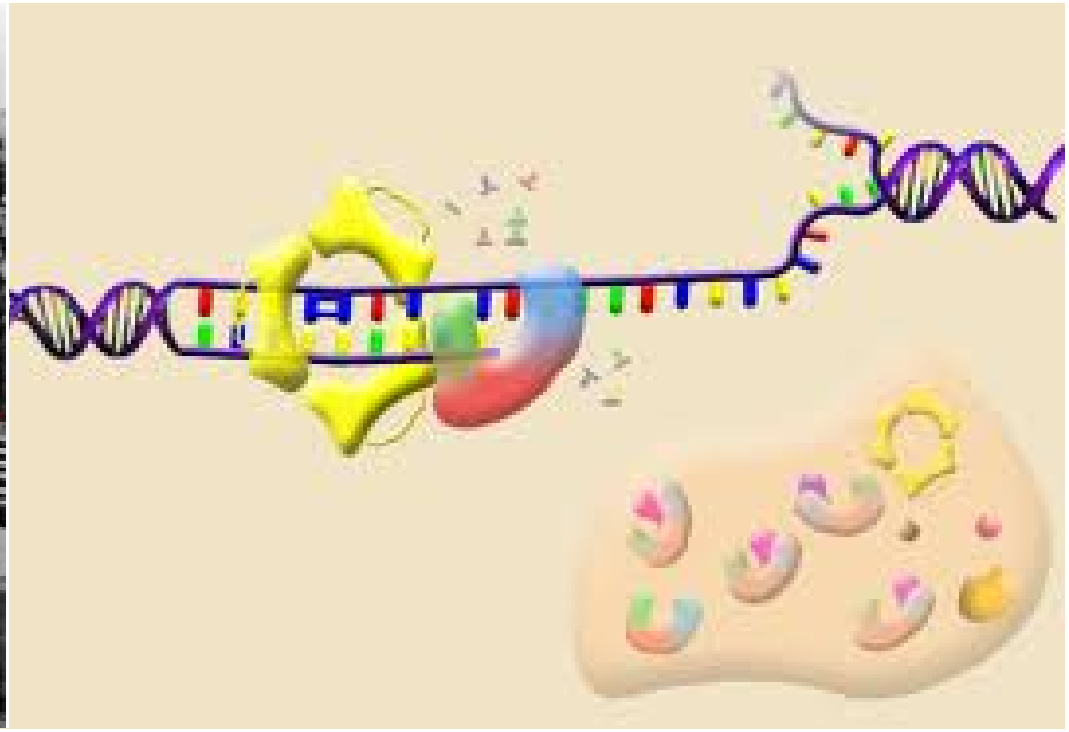
SYNTHETIC BIOLOGY

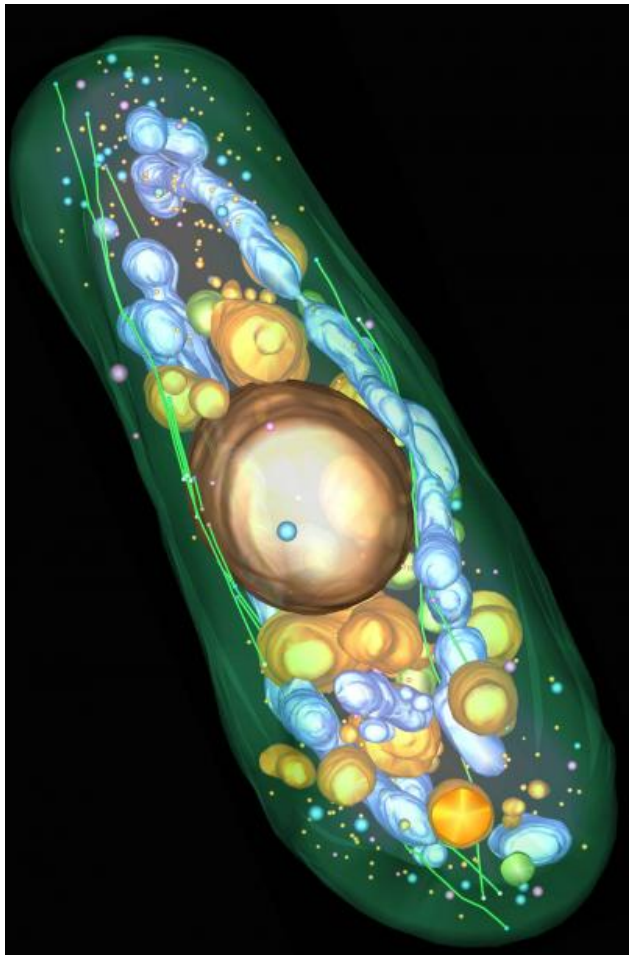
STANDARDS SETTING AND INTELLECTUAL PROPERTY

ANDREW W. TORRANCE (MIT & KU)
LINDA KAHL (STANFORD & SYNBERC)



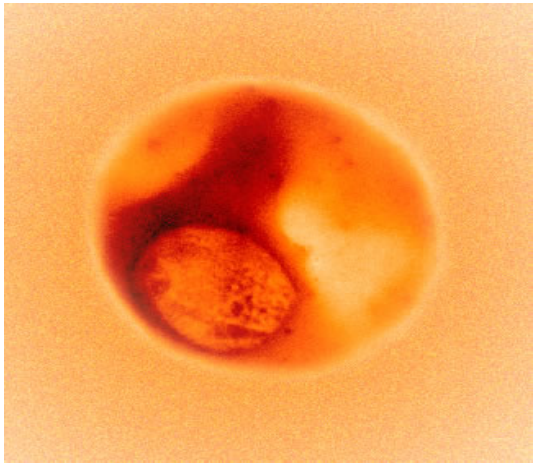
SYNTHETIC BIOLOGY

- Synthetic biology
  - The redesign and fabrication of existing biological components and systems
  - The *de novo* design and fabrication of biological components and systems that do not already exist in the natural world



NOTABLE SUCCESSES

- Artemisinin (2006)
  - Synthetic production of a precursor of artemisinin, a chemical with therapeutic effect against the malarial parasite (Keasling *et al.*)
- Synthetic genome (2010)
  - Entire genome of *Mycoplasma genitalium* ("laboratorium") synthesized, inserted into empty *Mycoplasma* plasma membrane, and then "booted up"
    - Also "booted up" the Presidential Commission for the Study of Bioethical Issues to study synthetic biology in its first report for President Obama
- Data storage (2012)
  - George Church encoded an entire book (*Regenesis: How Synthetic Biology Will Reinvent Nature and Ourselves in DNA*) in DNA (5.3Mb)

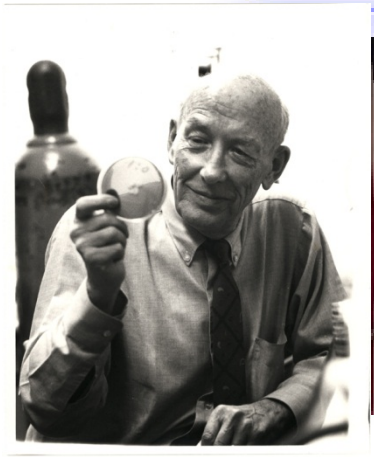


OUTLINE

- Synthetic biology
  - Milestones
  - Distinctive characteristics
  - Standards
  - Institutions
  - Successes
- Standards in synthetic biology
  - Technical standards
  - Biosecurity standards
  - Legal standards
- Intellectual property
  - Trade secrecy, copyright, and trademark
  - Patent
    - *Chakrabarty*
    - *Myriad*
    - *Prometheus*
- Conclusions

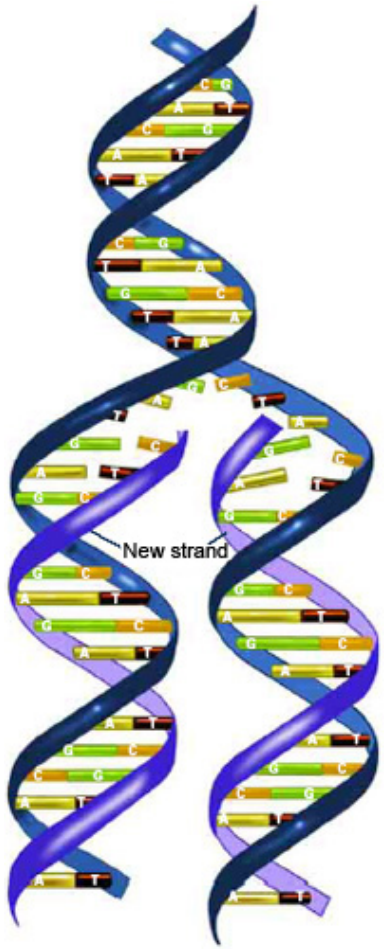
MILESTONES

- "Biological engineering"
  - 1963
    - Coined by Edward L. Tatum in his Nobel Prize speech
- Recombinant DNA
  - 1973
    - Cohen and Boyer constructed an rDNA organism
- DNA sequencing
  - 2000/2003
    - Complete human genome
- DNA synthesis
  - 2008
    - *Mycoplasma genitalium* genome synthesized and "booted up"



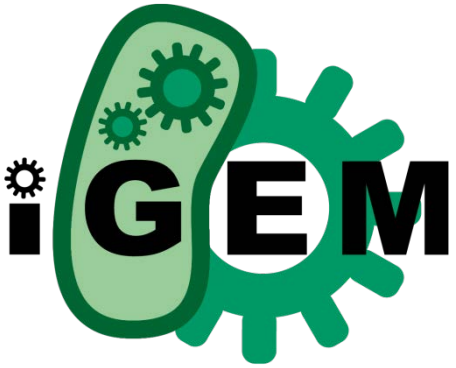
DISTINCTIVE CHARACTERISTICS

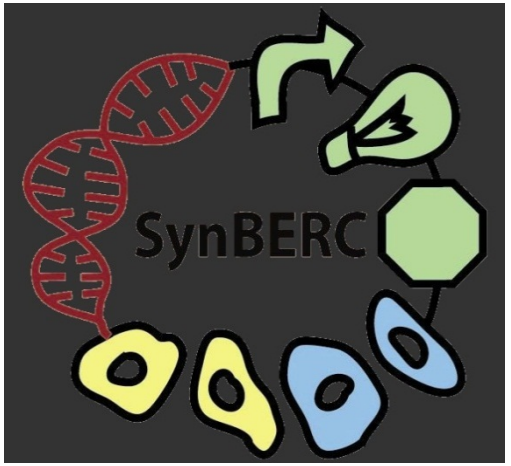
- Goals
  - Synthesis of large DNA molecules of specified nucleotide sequence
  - Design and implementation of genetic circuits constructed from basic genetic components
- Notable feature
  - Conscious reliance on engineering approaches
    - *E.g.*, standardization, decoupling, and abstraction (Endy 2005)
  - Engineers and computer scientists are prominent among the field's leaders



INSTITUTIONS

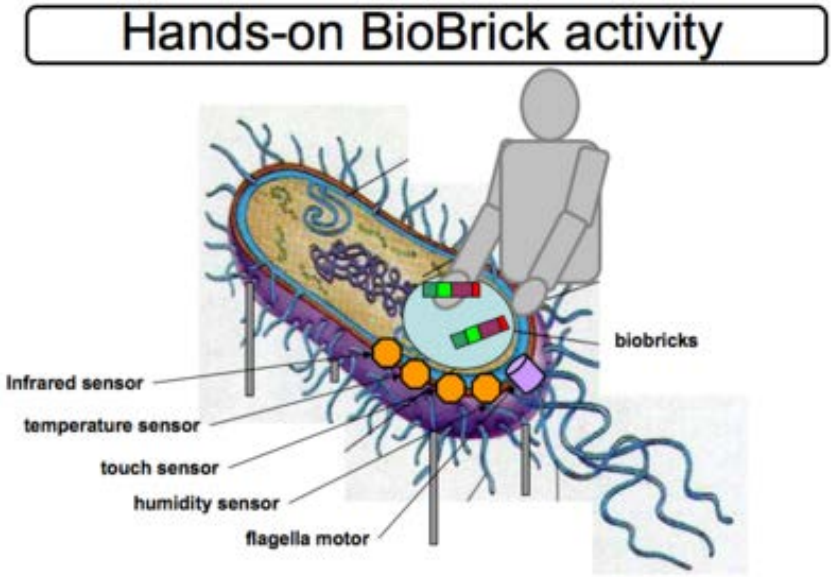
- The BioBricks Foundation ("BBF")
- The International Genetically Engineered Machine Foundation ("iGEM")
- The Registry of Standard Biological Parts ("Registry")
- The Synthetic Biology Engineering Research Center ("SynBERC"), BIOFAB:
- International Open Facility Advancing Biotechnology ("BIOFAB")
- 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")
- The International Consortium for Polynucleotide Synthesis ("ICPS")
- U.S. Department of Health and Human Services ("HHS")
- Do-It-Yourself Biology ("DIYbio")





THE BIOBRICKS FOUNDATION

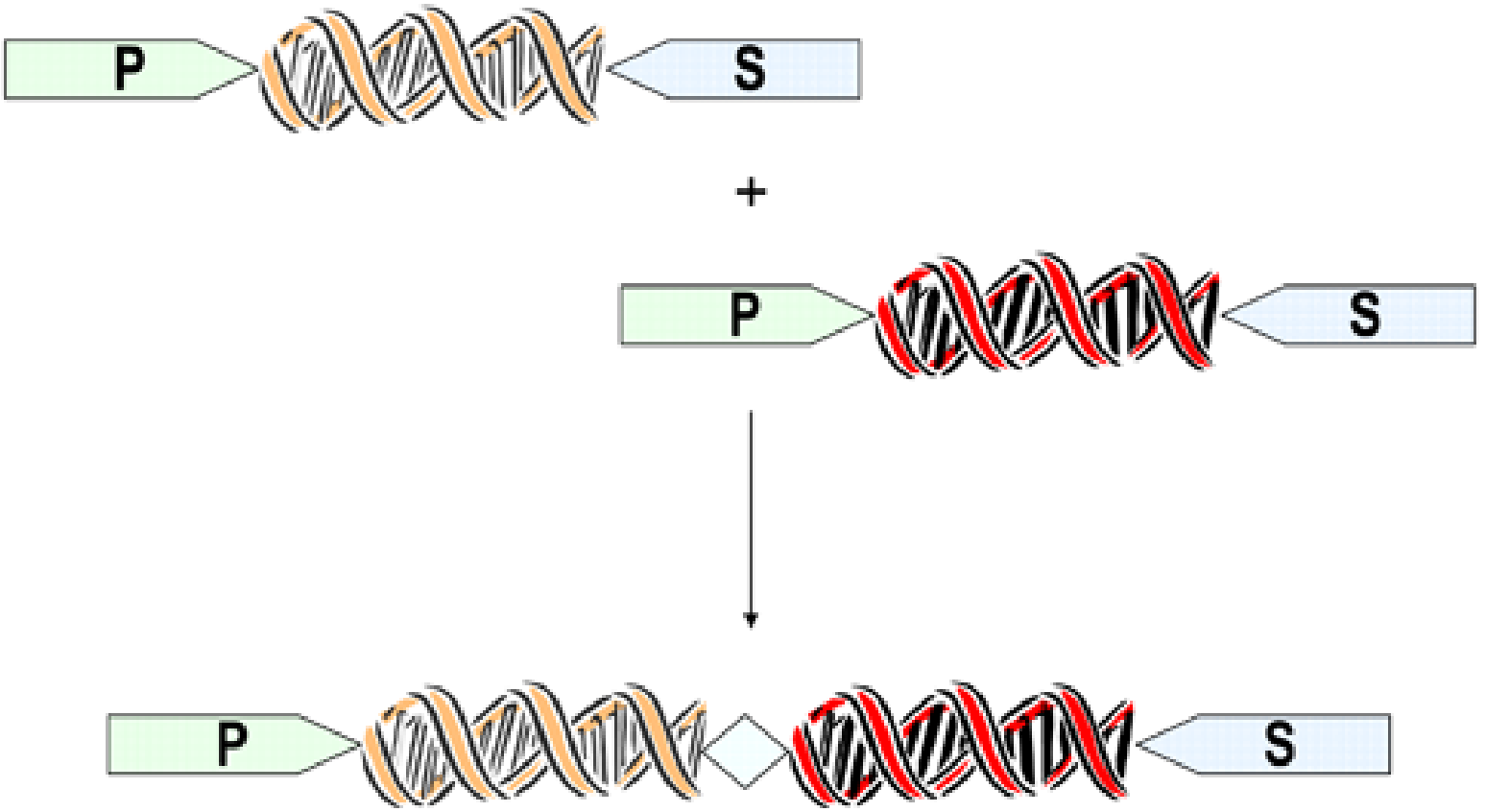
- Mission
  - Promote responsible synthetic biology
- Managed the Registry of Standard Biological Parts
  - BioBrick™ standard parts
- Ran the iGEM Olympics
- Ethic
  - Open works better than proprietary, especially for basic building blocks



REGISTRY OF STANDARD BIOLOGICAL PARTS

- Collection of ~7100 genetic parts
  - Growing rapidly in size
  - Can be mixed and matched to build synthetic biology devices and systems
- Based on the principle of "get some, give some"
- Founded in 2003 at MIT
- Provides a resource of available genetic parts to iGEM teams and academic labs
- Expectation
  - Users will contribute back information and data on existing parts and new parts to grow and improve this community resource

BioBrick™ FORMAT



BioBrick™ SPECIFICATIONS

- Standardized, continuous DNA sequence encoding a basic biological function
- Unique DNA sequence
- BioBrick™ parts defined by DNA sequence
- Composite BioBrick™ parts are "sequences" of BioBrick™ parts plus intervening "scars"
- BioBrick™ standard biological parts should conform to the BioBrick™ part assembly standard

Part:BBa_C0179 (lasR activator)

- atggccttgg ttgacggttt tcttgagctg gaacgctcaa gtggaaaatt ggagtggagc gccatcctcc agaagatggc gagcgacctt ggattctcga taccggaacc aactgccaaa agaactcgac cttgcgagtt caccttttaa cctcacctcg cggtaggagg tcttctaccg ctcgctggaa cctaagagct agatcctgtt cggcctgttg cctaaggaca gccaggacta cgagaacgcc ttcatcgtcg gcaactaccc ggccgcctgg cgcgagcatt acgaccgggc tctaggacaa gccggacaac ggattcctgt cggtcctgat gctcttgcgg aagtagcagc cgttgatggg ccggcggacc gcgctcgtaa tgctggcccg tggctacgcg cgggtcgacc cgacggtcag tcactgtacc cagagcgtac tgccgatttt ctgggaaccg tccatctacc agacgcgaaa gcagcacgag accgatgcgc gcccagctgg gctgccagtc agtgacatgg gtctcgcatg acggctaaaa gacccttggc aggtagatgg tctgcgcttt cgtcgtgctc ttcttcgagg aagcctcggc cgccggcctg gtgtatgggc tgaccatgcc gctgcatggt gctcgcggcg aactcggcgc gctgagcctc agcgtggaag aagaagctcc ttcggagccg gcggccggac cacatacccg actggtacgg cgacgtacca cgagcgccgc ttgagccgcg cgactcggag tcgcaccttc cggaaaaccg ggccgaggcc aaccgtttca tagagtcggt cctgccgacc ctgtggatgc tcaaggacta cgcactgcaa agcggtgccg gactggcctt gccttttggc ccggctccgg ttggcaaagt atctcagcca ggacggctgg gacacctacg agttcctgat gcgtgacgtt tcgccacggc ctgaccggaa cgaacatccg gtcagcaaac cggtggttct gaccagccgg gagaaggaag tgttgcagtg gtgcgccatc ggcaagacca gttgggagat atcggttatc gcttgtaggc cagtcgtttg gccaccaaga ctggtcggcc ctcttccttc acaacgtcac cacgcggtag ccgttctggt caaccctcta tagccaata tgcaactgct cggaagccaa tgtgaacttc catatgggaa atattcggcg gaagttcggt gtgacctccc gccgcgtagc ggccattatg gccgttaatt acgttgacga gccttcggtt acacttgaag gtataccctt tataagccgc cttcaagcca cactggaggg cggcgcatcg ccggtaatac cggcaattaa tgggtcttat tactctctaa taa

IGEM COMPETITION

- Undergraduate and high school synthetic biology competition (hundreds of teams; thousands of competitors)
- Teams given kit of biological parts from the Registry of Standard Biological Parts
- Teams use these parts, and new parts of their own design, to build biological systems and operate them in living cells
- Teams expected to give Registry new BioBrick™ parts

STANDARDS

- Engineering and computer science influence
  - Standards setting, interoperability, and interchangeability
- Ethos of open innovation
  - Prominent concerns about intellectual property (primarily patents)
- Roles of standards
  - "[T]he 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." (Endy 2005)
  - Structure, function, description, measurement, data, information exchange, software, biosafety and biosecurity, and even law

TECHNICAL STANDARDS

- Physical composition
  - Physical assembly of individual biological parts into multi-component systems
    - BBF RFC 10 uses iterative restriction enzyme digestion and ligation reactions to assemble small biological parts into larger composite parts
    - Gibson Assembly™, Seamless Ligation Cloning Extract ("SLiCE"), *etc.*, enable the seamless construction of large DNA molecules without sequence constraints on the design of biological parts
    - *De novo* DNA synthesis
- Functional composition
  - *E.g.*, Polymerase Per Second ("PoPS")
- Units of measurement
  - *E.g.*, Relative Promoter Unit ("RPU")
- Data exchange
  - *E.g.*, Synthetic Biology Open Language ("SBOL")

SSOs & IP POLICIES

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.

SBOL-COMPLIANT SOFTWARE TOOLS

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)
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)
Eugene	A human- and machine-readable language for the specification of biological constructs.	http://eugenecad.org	Bilitichenko et al. (2011)
GD-ICE	An open source registry platform for managing information about biological parts.	http://code.google.com/p/gd-ice/	Ham et al. (2012)
GenoCAD	A web-based application to design protein expression vectors, artificial gene network, and other genetic constructs	http://genocad.org	Czar et al. (2009)
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)
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)
TinkerCell	An application for bringing together models, information and algorithms.	http://www.tinkercell.com	Chandran et al. (2009)

BIOSECURITY STANDARDS

- Asilomar Conference (1975) on biosafety
- Synthetic Biology 2.0 (2006)
  - Discussion of biosecurity standards setting, but no consensus
- International Consortium for Polynucleotide Synthesis ("ICPS")
  - Oversight framework for the DNA synthesis industry
- International Association of Synthetic Biology ("IASB")
  - Developed a code of conduct for assessing the safety of DNA sequence orders
- HHS (2010)
  - Issued guidance which appears likely to be widely adopted

BIOSECURITY STANDARDS

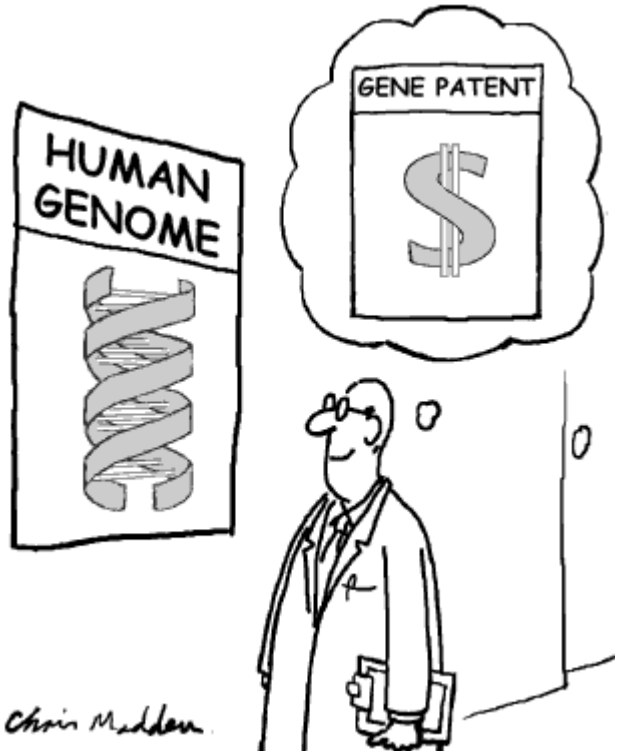
Standards Setting Organization	Year started	Biosecurity Standards
The International Consortium for Polynucleotide Synthesis (ICPS)	2007	The ICPS developed a plan for creating an effective oversight framework for the DNA synthesis industry.
International Association of Synthetic Biology (IASB)	2008	The 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.

LEGAL STANDARDS

- BioBrick Foundation
  - Designed two agreements to govern use and contribution of standardized synthetic biological parts
    - 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
  - Agreements encourage adoption of a legal standard on users or contributors BioBrick™ parts, and include provisions on attribution, safety, and intellectual property rights
  - BioBrick™ Public Agreement asks contributors to promise not to assert any patents they possess covering any parts they contribute under the contract

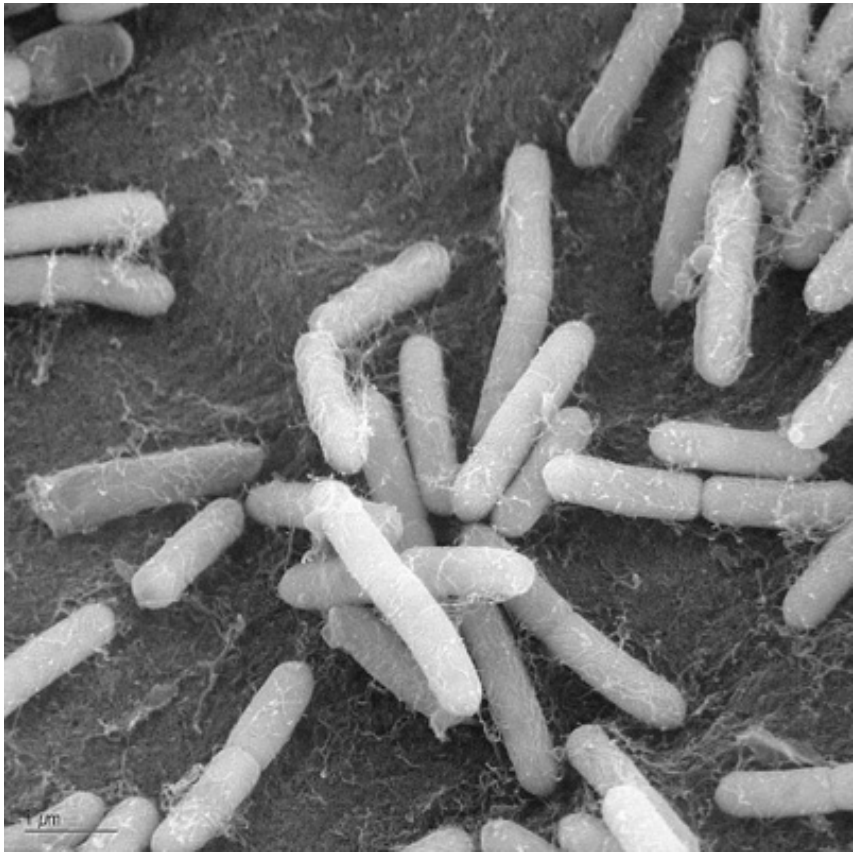
INTELLECTUAL PROPERTY

- Intellectual property
  - Trade secrecy
  - Copyright
  - Trademark
  - Patent
    - *Chakrabarty*
    - *Myriad*
    - *Prometheus*



CHAKRABARTY

- *Diamond v. Chakrabarty* (U.S. 1980)
  - One cannot patent
    - "[t]he laws of nature, physical phenomena, and abstract ideas have been held not patentable."
  - One can patent
    - "**anything under the sun that is made by man**"
      - Includes
        - Microorganisms
        - Plants
        - Animals
        - Genes
- Thousands of patents have claims to DNA
  - Natural source
  - Synthetic



GENE PATENT CONTROVERSY

- More than 20% of human genes are mentioned in patents (Jensen & Murray 2005)
- "To the person in the street, the grant of a patent covering all potential uses of these genes raises the visceral fear of corporate interests claiming ownership over our very bodies!" (Crease & Schlich 2003)
- "YOU, or someone you love, may die because of a gene patent. . . Gene patents are now used to halt research, prevent medical testing and keep vital information from you and your doctor." (Crichton 2007)
- Synthetic biology is likely susceptible to considerable risk of patent infringement


The United States of America

The Director of the United States Patent and Trademark Office

Has received an application for a patent for a new and useful invention. The title and description of the invention are enclosed. The requirements of law have been complied with, and it has been determined that a patent on the invention shall be granted under the law.

Therefore, this

United States Patent

Grants to the person(s) having title to this patent the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States of America or importing the invention into the United States of America for the term set forth below, subject to the payment of maintenance fees as provided by law.

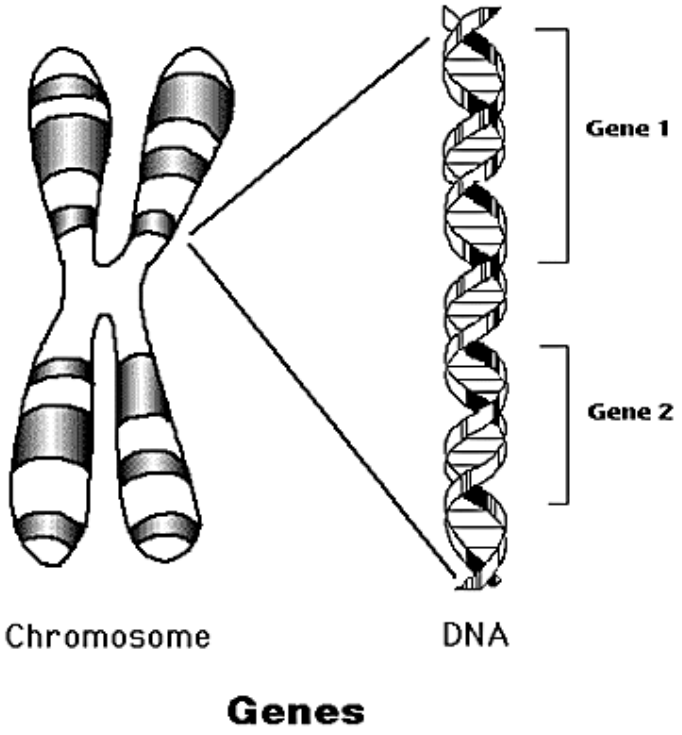
If this application was filed prior to June 8, 1995, the term of this patent is the longer of seventeen years from the date of grant of this patent or twenty years from the earliest effective U.S. filing date of the application, subject to any statutory extension.

If this application was filed on or after June 8, 1995, the term of this patent is twenty years from the U.S. filing date, subject to any statutory extension. If the application contains a specific reference to an earlier filed application or applications under 35 U.S.C. 120, 121 or 365(c), the term of the patent is twenty years from the date on which the earliest application was filed, subject to any statutory extensions.

Director of the United States Patent and Trademark Office

GENE PATENT LAW

- *In re Fisher* (CAFC 2005)
  - Cast doubt over EST patents
- Empirical evidence
  - Only 6 litigations on 13 human genes, and no findings of infringement
    - "not one of the 4,270 patents…has ever been found to have been infringed or been the basis of a preliminary injunction." (Holman 2007)
- Xavier Becerra
  - Proposed "Genomic Research and Accessibility Act of 2007" *etc.*
- America Invents Act §33

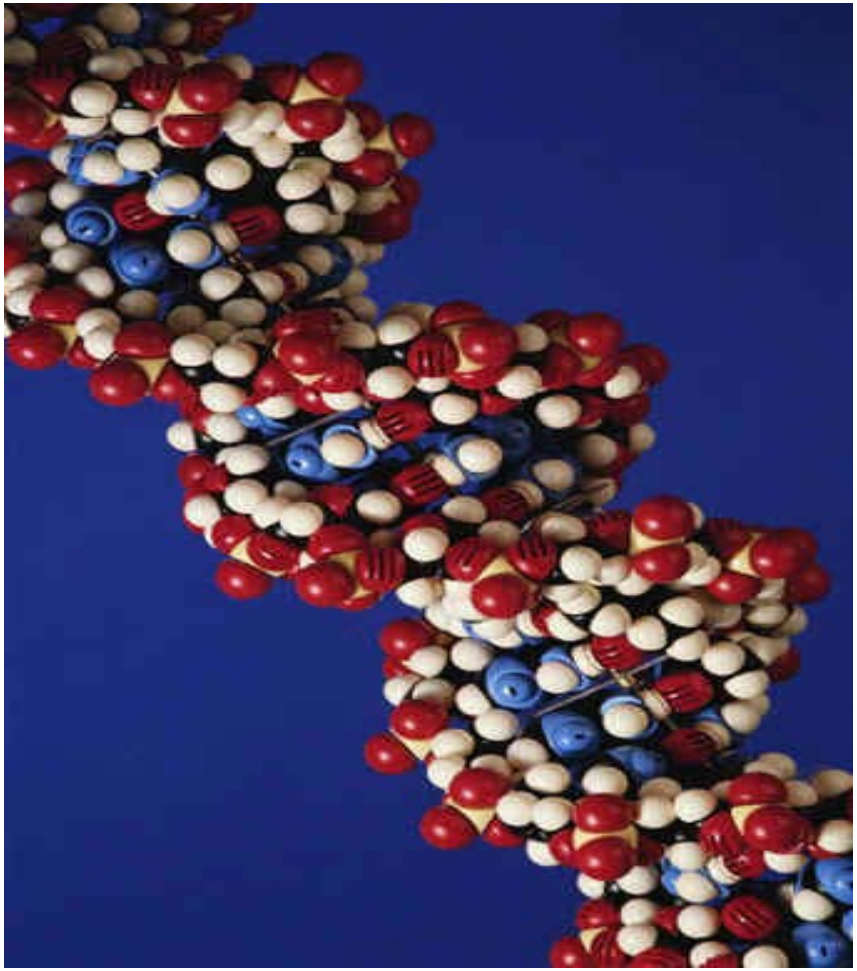


MYRIAD

- ACLU
  - "[e]very person's body contains human genes, passed down to each individual from his or her parents. These genes determine, in part, the structure and function of every human body. **This case challenges the legality and constitutionality of granting patents over this most basic element of every person's individuality.**"
- ACLU v. USPTO and MYRIAD
  - "[Genes'] purification from the body, using well-known techniques, renders it patentable by transforming it into something distinctly different in character. Many, however, including scientists in the field of molecular biology and genomics, have considered this practice a "lawyer's trick" that circumvents the prohibitions on the direct patenting of DNA in our bodies but which, in practice, reaches the same result…It is concluded that DNA's existence in an "isolated" form alters neither this fundamental quality of DNA as it exists in the body nor the information it encodes. **Therefore, [they] are deemed unpatentable subject matter under 35 USC 101.**"

U.S. JUSTICE DEPARTMENT

- Myriad appealed to Court of Appeals for the Federal Circuit ("CAFC")
- On October 29, 2010, the Department of Justice filed an *amicus curiae* brief in *ACLU v. USPTO and Myriad*
  - Unpatentable
    - "isolated but otherwise unmodified genomic DNA"
  - Patentable
    - "human-engineered DNA molecules"
  - May mark a new U.S. patent policy
  - Apparent departure from USPTO policy



PROMETHEUS

- On March 20, 2012, Supreme Court unanimously decided *Mayo v. Prometheus*
  - Cast substantial doubt on patentability of many biotechnology inventions
- On March 26, 2012, Supreme Court vacated and remanded CAFC case upholding gene patents
  - Ordered CAFC to reconsider in light of *Prometheus*
  - CAFC again upheld gene patents
  - On September 24, 2012, petition for appeal to Supreme Court filed
- Future of non-synthetic gene patents cloudy
  - Synthetic DNA likely to remain patentable

CONCLUSIONS

- Considerable emphasis on standards setting, but with limited success thus far
  - Unique demography
    - Non-biologists and DIYbiologists
  - Fast-evolving technology
  - U.S. guidance on biosecurity
- Despite flux in DNA patent law, synthetic DNA sequences likely to remain patentable
  - Potential threat of infringement, but little litigation
- Important and instructive to watch standards setting and intellectual property in synthetic biology