Published in final edited form as:

Nat Biotechnol. 2010 October ; 28(10): 1010–1012. doi:10.1038/nbt1010-1010.

Safe and effective synthetic biology

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The public outcry over the creation of "synthetic life" within a laboratory1 is both predictable and valuable. While it has been pointed out2 that the actual results represent an advance in DNA synthesis capabilities rather than what the sensational headlines have implied, the popular press has nonetheless evoked images of scientists that were previously only seen in science fiction. The lay public has a heightened awareness of synthetic biology and is both concerned and fascinated by the implications of this technology. The public's concerns should not be dismissed lightly. The field of synthetic biology is a consequence of numerous and inevitable advances in biological technologies. At the same time, interest and tools has arisen to apply a technology centric design-driven approach to complex biological systems3,4 to develop solutions for clinical and biotechnology challenges.

In the last four decades, the length of synthetic genes that can be produced in the laboratory has increased by four orders-of magnitude - from 10^2 to 10^6 base pairs5. At our limits, we can currently synthesize the DNA needed for simple bacteria1; extrapolating these trends into the future, however, provides a prediction that the synthesis of a complex genome (such as the human genome, 10^9 base pairs) will be feasible within the next 30 years. However, the rate has increased in the last decade, and the capability to synthesize such a complex genome may be achieved in as little as 10 years. Cost is a minor issue, but one that is quickly disappearing from the equation. The commercial cost to purchase / synthesize genes decreases significantly each year (decreasing at a rate of 30 % to 50 % per year6) – costs are expected to drop to $0.01 per base pair in the very near future7 – even without disruptive new methods, the current trend should reach this price point in 5 to 10 years.

Synthetic biology holds tremendous promise as both an investigative and therapeutic modality. The implications of engineering biologic systems were one of the topics discussed at the 2009 National Academies Keck Futures Initiative on Synthetic Biology (NAKFI-SB) 11. Experts were asked to consider such basic questions as what tools and technologies are required to advance the field, why man-made biologic systems are more fragile than natural ones, and how to create and improve inter-cellular communication. But also discussed were risk assessments, the religious and ethical implications of synthetic biology, and how best to leverage the technologies to explore other biological systems. While the primary focus of NAKFI-SB was to discuss future research and promote interdisciplinary cooperation, the conference also recognized the significant inherent risks and potential bioethical

implications of synthetic biology. The discussions at the NAKFI meeting included the value of revisiting the self-examination and self-regulation imposed on early adopters of recombinant DNA technology at the Asilomar meeting12 (an idea also suggested in13) in light of the increased complexity and ambitious goals for synthetic biology. The attendees also recognized the need for a "safety switch" to disable undesirable neo-organisms (see Table 1).

The recent meeting of the American Association for the Advancement of Science (AAAS) Center for Science, Technology and Security Policy focused on the U.S Government's perspective on minimizing the risk of synthetic biology9 and critiqued the recent U.S. Department of Health and Human Services draft set of voluntary guidelines entitled *Screening Framework Guidance for Synthetic Double-Stranded DNA providers* released in November 2009. The meeting included representatives from the U.S Government, gene-synthesis provider organizations, and the biotechnology and pharmaceutical industries as well as biosecurity experts and academics. This meeting was designed to solicit comments from industry players and other concerned parties rather than build a consensus to make specific recommendations or changes. The meeting summary is available from AAAS and is summarized below in Table 2, organized based on the participant's comments within specific "themes". As expected from the diverse nature of the participants, some of the concerns raised within each theme are contradictory, but the report does provide an important perspective from the major companies involved in commercial gene synthesis and highlights perceived weaknesses within the current strategy.

There are interesting differences between the results of the two conferences. NAKFI-SB was a broad evaluation of the current status of synthetic biology and the final recommendations focused on methods to advance the field. Besides outlining some technical improvements currently needed to improve productivity, the participants recognized the paramount importance of public communication and of lay participation in regulation and oversight to address potential bioethical issues. It also advocated specific technological steps to improve the stability of engineered biological systems including enhanced redundancy and adaptability as characterized by a capacity to evolve to improve efficacy. Gazing into the future, the conference suggested that synthetic biology could be employed to evaluate and synthesize more complex biological systems and that the field is likely to progress beyond using genes to create and regulate these novel entities.

The AAAS meeting was convened to comment on proposed U.S. Governmental safety regulations and the recommendations were understandably narrower. The conference emphasized the importance of improved oversight along the entire chain of production within synthetic biology. These included improvements in customer and end-product screening modalities and greater cooperation between governments, industry and academics both within the U.S. and internationally. Some of the AAAS participants noted that the increased financial burden required to comply with these regulations may impede private industry's investment in the technology.

Both conferences recognized that the promise of synthetic biology is associated with the potential for significant harm. We need to prepare for malicious acts using purely synthetic

or hybrid synthetic/natural neo-organisms. Additionally, we must have strategies to predict and prevent such events and to trace the source of such materials should they surface. Current prevention efforts rely on voluntary participation in a software-based matching system that checks orders against select agent sequences6,9 to head-off the commercial synthesis of select agent genes, but, as the AAAS report9 details, that system could be improved.

In addition, it is imperative to identify a strong method to label synthetic genes so they can readily be identified as such. Unencrypted watermarks14 have already been reported in published sequences of synthetic genes; it at first demonstrates the capability to tag synthetic genes with watermark sequences, but also highlights the lack of controls against surreptitious insertions. Natural DNA sequences that code for natural amino acids appears the simplest method to tag synthetic genes, but those sequences may be removed, modified or even counterfeited using conventional genomic tools. One potential solution would be to create a ‘serial number’ that could be traced back to individual synthesis laboratories or even individual synthesis machines and encoded into the synthetic gene using an appropriate combination of public-key and private-key encryption or hash algorithms.

It is important that the benefits of synthetic biology not be restrained by public fears and that the research proceeds in a coordinated, systematic fashion that promotes innovation and competitiveness. Synthetic biology offers technologies that may be able to address some of mankind’s basic needs –health, clean water and clean energy13. Regulations, funding and oversight are required and can best be accomplished by organizations (private and/or government) committed to safety and to fulfill the promise of synthetic biology.

This public/private cooperation is vital for safe and effective progress within synthetic biology. There must be a concerted effort to minimize the expenses associated with regulatory compliance; however the inherent risks of synthetic biology mandate rigorous oversight especially since the burdens of a major “accident” will be borne by the public. The financial expenditures that the synthetic biology industry will have to bear to proactively reduce the risk of potential misuse of the technology are substantially less that the estimated costs to respond to a biologic disaster. Safety must be designed into the system and not become a secondary concern. We are also concerned that an attempt to shift the oversight burden from the gene manufacturers to their customers via the creation of institutional “biosafety review boards” modeled after institutional animal care and use committees will be ineffective since it further decentralizes the review process and relies on committee structures that were not designed to preemptively detect hazardous modalities.

The AAAS9 and NAKFI-SB11 meetings were an excellent starting point and we strongly recommend that those discussions be expanded and that the subsequent safety recommendations become expeditiously implemented.

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Table 1

Summary Table for NAKFI-SB

Question	Response
What is needed to facilitate synthetic biology?	• Integration of biological vocabulary within computer programming. • Improved analytical and design modeling. • Novel cellular monitoring techniques. • Improved screening technologies. • Enhanced cell lines to improve productivity. • Cheaper technology. • Techniques to create complex entities. • “Fail-safe” systems. • A “kill switch” for new organisms.
What are the bioethical considerations?	• Synthetic biology is similar but not identical to other new techniques. • Implications require regulatory oversight. • Novel ethical issues necessitate specific risk/benefit evaluation. • On-going public communication and input is vital.
Is synthetic biology useful as an investigative modality?	• Can be utilized to evaluate intracellular systems. • Would require advances in current technology but that is expected. • A sharable library of results is essential but that requires standardization of a context sensitive archiving format.
Is synthetic biology useful for multi-cellular systems?	• Can be utilized to evaluate extra-cellular communication and integration. • Could create novel tissues, organs and complete organisms.
How do we make synthetic systems as stable as natural ones?	• Integrate redundancy. • Increase adaptability. • Improve evaluation techniques.
Is synthetic biology useful for multi-organism systems?	• Can evaluate inter-organism interaction. • Can search for unique genetic material. • Requires improved database administration.
Are there alternatives to using genes within synthetic biology?	• Chemical and physical interactions can be used to modify biological reactions.

Question	Response
	• Unique non-genetic compounds can be developed to influence outcomes. • Alternative engineering techniques (e.g. application of computer design tools) will likely improve results. • Create novel methods for system interfaces and interactions (e.g. optical inputs and outputs). • Isolate created functions from natural processes (e.g. create synthetic organelles or “subroutines”).
Is it important that synthetic biologic systems “evolve?”	• Provides adaptability. • Improved modeling would be valuable. • Need techniques to speed up process to be useful.
What is required to fulfill the potential of synthetic biology?	• Enhance education opportunities at all levels. • Improved and consistent public education and communication.

Table 2

Summary Table for AAAS Meeting

Theme	Comments / Recommendation
U.S. Health and Human Services Guidance	Comments • May inhibit competition and innovation. • How will proprietary information be protected? • No mechanism for “garage biology” oversight. • No mechanism for DNA providers to share customer information. • No ongoing, updated database of entities prohibited from obtaining synthetic biology technology. • DNA providers may refuse to fill orders for sequences that require additional expenses to participate in oversight programs. • No oversight of synthesis providers to assure security and safety. • While the purchase of synthesis technology is a private transaction, there is a lack of an established appeal process for refused orders.
	Recommendation • Coordinate customer and sequence screening to assure safety and security across all DNA providers. • Provide a mechanism to assure safety and security of synthetic biology technology providers. • Enhance accountability of all aspects of synthetic biology including reporting and appeal mechanisms.
Customer Screening	Comments • No mechanism to determine who is the end-user of technology. • Costs associated with compliance may be prohibitory.
	Recommendations • Supply precise customer screening modalities and criteria to assure safety and security. • Shift some compliance requirements from providers to customer institutions including “Biosafety Committee-like” review boards. • Compile, review and update a database of approved customers and consider a licensing requirement to allow purchase of synthetic biology technology.
Sequence Screening Methodology	Comments • Automated reviews of DNA sequences are inadequate. • Screening against a list does not consider the possible context of use since “sequence does not necessarily predict function.” • Innovation and discovery would be inhibited if orders are limited to previously described sequences. • Mandatory reporting of DNA sequence orders may compromise proprietary information.

Theme	Comments / Recommendation
	• Cannot identify sequences changed by end-users. • "Best match" determinations that search for sequences that are more similar to harmful than non-harmful patterns are better than "thresholds" but may be below current industry standards. • Labeling a sequence as potentially "of concern" does not determine actual harmful nature. • Proprietary screening software is inadequate. • 200 bp minimum size for sequence screening is inadequate.
	Recommendations • Human review of all sequence orders. • Compile, review and update a database of harmful sequences. • Promote research to determine the fundamentals of harmful sequences and use this information for screening. • Create and promote protocols for sequence screening "best practices." • Establish list of subject matter experts for each potentially harmful select agent. • Screen each order against any potentially harmful sequence not just those on select agent and Commercial Control Lists. • Mandate the use of open-source screening software that is continuously updated. • Screen all orders irrespective of sequence length.
Implementation and Evaluation	Comments • Success is determined by degree of implementation. • The costs of implementation are minimal when compared to other costs of doing business. • Regulatory compliance is difficult to determine.
	Recommendations • Ongoing, regular governmental communication and interaction with industry and research institutions is critical. • Models of illegal and non-compliance methods should be used to evaluate screening modalities. • Screening methods require continuous governmental and industry evaluations of effectiveness. • Screening methods require ongoing evaluation of financial impact on industry. • Effectiveness can be determined in part by the number of providers that claim compliance with regulations and by the number that perform follow-up screening. • DNA providers should be certified.
International Engagement	Comments • Voluntary compliance and cooperation is crucial to assure safety and security.

Theme	Comments / Recommendation
	Recommendations • Coordinate and streamline international screening of sequences, customers and industry providers.