National Institutes of Health
Office of the Director
Office of Biotechnology Activities

NATIONAL SCIENCE ADVISORY BOARD FOR BIOSECURITY

October 19, 2010
Held at the National Institutes of Health
Bethesda, Maryland

VOTING MEMBERS

Paul S. Keim, Ph.D. (Acting Chair)
Kenneth I. Berns, M.D., Ph.D.
Arturo Casadevall, M.D., Ph.D.
Murray L. Cohen, Ph.D., M.P.H., C.I.H.
Susan A. Ehrlich, J.D., LL.M.
J. Patrick Fitch, Ph.D.
Christine M. Grant, J.D.
Michael J. Imperiale, Ph.D.
Joseph Kanabrocki, Ph.D., C.B.S.P.
Stanley M. Lemon, M.D.
Stuart B. Levy, M.D.
Jeffery F. Miller, Ph.D.
Randall Murch, Ph.D.
David A. Relman, M.D.
James A. Roth, D.V.M., Ph.D., D.A.C.V.M.
Andrew A. Sorensen, Ph.D.
Anne K. Vidaver, Ph.D.

EX OFFICIOS/FEDERAL AGENCY DESIGNEES

Jason Boehm, Ph.D., U.S. Department of Commerce
Kay Marano Briggs, Ph.D., U.S. Department of the Interior
Parag R. Chitnis, Ph.D., National Science Foundation
Diane C. DiEuliis, Ph.D., Executive Office of the President
Amanda Dion-Schultz, Ph.D., Office of the Chief Scientist
Dennis M. Dixon, Ph.D., National Institutes of Health
CDR John Hardham, Department of Defense
Peter R. Jutro, Ph.D., U.S. Environmental Protection Agency
David Liskowski, Ph.D., National Aeronautics and Space Administration
Boris D. Lushniak, M.D., M.P.H., U.S. Food and Drug Administration
Theresa Lawrence, Ph.D., U.S. Department of Health and Human Services
Janet K.A. Nicholson, Ph.D., Centers for Disease Control and Prevention
David G. Thomassen, Ph.D., U.S. Department of Energy
Tru Twedt, D.V.M., C.B.S.P., Centers for Disease Control and Prevention

Edward You, Federal Bureau of Investigation, U.S. Department of Justice

Call to Order and Review of Conflict of Interest Rules

Dr. Paul Lewis, Executive Director of the National Science Advisory Board for Biosecurity (NSABB), convened the October 19, 2010, meeting of the NSABB at 8:45 a.m. He welcomed members and public participants to the meeting.

Dr. Lewis read into the record the rules of conduct and conflict of interest. The rules are explained in the report entitled "Standards of Ethical Conduct for Employees of the Executive Branch," which was received by each member when appointed to the NSABB. Members of the NSABB are considered Special Government Employees and were requested to review the steps to ensure that conflicts of interest are addressed. A Board member is required to recuse himself or herself in advance of any discussion in which he or she believes there to be a conflict of interest. This requirement may be waived for matters of general applicability because members are believed to be able to set aside their possible conflicts, but each member is asked to be alert for any matters that might create a genuine conflict of interest and recuse himself or herself when such conflicts arise. Questions should be addressed to the NIH Committee Management Officer, Ms. Lisa Rustin.

Introductions, Approval of the December 2008 Minutes, and Overview of Agenda

Dr. Keim welcomed the members and gave an overview of the agenda. Members of the Board introduced themselves.

NSABB Motion 1

Moved by Judge Ehrlich and seconded by Dr. Kanabrocki, the NSABB voted unanimously by voice to approve the December 3, 2009, NSABB meeting minutes that had been distributed in advance of this meeting.

Update of Relevant Federal Activities

Impetus for Report from National Research Council

Mary E. Groesch, Ph.D.
Senior Advisor for Science Policy
Office of Biotechnology Activities
Office of Science Policy, NIH

Dr. Groesch provided background for development of the National Research Council (NRC) report, noting the NSABB report entitled "Addressing Biosecurity Concerns Related to the Synthesis of Select Agents" (2007), gave as its Recommendation 4.2:

> Assemble a group of experts from the scientific community to determine if an alternative framework based on predicted features and properties encoded by nucleic acids, such as

virulence or pathogenicity, can be developed and utilized in lieu of the current finite list of specific agents and taxonomic definitions.

Then, in October 2007, participants in an NSABB–Recombinant DNA Advisory Committee (RAC) Roundtable on synthetic biology discussed the state of the science of synthetic biology, predicting function from sequence and structure, and risk assessment and risk management in a context of uncertainty. The content of this roundtable helped to inform the U.S. government's considerations of NSABB Recommendation 4.2, set forth above. The U.S. government acknowledged that it currently does not have the scientific capability to predict function from sequence with sufficient certainty to underpin regulation. Therefore, it concluded that it is premature to convene an expert panel to consider oversight based on predicted features. Rather, the expert panel should focus on establishing scientific milestones that would need to be achieved before a predictive oversight system could be implemented. When the needed science is available to underpin the risk assessment of predicted features, the U.S. government may consider using this approach in concert with the current oversight system but not in lieu of the current system. The U.S. government wanted to identify the list of scientific advances necessary before a predictive oversight system can be postulated, developed, evaluated and potentially implemented.

Based on the U.S. government's response, it charged the NRC committee to answer the following questions:

1. Does the current state of the science of predicting function from sequence support a predictive oversight system for select agents at this time?

2. If not, what are the scientific milestones needed before a predictive oversight system might be feasible?

3. What are the challenges in attempting to predict biological characteristics from sequence?

4. What would be the key scientific attributes of a predictive oversight system for select agents?

5. In qualitative terms, what level of certainty would be needed about the ability to predict biological characteristics from sequence data in order to have confidence in a predictive oversight system?

6. In what time frame might these milestones be realized? What kinds of studies are needed to achieve these milestones?

<u>NSABB Discussion</u>

There was no NSABB discussion.

National Research Council Report "Sequence-Based Classification of Select Agents: A Brighter Line"

India Hook-Barnard, Ph.D.
Study Director, Committee on Scientific Milestones for the Development of a Gene-Sequence-Based Classification System for the Oversight of Select Agents, National Research Council, National Academy of Sciences

Dr. Hook-Barnard presented an overview of the NRC's report considering a gene-sequence-based classification systems for the oversight of select agents. The NRC Committee on Scientific Milestones for the Development of a Gene-Sequence-Based Classification System for the Oversight of Select Agents was charged to "identify the scientific advances that would be necessary to permit serious consideration of developing and implementing an oversight system for select agents that is based on predicted features and properties encoded by nucleic acids rather than a relatively static list of specific agents and taxonomic definitions."

The Committee concluded that a sequence-based prediction system for oversight of Select Agents is not possible now or in the near future. The Committee considered a predictive oversight system to be far beyond current biological understanding. Before such a system is possible, the committee concluded, science must:

- Be able to predict the function of a protein from the sequence;
- Develop the ability to predict the output of biochemical, regulatory, and genetic pathways from genome sequence;
- Be able to predict the behavior of a whole microorganism from its genome sequence; and
- Develop the ability to predict the interactions of an organism in its natural environment from its genome sequence (e.g., how it interacts symbiotically or pathogenically with a host or other factors).

The committee found what it called "A Brighter Line … [a] sequence-based classification system for [Select Agents] SAs and a 'yellow flag' biosafety system for sequences of concern that could be developed using current technologies." Such a sequence-based classification would be strictly operational, a set of tools for drawing boundaries. It would establish an unambiguous procedure for deciding if a genome sequence is assigned one of the taxonomic names already on the select agent list. In other words, this use of DNA sequence information could better define select agents for regulatory purposes, establishing "a brighter line."

The committee recommended:

1. The sequence space around each taxonomic name on the select agent list should be clearly defined so that select agent status can be unambiguously determined from genome sequence; and
2. A sequence-based classification system should be considered and weighed against the cost and complexity of implementing such an augmentation of the current regulations.

Judge Ehrlich asked if intellectual property aspects were discussed in terms of the possible effect on research of expanded regulation and reporting to law enforcement. Dr. Hook-Barnard answered that this was not discussed although some consideration was given to how helpful a sequence-based classification system would be to accompany the current regulatory framework.

Dr. Miller noted that some microorganisms have open genomes so defining the sequence is not possible even in a practical sense; he wondered how such agents would be dealt with under the proposed system.

Dr. Casadevall wondered if the question should even be asked because asking it presupposes that virulence is an outgrowth of a microbe. He pointed out that virulence is an emergent property that cannot be predicted; it requires not just the organism but also a host. He gave as an example that, if everyone is vaccinated against the variola virus, it would not be pathogenic. He added that it is not feasible to make predictions from genome sequence, and he did not see how a sequence-based classification scheme can be implemented considering all the inherent problems. Dr. Hook-Barnard agreed with this observation, noting that this is a very complex problem and that biology cannot be made to fit regulation because biology is not binary yet the challenges must be met and policy decisions made. Right now, she said, not only are there no clear lines for what constitutes a select agent, it may not ever be possible to predict function from sequence, but a sequence-based classification system needs to be started. Dr. Lemon added that lists alone are not adequate because people tend to ignore things not on the list. He agreed with the content of the report and stated that these questions need to be looked at iteratively and continuously.

Dr. Keim pointed out that the select agent list exists only to establish a regulatory environment and that it is based on taxonomy. He noted that it actually does not state that the agent has to be pathogenic; the agent can be fully attenuated, yet someone working with it can still be violating the rules. He continued that genomic sequence is to support a cladistic approach; there is nothing in a sequence that says an organism is pathogenic, but the way organisms now are identified is sequence based. Using a sequence-based system to identify *future* select agents might be nonsensical, he posited, but current agents can be identified using sequence data and evolutionary and taxonomic methods.

Dr. Imperiale commented that developing the technology for sequence-based prediction might in itself be dual use and wondered if the Committee had discussed this. He asked whether there was any impetus to move forward nonetheless, and whether this should be done in a classified manner. Dr. Hook-Barnard explained that the Committee considered this to be the future of biology and that developing an understanding of pathogenicity and function are big goals. Trying to predict pathogenicity from sequence data and having that drive the biology is another matter, she said, adding that even developing common databases would be helpful for biology. She further noted that Committee members were very uncomfortable with the idea of specifically having a program to try to predict pathogenicity and what would be a good bioweapon and considered it a misalignment of priorities.

Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA

Jessica M. Tucker, Ph.D.
Senior Policy Analyst
Office of Assistant Secretary for Prepardness and Response
(Contractor) for Department of Health and Human Services

Dr. Tucker offered a summary of the screening framework guidance for synthetic double-stranded DNA published in the *Federal Register* on October 13, 2010. She noted that the guidance is voluntary, not regulatory.

1. All orders of synthetic double-stranded DNA (dsDNA) should be subject to a screening framework that incorporates both sequence screening and customer screening.

2. Regarding sequence screening software and expertise, the recommendations are that:

- Providers select sequence screening software that uses a local sequence alignment technique; and
- Providers have in-house the necessary technical expertise to run the sequence screen, analyze the results, and conduct any research needed to evaluate the significance of dubious sequence matches.

3. The recommendation for records retention is that providers retain records of all customer orders for at least 8 to 10 years.

NSABB Discussion

Dr. Imperiale noted that recent research has developed techniques to assemble fairly long sequences of DNA from single-stranded DNA and asked to hear the U.S. government position on that point. Dr. Tucker indicated that the consensus right now is that the greatest risk still stems from dsDNA because the technical difficulties of developing a functional organism from dsDNA are not as great as starting from oligonucleotides.

Dr. Keim noted that manufacturers are already concerned about export controls and were already screening dsDNA for export because that is mandated in the Commerce Control List (CCL).

Dr. Levy wondered how much interaction is taking place between the U.S. government and the international community. He noted that this concern was discussed at the previous NSABB meeting when the observation was made that regulation can drive people from the U.S., leaving the government with no control over them. An international agreement is needed, he said.

Dr. Tucker assured participants that conversations on this topic are being held with other countries. The U.S. is definitely engaged, and other countries are interested in incorporating the principles of this Guidance into their own policies.

NIH Guidelines to Address Synthetic Nucleic Acids

Jacqueline Corrigan-Curay, J.D., M.D.
Executive Secretary, NIH Recombinant DNA Advisory Committee
Acting Director, Office of Biotechnology Activities, NIH

Dr. Corrigan-Curay provided background on updates to the *NIH Guidelines for Research Involving Recombinant DNA.* She said that, currently, the NIH is reviewing the guidelines to ensure they are adequate for work with synthetic nucleic acids and that the new proposed revision defines synthetic DNA as:

1. Molecules that are constructed by joining nucleic acid molecules and that can replicate in a living cell, i.e., recombinant nucleic acids;
2. Molecules that are chemically or by other means synthesized or amplified, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules, i.e. synthetic nucleic acids; or
3. Molecules that result from the replication of those described in 1 or 2 above.

She reported that a new proposed Section F-1 of the *Guidelines* will exempt synthetic nucleic acids that can neither replicate nor generate nucleic acids that can replicate in any living cell, are not designed to integrate into DNA, do not produce a toxin that is lethal to vertebrates at an LD_{50} less than 100 ng/kg body weight, and are not considered human gene transfer under Section III-C of the *NIH Guidelines*.

The proposed Section III-C stated that human gene transfer is the deliberate transfer into human research participants with either:

- Recombinant DNA molecules or DNA or RNA derived from recombinant DNA molecules.
- Synthetic DNA or RNA that:
  - Contains more than 100 nucleotides.
  - Possesses biological properties that enable integration into the genome.
  - Has the potential to replicate in a cell.
  - Can be translated or transcribed.

She added that the review process also looked at risk assessment, noting that advances in technology might make it possible someday to develop organisms containing sequences from multiple organisms, so that the parents are not obvious. In such a case, she added, the risk assessment must take into account both the risk associated with the groups of organisms from which the sequences are derived, and the function of the sequences in their original host context.

The RAC approved final recommendations at a meeting on June 16 and 17, and a draft *Federal Register* notice is under review.

NSABB Discussion

There was no NSABB discussion.

U.S. Government Deliberation on Dual Use Research Oversight: Status Update
Mary E. Groesch, Ph.D.

Dr. Groesch gave a status update on government deliberations on dual use research. In June 2007, NSABB issued its report, "Proposed Framework for the Oversight of Dual Use Life Sciences Research: Strategies for Minimizing the Potential Misuse of Research Information." The NSABB recommendations are now being considered through a trans-federal policy coordination process, leading toward development of a draft policy, which will be revised in an iterative process that includes consultation with stakeholders. An opportunity for public comment on the policy via an announcement in the *Federal Register* will be provided.

NSABB Discussion

Dr. Lemon asked Dr. Groesch to elaborate on who were the stakeholders involved in the public consultations. She replied that this working group included representatives of government agencies and others across the scientific community, including NSABB members Judge Ehrlich and Dr. Imperiale.

Judge Ehrlich asked when NSABB can expect to see the draft published. Dr. Groesch answered that no firm timeline has been established because the internal review is still ongoing. Many agencies are involved, and obtaining sign-off from all of them requires time.

Dr. Cohen wondered how different the report to be published in the *Federal Register* is from the NSABB report. Dr. Groesch stated that it is premature to say exactly how different the government's draft policy report will be from NSABB recommendations but that the draft will still be comparable to the NSABB's recommendations. Some small gaps were present, but no institutional review has been finalized, and the trans-federal working group is trying to add some substance in those instances.

Several Board members remarked that the document was completed by NSABB and sent to the U.S. government for review with the understanding that it would come back for NSABB review before the document was made final for the purpose of U.S. government review. They asked if "stakeholders" include NSABB. Dr. Groesch answered that stakeholders include the entire scientific community.

Dr. Levy added that the way the letter accompanying the document was addressed to the U.S. government was a key point: it was sent for review and was to come back to NSABB. Apparently, instead, the U.S. government appears to be drafting the guidelines and they will come back to NSABB as finalized federal policy. NSABB members understood this process to be one of consultation. This was implicit when NSABB's recommendations were sent in for review.

Judge Ehrlich explained that NSABB members understood that they were sending a concept paper to see if the work was going in the right direction, not a report for federal agencies to act on at that time. The expectation was that NSABB would receive feedback saying either "yes, this is the right direction" or "work on it more."

Dr. DiEuliis suggested that the draft NSABB recommendations were acted on, so that constitutes positive feedback.

Dr. Sorensen noted that NSABB understood that it would get the penultimate version of the federal guideline and have the opportunity to comment on it, but it appears as if that will not occur.

Dr. Keim commented that the process appears to have left out return of the document to NSABB formally. He suggested that NSABB comment on the draft as members of the public, i.e., as individuals, or can react as a group if it wishes to make a consensus recommendation.
Dr. DiEuliis answered that comments delivered by the group as a whole would be cohesive and powerful, and suggested that it makes sense to have a response from NSABB as a group but that members can certainly also respond as individuals. When the draft becomes available, NSABB can see it and respond as a group accordingly.

Several NSABB members stated their preference that the full NSABB consider the document via a face-to-face versus via teleconference.

Dr. Keim summarized the discussion indicating NSABB requests an opportunity to review the draft federal guidance either at an NSABB meeting or as part of the public comment process.

Overview of Executive Order on Optimizing the Security of Biological Select Agents and Toxins in the United States

Mary E. Groesch, Ph.D.

Dr. Groesch highlighted several key elements of particular interest in Executive Order 13546, "Optimizing the Security of Biological Select Agents and Toxins in the United States."

- A robust and productive scientific enterprise that uses Biological Select Agents and Toxins (BSAT) is essential to national security.
- BSAT shall be secured in a manner appropriate to their risk of misuse, theft, loss, and accidental release.
- Security measures shall be taken in a coordinated manner that balances their efficacy with the need to minimize the adverse effect on their legitimate use.

Mandated activities included in the executive order include:

- Risk-based tiering of the SA list.
- Revision of regulations, rules, and guidance to accommodate a tiered SA list.
- Coordination of federal oversight for BSAT security.
- Implementation: establishment, operation, and functions of a federal experts security advisory panel; a role for NSABB.
- Sharing of Select Agent Program information within the U.S. government.

The Federal Experts Security Advisory Panel (FESAP), constituted in response to the Executive Order, will make technical and substantive recommendations on BSAT security. Membership on this panel will come from across the U.S. government, and it is co-chaired by the U.S. Department of Health and Human Services (HHS) and the U.S. Department of Agriculture (USDA).

The potential role for NSABB includes technical advice and serving as a conduit for public consultation, as needed, on topics of relevance to the Select Agent Program.

<u>NSABB Discussion</u>

Dr. Casadevall commented that he is a big proponent of reducing the size of the select agent list, and he hopes that a hard look will be taken at the agents on the list. He noted that over the last 10 years, since the community has had access to the toxin of the non-encapsulated strains of *Bacillus anthracis,* such as the Sterne strain, but not the strains categorized as select agents,

either the encapsulated strain not expressing a toxin such as the Pasteur strain or the encapsulated strain expressing a toxin such as the Ames strain, the ratio of papers in the literature is now 10 to 1—good evidence that, when something is placed on the Select Agent list, it can translate into scientific limitations.

Dr. Berns said that the biggest concern that some have is that the select agent law was written in a way so as to broaden the agents put on the list when one of them is a related construct. The classic case is smallpox and vaccinia virus; it took an advisory letter from the U.S. Department of Justice that research could be conducted with vaccinia virus. Right now there is great concern about 1918 influenza, not about working with the agent itself but with related constructs. Dr. Berns strongly encouraged provisions to facilitate clarification of which agents are really on the list and those that are only technically related.

Consideration of Advances in Synthetic Biology in Relation to the NSABB Report "Addressing Biosecurity Concerns Related to Synthetic Biology": (1) Emerging Scientific Advances and (2) Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome

David A. Relman, M.D.
Professor of Microbiology & Immunology and of Medicine
Stanford University

Dr. Relman offered a summary of recent advances in synthetic biology with the intent of looking at whether NSABB recommendations are still applicable. He structured his comments around a review of developments in synthetic biology, a review of a few advances in the field, with particular emphasis on the paper by Daniel Gibson et al. "Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome," that appeared in *Science* in July 2010.

Dr. Relman summarized the NSABB recommendations concerning synthetic biology. The NSABB's Synthetic Genomics Working Group had two phases to its charge. The first was to examine the potential biosecurity concerns presented by the synthesis of select agents. The second was to identify, assess, and recommend strategies to address potential dual use concerns that may arise from work being performed in synthetic biology. These tasks both have been completed and reports have been issued. The December 2006 report on the first phase made four basic recommendations:

1. Develop and disseminate a harmonized guidance;
2. Develop standards and practices for sequence providers to include nucleic acid screening;
3. Review current biosafety guidelines to ensure that they are adequate for synthetically derived DNA; and
4. Consult with experts to develop a predictive framework for determining pathogenicity.

The second report by the Working Group, issued in April 2010, also contained four basic recommendations:

1. The NSABB paradigm should adequately address dual use research issues associated with synthetic biology;

2. Oversight should extend beyond the boundaries of life sciences and academia;
3. Outreach and education strategies should engage the diverse research communities; and
4. The U.S. government should include advances in "tech-watch" endeavors.

NSABB recommended that the U.S. government should ensure institutional review and oversight of synthetic biology because some aspects of the field pose biosecurity risks. Responses to dual use and synthetic biology risks should be made when appropriate. The current oversight paradigm ought to be adequate for current issues in synthetic biology. However, looking at recent developments in this field in the last year raises the question whether previous NSABB recommendations still apply.

Recent advances in science and technology include metabolic engineering, a top-down approach, which allows modifying existing organisms for functions of interest. A paper published by Parayil Kumaran et al. (2010) in *Science* describes engineering a strain of *Escherichia coli* to produce taxadiene, the first intermediate step in the production of the chemotherapeutic agent taxol. This agent requires the use of a rare plant in its usual production process, but the investigators used metabolic engineering to produce *E. coli* that can produce this precursor for a family of chemical compounds, taxol being one of them.

Travis Bayer et al. (2009) reported in the *Journal of the American Chemical Society* that the metabolic engineering of *Saccharomyces cerevisiae* to produce methyl halides in a co-culture with the bacterium *Actinotalea fermentans* from a variety of non-food agricultural products. Here, the researchers were able to engineer a system to provide optimal production by microbes. They took every sequence predicted to produce methyl halides and tested them for the highest activity, then engineered that into *Saccharomyces* to produce methyl halide in partnership with another organism.

Another example recently published by Howard Salis et al. (2009) in *Nature Biotechnology* is not focused on a single organism but is about creating synergistic interacting partners—ribosomal modules that can regulate expression. This technology could have widespread applicability.

Research by Jeffrey Tabor et al. (2009) in *Cell* is another example of a combination of components that allowed production of a bacterium with the ability to recognize a boundary condition. This was a proof-of-principal study that may have widespread commercial applicability. The investigators re-engineered organisms that could recognize not only when they are in the light or the dark, but also when they are at the boundary, which is much more complicated and interesting. These capabilities have been engineered in a top-down manner, and the technology may have great significance.

A recent publication by Daniel Gibson et al. (2010) in *Nature Methods*, October 2010, shows the evolution of the ability to assemble DNA from smaller and smaller pieces. This paper reports the semi-automated assembly of the entire mouse ribosomal genome from 600 overlapping 60-mer oligonucleotides, with very little need for monitoring. Such a technology could make DNA synthesis much more expeditious and efficient and raises the question of whether a bottom-up capability can be developed in the near term. This could have a number of applications,

including synthetically reconstructing natural systems to study disease mechanisms, engineering drug or chemical production, and biosensing of hazardous wastes, etc.

Dr. Relman noted that, with recent advances, a growing number of genetic circuits and modules are being developed, some with robust and predictable behavior. These could lead to more bottom-up capability. The number of success stories is growing based on naturally occurring organisms (top-down approaches). Novel scenarios are being reported, such as the example of a synergy between an engineered yeast and a bacterium. Capabilities in DNA construction have far outpaced the capability of design. These advances may quickly make the federal guidance outdated.

Dr. Relman focused the remainder of the discussion on the paper "Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome." The investigators assembled a full-scale genome of approximately 1-M base pairs and moved this synthetic genome into an existing cell with its native genome removed. The cell can replicate itself, so this represents a novel form of independent life.

The word "Creation" in the title should be highlighted, Dr. Relman said, because it is somewhat misleading. Actually, this work follows on a series of findings by the same group, which has been interested in this for some time. About a year ago, they described the synthesis of a bacterial genome that did not work and the ability to move it into a new cell. Much of this technology already has been described, including the key features that enabled it. This latest report is of a development in a series of developments with a stated clear goal: reverse engineer a genome, translate it into an existing cell, and show that it can replicate. This is technically limited to a specialized genus of bacteria, *Mycoplasma*, which have no cell wall, making it easier to move the genome into the recipient cell. This was actually an incremental, predictable advance, and, because of its demonstration in an unusual type of bacterium, it may have limited applicability. It is not clear whether it can be used immediately for other cell types. In addition, whether it means that a radically new organism can be designed is a much bigger unknown, although that is likely at some future time. However, this advance relates to the ability to design an organism with predictable function, although at present there is not enough information to make it viable.

<u>NSABB Discussion</u>

Dr. Casadevall agreed that much hype has surrounded this paper and that "incremental" is the right word to describe the advance. It could have been predicted based on what had been done and was not transcendental science. Dr. Relman noted that an organism having the ability to replicate its own distinct genome independently carries some significance and has been the basis for a lot of the attention.

Dr. Berns noted that this was not entirely synthetic because, once the genome reached a certain size, the investigator had to put it into an existing cell to complete the construction. More challenging, when the genome went into the cell, it was put into one that was extremely closely related to the new genome. The fact that all the other machinery was already completely primed was extremely important. The ability to create something *de novo* is not there yet.

Judge Ehrlich pointed out that this must be considered in the environment of the general public. Advances have been continuous since the human genome was sequenced, and the public is increasingly concerned. Further, as the knowledge base increases, the public becomes less familiar with these areas of science. This compels the scientific community to communicate better if scientists are to alleviate some of the concerns or the result will be a loss of trust and more regulation and scientists will be less able to do research.

Dr. Keim noted that NSABB has made a strong recommendation about having a communication plan when such a paper is to be released. In this instance, there was a communication plan, but it was not exactly what NSABB envisioned. In spite of that, he believed that the public reaction was not as severe as it might have been.

Dr. Imperiale stated that discussion of the predictability of this result is justified, but it is also important to consider the predictability of the top-down process. Researchers thought that they could assemble pathways, but they learned by trial and error that this is very complicated, with feedback loops, for example, so they have learned how to engineer things that work. Improvement in the predictability of making things that work is an important thing to focus on. This will reach a threshold where someone can easily take the technology and put it to misuse. There is no way to know how close that possibility is, but it is something of which to be aware.

Dr. Keim noted that this research was all done with private money, so it did not come under the *NIH Guidelines*. He also pointed out that the committee has discussed the question of how it is possible to reach into a laboratory when it is outside federal regulation. This is a clear example of the potential problem.

Dr. Levy noted that that the word "creation" is potentially inflammatory. The public could have picked up on that term. Dr. Relman agreed, noting that those points of view were heard even though it is not clear they had much of an impact on the final product. However, they were heard late in the process.

Dr. Casadevall agreed with the value of keeping an eye on predictability but thought that predictability was not really possible. Predictability may be impossible now, but the stated goal of some practitioners of synthetic biology is to make biological systems predictable. This must be kept in mind.

Dr. Berns pointed out that the paper is much more conservative than the press conferences were. He suggested that all the experiments reported in the paper appear to be exempt under the *NIH Guidelines*. The potential concerns raised by this research highlight the fact that they transcend areas the *Guidelines* address.

Dr. Relman suggested that this discussion on emerging technologies should take place every time NSABB meets. NSABB needs to consider ways to be more proactive in recognizing developments of importance as they happen, highlighting them in the appropriate manner, and discussing them with the broader community.

NSABB Activities

Stanley M. Lemon, M.D.
Co-Chair, NSABB Working Group on Culture of Responsibility (CRWG)
Professor, Division of Infectious Diseases
University of North Carolina School of Medicine

Paul S. Keim, Ph.D.
Co-Chair, NSABB Working Group on Culture of Responsibility (CRWG)
Division Director, Pathogen Genomics
The Translational Genomics Research Institute
Cowden Endowed Chair of Microbiology
Northern Arizona University

Dr. Lemon began by noting that the CRWG's aims are to identify strategies and develop guidance for enhancing the culture of responsibility among individuals with access to BSAT. This involves not only personnel reliability but also implementation of such a culture at the local level and assistance for institutional and laboratory leadership. Ultimately, the goal is to broadly engage the scientific community to promote such a culture.

The Working Group's approach was to review and elaborate on recommendations made in the NSABB report on personnel reliability and to identify additional practices for promoting a culture of responsibility. The Working Group held a series of roundtable meetings with experts from the public on how to enhance the culture of responsibility at the local level and what the culture of responsibility should be, particularly in high containment laboratories.

The basic premise is that personnel reliability is the responsibility of the local institution, which needs a strong culture of responsibility toward biosecurity and biosafety. Nobody knows local personnel better than does the local institution. Leadership is the most effective tool overall in implementing a culture of responsibility. With few exceptions, the strategies proposed are applicable across all life sciences and, in many cases, could apply to all sciences. The Working Group is hopeful that the report will have broad use, helping to build greater awareness and institutional leadership.

Several categories of practices potentially can enhance personnel reliability and a culture of responsibility. "Best" practices are both widely agreed on and widely applicable. "Potentially useful" practices are less broadly applicable, and their use should be subject to local risk assessment. "Other practices that have been considered" are more controversial and may be subject to federal, state, and local laws. Their use also is subject to their applicability in the local context.

Among those best practices considered by the working group are:

1. Good hiring and employment practices;
2. Encouragement of biosecurity awareness and promotion of responsible conduct at the institutional and laboratory levels;

3. Institutional leadership, including explicitly articulating the institution's expectations of employees;
4. Peer reporting of behavior that is of concern;
5. A system whereby a person may opt out of research using BSATs; and
6. Local review and risk assessment of all BSAT research.

The second category considered by the Working Group is that of potentially useful practices, including:

1. Video monitoring of BSAT labs; and
2. Two-person rule.

The third category is "other practices that have been considered," including:

1. Drug and alcohol testing, which may be prohibited by state and federal laws;
2. Criminal background checks;
3. Credit checks; and
4. Search of social networks.

Finally, metrics and methods are needed to evaluate the effectiveness and impact of these practices. Developing ways to assess practices is always a challenge.

Dr. Keim added that the Working Group is struggling with the "other practices" category. However, rather than ignore it and leave it out, the approach is that it should be brought to the forefront and discussed. Why are these things problematic? A favorite example is polygraph testing, which is widely used in personnel-reliability evaluations but is not admissible in court. Perhaps the entire NSABB needs to consider which practices it wants on the list.

NSABB Discussion

Dr. Murch emphasized the need to obtain local buy-in because that is where practices are implemented. It is appropriate for NSABB to recommend guidelines, but all policies are local. The institution must create an environment where a culture of responsibility can flourish.

Dr. Vidaver asked if the Working Group had considered checking academic credentials. Dr. Lemon answered affirmatively but added that the Working Group considered it important to go beyond that and not simply take a letter of reference as evidence that someone is reliable but actually speak with the candidate's former employers.

Dr. Vidaver considered the list described by Dr. Lemon appropriate for public institutions but wondered if the Working Group had thought about what might be appropriate in the private sector. Dr. Lemon said that these factors seem appropriate for private universities but that the Working Group had not spent much time discussing industry or whether there should be differences. Industry likely does a better job in its pre-employment practices than academia typically does. Most of these recommendations appear applicable across the board, including the

local risk assessment. If done properly, such practices will have an impact beyond the biological sciences.

Dr. Sorensen noted practices typical in recruiting scientists; search committees often restrict their "due diligence" inquiries to checking with the people recommended by the candidate, and, in an astonishing number of cases, the letters and conversations are assumed to be accurate and true. This leads to a failure to detect people who are being dumped for incompetence or for some other reason.

Dr. Kanabrocki suggested that good hiring practices do not end at the time of the hire; they should include regular performance reviews, evaluations and accountability.

Ms. Grant agreed and suggested building on this during employment with better practices such as team building, project-oriented practice, and sensitivity to what is going on in people's lives.

Dr. Murch pointed out that government employees typically have their backgrounds reviewed about every 5 years; this might be a useful practice to implement in other sectors. If supervisors meet one-on-one with employees on a regular basis every 3 to 5 years, they are reviewed more carefully.

Dr. Lemon noted that local and state laws on privacy might preclude this, so legal implications are possible and whatever recommendations the Working Group comes up with must recognize this. Laws vary from state to state, and policy is still evolving. For example, the United States Supreme Court is now looking at this.

Judge Ehrlich noted that the case is about whether informational privacy is possessed by federal contract employees in the Jet Propulsion Lab operated by the California Institute of Technology. This case's outcome will give some guidance about informational privacy. There is the federal Privacy Act and a myriad of other federal and state laws that vary in their applicability to these issues. The CRWG intends to discuss whether any such legal rights may be waived, noting credit checks and whether employers should demand a detailed look at employees' lives every few years.

Dr. Murch stated that it might not be possible to come up with a grand unified policy approach on this; the CRWG can give its best judgment with a set of recommendations and the various states can equilibrate something they can accept.

Judge Ehrlich agreed that this is the Working Group's goal. For some personnel positions, waivers and credit checks may be entirely appropriate, for others not. This is where local review and determination are critical. The Working Group needs to lay out the pros and cons even on matters to which all of its members are highly committed.

Dr. Relman noted the importance of not going too far in the recommendations with the expectation that institutions can adjust their policies or states their laws. In many instances, those involved in BSAT research are a very small number and might be considered expendable.

Dr. Murch noted that it is next to impossible to write one overall policy.

Dr. Relman asked for feedback on Institutional Biosafety Committee (IBC) review of research, although the actual report will not specify an IBC.

Dr. Kanabrocki responded that all IBCs with which he has worked have oversight over infectious agents whether or not the agents are Select Agents or recombinant DNA. This is common practice and he stated his full support of it.

Dr. Relman reiterated that the Working Group should not specify an IBC, just some sort of oversight entity, and noted a consensus that there should be public representation on such a committee. This redounds to the credit of the institution because it is a way for the institution to gain community trust.

Dr. Fitch agreed but noted that especially large organizations will find it challenging to get volunteers to come to meetings. It is not clear whether a community member would come to every safety meeting without being paid as a part-time job. Guidelines are appropriate, but care must be taken not to become overly prescriptive.

Dr. Nicholson noted that local review and reliability of all staff are two different things. One is to look at the research being proposed or being done, and the other is to look at the people doing it and whether they are reliable, appropriately trained, etc. Particularly at the CDC, where a great deal of this type of work is ongoing, it must be reviewed efficiently and public representation on review panels would present a challenge both because of the extent of the ongoing work and concern about letting everybody know specifically what is going on.

Dr. Kanabrocki commented that evaluating the performance of a given laboratory based on safety audits and evaluating the training record of the people working in the laboratory are the sorts of things that give a good understanding of what is going on in the lab, not just what is written in the protocol. He stated that he understands and is sensitive to the problem of volume, but perhaps IBCs and safety committees need to be thoughtful about their review processes. Do they require an extensive review every time a new grant is written or do they look at it from a Principal Investigator-based approach, which could reduce the number of full reviews?

NSABB International Engagement Working Group (IWG)

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Dr. Levy summarized the activities of the IWB, specifically the NSABB hosting a webcast series that focuses on dual use research on topics of NSABB and U.S. government interest and facilitating international engagement activities in support of NSABB efforts. These include face-to-face international discussions and facilitating participation at international meetings.

The IWG has hosted a webcast series, holding three conferences, one in Bethesda and two internationally, to help develop an international framework. The Working Group realized that these conferences can reach a certain number of people, but they are quite costly. Technology can broaden the audience and capture people who will not or cannot travel for reasons of expense. The first webcast focused on the region of the Americas. The second, held in September 2010, focused on Europe. The idea is to set up an event with questions and answers and webcast the event. It also can be videotaped and put on the NSABB website after the event. Both the event itself and the archived event are available for viewing on the web.

The title of the most recent webcast event was "Does Your Research Raise Security Concerns?" held on September 22, 2010. The event gained a great deal of publicity from the European partners, which included the Institut Pasteur, the European Science Foundation, the European Molecular Biology Organization, and the European Society of Clinical Microbiology and Infectious Diseases. The region of focus determines the groups that get involved. This webcast introduced the concept of obtaining partners to assist with advertising the event.

This event provided an opportunity to establish partnerships and liaisons with these groups. The objectives of this webcast were about what dual use life sciences research is. This was done by providing case examples and commentary. Strategies for promoting responsible conduct of research (RCR) were discussed with presentations on relevant European examples. This was followed by a general panel discussion and audience participation. The panelists were Drs. Amy Patterson (NIH), Gerald Parker (HHS), David Franz, Stuart Levy, and David Relman (NSABB members), and European representatives, Drs. Andres Gorski, Mihail Kritkos, Oscar Kuipers, Guenael Rodier, and Markus Schmidt. The webcast was 2.5 hours long.

The IWG received much e-mail and feedback from viewers. There were some technical difficulties. The primary system for the webcast was Flash software, but it did not work, so the backup was RealPlayer. Many participants did not have access to this software, and those who could not move from Flash to RealPlayer were not able to participate in the webcast. Nonetheless, a total of 173 viewed the webcast in live time, and 94 viewed the archived video. More groups are still signing on to the archived event, so it is proving valuable. The webcast is a potentially useful way of reaching a larger community and has provided ideas for a third IWG activity.

What the IWG has seen is a modest live and archived viewership from a wide geographic diversity. In the Americas version, the archive viewership is now about 500 whereas the live viewership was about 200.

The next activity will involve collaboration with another working group and will be entitled "Strengthening the Culture of Responsibility with Respect to Dual Use Research and Biosecurity." This will be a satellite video teleconference from Beijing, China, with a participating group at the NIH. This event will be videotaped, not webcast, so it can be edited and put together for a satellite symposium and then put on the web. The event is a collaboration between the NIH and the Chinese Academy of Sciences. The event will be organized as a satellite session during the Biological Weapons Convention Science and Technology Workshop to assess implications of scientific and technical developments for biosecurity. The

teleconference will consist of a one-hour session, with co-moderators Dr. Li Huang in Beijing and Dr. David Franz in Bethesda. Panelists will be Amy Patterson, Susan Ehrlich, Paul Keim, and Stuart Levy. The format will include a structured question-and-answer session with conference participants focusing on (1) principal features or attributes of a culture of responsibility and (2) strategies for promoting, creating, and sustaining a culture of responsibility.

Future working group activities include an international interactive webcast in 2011, possibly with a focus on Asia. The working group has been pleased with the costs of the webcast format and the combined approach. The goal is to expand the ways the IWG publicizes, expands to Asia, and does more in the Americas.

NSABB Discussion

Dr. Keim asked about language barriers.

Dr. Levy answered that the first webinar was done in Spanish and English but that the second was in English only; however, the videotape could be edited to accommodate various languages. He commented that the costs of doing this are enormously fewer than bringing people together physically.

Dr. Imperiale noted that, although this is largely intended to be a non-governmental effort, there is a thriving organization of science counselors from the embassies that have a presence in Washington. This might be a group worth engaging informally or by specific invitation.

NSABB Outreach and Education Working Group (OEWG)

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Dr. Imperiale explained some history of the OEWG, and summarized the original charge and progress. This update is the basis of the OEWG's report that will be ready at the next NSABB meeting.

Dr. Imperiale noted that a number of activities aimed at fulfilling the OEWG charge are ongoing. These include the web site as the portal for information on NSABB, presentations and workshops to key constituencies, exhibits at major meetings, poster presentations at meetings and conferences, and a video and educational brochure. He noted that participants' folders include a copy of the video. This video has received about 1,500 hits.

For a number of reasons having to do with the changing nature of biotechnology research, the Working Group, via NSABB, has been given a new charge. Among the important changes driving the need for this is the relative democratization of research. Projects that once cost millions of dollars can now be completed for a few thousand; genome sequencing is a prime example. A second change is the increasing accessibility of biotechnologies to individuals outside traditional institutions. There is a growing hobbyist community of do-it-yourselfers and other amateur biologists. A lack of institutional infrastructure for training and oversight presents a host of biosafety and biosecurity concerns, including the important question of how to reach these people and ensure they are trained in biosafety and biosecurity.

In light of these changes, the Working Group's new charge notes that outreach efforts limited to life scientists at established institutions are insufficient and presents the question of how to reach others. The federal government has now charged the NSABB to recommend outreach strategies to amateur biologists and scientists in non-biology fields. Over the last few months, the Working Group has held a series of teleconferences to get input from various stakeholders. It is interested in what the full NSABB considers missing.

Ms. Grant noted that amateur biologists work with biology as an avocation on their own time and frequently alone but also as part of a community with community labs. These are do-it-yourself biologists. Some of them have organized around a group they call "DIYbio," but this community approach represents a new way of operation. There is really no way to know the total. The DIYbio listserv has about 2,000 participants, but some are just watching. Many are not formally trained. They mostly do low biosafety level work. They are highly creative, curious, young, and early adopters of new technologies, and they work outside settings with infrastructure and oversight. They may assemble into community groups. Many of them do not consider themselves researchers. Their organization is encouraging community labs with shared equipment.

The scientists in non-life science disciplines who are of interest are those participating in life science research and collaborations. They span many fields, including engineering, chemistry, computer science, mathematics, and physics, among others. They are not typically trained in biosafety and biosecurity, may not be subject to IBCs, Institutional Review Boards and Institutional Animal Care and Use Committees, and might be less familiar with oversight requirements.

The OEWG's approach to understanding these new audiences included interviews with individuals who are members of or familiar with the two groups. A number of observations arose out of these interviews. Beginning with the amateur biologists, to the extent they are organized, it is under such groups as DIYbio, BioCurious, and genSpace. The indicated strategy for reaching them is to understand that these organizations are key to reaching amateur biologists and should be sought as partners in outreach and education efforts.

The second observation is striking and consistent; the community culture values its reputation as good citizens and responsible users of technology. The Working Group should build on this premise. The need to be aware of the dual use message resonates with these people. The

indicated strategy is that the message should involve broader concepts such as personal and social responsibility.

A third observation is that they have expressed a desire to interact with many federal agencies such as the Food and Drug Administration and the USDA. The strategy indicated by this is to create opportunities for broader federal engagement. However, because they are somewhat skeptical of government interest, message points about dual use should focus on the possibility that amateur biologists can develop findings and technologies that could be abused.

A fourth observation is that amateur biologists tend to be tech savvy. They use Internet social networking tools such as mobile devices, blogs, Twitter, Facebook, and Google groups. The indicated strategy is to use the value of such electronic modes of communication.

A fifth observation is that their youth and natural curiosity lead them to migrate to novelty devices and games. The indicated strategy is that novelty and unconventional items can be effective conduits of information for reaching members of this group.

A sixth observation is that amateur biologists have an interest in adhering to biosafety standards and want this knowledge as an extension of their own goals of personal protection and social responsibility. The indicated strategy is to join message points about dual use research with information about biosafety practices.

A final observation is that younger scientists tend to be more receptive to the dual use message and that educational strategies have a more lasting impact on them; with them, a true culture shift is more likely to occur. The educational intervention needs to start early in their education and be frequently reinforced. This points out the need to figure out how to reach those training in the non-life sciences with the message on dual use research prior to doctoral-level training. Many educational tools already developed have broad applicability and future educational tool development should be aimed at a scientifically diverse audience.

NSABB Discussion

Dr. Levy stated that he appreciated the interviews; however, they were pre-selected, and it might have been useful to talk to somebody who disagreed. Those interviewed all agreed with the need to conduct research responsibly. He suggested using them as the messengers to spread the message, i.e., use youth to teach their peers. The NSABB discussed reaching younger people, even as far as the 10th or 11th grade so that they could develop the message for those even younger.

Dr. Imperiale noted that recommendations had been made in an early NSABB report to develop a toolkit for training at the high school level. Those efforts could be pursued or reinvigorated to get the message of dual use research of concern into the school science curricula. When these students grow up and "graduate" into being do-it-yourselfers, they will already have been exposed to the concept of dual use research. He advocated proceeding with caution, mainly because a workshop convened by the National Academies brought together scientists interested in education and expert educators, and their report just came out. A take-home message from that

meeting is that there must be care in how these ideas are targeted to younger people. The risk is turning them off if the "bad" side is emphasized too much so that they don't have the excitement about going into research. He suggested the need to back off from that audience at this point until a better understanding is available of what type of message to give to that audience. Certainly their teachers can be approached, but otherwise the need is to focus on older students, college age and up.

Dr. Lemon asked to what extent these amateur biologists use commercial products, such as restriction enzymes, and wondered if there is an opportunity to engage such companies in providing educational materials.

Ms. Grant replied that there had been no attempt to quantify that. They are clearly using commercial suppliers, and there is a whole world of high school experiments in which a person can obtain an alga or a bacterium and perhaps insert a luminescent feature.

Dr. Levy responded that he was not interested in putting forth the dangers. His interest is in educating about what dual use research is. It is not hard to think about communicating dual use research concepts to students without frightening them away. Teachers could do it as part of a regular class where there is an opportunity to discuss the process of research.

Dr. Berns expressed interest in getting feedback from science educators on the question of at what level the notion of dual use research can be introduced.

Dr. Murch agreed with Dr. Levy that this is not about communicating the danger but rather the responsible side of science, which cannot be started too early if it is done properly. Vignettes can be used as examples showing that things can be done in a harmful way, and it is not too early to start thinking about it.

Dr. Relman agreed with the value of thinking about a positive message to be given early; he expressed concern about being too caught up in a small segment of the life science research community that has turned a bright spotlight on itself. He suggested that being missed is a much larger group doing research with clear dual use research implications, e.g., all the people doing management consulting work, looking at process engineering. Where are the critical vulnerabilities in a process? Many people are doing very sophisticated analyses of vaccine infrastructure. Where are the critical parts that can break down or be manipulated? Many are in business schools, consulting firms, and the private sector, who do this kind of thing all the time. They are not getting the message at all. Likewise, in the engineering fields, many in the private for-profit and nonprofit areas are doing work that all would agree is clearly relevant and very sophisticated and powerful. None of them are talking to NSABB; they are just doing their work.

Ms. Grant thought this was a great message to think about as the Working Group considers who to interview from the non-life sciences. The Working Group charge needs to be brought to closure. Part of that charge is to look at the do-it-yourself community, and the Working Group will do that. The second part is to look at non-life sciences, which could include some of the process people if they are considered part of the group.

Dr. Casadevall stated that he was not sure the amateur biologists are really doing research or if the concept of dual use research actually applies to them. Anyone connected with popular culture is familiar with the idea that science can come up with bad things. He suggested that this represents a different subset from what NSABB has been trying to do, which is to identify legitimate research that has or can have two sides to it. It might be necessary to keep an eye on amateur biologists, but they are a different issue.

Mr. You related an incident at Virginia Tech, where the Bioinformatics Institute hosted a seminar on dual use research. Students took the seminar and expanded it as a summer project, using the federal guidance on biosecurity for DNA providers and developing a screening tool using federal parameters. This is a perfect amalgam of the federal agency providing tools and the young people leveraging the tools to deal with real, concrete biosecurity issues. The materials must be provided and the right approach used, but the results can be phenomenal. This is not onerous or repressive if it is done right. NSABB can address not only innovation but also security and risk questions.

NSABB Journal Review Policies Working Group

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The co-chairs summarized the working group's objectives:

1. Gain an understanding of current practices in conducting reviews of manuscripts for content with dual use potential;
2. Solicit input from journal editors and publishers on the current NSABB guidance;
3. Continue to raise awareness about dual use research of concern; and
4. Provide information and support to facilitate the incorporation of current or novel practices for the review of research for possible dual use research of concern into the policies of publishing scientific literature.

To date, work on a review of journals' current policies has included an online survey of select journals and publishing-related organizations. This has been largely anecdotal, not systematic, but it has revealed practices. These practices pertaining to dual use contents vary from journal to journal.

Major themes that emerge from a review of current policies are:

1. Some journals ask authors to assess dual use potential;
2. Some ask reviewers to assess dual use potential;
3. Some call on expert opinion to assess dual use potential;

4. Most ask their associate and senior editors to do an initial screen for dual use potential;
5. If editors see grounds for concern, the managing editor and editor-in-chief are called on; and
6. No journal has a policy on manuscripts that raise dual use concern but are rejected on scientific merit.

One-on-one discussions with editors have focused on their journals' current position or policy on review of manuscripts for dual use content; the process of review; the outcomes and impacts of reviews such as actions taken, changes over time, and lessons learned; the utility of NSABB's communication tool; and the need for further guidance.

Preliminary findings are that different models are working, that there are a few instances of concern, and that there is a need for guidance.

The Working Group plans to hold a Journal Editors' Roundtable on January 13, 2011. It has been organized to get input from the target participants, who comprise 10 to 15 editors of leading bioscience journals, some with and some without a dual use research review policy.

Dr. Casadevall added that he has found this process to be very enlightening. Even with such a small number of journal editors interviewed, there is great variation in policies. For example, the American Society of Microbiologists (ASM) has taken the NSABB criteria and made them a necessary component for when a manuscript goes through the review process. It may have benefited from the fact that the original NSABB membership included at least three ASM editors.

The other point is that just talking to editors makes them aware of some of the problems. One said that at the next editors' meeting, these issues will be brought up for discussion and asked for the NSABB documents. Just making the connection seems to alter the system. Engagement makes them realize that problems exist, which they would not necessarily otherwise have known about.

Dr. Miller noted his surprise at how many top journals do not seem to have stated policies for dual use research review; maybe the interviews will reveal ad hoc policies. Another area of concern is frequency, the number of manuscripts that are flagged or considered of concern. This number seems to be really small. He wondered if this is because the numbers really are low or if it stems from the system not identifying manuscripts that should be considered, a sort of specificity/sensitivity question that needs to be looked at.

Dr. Casadevall commented that he has always believed that making a list is an act of dual use. This can be seen in the journal review system. For example, the journals' "radar" is totally geared to detect select agents. If a manuscript is about a select agent, it triggers a review; otherwise, it does not, even though it might be research of dual use potential.

<u>NSABB Discussion</u>

Dr. Imperiale asked if the editors with whom the Working Group spoke give any guidance to their authors or reviewers.

Dr. Casadevall answered that only ASM gives guidance. A reviewer gets to ask certain questions, and there is a pop-up of the NSABB recommendations. Then the reviewer has to click that (s)he is not concerned about the research in light of those recommendations. That is the only system of which he is aware that uses this process; however, this journal represents a significant amount of the microbiological research being published. Another journal used the select agent list, and, if the research included an organism on the list, it took a closer look at it; however, if not on the list, the manuscript received no attention.

Dr. Imperiale asked if the reviewers know for what they are looking when they take a further look at the manuscript.

Dr. Lemon recalled an exercise when NSABB looked at sample papers and tried to judge whether they met the NSABB criteria for dual use research of concern. Even within NSABB, there was tremendous disparity although this issue had been discussed extensively. He asked how the Working Group intends to get at the question of sensitivity.

Dr. Casadevall answered that they can look at the numbers of manuscripts that are flagged but maybe some are missed.

Dr. Miller suggested that it might not be possible to identify the number of papers that should have been reviewed by asking the journals, and it may be necessary to do an independent assessment.

Dr. Cohen asked if it might make sense to include journals and associations not related to the biosciences in the roundtable planned in January.

Dr. Casadevall thought this a reasonable suggestion, but NSABB's recommendations are geared toward the biosciences. The issue, relevant to the biosciences, may not be applicable to areas outside this discipline

One point that was evident from these interviews with the editors is that they want to have a mechanism for obtaining guidance. This could come back to NSABB, although the NSABB is to advise the U.S. government, not journal editors. Perhaps some kind of an advisory panel or a listing of experts can be created, not via NSABB per se, when a specific question comes, editors would like to have somebody they can ask.

Dr. Keim suggested this could take place in the screening process when a paper is flagged and comes back for review.

Dr. Keim remarked that the reader is supposed to be able to repeat another scientist's work from the published account. He noted that one of his papers was flagged by ASM, and he volunteered to take out the detailed methodology. The journal editor stated that the methods are standard, so they should be left in because anybody could figure them out. If it is really a standard procedure,

the sensitivity is real, but it is also a philosophical problem because a reader needs to be able to repeat the experiment.

Dr. Keim suggested that it is clearly better to engage the authors from the start. If a paper is rejected based on bad science, there is no further engagement. On the other hand, many have seen a paper that gets rejected go to another journal and it probably will be published somewhere. Engaging and working with the author can be viewed as a moral responsibility for the editors.

Dr. Vidaver wondered if, after the look at journals has been completed, patent applications should be looked at as these typically include very extensive methods, described very explicitly. She wondered if that is an area of concern or not.

Dr. Casadevall stated that this was not discussed.

Dr. Keim noted that this was looked at by the Communications Working Group, but it reached no solution.

NSABB Codes of Conduct Working Group

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Dr. Sorensen noted that the Codes of Conduct Working Group's aims are to promote the dissemination, awareness, and adoption of codes of conduct by academic institutions as well as by professional societies and individuals engaged in dual use research.

The Working Group's premises are that the development and implementation of codes of conduct should be voluntary activities on the part of professional societies, institutions, and groups of researchers (e.g., a laboratory team). Codes are optimally used for the purposes of educating and raising awareness among scientists. The Working Group has been charged with advising on ways to promote the adoption of codes by academic institutions and scientific societies. Codes should be thought of as living documents.

Dr. Sorensen noted that the Working Group will have a roundtable on October 20th. This will gather experts from various institutions, scientific societies, and the U.S. government in an attempt to increase and enhance NSABB's knowledge. The task is to get codes into the institutions in a way that they will be used. To prepare for the roundtable, the Working Group

conducted an online survey to identify organizations with dual use research–related codes. A previous survey was completed in 2006 and found that only five associations had such a code, only two of which were scientific. Dr. Dan Davis (NIH Office of Biotechnology Activities) suggested that the 2010 survey, done by the Working Group in the last few months, could be viewed as a kind of pulse-taking activity.

There are a number of limitations to this survey. First, it was done online. Second, the survey was also limited because it did not deal at all with academic institutions. The Working Group also conducted a literature review, including the historical background of the development of codes, the justification for developing them, the types of codes, the relationship of codes to the conduct of science and to legal systems, best practices, gaps in policies or implementation mechanisms, and how to implement the code of conduct once developed.

A question the Working Group intends to probe is what makes a code effective in achieving its aims. The Working Group's aims are for the most part educational or consciousness raising.

A second question is what are the best practices in implementing codes and make them living documents.

The third question was highlighted when the Working Group encountered individuals who were skeptical of the notion of implementing codes of conduct for fear they would be used as regulatory devices.

Dr. Berns commented that scientists work for institutions that pay their salaries, so the question of whether they adhere to the code of conduct can be significantly enhanced by their institutions. Do institutions consider this another unfunded mandate? This is a question to which NSABB must be extremely sensitive.

The roundtable will finish with people who are leaders in the RCR field and have given serious thought to the value of codes of conduct as an educational tool that can be integrated into RCR education modules. Experts will be asked to provide advice on how codes of conduct can be used in the educational setting.

NSABB Discussion

Judge Ehrlich wondered how this will dovetail with President Obama's mandate that every federal agency develop a code of integrity.

Dr. Berns answered that, within a federal agency, the code of integrity is essentially the word of law and determines the conduct within the agency.

Dr. Imperiale commented that in one of NSABB's reports, there was a recommendation for some sort of mandatory training but that NSABB seems to be viewing codes as educational. Why not make the codes also mandatory? Surveys and asking if associations have codes of conduct related to dual use have been spoken of, but NSABB is also engaging the RCR people where the context is much broader. The question is whether NSABB is thinking about dual use codes of

conduct as incorporated into a larger context that discusses plagiarism, ethical standards, and other issues taught in RCR, or whether NSABB is thinking about these codes as stand-alone vehicles.

Dr. Berns replied that it is all part of how the scientist responsibly conducts him/herself. In that sense, it is perfectly logical to include dual use considerations in an RCR course. Mandating making people aware of dual use concerns is quite a different thing from mandating a very specific dual use code. That type of mandate departs from the voluntary nature of what NSABB has been talking about. It makes more sense to allow individual institutions to choose the way they approach how their faculty conduct themselves.

Dr. Cohen asked whether this continues where the original Codes of Conduct Working Group and its report ended. `

Dr. Berns replied that it will cover advances since that time and will point out whether any progress has been made.

Dr. Sorensen said his hope is that every university with scientists engaging in dual use research will adopt a code of conduct specific to that institution. However, the exact nature of the code will vary from institution to institution just as there is a universal code on plagiarism but no institution has a specific code of conduct on plagiarism.

Dr. Levy said that NSABB talks about the problem of "turf." As a scientist looking at the Culture of Responsibility Working Group and this group's work, he is being asked to align himself with a culture of responsibility and at the same time to sign onto a code of conduct. He expressed some confusion about the constituency and the message. A scientist is dedicating himself to the institution's code, but (s)he has her/his own culture of responsibility, which seems to come back to the institution's culture of responsibility.

Dr. Lemon suggested looking at a code as a best practice. The process of developing a code was as important as having a code; thus, one of the important elements of a code is having it developed locally.

Dr. Berns noted that, at his university, the notion of something starting at the faculty level and coming up to the university level creates internal agreement. The point here is the notion of buy-in. If people buy in from the beginning, as opposed to having something foisted on them, a better outcome results.

Dr. Lewis commented that what is being discussed is exactly what the Working Group grappled with in developing a code of conduct not as a legal requirement. The Working Group looked at this as a voluntary, moral activity, and how a person, how an organization, and how an institution should be operating.

Dr. Lemon commented that there can be a code of conduct that addresses dual use research or there can be elements of such a code in a much broader code.

Dr. Levy stated that this will be a challenge, not only to NSABB, but also to the intended constituencies as they wrestle with the many questions.

Public Comment

David Silberman, Director of the Health and Safety Programs Office at Stanford University School of Medicine, stated that he anticipates the NSABB's recommendations will be considered as regulations by the U.S. government and that it is not clear what impact they will have on a community of researchers that already finds itself in an unintended state of marginal noncompliance with existing regulations, laws, and standards. People recognize that mandates cost money and time, and will take away from the research intended to protect, and, it does not have to be that way.

Member Activities

Dr. Cohen reported on presentations made around the world in late spring and early summer, with special focus on dual use research and dual use research of concern. Last April, Switzerland opened a BSL-4 facility near Zurich, and there were specific presentations on not just the concept of dual use research and dual use research of concern but also on the specifics of NSABB work. The presenters were primarily European, and it was interesting how much they were using NSABB work products. On the other hand, the tone of life scientists in Europe was disconcerting as it presumed that what is being done in the U.S. for biodefense is really thinly veiled bioweapons work. Nonetheless, the Europeans are putting it into the context of what NSABB is trying to do in the U.S., i.e., to educate the scientific community and representatives of the U.S. government. A second meeting was the Asia-Pacific Biological Safety Association 5th annual meeting in Seoul in June. Specific presentations were made on dual use research of concern and codes of conduct among other topics, all based on familiarity with, and direct use of, the work product of NSABB.

Dr. Kanabrocki mentioned attending a meeting in Amman, Jordan, sponsored by the American Association for the Advancement of Science (AAAS) and the Jordanian Academy of Science. Participating countries included Middle Eastern and African countries and the U.S., Afghanistan, Pakistan, Iraq, Jordan, Kuwait and Morocco among others. The intent of the meeting was to stimulate scientific collaborations between the region and the United States. A series of follow-up meetings will be held to continue that promotion. He noted that Dr. Kavita Berger of the AAAS was present and asked her to expand on this.

Dr. Berger explained that the AAAS had received a grant from the U.S. Department of State to host a series of meetings related to the bioengagement program. The decision was to host the meeting on international collaboration in part because there is very little engagement on biosafety and biosecurity, and thus very little follow-up, in these countries.

Dr. Vidaver reported having just attended the world's first *Gesneriad* research conference. This is a genus of plants in a group with about 20,000 species of which the African violet is perhaps the best known. The conference consisted primarily of people doing phylogeny and ornamental work. Considering that the conference was worldwide and included about 100 people, there was no mention of concern about microorganisms, much less dual use. It was striking that, as people

showed pictures, mostly concerned with the flowers, a number of the specimens clearly had disease.

Dr. Keim reported that in May, as acting chair of NSABB, he was approached by the White House Office of Science and Technology Policy (OSTP) and in fact received the Venter paper on the synthetic bacterial genome that was discussed earlier. He reviewed the paper for its dual use potential prior to publication, along with Drs. Amy Patterson and Anthony Fauci, and then went to the OSTP where Craig Venter gave a presentation. Dr. John Holdren, the OSTP Director, also attended this meeting and presentation. Dr. Keim offered an opinion on the technology's potential for dual use and was involved in the process at the time it occurred.

Next Steps

Paul S. Keim, Ph.D.

Dr. Keim announced that the next NSABB meeting is tentatively scheduled for February 8, 9, and 10. Exact dates are being finalized, and members will be notified on the specifics as the agenda is developed. The meeting will be announced in the *Federal Register.* Based on the reports from the NSABB working groups, it is anticipated that several will be presenting their draft reports at the February meeting or in upcoming meetings in 2011.

Closing Remarks and Adjournment

Dr. Keim thanked the members of the NSABB and everyone else present for their insightful comments. He adjourned the meeting at 4:00 p.m.

Date: _____

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Paul I. Lewis, Ph.D.
Executive Director
National Science Advisory Board for
Biosecurity

I hereby acknowledge that, to the best of my knowledge, the foregoing Minutes and Attachments are accurate and complete.

These Minutes will be formally considered by the NSABB at a subsequent meeting; any corrections or notations will be incorporated into the Minutes after that meeting.

Date: _____ _____

Paul S. Keim, Ph.D
Acting Chair
National Science Advisory Board for Biosecurity