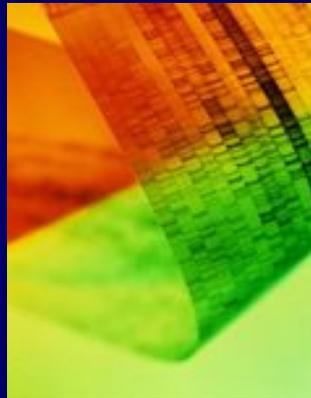


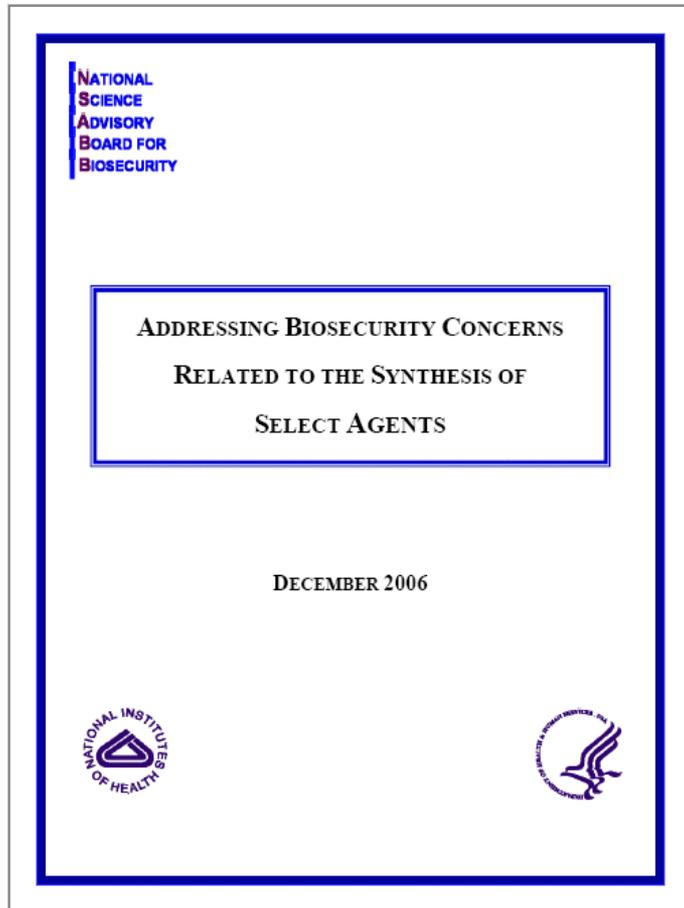
Impetus for NRC Report on Sequence-Based Classification of Select Agents



October 19, 2010



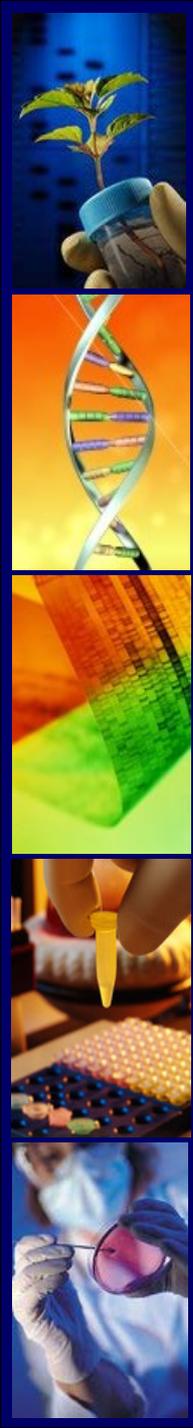
NSABB Report: Recommendation 4.2



“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.”

October 2007 NSABB-RAC Roundtable on Synthetic Biology

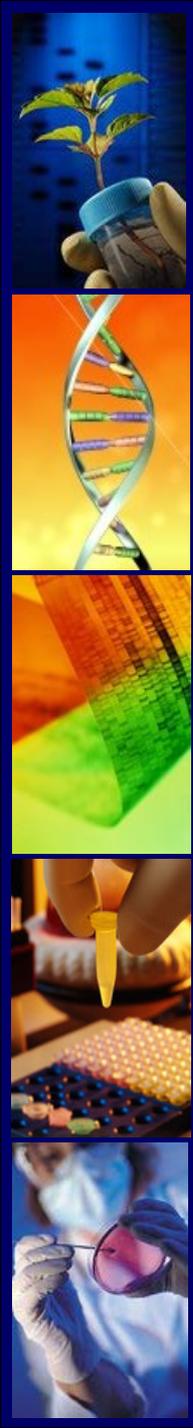
- **State of the Science of Synthetic Biology**
 - Roger Brent
 - Steven Benner
 - Ron Weis
 - Steen Rasmussen
- **Predicting Function from Sequence and Structure**
 - William Goldman
 - James Musser
 - Marc Kirschner
 - Owen White
- **Risk Assessment and Risk Management in a Context of Uncertainty**
 - Rocco Casagrande
 - Lawrence McCray



October 2007 NSABB-RAC Roundtable on Synthetic Biology

■ **Session on Predicting Function**

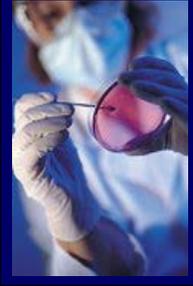
- Form and Context in Predicting Biological Function
- Genotype to Phenotype
- Design Considerations for Robustness and Vulnerability in Biological Systems
- Design and Use of Predictive Tools: State of the Art



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■ Session on Predicting Function: Questions for Speakers

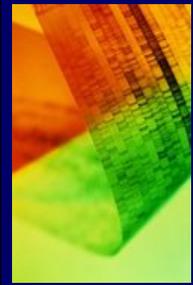
- How accurately can virulence be predicted on the basis of sequence alone?
- How does our current understanding of lateral gene transfer in nature help us predict the degree to which virulence and other relevant phenotypes can be deliberately manipulated or created de novo?
- What are the major challenges and unmet needs that hinder recognition and prediction of virulence?
- What are the considerations for predicting function within systems?
- To what can we construct entirely new systems or organisms with predictable behaviors?
- What are the capabilities and limitations of current tools/approaches for predicting function from sequence? What are the major challenges and goals for developing more accurate predictive tools?



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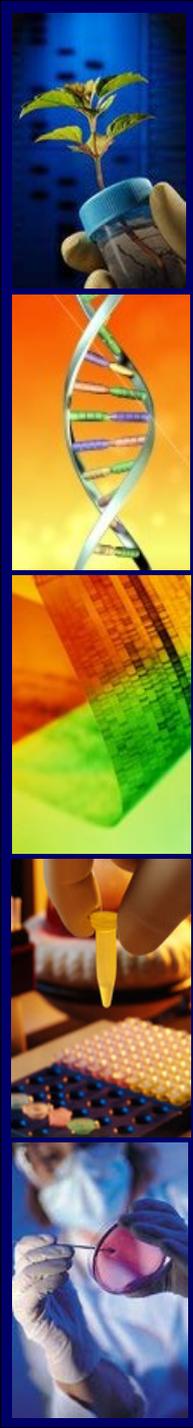
■ Predicting Biological Function: Lessons Learned

- Function/behavior is often context dependent, and sequence information will not tell you that
 - E.g., a particular sequence that encodes a virulence factor for one organism can encode an entirely different function in another organism, and none of this comes from sequence information
- Single nucleotide changes can contribute significantly to phenotype
- Components of biological systems do not vary all that much, but what does change is regulation. There is considerable evidence that regulation might be as important, if not more so, than sequence in modulating function/behavior
- **We know very little about predicting function. A sequence-based predictive model of behavior is currently not possible.**



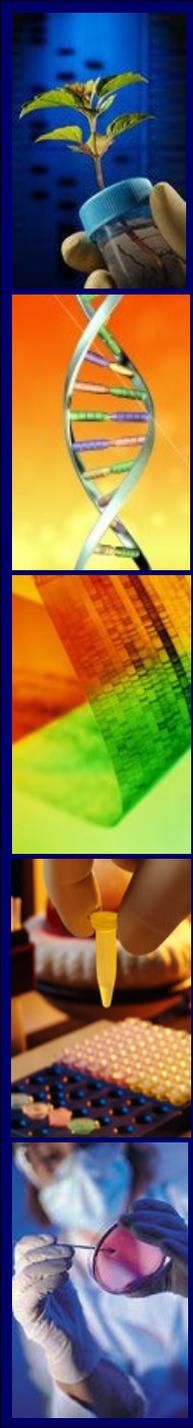
USG Considerations of NSABB Recommendation 4.2

- We currently do not have the scientific capability to predict function from sequence with sufficient certainty to underpin regulation
 - Therefore 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



USG Considerations (cont.)

- Once the science is available to underpin risk assessment of predicted features, it may be possible to utilize this approach *in concert with* the current oversight system, *rather than in lieu of* the current approach



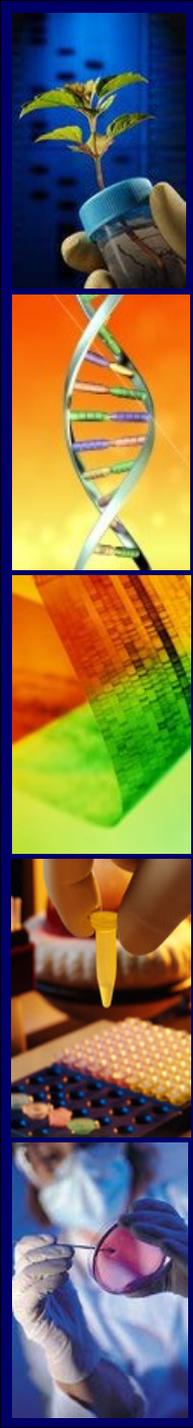
USG Policy Decision on NSABB Recommendation 4.2

- Identify the list of scientific advances necessary before a predictive oversight system can be postulated, developed, evaluated and potentially implemented



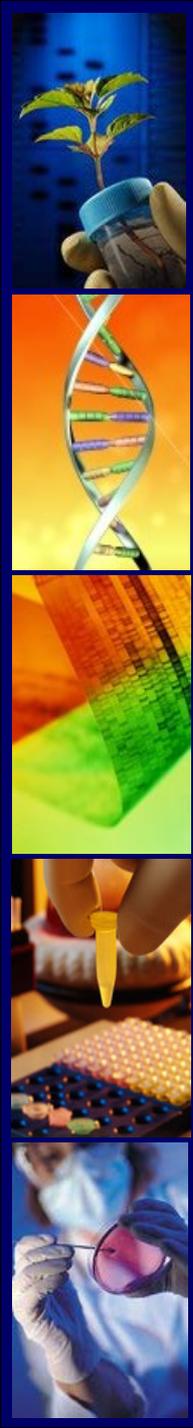
Questions for the NRC Committee to Address

- Does the current state of the science of predicting function from sequence support a predictive oversight system for select agents at this time?
- If not, what are the scientific milestones that would need to be realized before a predictive oversight system might be feasible?



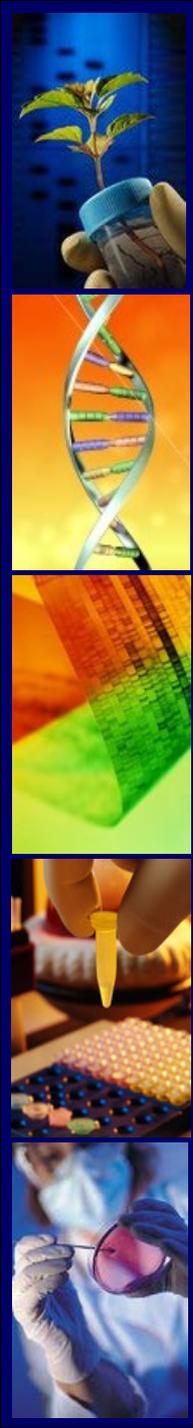
Questions for the NRC Committee to Address (cont.)

- What are the challenges in attempting to predict biological characteristics from sequence?
- What would be the key scientific attributes of a predictive oversight system for select agents?



Questions for the NRC Committee to Address (cont.)

- **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?**
 - **What are potential implications of certainty/uncertainty of predicted function on**
 - consistency in interpretation
 - ability of investigators to comply
 - enforcement decisions



Questions for the NRC Committee to Address (cont.)

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

