THE NATIONAL ACADEMIES

SYNTHETIC BIOLOGY STANDARDS AND INTELLECTUAL PROPERTY

Andrew W. Torrance[1] & Linda J. Kahl[2,3]

I. INTRODUCTION

In his 1958 Nobel Prize acceptance speech, Edward Tatum described the application of biology to "the improvement of all living organisms by processes which we might call biological engineering."[4] "Synthetic biology" has emerged over the past decade as a presumptive heir to Tatum's vision. Synthetic biology has developed two broad emphases.[5] One involves the synthesis of large DNA molecules of specified nucleotide sequence. A competitive industry of gene synthesis companies has emerged to synthesize made-to-order DNA molecules on a commercial scale, and speed and cost improvements of DNA synthesis are making this technology increasingly accessible. The second emphasis involves the design and implementation of genetic circuits constructed from basic genetic components. A distinct feature of synthetic biology is its conscious reliance on engineering approaches.[6] In fact, influences from engineering, as well as computer science, have led to more consideration of standards setting, interoperability, and interchangeability in synthetic biology than is usual in other areas of biology. Many in the synthetic biology community also support an ethos of open innovation,

---

[1] Professor, University of Kansas School of Law; A.M., Ph.D., J.D., Harvard University; B.Sc., Queen's University, Ontario, Canada. Dr. Torrance is currently a Visiting Scholar at the MIT Sloan School of Management.
[2] Legal Scholar, Department of Bioengineering, Stanford University; Ph.D., Princeton University; J.D. Santa Clara University School of Law; B.S. University of California at Los Angeles. Dr. Kahl currently leads the Ownership, Sharing, Access and Innovation Systems (OASIS) project for SynBERC, a multi-university NSF Synthetic Biology Engineering Research Center.
[3] The authors gratefully acknowledge the research assistance of Cliff Brazil.
[4] The Nobel Prize, *Edward Tatum – Biography*, Nobelprize.org. 31 Aug 2012 http://www.nobelprize.org/nobel_prizes/medicine/laureates/1958/tatum-bio.html
[5] Tal Danino, et al., *A Synchronized Quorum of Genetic Clocks*, 463 NATURE 463:7279, 326–330 (2010) (explaining how "'[s]ynthetic biology' can be broadly parsed into efforts aimed at the large-scale synthesis of DNA and the forward engineering of genetic circuits from known biological components.").
[6] Drew Endy, *Foundations for Engineering Biology*, 438 NATURE 449, 449 (2005).

and have concerns about the adverse effects intellectual property rights (primarily patents) could have on the development of their field.

Numerous standards have been proposed in synthetic biology, including those relevant to structure, function, description, measurement, data, information exchange, software, biosafety and biosecurity[7], and even law. Adoption of most of these proposed standards has thus far been quite modest. A notable exception involves biosecurity, where standards for screening DNA synthesis orders have been widely adopted. The simultaneous wealth of proposed standards and dearth of adopted standards may be due, in part, to the relative youth of the synthetic biology field and its rapid technical evolution. For example, early enthusiasm for structural and assembly standards may become less urgent as the technology of large-molecule DNA synthesis improves. Nevertheless, interest in standards setting remains a prominent feature of the synthetic biology field.

Numerous institutions have been created with standards setting in synthetic biology as an important goal. These include the BioBricks Foundation ("BBF"), the International Genetically Engineered Machine Foundation ("iGEM"), the Registry of Standard Biological Parts ("Registry"), the Synthetic Biology Engineering Research Center ("SynBERC"), BIOFAB: International Open Facility Advancing Biotechnology ("BIOFAB"), the Synthetic Biology Open Language ("SBOL") Team, the semi-annual International Meeting on Synthetic Biology conference series ("SB1.0", "SB2.0", *etc.*), the International Association of Synthetic Biology ("IASB"), and the International Consortium for Polynucleotide Synthesis ("ICPS"). Another prominent player has been the U.S. Department of Health and Human Services, which, in 2010, issued guidance on how to screen DNA synthesis orders that has been widely adopted by the DNA synthesis industry. At a more informal level, many scientists and a number of commercial firms have proposed standards relevant to various aspects of synthetic biology. In addition, there has been considerable interest in standards within the Do-It-Yourself Biology ("DIYbio")

[7] The term "biosafety" refers to issues related to the safety of humans, nonhuman organisms, or ecosystems from the potential for accidental or uncontrolled release of experimental organisms, standards for which are presented in the *NIH Guidelines for Research Involving Recombinant DNA Molecules (October 2011*) and amendments that modify the scope of the NIH guidelines (announced September 5, 2012) available at http://oba.od.nih.gov/rdna/nih_guidelines_oba.html. This report will focus on standards for "biosecurity" which encompasses safety issues that arise from the potential for intentional or malevolent release of harmful organisms, whether natural or experimental.

movement, whose success in attracting wide participation may be influenced by the existence of standard components and protocols capable of use by amateur biologists.

Many in the synthetic biology community have voiced concerns that excessive intellectual property rights may have an adverse impact on the progress of the field. In theory, negative effects caused by patent rights covering commonly used components or methods in synthetic biology could be exacerbated if those patented components or methods were to be adopted as standards. However, little evidence exists to suggest that this is currently the case. In practice, the past few years have seen tremendous flux in how courts interpret the patent-eligibility of both methods (*e.g.*, diagnostic tests) and components (*e.g.*, isolated DNA molecules) essential to synthetic biology. There is a substantial likelihood that the scope of subject matter in biotechnology currently considered patent-eligible will narrow, perhaps significantly. Copyright may be particularly suited to providing an alternative to patent protection for synthetic DNA, though its applicability to DNA is currently uncertain.

This report resulted from a study of standards setting efforts by the institutions, firms, governments, and individuals within the field of synthetic biology. It is based on a review of the relevant published literature and web-based information. Section II provides a brief introduction to the field of synthetic biology. Section III surveys standards, standards setting efforts and related institutions. Section IV discusses intellectual property issues rights relevant to synthetic biology and standards setting. Section V summarizes the findings of the report.

II. SURVEY OF SYNTHETIC BIOLOGY

Synthetic biology tends to differ markedly from most other fields within biology. Endy (2005) has suggested standardization, decoupling, and abstraction as important principles in making synthetic biology more similar to engineering. He has described standardization as "the definition, description and characterization of the basic biological parts, as well as standard conditions that support the use of parts in combination and overall system operation."[8]

[8] Endy, *supra* note 6, at 450.

However, he has also acknowledged the possibility that biology may be too complex to yield easily to engineering approaches.

Biology differs substantially from the physical and computer sciences. Biological systems tend to be more complex and less predictable, making both understanding and (re)designing them challenging. There may be theoretical limits on the ability to describe and reconstruct any but the simplest biological systems, with little prospect of overcoming these limits in the near future.[9] In addition, practical limitations include the difficulty in defining and measuring the functions of standard biological parts (e.g., BioBricks), the unpredictability of genetic circuitry (necessitating exactly the kinds of trial and error experimentation synthetic biology is meant to avoid), the challenges posed by biological complexity, the mutual incompatibility of many standard parts, and the tendency for variability within biological units to render biological systems prone to failure.[10] For example, synthetic gene networks tend to be resistant to precisely programmed behavior due to cell-by-cell variability and intrinsic stochasticity.[11] Stricker et al. (2008) have urged "caution must be exercised when making simplifying assumptions in the design of engineered gene circuits."[12]

The applied nature of synthetic biology has resulted in a small industry. Commercial synthetic biology represents a modest fraction of the biotechnology industry, and firms have experienced mixed success. Among the most prominent are DNA 2.0, Inc., and Blue Heron Biotech, LLC, providers of synthetic genes, Amyris, Inc., which engineered a pathway for synthesizing a precursor to the anti-malarial artemisinin, LS9, Inc., and Qteros, Inc., developers of biofuels, Ginkgo BioWorks, a biological engineering company, and Synthetic Genomics, Inc., a developer of synthetic genomics technologies, such as Gibson Assembly™,[13] and owner of a substantial patent portfolio.[14] Codon Devices, Inc., an early DNA synthesis firm, went bankrupt

[9] Christof Koch, *Modular Biology Complexity*, 337 SCIENCE 6094, 531–2 (2012).
[10] Kwok, R., 2010. Five hard truths for synthetic biology. 463 NATURE 463, 288–290.
[11] Danino et al., *supra* note 5.
[12] Jesse Stricker et al., *A Fast, Robust and Tunable Synthetic Gene Oscillator*, 456 NATURE 7221, 516–9 (2008).
[13] www.syntheticgenomics.com/products/
[14] Among the patent applications owned by Synthetic Genomics are U.S. 2007/0122826 ("Minimal Bacterial Genome"), U.S. 2007/0264688 ("Synthetic Genomes"), and U.S. 2011/0053273 ("Methods for Cloning and Manipulating Genomes").

in 2009,[15] although a new venture, Gen9, Inc., has since emerged and is developing technology to support synthesis and assembly of larger DNA constructs.

A prevalent theme within the synthetic biology community is the value of an open science ethos.[16] This ethos often promotes open sharing of information among biologists as well as considerable attention to the effects that patent rights may have on the evolution of the field. For example, the BioBricks Foundation and the Registry have tended to promote open sharing of both parts and information, while trying to develop methods for detecting and avoiding patents that might interfere with such openness.[17] However, it appears highly likely that universities and firms have already acquired considerable patent rights in various aspects of synthetic biology – patent rights that could interfere with open science practices. Thus far, there is little evidence that patents covering aspects of synthetic biology have, in fact, been used in this manner.

One notable feature of standards setting and intellectual property in synthetic biology is the recurring participation of a relatively small group of academic scientists, a substantial minority of them with formal training as engineers, who have serially founded and led many of the institutions noted above.

III. STANDARDS AND STANDARDS-SETTING IN SYNTHETIC BIOLOGY

A. TECHNICAL STANDARDS

Within the synthetic biology community, researchers are actively working to develop technical standards for genetically encoded functions that will enable the efficient production, distribution and re-use of biological parts. To date, technical standards relevant to synthetic

[15] Todd Wallack, *Codon Devices Closing as Financing Dwindles*, THE BOSTON GLOBE, Apr. 3, 2009, http://www.boston.com/business/healthcare/articles/2009/04/03/codon_devices_closing_as_financing_dwindles/.
[16] Stephen M. Maurer, *Before It's Too Late – Why Synthetic Biologists Need an Open-Parts Collaboration – and How to Build One*, EMBO 10(8): 806-809; Joachim Henckel & Stephen M. Maurer, *The Economics of Synthetic Biology*, 3 MOL. SYST. BIOL. 117; David Cohn, *Open-Source Biology Evolves*, WIRED (Jan. 17, 2005), http://www.wired.com/medtech/health/news/2005/01/66289?currentPage=all.
[17] An example of this is the development by the BBF of the BioBrick™ User and Public Agreements, found at https://biobricks.org/bpa/, and the requirement that all participants in the iGEM competition register with iGEM before receiving BioBrick™ parts.

biology applications are being developed in at least four broad categories: physical composition, functional composition, units of measurement and data exchange.

Physical composition standards support the physical assembly of individual biological parts into multi-component systems. One of the earliest examples of a physical composition standard in synthetic biology is the original BioBrick™ assembly standard (BBF RFC 10) which uses iterative restriction enzyme digestion and ligation reactions to assemble small biological parts into larger composite parts.[18] This standard initially served as the primary means for physical assembly of biological parts by teams participating in the International Genetic Engineering Machines (iGEM) competition (http://igem.org), and thousands of parts in the Registry of Standard Biological Parts (http://partsregistry.org) have been constructed following this standard. As technology has advanced, the BioBrick™ assembly standard has undergone a number of refinements and other physical composition standards that provide additional flexibility for the physical assembly of biological parts have been introduced.[19]

Although the BioBrick™ assembly standard and other methods that build upon this standard have proven useful to many groups,[20] it is now possible to assemble biological parts

[18] Thomas Knight, *Idempotent Vector Design for Standard Assembly of Biobricks* (2003) (MIT Artificial Intelligence Laboratory; MIT Synthetic Biology Working Group), *available at* http://hdl.handle.net/1721.1/21168.
[19] *See, e.g.*, Ira Phillips & Pamela Silver, *BBF RFC 23: A New BioBrick Assembly Strategy Designed for Facile Protein Engineering*, Apr. 18, 2006, *available at* http://hdl.handle.net/1721.1/32535; Thomas Knight, *BBF RFC 2: Draft Standard for Biobrick BB-2 Biological Parts*, Nov. 19, 2008, *available at* http://hdl.handle.net/1721.1/45139; Reshma P. Shetty, Drew Endy & Thomas F. Knight, *Engineering BioBrick Vectors from BioBrick Parts*, J. BIOL. ENG. 2:5 (2008); Michael Ellison et al., *BBF RFC 47: BioBytes Assembly Standard*, Oct. 29, 2009, *available at* http://hdl.handle.net/1721.1/49518; Katja Arndt et al., *BBF RFC 25: Fusion Protein (Freiburg) BioBrick Assembly Standard*, Apr. 18, 2009, *available at* http://hdl.handle.net/1721.1/45140; Sergio G. Peisajovich et al., *BBF RFC 28: A Method for Combinatorial Multi-Part Assembly Based on the Type IIs Restriction Enzyme AarI*, Sept. 16, 2009, *available at* http://hdl.handle.net/1721.1/46721; J. Christopher Anderson et al., *BglBricks: A Flexible Standard for Biological Part Assembly*, J. BIOL. ENG. 4:2 (2010); Sean C. Sleight et al., *In-Fusion BioBrick Assembly and Re-engineering*, NUCL. ACIDS RES. 38:8, 2624–36 (2010); Reshma Shetty et al., *Assembly of BioBrick Standard Biological Parts Using Three Antibiotic Assembly*, METHODS ENZYMOL. 498, 311–26 (2011).
[20] *See, e.g.*, Karmella A. Haynes et al., *Engineering Bacteria to Solve the Burnt Pancake Problem*, 2 J. BIOL. ENG. 8 (2008); Bruno Afonso et al., *A Synthetic Circuit for Selectively Arresting Daughter Cells to Create Aging Populations*, 1 NUCL. ACIDS RES. 9, 2727–35 (2010); Raik Grunberg et al., *Building Blocks for Protein Interaction Devices*, 38 NUCL. ACIDS RES. 8, 2645–62 (2010); Hsin-Ho Huang et al., *Design and Characterization of Molecular Tools for a Synthetic Biology Approach towards Developing Cyanobacterial Biotechnology*, 38 NUCL. ACIDS RES. 8, 2577–93 (2010); Marco Constante et al., *A Biobrick Library for Cloning Custom Eukaryotic Plasmids*, 6 PLOS ONE 8, e23685 (2011); Elisabeth Linton et al., *Translocation of Green Fluorescent Protein by Comparative Analysis with Multiple Signal Peptides*, 7 BIOTECHNOL. J. 5, 667–76 (2012); Raul Cuero, J. Lilly & David S. McKay, *Constructed Molecular Sensor to Enhance Metal Detection by Bacterial Ribosomal Switch-Ion Channel Protein Interaction*, 158 J. BIOTECHNOL. 1–2, 1–7 (2012); Liping Du et al., *Multigene Expression In Vivo: Supremacy of Large Versus Small Terminators for T7 RNA Polymerase*, 109 BIOTECHNOL. & BIOENG. 4, 1043–50 (2012).

without the use of restriction enzymes. Methods such as Gibson Assembly™,[21] Seamless Ligation Cloning Extract (SLiCE)[22] and others,[23] enable the seamless construction of large DNA molecules and do not impose sequence constraints on the design of biological parts. Yet another approach, often used in conjunction with other physical assembly methods, is *de novo* DNA synthesis. With continued improvements in the capacity to synthesize DNA constructs at ever more affordable prices, *de novo* synthesis of multicomponent devices and systems may become feasible.[24] So far, no single approach has become a *de facto* standard for the physical assembly of biological parts and physical composition standards will likely continue to evolve.

Functional composition standards support the ability of assembled biological parts to function in a predictable manner. As an example, the Expression Operating Unit (EOU) is a genetic layout architecture that enables forward engineering at the genome scale by ensuring that independent expression elements perform reliably across different genetic contexts.[25] Another tool that has proven particularly useful in the functional composition of biological devices (e.g., genetic circuits) is Polymerase Per Second, or PoPS.[26] PoPS reflects the rate of gene expression and is defined as the number of times that an RNA polymerase molecule passes a specific point on DNA per unit time (e.g., from the 3' end of a promoter part into the 5' end of a downstream part such as a ribosome binding site).[27] Tools that help rationally predict the modulators of gene expression, such as the ribosome binding site (RBS) calculator[28] and calculators for promoter

[21] Daniel G. Gibson et al., *Enzymatic Assembly of DNA Molecules up to Several Hundred Kilobases*, 6 NAT. METHODS 5, 343–5 (2009);
[22] Yongwei Zhang et al., *SLiCE: A Novel Bacterial Cell Extract-Based DNA Cloning Method*, 40 NUCL. ACIDS RES. 8, e55 (2012).
[23] *See e.g.*, Baogong Zhu et al., *In-Fusion Assembly: Seamless Engineering of Multidomain Fusion Proteins, Modular Vectors, and Mutations*, 43 BIOTECHNIQUES 3, 354–9 (2007); Carola Engler et al., *A One Pot, One Step, Precision Cloning Method with High Throughput Capability*, 3 PLOS ONE 11, e3647 (2008); Jiayuan Quan & Jingdong Tian, *Circular Polymerase Extension Cloning of Complex Gene Libraries and Pathways*, 4 PLoS ONE 7, e6441 (2009); Patrick M. Boyle et al., *A BioBrick Compatible Strategy for Genetic Modification of Plants*, 6 J. BIOL. ENG. 8 (provisional) (2012); Arjen J. Jakobi & Eric G. Huizinga, *A Rapid Cloning Method Employing Orthogonal End Protection*, 7 PLOS ONE, 6, e37617 (2012).
[24] Peter A. Carr & George M. Church, *Genome Engineering*, 27 NAT. BIOTECHNOL. 12, 1151–62 (2009).
[25] Vivek K. Mutalik et al., *Precision Gene Expression Via Reliably Reusable Standard Genetic Parts*, (2012) (not yet published).
[26] Prasanna Amur Varadarajan & Domitilla Del Vecchio, *Design and Characterization of a Three-Terminal Transcriptional Device through Polymerase Per Second*, 8 IEEE TRANS. NANOBIOSCIENCE 3, 281–9 (2009).
[27] Drew Endy, Isadora Deese & The MIT Synthetic Biology Working Group, and illustrated by Chuck Wadey, *Adventures in Synthetic Biology*, a comic book available at http://mit.edu/endy/www/scraps/comic/AiSB.vol1.pdf.
[28] Howard M. Salis, Ethan A. Mirsky & Christopher A. Voigt, *Automated Design of Synthetic Ribosome Binding Sites to Control Protein Expression*, 27 NAT. BIOTECHNOL. 10, 946–50 (2009).

strength,[29] also are useful as an approach for the functional composition of assembled biological parts.

Standards for units of measurement enable independent researchers to make measurements of genetically encoded functions that account for variation introduced by differences in experimental conditions and instruments and are sharable across multiple laboratories. As an example, the Relative Promoter Unit (RPU) is a standard unit for reporting promoter activity, where RPU is defined as a ratio of the absolute activity of a sample promoter relative to the absolute activity of a standard reference promoter.[30] Because the RPU is a relative measure, as opposed to an absolute measure, it is not tied to a single measurement procedure and so different laboratories are free to select whatever procedures they find most convenient and suitable. The concept of the RPU was initially demonstrated using promoters in *E. coli*, and has since been extended for promoter characterization in mammalian cells.[31]

Data exchange standards enable researchers to query and retrieve information needed to more efficiently design new biological parts, devices, and systems for synthetic biology applications. As an example, Synthetic Biology Open Language (SBOL) is a software standard for the electronic exchange of specifications and descriptions of genetic parts, devices, modules, systems, and engineered genomes.[32] The SBOL semantic was used to create the Standard Biological Parts Knowledgebase (SBPkb), which has been populated with the 13,000 parts from the Registry of Standard Biological Parts and is anticipated to serve as the first node in a framework for a semantic web of distributed knowledge in synthetic biology.[33] In addition, SBOL visual (SBOLv) has been proposed as a graphical notation standard for the visual display of information about the physical composition of basic and composite parts used in the development of biological devices.[34] Additional standardization efforts for data exchange have focused on the development of datasheets that describe the formal specifications for basic and

[29] Virgil A. Rhodius, Vivek K. Mutalik & Carol A. Gross, *Predicting the strength of UP-elements and full-length E. coli σ^E promoters*, 40 NUCLEIC ACIDS. RES. 2907-24 (2012).
[30] Jason R. Kelly et al., *Measuring the Activity of BioBrick Promoters Using an In Vivo Reference Standard*, 3 J. BIOL. ENG. 4 (2009).
[31] Lars Velten et al., *Units for Promoter Measurement in Mammalian Cells*, BioBrick Foundation Request for Comment 41, Oct. 21, 2009, *available at* http://hdl.handle.net/1721.1/49501.
[32] SBOL Team, *Synthetic Biology Open Language*, *available at* http://www.sbolstandard.org.
[33] Michal Galdzicki et al., *Standard Biological Parts Knowledgebase*, 6 PLOS ONE 2, e17005 (2011).
[34] Cesar Rodriguez et al., *BBF RFC 16: Synthetic Biology Open Language Visual (SBOLv) Specification*, Nov. 01, 2009, *available at* http://hdl.handle.net/1721.1/49523.

composite parts, and example datasheets summarizing the relevant physical characteristics and performance features of biological parts have been proposed.[35]

B. TECHNICAL STANDARDS-SETTING ORGANIZATIONS

As in other engineering disciplines, standards are best developed by consensus and this is no less true in synthetic biology (Table 1). An organizational framework to help define, evaluate and propose technical standards in synthetic biology has been created by the BioBricks Foundation (http://biobricks.org). This framework, known as the BioBrick™ Request for Comments (RFC) process, has been instrumental in facilitating discussion and coordinating the efforts of multiple researchers in technical standards development. Initiated in 2008, the BioBrick™ RFC process was inspired by and modeled upon the RFC process of the Internet Engineering Task Force, and currently contains nearly 90 technical documents.[36] These documents may propose a technical standard, describe best practices or protocols, or simply provide information. As new BioBrick™ RFCs are added, they may comment upon, extend or replace earlier RFCs, and in this way the BioBrick™ RFC process serves as a convenient, useful vehicle for documenting and distributing information so that a general consensus may eventually emerge and lead to the widespread adoption of technical standards.

Technical standards development efforts also have been initiated by the BIOFAB: International Open Facility Advancing Biotechnology (BIOFAB). The concept for creating a BIOFAB was initially proposed in 2006.[37] Drawing upon analogies to the semiconductor industry, the idea was put forth that a fabrication platform using standardized methods and libraries of compatible biological parts could empower engineers to design and build sophisticated biological devices and systems with greater efficiency and speed than is possible using conventional molecular biology approaches. Towards that end, the world's first biological design-build facility was founded in 2009 and located in Emeryville, California (http://biofab.org). Funded by a 2-year grant from the National Science Foundation, the

[35] *See, e.g.*, Barry Canton, Anna Labno & Drew Endy, *Refinement and Standardization of Synthetic Biological Parts and Devices*, 26 NAT. BIOTECHNOL. 787–93 (2008); Taek S. Lee et al., *BglBrick Vectors and Datasheets: A Synthetic Biology Platform for Gene Expression*, 5 J. BIOL. ENG. 12 (2011); Kenneth Evan Thompson et al., *SYNZIP Protein Interaction Toolbox: In Vitro and In Vivo Specifications of Heterospecific Coiled-Coil Interactions Domains*, 1 ACS SYNTH. BIO. 118–29 (2012).
[36] Daniel Tarjan et al., *BBF RFC 0: Instructions to BBF RFC Authors*, Nov. 10, 2008, *available at* http://hdl.handle.net/1721.1/44960.
[37] David Baker et al., *Engineering Life: Building a FAB for Biology*, 294 SCI. AM. 44–51 (2006).

Emeryville BIOFAB was operated in partnership with Lawrence Berkeley National Laboratory, the BioBricks Foundation, and the Synthetic Biology Engineering Research Center (SynBERC).[38] There, the BIOFAB team developed a mathematical framework for quantifying the intrinsic activities of genetic elements and designed a genetic layout architecture to help eliminate the functional uncertainty that arises from the reuse of transcription and translation control elements with sequence-distinct protein coding regions.[39] A second BIOFAB, founded at Stanford University in 2012 and supported by the BioBricks Foundation, aims to map the central dogma of yeast and contribute BioBrick™ parts to the public domain.[40] The goal is to build a network of BIOFABs around the world to create synergy and foster the development of community-driven technical standards and production of standardized biological parts.

Additional efforts in technical standards development have been initiated by the Synthetic Biology Open Language (SBOL) Team. SBOL is an open-specification, open-source project in which a diverse community of individuals from academia, industry and public benefit organizations work collaboratively to create data exchange standards for describing and communicating information about genetic parts, devices, modules, and systems (http://www.sbolstandard.org). Development of the SBOL standard began in 2008 (then in a format known as Provisional BioBrick™ Language, or PoBoL),[41] and this community-based effort has consistently grown in size and sophistication as the SBOL standard continues to evolve to meet the needs of synthetic biology researchers and engineers.[42] The core data model for the SBOL standard supports organization of the essential information for synthetic DNA sequences,[43] and extensions to the core data model support visualization of biological designs and the communication of additional information.[44] The SBOL standard underlies the Standard Biological Parts knowledgebase (SBPkb), which is a semantic web resource that allows

[38] The Emeryville BIOFAB facility maintains a neutral posture with respect to intellectual property rights so that the facility will be able to support partnerships with academic and commercial entities, some of whom might work with the BIOFAB in developing both improved open access and propriety parts. *See* SynBERC Parts on Demand at http://biofab.org/projects (last visited September 1, 2012).
[39] Vivek K. Mutalik et al., *Scalable Estimation of Activity and Quality for Functional Genetic Elements* (2012) (not yet published); Mutalik, *supra* note 23.
[40] *See* Stanford BIOFAB at http://biobricks.org/programs/technical-program (last visited September 1, 2012).
[41] Michal Galdzicki et al., *BBF RFC 31: Provisional BioBrick Language (PoBoL)*, May 15, 2009, *available at* http://hdl.handle.net/1721.1/45537.
[42] Michael Galdzicki et al., *BBF RFC 87: Synthetic Biology Open Language (SBOL) Version 1.1.0.* (2012).
[43] Jean Peccoud et al., *Essential Information for Synthetic DNA Sequences*, 29 NAT. BIOTECHNOL. 1, 22 (2011).
[44] Rodriguez, *supra* note 34; Jeffrey Johnson et al., *BBF RFC 68: Standard for the Electronic Distribution of SBOLv Diagrams*, Dec. 05, 2010, *available at* http://hdl.handle.net/1721.1/60086.

researchers to query and retrieve information about biological parts from the Registry of Standard Biological Parts.[45] In addition, several SBOL-compliant software tools have been developed for synthetic biology (Table 2).[46]

Synthetic biology standards also have been addressed by the Synthetic Biology Standards Network (SynBioStandards Network), an interdisciplinary network for UK academics working in synthetic biology. The SynBioStandards Network was funded for three years from June 2008 by the Arts & Humanities Research Council, the Biotechnology and Biological Sciences Research Council, Economic & Social Research Council, and the Engineering and Physical Sciences Research Council (http://www.synbiostandards.co.uk). Though it does not consider itself to be a standards setting organization, the SynBioNetwork aims to develop a common language among researchers from the fields of engineering, biological sciences, computer science and the social sciences and to develop approaches, tools and protocols that may become gold standard and adopted by synthetic biology researchers worldwide.

Standards setting efforts have been prominent throughout the development of synthetic biology, at least in part due to participation in the field by engineers, computer scientists, and others who are familiar and comfortable with technical standards. One worry has been that imposition of standards too early in the evolution of synthetic biology might canalize the trajectory of the field, discouraging alternative directions and impeding innovation. However, little evidence exists to support this worry. None of the technical standards proposed thus far have been made mandatory for the field as a whole, and no governance body with the authority to impose mandatory technical standards for synthetic biology has yet been established. In fact, even the most promising technical standards seem to have served in a transitory capacity given the speed at which scientific and technical advances in synthetic biology occur. For example, a number of proposed technical standards pertaining to the physical assembly of DNA fragments into larger DNA molecules are being displaced by distinctly different methods, such as Gibson Assembly™ and *de novo* DNA synthesis. The iterative and progressive nature of technical standards development has been embraced by the synthetic biology research community, as

[45] Galdzicki, *supra* note 33.
[46] A vast array of software tools have been developed for synthetic biology, some of which are SBOL-compliant. For recent review see Adrian L. Slusarczyk, Allen Lin & Ron Weiss, *Foundations for the design and implementation of synthetic genetic circuits*, 13 NATURE 406-20 (2012).

evidenced by the BBF RFC process, which provides an avenue for the improvement, and even outright replacement, of earlier proposed technical standards. Only in the realm of biosecurity has any standard risen to the level of wide acceptance within the synthetic biology community, and there the primary proponent of the standard adopted was the U.S. federal government. At the present time, standards setting efforts do not appear to have affected the development of synthetic biology adversely.

Table 1. Standard Setting Organizations and Intellectual Property Policies in Synthetic Biology

Standards Setting Organization	Year started	Example Technical Standards	Intellectual Property Policy
BioBrick Request For Comments (RFC) process	2006	**Physical Composition:** BioBrick standard (BBF RFC 10) BglBrick standard (BBF RFC 21) BioFusion standard (BBF RFC 23) Freiburg standard (BBF RFC 25) AarI cloning standard (BBF RFC 28) **Units of Measure:** Relative Promoter Unit (RPU) (BBF RFC 19) Relative Mammalian Promoter Unit (RMPU) (BBF RFC 41)	The BioBricks Foundation advocates open technology platforms and technical standards, and encourages the donation of basic bioengineering knowledge into the public domain. The BioBricks Foundation does not hold any patents relating to technical standards and retains copyright to documents filed in the RFC process.
Synthetic Biology Open Language (SBOL) Team	2008	**Data Exchange:** Standard Biological Parts Knowledgebase (SBPkb) SBOL visual (SBOLv)	SBOL is an open-specification, open-source, community-based project. SBOL has been submitted to the BioBrick RFC process (BBF RFC 87) as a software standard for the electronic exchange of specifications and descriptions of genetic parts, devices, modules, systems, and engineered genomes.
BIOFAB: International Open Facility Advancing Biotechnology (BIOFAB)	2009	**Functional Composition:** Expression Operating Unit (EOU)	The Emeryville BIOFAB facility maintains a neutral posture with respect to intellectual property rights so that the facility will be able to support partnerships with academic and commercial entities. The Stanford BIOFAB aims to contribute BioBrick™ parts to the public domain.

Table 2. SBOL-compliant Software Tools for Synthetic Biology

Software Tool	Description	URL	Reference
ClothoCAD	A data model-based tool and plugin environment that provides a data model for representing biological objects, a common API for manipulating these objects, and a common platform for developing Apps for designing synthetic biological systems.	http://www.clothocad.org	Xia et al. (2011)[47]
DeviceEditor	A web-based visual design environment that mimics the intuitive visual whiteboard design process practiced in biological laboratories.	http://j5.jbei.org	Chen et al. (2012)[48]
Eugene	A human- and machine-readable language for the specification of biological constructs.	http://eugenecad.org	Bilitichenko et al. (2011)[49]
GD-ICE	An open source registry platform for managing information about biological parts.	http://code.google.com/p/gd-ice/	Ham et al. (2012)[50]
GenoCAD	A web-based application to design protein expression vectors, artificial gene network, and other genetic constructs	http://genocad.org	Czar et al. (2009)[51]
iBioSim	A project-based tool for the analysis of genetic circuits, metabolic networks, cell signaling pathways and other biological and chemical systems.	http://www.async.ece.uth.edu/iBioSim	Myers et al. (2009)[52]
SBPkb	A semantic web resource that allows researchers to query and retrieve standard biological parts for research and use in synthetic biology.	http://www.sbolstandard.org/sbol-in-use/sbpkb	Galdzicki et al. (2011)[53]
TinkerCell	An application for bringing together models, information and algorithms.	http://www.tinkercell.com	Chandran et al. (2009)[54]

[47] Bing Xia et al., *Developer's and User's Guide to Clotho v2.0: A software platform for the creation of synthetic biological systems.* 498 METH. ENZYMOL. 97-135 (2011).
[48] Joanna Chen et al. *DeviceEditor visual biological CAD canvas,* J. BIOL. ENG. 6:1 (2012).
[49] Lesia Bilitchenko et al., *Eugene – A domain specific language for specifying and constraining synthetic biological parts, devices, and systems.* 6 PLOS ONE e18882 (2011).
[50] Timothy S. Ham et al., *Design, implementation and practice of JBEI-ICE: an open source biological part registry platform and tools,* NUCLEIC ACIDS RES. 1-8 (2012).
[51] Michael J. Czar, Yizhi Cai & Jean Peccoud, *Writing DNA with GenoCAD™*, 37 NUCLEIC ACIDS RES. W40-47 (2009).
[52] Chris J. Myers et al., *iBioSim: a tool for the analysis and design of genetic circuits,* 25 BIOINFORMATICS 2848-9 (2009).
[53] Galdzicki, *supra* note 33.
[54] Deepak Chandran, Frank T. Bergmann & Herbert M. Sauro, *TinkerCell: modular CAD tool for synthetic biology,* J. BIOL. ENG. 3:19 (2009).

C. BIOSECURITY STANDARDS SETTING

The development and implementation of standards for biosecurity has been of paramount importance in the field of synthetic biology. As in other fields, research in synthetic biology may generate "dual use" findings that could be socially beneficial (e.g., new therapies, diagnostic methods, crops, industrial processes) as well as harmful (e.g., new pathogens, toxins, biological weapons). Consequently, an early topic of discussion and planning among the synthetic biology community was how to minimize the risk of harmful applications of the technology. As early as 2005, researchers, policy analysts and security experts in universities, research institutions, commercial firms, and government organizations have worked to develop biosecurity standards for synthetic biology (Table 3).

At the first Synthetic Biology conference ("SB 1.0"), in 2005, there was some discussion of biosecurity issues among the synthetic biology community. Leading up to, and during, SB 2.0, in 2006, a discussion about biosecurity led to a formal proposal that synthetic biologists adopt a set of community biosecurity standards. With funding from the Carnegie Corporation Foundation and MacArthur Foundation, Stephen Maurer, Director of the Berkeley Information Technology and Homeland Security Project, led a project that proposed six resolutions related to promoting an ethic of biosecurity.[55] Another effort, funded by the Alfred P. Sloan Foundation, resulted in the development of a number of policy, technical, and other options to address the risks and benefits posed by dual-use nature of synthetic biology research.[56]

In the wake of SB 2.0, two consortia of DNA synthesis companies developed their own standards for detecting orders for DNA sequences of concern. The International Consortium for Polynucleotide Synthesis ("ICPS") developed a plan for creating an effective oversight framework for the DNA synthesis industry.[57] A rival German effort, led by the International Association of Synthetic Biology ("IASB"), developed a code of conduct for assessing the safety of DNA sequence orders that would rely on both (1) automated searches for matches with sequences of concern (e.g., the U.S. list of sequences of concern) and (2) human double-

[55] Stephen M. Maurer, *End of the Beginning or Beginning of the End? Synthetic Biology's Stalled Security Agenda and the Prospects for Restarting It*, 45 VAL. U. L. REV. 1387 (2011).
[56] Michele S. Garfinkel et al. *Synthetic Genomics: Options for Governance*, 5 BIOSECUR. BIOTERROR. 359-62 (2007).
[57] Hans Bügl et al., *DNA synthesis and biological security*, 25 NAT. BIOTECHNOL. 627-30 (2007).

checking.[58] In addition, the U.S. Department of Health and Human Services ("HHS") issued guidance aimed at reducing the risk that synthetic DNA will be misused deliberately to create dangerous organisms.[59] Efforts to articulate and refine biosecurity standards for dual-use research in synthetic biology and other life science fields are ongoing.[60]

Table 3. Biosecurity Standards in Synthetic Biology

Standards Setting Organization	Year started	Biosecurity Standards
The International Consortium for Polynucleotide Synthesis (ICPS)	2007	The ICPS developed a plan for creating an effective oversight framework for the DNA synthesis industry.
International Association of Synthetic Biology (IASB)	2008	The IASB established a code of conduct for best practices in gene synthesis, which is primarily based on a self-policed system among gene synthesis and assembly firms.
U.S. Department of Health and Human Services (HHS)	2010	The HHS recommendations include screening customers as well as DNA sequences, follow-up screening as necessary, and consulting with U.S. government contacts as needed.

D. LEGAL STANDARDS SETTING

The development of legal standards to enable synthetic biology researchers to use and share biological parts was first proposed by Drew Endy in 2005.[61] Over several years beginning late in 2008, the BioBrick Foundation developed two legal agreements designed to standardize the use and contribution of standardized biological BioBrick™ parts.[62] The BioBrick™ User Agreement is designed to oblige signors to abide by a set of rules for using BioBrick™ parts responsibly. The BioBrick™ Public Agreement is designed to govern the responsible contribution of BioBrick™ parts to the Registry. The agreements purport to impose a legal standard on users or contributors BioBrick™ parts, and include provisions on attribution, safety, and intellectual property rights. Of special note, contributors who sign the BioBrick™ Public

[58] International Association Synthetic Biology, *The IASB Code of Conduct for Best Practices in Gene Synthesis,* Cambridge, MA, November 3, 2009, available at http://www.ia-sb.eu/tasks/sites/synthetic-biology/assets/File/pdf/iasb_code_of_conduct_final.pdf (last visited September 1, 2012).
[59] U.S. Department of Health and Human Services, *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA,* October 13, 2010, available at http://www.phe.gov/syndna (last visited September 1, 2012).
[60] *See e.g.,* National Science Advisory Board on Biosecurity (NSABB), *Enhancing responsible science: Considerations for the development and dissemination of codes of conduct for dual use research,* available at http://oba.od.nih.gov/oba/biosecurity/documents/COMBINED_Codes_PDFs.pdf (last visited September 1, 2012).
[61] Endy, *supra* note 6, at 450 (stating "…legal standards are needed to define means by which large collections of parts encoding basic biological functions, from a myriad of sources, can be easily shared and used in combination to realize many applications.")
[62] https://biobricks.org/bpa/

Agreement promise not to assert any patents they possess to any parts they contribute under the contract.

IV. INTELLECTUAL PROPERTY AND SYNTHETIC BIOLOGY STANDARDS

Four principle types of intellectual property protection are relevant to the protection of synthetic biology inventions: (1) patent, (2) trade secrecy, (3) copyright, and (4) trademark. Thus far, only patent and trade secrecy have played substantial roles in protecting such inventions, though both copyright and trademark have been suggested.[63] The subject matter protectable by patent or trade secrecy is broad, spanning such innovations as new DNA, RNA, and polypeptide molecules, genomes, cells, and organisms, and myriad methods of using them either singly or in combination. Because trade secrets are, by their very nature, difficult to catalogue, discussion here focuses on patents. Patent protection for DNA molecules, such as those deposited into the Registry, will serve as an additional focus, though the patent law principles discussed are applicable to other products and methods of synthetic biology.

A. PATENT

The United States Patent and Trademark Office ("USPTO") has granted patents claiming isolated or purified DNA molecules since at least the 1970s.[64] The 1990s race to sequence the entire human genome precipitated a flood of patent applications (many later maturing into patents) claiming human DNA that peaked around 2000.[65] Patenting DNA has been criticized as unethical[66] and for causing a genetic "tragedy of the anticommons."[67] By one account, roughly 20% of known human genes are claimed in a U.S. patent.[68] Although a recent empirical study

[63] Andrew W. Torrance, *Synthesizing Law for Synthetic Biology*, 11 Minn. J. L. Sci. & Tech. 2, 629–665 (2010).
[64] Andrew W. Torrance, *Gene Concepts, Gene Talk, and Gene Patents*, 11 MINN. J. L. SCI. & TECH. 2, 157–191 (2010).
[65] *Id*.
[66] Tom Hollon, *NIH Researchers Receive Cut-Price BRCA Test*, 6 NAT. MED. 6, 610 (2000).
[67] Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCIENCE 5364, 698–701 (1998).
[68] Kyle Jensen & Fiona Murray, *Intellectual Property Landscape of the Human Genome*, SCIENCE 310:5746, 239–40 (2005).

has brought this estimate into question,[69] if such assessments are even somewhat accurate, synthetic biologists may be at substantial risk of infringing prodigious numbers of patent claims to DNA sequences. As such, existing patent rights may encumber the products and methods of synthetic biology.

Since at least 2005, uncertainty has been rising about whether or not isolated or purified natural-source DNA constitutes legitimate patentable subject matter. In 2005, a Court of Appeals for the Federal Circuit ("CAFC") panel held that a set of patent claims expressed sequence tags ("ESTs") lacked utility and enablement, casting doubt on the patentability of partial-gene DNA sequences. In 2007, Xavier Becerra (Democrat Congressman from California) and Dave Weldon (Republican Congressman from Florida) unsuccessfully championed passage of the *Genomic Research and Accessibility Act*. Section 106 of this Act would have barred genes from patent eligibility, stipulating that "[n]otwithstanding any other provision of law, no patent may be obtained for a nucleotide sequence, or its functions or correlations, or the naturally occurring products it specifies." Although this proposal has never been passed by the U.S. Congress, Section 33 of the America Invents Act ("AIA") of 2011 did amend U.S. patent law to ban the patentability of any invention "directed to or encompassing a human organism." Lacking legislative history, court interpretation, and formal incorporation into the U.S. Code, it is as yet unclear what legal influence Section 33 may have on the patentability of human DNA sequences.

Most relevant to synthetic biology is an ongoing litigation initiated in 2009 by the American Civil Liberties Union ("ACLU") and its allies against the biotechnology firm Myriad Genetics ("Myriad") and the USPTO.[70] Myriad owns rights to several patents claiming, among other inventions, human BRCA1 and BRCA2 gene variants predictive of breast and ovarian cancer. In its initial complaint in this action for declaratory judgment, the ACLU stated its opposition to the patent-eligibility of human genes, and challenged "the legality and constitutionality of granting patents over this most basic element of every person's individuality." In October 2010, Judge Sweet, of the Southern District of New York, decided that genes "containing sequences found in nature … are deemed unpatentable subject matter."

[69] Christopher M. Holman, *Debunking the myth that whole-genome sequencing infringes thousands of gene patents,* 30 NAT. BIOTECHNOL. 240-4 (2012).
[70] Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office, 669 F. Supp. 2d 365 (S.D.N.Y. 2009).

Myriad appealed the decision to the CAFC. On July 29, 2011, a panel of three judges largely reversed the lower court, and restored the patentability of DNA.

In response, the ACLU filed a petition for a writ of *certiorari* to the U.S. Supreme Court, which vacated the CAFC decision on March 26, 2012, and instructed that court to reconsider the patentability issues in light of *Mayo v. Prometheus*, a patentability decision the Court had made a week before.[71] The patent claims at issue in *Mayo v. Prometheus* were directed to methods of diagnosis using human metabolites, not to DNA molecules *per se*. However, the Supreme Court clearly signaled its discontent with the CAFC panel decision. On August 16, 2012, the same panel of CAFC judges broadly reaffirmed their earlier panel decision, again upholding the patent-eligibility of isolated DNA.[72]

The Supreme Court order vacating the first CAFC panel decision may suggest skepticism by that court that isolated DNA should be considered patentable subject matter. The CAFC may decide to reconsider the latest panel decision itself by rehearing the case *en banc*. In addition, there is substantial likelihood that the Supreme Court would eventually grant *certiorari* to decide this case itself. If so, the logic of *Mayo v. Prometheus* may render some types of DNA molecules ineligible patent subject matter.

Most existing patents directed to DNA claim nucleotide sequences identical or similar to those derived from naturally occurring genomes. Cost, speed, and accuracy improvements in DNA synthesis technology have increasingly facilitated the design and production of synthetic DNA of any nucleotide sequence. Even if legal trends in patentable subject matter were to render natural-source DNA unpatentable, human-designed synthetic DNA is likely to remain patent-eligible. In an *amicus curiae* brief filed before the first CAFC panel decision, the U.S. Department of Justice argued that "isolated but otherwise unaltered genomic DNA is not patent-eligible subject matter under 35 U.S.C. §101,"[73] but that DNA molecules that are "the synthetic results of scientists' manipulation of the natural laws of genetics" could be patent-eligible.[74]

[71] Mayo Collaborative Servs. V. Prometheus Labs., Inc., 132 S. Ct. 1289 (2012).
[72] Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office, 2010 U.S. App. LEXIS 17077 (Fed. Cir. 2010).
[73] U.S. Department of Justice amicus brief, page 18.
[74] *Id.*, page 15.

Currently, there is considerable uncertainty about the patentability of DNA molecules. This uncertainty may be resolved by the CAFC or Supreme Court within the next few years. In the meantime, there remains substantial risk that synthetic DNA molecules, such as BioBrick™ parts, could infringe patent rights. Moreover, barring the improbability of an extreme legal rule excluding all DNA from patent-eligibility, there is a strong prospect that human-designed synthetic DNA will remain patentable.

B. TRADE SECRECY

Many owners choose to keep the details, or even the very existence, of their intellectual property secret. Some information is difficult to protect by trade secrecy, particularly products or services whose intellectual property is self-disclosing. For example, it would be difficult to maintain secrecy about the nucleotide sequence of a synthetic DNA construct due to the ease of reverse engineering that construct using routine DNA sequencing methods followed by DNA synthesis. By contrast, trade secrets inherent in a protein product whose desired functioning depended on a particular folding pattern would be easier to preserve due to the great difficulty in reverse engineering tertiary and quaternary structure.[75] By the very nature of this form of intellectual property protection, little is known about the extent of reliance on trade secrecy across industries or technological fields, in general, or in synthetic biology, in particular.

In a confluence of patent and trade secrecy law, §273 of the AIA added a defense to patent infringement for prior commercial use of an invention claimed in a patent not owned by a university. This defense is available only for commercial uses (§273(a)), though the patent statute defines such uses to include premarketing regulatory review (§273(c)(1)) and nonprofit laboratory uses (§273(c)(2)). Since this amendment to U.S. patent law has yet to be interpreted by the courts, it is unclear how it might affect patents and trade secrets in the field of synthetic biology. Nevertheless, it appears to place a modest limit on how patent rights may affect long-standing commercial and research uses of synthetic biological products and processes.

[75] The Biologics Price Competition and Innovation Act of 2009, passed as part of the Patient Protection and Affordable Care Act of 2010, allows the developer of a biologic to maintain regulatory data exclusivity for at least 12 years after the biologic is licensed by the FDA. Specifically, 42 U.S.C. §262 grants biologics developers a new form of data-based exclusive rights in exchange for potential loss of patent term caused by entry into the market of generic biologics competitors.

C. COPYRIGHT

Copyright protection is relevant to standards development in synthetic biology in several respects. The documents created to describe technical standards, such as those of the BioBrick™ RFC process, are subject to copyright protection. Software tools developed for synthetic biology applications, including the SBOL standard, also are subject to copyright protection. A third way in which copyright protection may be relevant to standards development in synthetic biology is the potential for copyright protection of DNA sequences.

Copyright eligibility for DNA sequences has been discussed for many years.[76] Though not all scholars agree, the case has been made that synthetic DNA sequences may be especially strong candidates for copyright protection, in part because the deliberate design of nucleotide sequences allows considerable scope for creative expression. For example, when Synthetic Genomics synthesized the first mycoplasma genome, it included several decipherable sentences among within the genome.[77] At least one firm has already asserted copyright protection for synthetic DNA sequences,[78] although to date there has been no litigation.

Copyright affords legal protection against unauthorized copying for "original works of authorship fixed in any tangible medium of expression, now known or later developed".[79] In addition to conventional targets for protection, such as books and paintings, copyright law has proved capable of adapting to cover additional forms of creative expression like architecture and computer software. Like patent protection, copyright protection for DNA sequences originating in naturally occurring genomes is least justifiable. The case for copyright protection would likely strengthen as a DNA sequence of interest acquired more characteristics of human design and synthetic production. Of course, the case for copyright protection would be far weaker for

[76] Duncan M. Davidson, *Common Law, Uncommon Software*, 47 U. PITT. L. REV. 1037, 1104–05 (1986); Irving Kayton, *Copyright in Living Genetically Engineered Works*, 50 GEO. WASH. L. REV. 191 (1982); Donna Smith, Comment, *Copyright Protection for the Intellectual Property Rights to Recombinant Deoxyribonucleic Acid: A Proposal*, 19 ST. MARY'S L.J. 1083, 1096–1108 (1988); Dan L. Burk, *Copyrightability of Recombinant DNA Sequences*, 29 JURIMETRICS J. 469, 531–32 (1988–89); Andrew W. Torrance, *DNA Copyright*, 46 VAL. U. L. REV. 1, 1-46 (2011); Christopher M. Holman, *Copyright for Engineered DNA: An Idea Whose Time Has Come?*113 WEST VIRGINIA LAW REVIEW 699-738 (2011).

[77] Daniel G. Gibson et al., *One-Step Assembly in Yeast of 25 Overlapping DNA Fragments to Form a Complete Synthetic Mycoplasma genitalium Genome*, 105 PNAS 51, 20404–9 (2008).

[78] Illumina, Inc., asserts copyright protection for some of the oligonucleotide primers compatible with its DNA sequencing machines in a letter it has sent to customers: http://www.bioinfo.uh.edu/IMDSC/Release_of_Oligo_Sequences_Letter_for_Customers1.pdf..

[79] 17 U.S.C. §102 (2012).

DNA sequences designed using directed evolution approaches since DNA sequences would evolve as a consequence of natural selective processes, and not as a result of DNA sequence design by human authors.

Copyright eligibility for DNA sequences, were it available, would create a much quicker and cheaper route to protection than does patent protection, and the resulting protection could last almost an order of magnitude longer. On the other hand, doctrines such as fair use could permit more uses by others - especially for purposes of scholarship or education - of copyrighted DNA sequences than does patent protection, and a DNA copyright framework might allow the application of open source principles to synthetic biology.[80] If many or all DNA molecules lose their eligibility for patent protection as the law of patentable subject matter evolves, copyright could provide a ready alternative for protection. Nevertheless, copyright eligibility for DNA remains uncertain and untested.

D. TRADEMARK

Trademark protection may be available for a mark that indicates a single origin for goods or services bearing that mark. Trademark law imposes few restrictions on eligible subject matter, as long as the mark achieves its purpose as an indicator of origin, and customer confusion is avoided. Even synthetic DNA sequences might qualify as trademarks if they were used in commerce, and served as designations of origin for products or services.

The BBF has registered "BioBrick" as a U.S. trademark.[81] Currently, the BBF may use this trademark as a mild form of leverage to support its standards. In relevant part, §3(a) of the BioBrick™ User Agreement requires that "User agrees not to remove or alter any BioBrick™ identification tag…included in the Materials…" The BioBrick™ Contributor Agreement defines this aspect of the "Materials" in its preamble as "the particular standardized genetic material(s)…and any associated sequence…information," and §2 of the Contributor Agreement requires contributors to allow the addition of a "BioBrick™ identification tag" to any genetic

[80] Note that, as with open source software code, coexistent patent rights could still create risks of infringement for making, using, selling, offering to sell, or importing synthetic DNA sequences.

[81] "BioBrick" is a registered trademark of the BioBricks Foundation under U.S. registration #3836261. It is registered in international classes 41 and 42. Its description in class 42 is "Research and development services in the fields of biology and biological engineering; providing information in the fields of biology and biological engineering."

material they contribute. If desired, the BioBricks Foundation could assert its trademark rights more vigorously to promote its BioBrick-related standards by restricting the descriptor "BioBrick" to only those DNA molecules fully conforming to specified standards.

E. SYNTHETIC BIOLOGY, BIOTECHNOLOGY, AND INTELLECTUAL PROPERTY

Many of the intellectual property issues that arise in specific context of synthetic biology also pertain to the broader field of biotechnology. However, synthetic biology differs in its reliance on approaches from engineering and computer science, including an emphasis on standards. Due to their unique features, some synthetic biological inventions may be eligible not only for patent protection, but also for copyright, and even trademark, protection. Innovations in synthetic biology may become subject to complicated policy debates about which forms of intellectual property protection are most appropriate, just as innovations in software were a generation ago.[82] As such, it is important to address the potential confusion surrounding intellectual property issues in synthetic biology, particularly with regards to standards setting initiatives, in order to avoid the prolonged uncertainty that could undermine the necessary commercial investment for bringing useful synthetic biology applications to market.

V. CONCLUSIONS

There has been considerable discussion and activity surrounding standards setting in synthetic biology. This may be due, in part, to the interdisciplinary backgrounds of many of the field's leading participants. A number of institutions within synthetic biology have made standards setting a priority, and many standards have been proposed, including those pertaining to the structure, function, and description of genetic components, data sharing, biosecurity, and law. Despite this interest in standards, progress in standards setting has been quite modest so far. Standards for physical assembly of DNA fragments are continuing to evolve, and methods such as Gibson Assembly™ and *de novo* DNA synthesis are gaining acceptance as alternate approaches for the construction of large DNA molecules. Moreover, standards for other technical aspects of synthetic biology have begun to emerge, including functional composition standards

[82] Arti Rai and James Boyle, *Synthetic Biology: Caught between Property Rights, the Public Domain, and the Commons*, 5 PLOS 3, 389-393 (2007).

that support the ability of assembled biological parts to function in a predictable manner, standards for units of measurement, and data exchange standards. At the present time, standardization efforts do not appear to have impeded innovation in synthetic biology and no single technical standard appears to have dominated the field of synthetic biology. By comparison, standards covering policies in biosecurity appear to be better established, and a U.S. government-proposed biosecurity guidance governing commercial orders for synthetic DNA has been widely adopted.

Patent rights that encumber components and methods have long been a concern among those in synthetic biology, especially as a perceived threat to the field's prominent ethos of open biological innovation. Currently, there is little evidence that patent rights adversely affect synthetic biological research. In fact, the patent-eligibility of DNA molecules has been put in doubt by several conflicting U.S. court decisions, and the new AIA has created a new defense of prior commercial use that offers some protection from patent infringement for some uses of synthetic biological products and processes. Copyright and trademark may provide alternatives mechanisms for conferring rights in synthetic biological inventions, setting and reinforcing standards, or promoting open innovation. Among the standards-setting groups that have formed within the synthetic biology community, most have expressed a preference that standards remain open and accessible to the community as a whole. This preference, however, has not yet been incorporated into formal policies requiring the disclosure and licensing of intellectual property rights covering technical standards. Whether such policies could be made mandatory or would ultimately be beneficial to the field of synthetic biology remain open questions. What is certain is that the synthetic biology community is unusually attuned to debates surrounding intellectual property and standards setting, and views its engagement in these debates as vital to ensure the continued success of synthetic biology.