clearly pointed out, or engineered diseases.

We're probably wanting to consider how we transition from threat specific based defenses to general capabilities based defenses where we can quickly identify, analyze, and respond to new agents as they arise or if, God forbid, they emerge or are engineered and are released. Thank you.

CHAIRPERSON KASPER: Thank you. Are there other comments from people in the audience?

(No verbal response.)

CHAIRPERSON KASPER: Okay. This is the conclusion of the first meeting of NSABB. On behalf of the Board I'd like to thank the speakers and panelists for coming and sharing their expertise and insights with us.

We also thank all of you who have attended the proceedings either in person or by webcast and express our gratitude for your comments. I believe

the inaugural meeting of NSABB was really productive and marks a significant starting point for this body.

In laying out the ground work for these working groups, I believe we've established a solid base for the future of NSABB. Over the coming months there's sure to be cause for the adaption of working group action items as we track the current issues at hand regarding bio-security and public health.

These working groups will provide us with the flexibility that this board will need in responding to the dynamics of life sciences research.

There's undoubtedly a lot of very important work ahead of us. The fact that the topics discussed at this meeting are broad-ranging issues to all life sciences, speaks to the importance of continued contributions from academia, industry, government and the general public in order to achieve the appropriate balance necessary for effective bio-security without unduly encumbering research efforts.

To conclude, I would once again like to thank the NSABB Board members and staff. The meeting is adjourned. Thank you.

(Whereupon, at 12:15 p.m. the above-entitled matter was concluded.)